TITLE PAGE

STUDY PROTOCOL

Protocol Title: A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Protocol Number: ATI001-204

Phase: II

Date of Protocol:
Amendment 2: 08 January 2020
Amendment 1: 09 May 2019
Original: 07 February 2019

Sponsor: Ziopharm Oncology, Inc.
[redacted]

Medical Monitor: [redacted]

Safety Reporting: [redacted]

1. CLINICAL PROTOCOL SYNOPSIS

Title	A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma
Protocol Number	ATI001-204
Clinical Phase	Phase II
Research Hypothesis	Among subjects with recurrent or progressive glioblastoma, Ad-RTS-hIL-12 and veledimex in combination with cemiplimab-rwlc (Libtayo®) can be safely administered, show evidence of efficacy, and can induce signals of immune activity.
Study Objectives	**Primary Objectives** To determine the safety and efficacy of intratumoral [redacted] (Ad-RTS-hIL-12) and oral (PO) veledimex [redacted] in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively. **Secondary Objectives** • To determine the survival rates at 6, 12, 18 and 24 months • To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months • To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months • To determine the tumor response rates at 6, 12, 18 and 24 months [redacted]
Investigational Product(s)	Ad-RTS-hIL-12 + veledimex: [redacted]

	[redacted] Cemiplimab-rwlc Cemiplimab-rwlc (Libtayo®) is a programmed death receptor-1 (PD-1) blocking antibody.
Number of Centers	Approximately 10 centers
Number of Subjects	Approximately 36 subjects
Study Design	This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 [redacted] and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively, in the presence of variable systemic corticosteroid exposure. This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility. [redacted] Subjects will receive cemiplimab-rwlc on Day -7 (±3days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection of Ad-RTS-hIL-12 and Ad-RTS-hIL-12 ([redacted] will be administered by freehand injection. Ad-RTS-hIL-12 will be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). [redacted] The total amount of virus delivered to each site will be recorded in the electronic Case Report Form (eCRF). If the total administered (injected) volume is less than

	planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations. After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing. Subjects will receive a dose of cemiplimab-rwlc (350 mg) on Day 15 and every three weeks thereafter (Q3W) until confirmed progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the safety follow-up period. Delays in cemiplimab-rwlc dosing due to toxicity are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days. A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor. After the first six subjects have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused. The SRC will review safety data after the 6th subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products. The primary endpoint for evaluation of safety is: • The safety profile The primary endpoint for evaluation of efficacy is: • Overall survival (OS) Secondary endpoints include: • Overall Survival rate at 6, 12, 18 and 24 months • PFS, and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months • Objective Response Rate at 6, 12, 18 and 24 months • To determine the tumor response rate at 6, 12, 18 and 24 months [redacted]

Dose & Schedule	**Ad-RTS-hIL-12:** intratumoral [redacted] vp administered on Day 0 **Veledimex**: 20 mg PO QD on Days 0 to 14 **Cemiplimab-rwlc**: 350 mg IV on Day -7, Day 15, and approximately every 3 weeks (Q3W) until confirmed progression (iRANO), unacceptable toxicity or subject withdrawal.
Therapy Duration	From administration of the first study drug (cemiplimab-rwlc) until the subject has confirmed progressive disease per iRANO, unacceptable toxicity, the subject withdraws consent, or the end of the follow-up period.
Eligible Population	The eligible study population includes adult subjects with recurrent or progressive glioblastoma for which there is no alternative curative therapy. **Eligibility Criteria** Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells. **Inclusion Criteria** 1. Male or female subject ≥18 and ≤75 years of age 2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures 3. Histologically confirmed glioblastoma from archival tissue 4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy. Multifocal disease is allowed, but subjects must not have more than 5 enhancing lesions. 5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be

	allowed only after consultation with the Medical Monitor) a. Nitrosoureas: 6 weeks b. Other cytotoxic agents: 4 weeks c. Antiangiogenic agents: 4 weeks d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks e. Vaccine-based or CAR-T therapy: 3 months 6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment 7. Karnofsky Performance Status ≥70 8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements: a. Hemoglobin ≥9 g/L b. Lymphocytes >500/mm^3 c. Absolute neutrophil count ≥1500/mm^3 d. Platelets ≥100,000/mm^3 e. Serum creatinine ≤1.5 x upper limit of normal (ULN) f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN g. Total bilirubin <1.5 x ULN h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) within normal institutional limits 9. Female of child bearing potential* and sexually active male subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine

device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrhoeic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Normal cardiac and pulmonary function as evidenced by a normal ECG with QTc ≤450 msec and peripheral oxygen saturation (SpO2) ≥92% on Room air by pulse oximetry

Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment of disease with bevacizumab [redacted]
3. Subjects receiving systemic corticosteroids for treatment of disease-related symptoms during the 4 weeks prior to Day -7
4. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
5. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

NOTE:

- Subjects with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are

	permitted. For Subjects with controlled HIV infection, monitoring will be performed per local standards. • Subjects with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Subjects with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug. • Subjects who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted. 6. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively. 7. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed. 8. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer 9. Nursing or pregnant females 10. Prior exposure to veledimex 11. Use of an investigational product within prior 30 days. 12. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells

	13. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor 14. Presence of any contraindication for a neurosurgical procedure 15. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of deep vein thrombosis (DVT) may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor. 16. Unstable or clinically significant medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples include, but are not limited to, a history of myocarditis or congestive heart failure (as defined by New York Heart Association Functional Class III or IV), unstable angina, serious uncontrolled cardiac arrythmia, myocardial infarction within 6 months of screening, active interstitial lung disease (ILD)/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids uncontrolled asthma, or colitis.
Stopping Rules	From Day -7 to 30 days after completion of Ad-RTS-hIL12 + veledimex dosing, if any subject experienced a death (other than death related to progressive disease); or if any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.

Statistical Methods	**Analysis Populations** • The safety population will be comprised of all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex • The per protocol population will be comprised of subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post Ad-RTS-hIL-12 dose of veledimex, at least 1 post Ad-RTS-hIL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation (i.e., subjects who have had minor protocol violation(s) that are deemed not to impact efficacy will be included in this analysis population.) • [redacted] **Safety Evaluation** Safety will be evaluated based on frequency, severity and relatedness of adverse events (AEs), Serious adverse events (SAEs), laboratory abnormalities, electrocardiograms (ECGs), vital signs and physical/neurologic examination findings. The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5. Relatedness of adverse events will be assessed by the investigator and sponsor independently. The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug. **Efficacy Evaluation** • The primary analysis for efficacy is based on the per protocol population. • Secondary analyses for all efficacy endpoints will be based on the Safety population. The primary endpoint for evaluation of efficacy is: • The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.

- The per protocol population will be followed from the first date of treatment up to 2 years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

Secondary endpoints include:

- The OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

<u>Tumor Response Assessments:</u>

The Per Protocol Population will be evaluated for ORR, PFS, PSP, and OS. Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, efforts will be made to encourage obtaining additional to confirm disease progression.

- Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression

	(estimate of PFS). A baseline MRI will be performed within 24 hours (a +48-hour window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines • Independent tumor response assessments, as well as post-treatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines. • Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bi-dimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD). [redacted]

	[redacted]
Sample Size Determination	We plan to accrue up to 36 subjects to obtain approximately 25 subjects evaluable for efficacy. This subject population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS at 12 weeks. A sample size of approximately 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19. Note: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that enough subjects have measurable disease for evaluation of overall response rate per iRANO criteria. In addition, a toxicity boundary based on repeated significance testing provides a guideline for stopping the trial if the number of subjects experiencing unacceptable toxicity exceeds the proportions below, assuming a 30% toxicity rate is acceptable and 60% would be unacceptable: Low boundary: 3/5 5/10 8/15 9/20 11/25 High boundary: 3/5 6/10 8/15 10/20 11/25 Note: A sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) a 10% standard error of the estimate assuming the binomial estimation method.
Study Duration	The duration of this study from the time of initiating subject screening until the completion of survival follow-up is anticipated to be approximately 36 months, including 12 months for enrollment and 24 months of follow-up. The start of study is defined as the date when the first subject is consented into the study and the study stop date is the date of the last subject's last visit.

Table 1: Schedule of Study Procedures

Activity	Screening	Treatment							
	Day -30 to -8*	**Day -7 ****	**Day 0[a]**	**Day 1**	**Day 2**	**Day 3**	**Day 4 to 6**	**Day 7**	**Day 8 to 13**
Informed consent	X								
Medical/Cancer history[d]	X								
Physical exam[e], including targeted neurological exam	X	X	X	X	X	X		X	
Karnofsky PS[f]	X	X	X						
Height (screen) and weight	X							X	
Vital signs[g]	X	X	X	X	X	X		X	
Adverse events[h]	CONTINUOUS								
Concomitant medications[h]	CONTINUOUS								
Survival status[i]	CONTINUOUS								
Pregnancy test[j]	X	X	X						
Hematology[k]	X	X	X[a]	X	X	X		X	
Coagulation[l]	X		X[a]	X		X		X	
Serum chemistry[m]	X	X	X[a]	X	X	X		X	
Urinalysis[n]	X	X	X[a]			X		X	
Thyroid panel[o]	X								
ECG[p]	X		X			X		X	
Confirm eligibility		X[q]							
Cemiplimab-rwlc dose[q]		X							
Ad-RTS-hIL-12			X[r,s]						
Veledimex dose and diary[v]			X[s, t]	X[s, t]	X	X[u]	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]					[redacted]			
MRI scans[z]	X[z]			X[z, aa]					
[redacted]			[redacted]						
[redacted]	[redacted]							[redacted]	

Table 1: Schedule of Study Procedures (continued)

Activity	Treatment							Long Term Follow-up
	Day 14	Day 15	Day 22	Day 28	Day 36 ±3 days	Day 57 ±3 days	Every 3 weeks[b] ±7days	Every 8 weeks[c] ±7days
Informed consent								
Medical/Cancer history[d]								
Physical exam[e], including targeted neurological exam	X				X		X	
Karnofsky PS[f]	X				X		X	
Height (screen) and weight	X				X			
Vital signs[g]	X				X		X	
Adverse events[h]	CONTINUOUS							
Concomitant medications[h]	CONTINUOUS							
Survival status[i]	CONTINUOUS							
Pregnancy test[j]				X	X		X	
Hematology[k]	X		X		X	X	X	
Coagulation[l]	X				X			
Serum chemistry[m]	X		X		X	X	X	
Urinalysis[n]	X		X			X	X	
Thyroid panel[o]	X				X	X	X	
ECG[p]	X				X		X	
Confirm eligibility								
Cemiplimab-rwlc dose[q]		X			X	X	X	
Ad-RTS-hIL-12								
Veledimex dose and diary	X[v]							
[redacted]	[redacted]			[redacted]				
[redacted]	[redacted]			[redacted]				
[redacted]	[redacted]			[redacted]				
MRI scans[z]						X[z]		X[z]
[redacted]								
[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	

[redacted] Screening assessments must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex.
[**] Day -7 dosing with cemiplimab-rwlc may be performed within ± 3 days.
[a] The PI will review all results of laboratory tests drawn within 24 hours prior to surgery.
[b] Every 3 weeks from Day 57
[c] Every 8 weeks from Day 57 in addition to assessments performed every 3 weeks
[d] Medical history includes demographic information, relevant medical and surgical history. Cancer history includes current cancer diagnosis, prior treatment (regimen[s], doses, start and stop dates, and

any associated residual toxicity), and best response for each regimen.

[e] A complete physical examination including a neurological exam and mental status is required at baseline and discharge from hospital. Targeted neurological exams thereafter.

[f] KPS is required at Screening, Day -7, Day 0, Day 14, Day 36 and every 3 weeks thereafter.

[g] Blood pressure, pulse, temperature, and respiration will be recorded. Pulse oximetry peripheral oxygen situation (SpO2) will be recorded at Screening, Day -7, Day 0, Day 3, Day 7, Day 14, Day 36 and every 3 weeks from Day 57. Blood pressure should be monitored closely, with hydration as needed to prevent hypotension after veledimex administration. Subjects must be instructed to maintain adequate oral hydration on and between veledimex dosing days; sites must closely monitor hydration status.

[h] Concomitant medications will be monitored and recorded throughout the study. Medications received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.

[i] Subjects will be followed to document start of new anticancer therapies and survival status for 2 years following administration of Ad-RTS-hIL-12.

[j] Serum pregnancy test at Screening for females of childbearing potential, must be within 72 hours prior to first dose of cemiplimab-rwlc; urine or serum pregnancy test on all other days.

[k] Hematology: Complete blood count, white blood count with differential, red blood cell count, red blood cell indices, hematocrit, hemoglobin, and platelet count. The Day 0 testing should be obtained prior to veledimex dosing.

[l] Coagulation: aPTT, INR, erythrocyte sedimentation rate and C-reactive protein. The Day 0 testing should be obtained prior to veledimex dosing.

[m] Serum Chemistry: AST, ALT, lactate dehydrogenase, alkaline phosphatase, lipase, amylase, creatinine, total bilirubin, total protein, albumin, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate. The Day 0 testing should be obtained prior to veledimex dosing.

[n] Urinalysis Panel (dipstick): appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals and cells may be done if indicated. The Day 0 testing should be obtained prior to veledimex dosing.

[o] Thyroid Panel: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)

[p] Standard 12-lead ECG; single measurement at each time point. The Day 0 testing should be obtained prior to veledimex dosing.

[q] Eligibility must be confirmed within 24 hours prior to dosing with cemiplimab-rwlc. In the event of toxicities likely related to cemiplimab-rwlc, the PI and the Medical Monitor will individualize the management of cemiplimab-rwlc dosing in general accordance with the Investigator's Brochure. Doses must be at least 21 days apart. Delays of up to 14 days are acceptable for toxicity, in consultation with the medical monitor.

[r] Ad-RTS-hIL-12 intratumoral injection should be administered by freehand injection. Subjects must be instructed to maintain adequate oral hydration during the Treatment Period; sites must closely monitor subjects' hydration status. Because of the potential for toxicity (e.g., fevers, chills, fatigue, and dehydration), administration of prophylactic antipyretics is recommended after injection of Ad-RTS-hIL-12.

[s] Each subject will be carefully monitored for any local reactions and/or hypersensitivity reactions following the Ad-RTS-hIL-12 injection and veledimex administration. Subjects should be instructed to call the clinical site if headache, hemiparesis, seizure, or other local reactions develop anytime and especially between study visits.

[t] The first post-resection veledimex dose will be given on the next day, designated as Day 1, under supervision of the clinical staff to ensure there are no difficulties swallowing the capsule. Subsequent veledimex doses are to be taken once daily, in the morning and within 30 minutes of a regular meal.

[u] The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.

[v] Study sites must assess compliance of veledimex dosing. Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time of the daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff for assessment of compliance.

[redacted]

[y] Optional assessment, as total blood volume for phlebotomy clinically permits

[z] Appropriate cancer staging procedures should be performed during screening. If a pre-operative MRI for surgical planning is obtained it will be collected by Sponsor. All imaging should be of diagnostic quality. The brain will be imaged using the same method(s) throughout the study. Measurable target lesions should be selected and measured per iRANO guidelines. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Additional tumor response assessments as well as a posttreatment diagnostic brain biopsy may be performed at the discretion of the Investigator as part of standard-of-care treatment, per current iRANO guidelines. MRI scans are required for all subjects, including those with unconfirmed disease progression, to ensure that more slowly declining tumor burden in response to therapy is noted. For 2 years, subjects without confirmed disease progression should continue to have tumor assessments every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation). MRI scans should be available for collection upon Sponsor request. If appropriate, in accordance with iRANO, subjects should continue to receive cemiplimab-rwlc until progression has been confirmed.

[redacted]

Figure 1: Study Schema

* Tumor sample to be obtained at repeat resection or via biopsy to confirm progression.

2. TABLE OF CONTENTS

3. LIST OF TABLES

4. LIST OF FIGURES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ab	Antibody
Ad	Ad-RTS-hIL-12 or Ad-RTS-mIL-12, depending on context
[redacted]	[redacted]
[redacted]	[redacted]
ALVAC	Canarypox virus viral vectors
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
BBB	(Putative) blood-brain barrier
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
CHO	Chinese hamster ovary
CR	Complete response
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP3A4 or CYP450 3A4	Cytochrome P450 3A4
DIPG	Diffuse intrinsic pontine glioma
DP	Drug product
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report form
EIAED	Anti-epileptic drugs

Abbreviation or Specialist Term	Explanation
EMCV	Encephalomyocarditis virus
ESR	Erythrocyte sedimentation rate
FDA	U.S. Food and Drug Administration
Gal4-EcR	Fusion protein between Gal4 DNA binding domain and ecdysone receptor ligand binding domain
GalRE/P	Gal4 responsive promoter
GBM	Glioblastoma (multiforme)
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
hIL-12	Human interleukin-12
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-β	Interferon-beta
IFN-γ	Interferon-gamma
INR	International normalized ratio
IL-2	Interleukin-2
IL-12	Interleukin-12
IP-10	IFN-γ-induced protein 10
iRANO	Immunotherapy Response Assessment for Neuro-Oncology
IRB	Institutional Review Board
IV	Intravenous(ly)
IRES	internal ribosome entry site
IUD	Intrauterine device
KDa	kilo (K)- unified atomic mass units (Daltons or Da)
LDH	Lactate dehydrogenase
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

Abbreviation or Specialist Term	Explanation
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NK	Natural killer
NOS	Not otherwise specified
NPO	Nothing by mouth (literally, nil per os)
ORR	Objective response rate
OS	Overall survival
OSP	Overall Safety Population
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PKP	Pharmacokinetics Population
PO	Oral(ly)
polyA	polyadenylation signal
PR	Partial response
PSP	Pseudo-progression
PUbC	Ubiquitin C promoter
Q	Each/every (*quaque*), as in Q3W (every 3 weeks)
QD	Each day (*quaque die*)
rAd	Recombinant adenovirus
RANO	Response Assessment for Neuro-Oncology
RBC	Red blood cell
rhIL-12	Recombinant human IL-12
[redacted]	[redacted]
RXR	Retinoid X receptor
SAE	Serious adverse event
SD	Stable disease
SpO_2	Saturation of peripheral oxygen
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
Th1	T-helper cell type 1

Abbreviation or Specialist Term	Explanation
ULN	Upper limit of normal
V	Veledimex
v	Version (followed by number)
vp	Viral particles
VP16-RXR	Fusion between VP16 transcriptional activation domain and a chimeric RXR
WBC	White blood cell

6. INTRODUCTION

6.1. Immunotherapy in Glioblastoma

The revised 2016 World Health Organization Classification of Tumors of the Central Nervous System makes use of molecular genetic findings in addition to histology to define tumor entities based on combined phenotypic and genotypic features to generate "integrated diagnoses" (Louis et al. 2016). It has resulted in substantial restructuring of the diffuse gliomas, as compared with the 2007 CNS WHO Classification. In the revised classification the diffuse gliomas include the anaplastic astrocytomas (anaplastic astrocytoma, IDH-wildtype; anaplastic astrocytoma, IDH-mutant; and anaplastic astrocytoma, NOS [Not Otherwise Specified]) and anaplastic oligodendroglioma (with IDH-mutant and 1p/19q-codeleted subtypes) that are classified as WHO Grade III and the glioblastomas (glioblastoma, IDH-wildtype including giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma subtypes; glioblastoma, IDH-mutant; and glioblastoma, NOS) that are classified as WHO Grade IV. Of the WHO Grade III and Grade IV tumors, glioblastomas make up 60% to 70%, anaplastic astrocytomas 10% to 15%, and several other anaplastic subtypes the rest (Central Brain Tumor Registry).

Glioblastomas are by far the most frequent malignant glioma and are associated with a particularly aggressive course and dismal prognosis (Lieberman 2017). Standard of care treatment for glioblastomas is based on surgical resection with the intent to remove as much of the tumor as is feasible (Fernandes et al. 2017, Paolillo et al. 2018). Resection is then followed by radiotherapy and concomitant adjuvant temozolomide. However, such aggressive treatment is associated with only modest improvements in survival. Newly diagnosed glioblastoma subjects have a median overall survival (OS) of 12 to 15 months (Ahmed et al. 2014) and 2-year OS rate of up to 27% (Omuro et al. 2013), while OS in subjects that have failed TMZ and bevacizumab, or equivalent salvage chemotherapy, is reported as being as short as 3 to 5 months (Omuro et al., 2013; Iwamoto et al., 2009). To date, no salvage treatment has been validated by Phase III data for recurrent or progressive glioblastoma. For subjects with recurrent glioblastoma, the median OS is 6 to 7 months (Omuro et al. 2013), and median progression-free survival (PFS) is 2 to 3 months.

The lack of standard and validated salvage therapies has prompted the use of nitrosoureas, temozolomide rechallenge, bevacizumab, and other targeted agents that are unsatisfactory treatment options. This likely reflects the complexities of disease heterogeneity, and the treatment limitations of brain tumors given the low activity of antineoplastic agents, de novo or acquired drug resistance, the sensitivity of the brain to irreversible damage in response to treatment and the presence of the blood brain barrier (BBB), which maintains the brain as a privileged compartment. Surgical resection may be offered for subjects with recurrent disease, with the goal of alleviating mass effect, improving symptoms, and achieving cytoreduction. Surgical resection, however, is limited by the infiltrative nature of the disease and the lack of clear margins delimitating the tumor. Given the poor overall prognosis and lack of effective treatments, new therapeutic approaches for malignant gliomas are needed.

Immunotherapy for brain tumors is actively being investigated with an array of newer therapeutic modalities. Only about a third of glioblastomas have been reported to demonstrate a robust CD8+ cell population present within the tumor microenvironment (Heimberger et al. 2008), and these cells are anergic (i.e., not secreting interferon gamma [IFN-γ] or incapable of cytolytic activity). The immune infiltration in glioblastomas is highly variable and is likely

driven by the genetic composition and mutational load of the tumor (Beier et al. 2012, Doucette et al. 2013). The anticipated specificity and efficiency of cytotoxic T-cells (CD8+), activated by local production of IL-12, is particularly attractive and may both spare normal brain cells and minimize systemic toxicity. We have shown in an orthotopic mouse model that survival and tumor killing was greatly enhanced by combining a checkpoint inhibitor and Ad-RTS-mIL-12 + veledimex (Barrett et al. 2016b). Early clinical trials suggest that combining immunotherapeutic approaches with surgery, radiation, and chemotherapy may improve outcomes (Mitchell et al. 2008). Preliminary results from the CheckMate 143 (NCT 02017717) randomized clinical trial in first recurrence of glioblastoma, announced in a World Federation of Neuro-Oncology Societies (WFNOS) 2017 abstract, demonstrated a failure of nivolumab to prolong overall survival of patients with recurrent GBM, and this monotherapy arm of the trial was prematurely terminated (Filley et al 2017). However, an encouraging example of a *combination* immunotherapy approach to treating glioblastoma is a study of the safety and activity of nivolumab (human programmed death receptor-1 [PD-1] blocking antibody) in combination with ipilimumab (anti-cytotoxic T lymphocyte associated antigen 4 [CTLA-4] antibody) in patients with recurrent disease (Reardon et al. 2016). In this ongoing dose escalation study, combination therapy was tolerable, with 12-month overall survival (OS) ranging from 25% to 40%.

In Ziopharm's ongoing Phase I trial of intratumoral viral delivery of Ad-RTS-hIL-12 + veledimex to date 31 subjects have been orally dosed in 4 cohorts: 10 mg (n=6), 20 mg (n=7), 30 mg (n=4), 40 mg (n=6), and an expansion cohort of 20 mg (n=8). Results show that veledimex crossed the blood-brain-barrier, with approximately 40% of plasma levels detected in the brain tumor. Subjects in the 20 mg dose cohort (n=15) have better median OS (12.7 months) than in other cohorts.

Immune checkpoint inhibitors penetration across the blood-brain-barrier to the tumor tissue remains controversial, but the goal is to achieve maximum therapeutic effect while limiting systemic toxicity, especially when CD8+ cells have been mobilized to the tumor as we have documented following treatment with Ad-RTS-hIL-12 + veledimex.

6.2. Interleukin-12 and Cancer Immunotherapy

Interleukin-12 (IL-12) is a pro-inflammatory cytokine and has been recognized as a master regulator of cell mediated immunity in response to intracellular pathogens and neoplastic transformation. Structurally, IL-12 is a heterodimeric protein composed of p35 and p40 subunits covalently linked to form the biologically active IL-12 p70 molecule (Carra et al. 2000). The expression of the p40 subunit is tightly regulated and requires specific priming and amplification signals through complex combinatorial matching of Toll receptor agonists and specific cytokines, thus limiting the cell types that can produce native biologically active IL-12 to activated antigen-presenting cells, neutrophils, and macrophages (Trinchieri 2003). On a secondary level, IL-12 production can also be negatively regulated through various mechanisms including production of IL-10 and transforming growth factor β (TGFβ).

Initial studies identified that IL-12 was produced by innate immune cells in response to pathogens and that it led to the production of interferon gamma (IFN-γ) and tumor necrosis alpha (TNFα) by T and natural killer (NK) cells (Micallef et al.1996, Trinchieri 2003). When it was discovered that IL-12 could drive naïve T-helper cell differentiation to the inflammatory T-helper cell type 1 (Th1) phenotype (Hsieh et al. 1993), a role for IL-12 was established as a bridge between innate immune cells and the adaptive immune response through polarization of

naïve CD4+ cells. More recent data demonstrate additional functional roles of IL-12 directly influencing CD8+ T-cell differentiation (Curtsinger et al. 2003, Kalinski et al. 1999) and the reactivation and survival of memory CD4+ T-cells (Yoo et al. 2002). This is particularly important in the context of the tumor microenvironment where high levels of IL-12 have been shown to repolarize antigen-experienced CD4+ T-cells back to the functional antitumor Th1 phenotype (Wesa et al. 2007).

Evidence that IL-12 is able to trigger innate and adaptive immunity and modulate the tumor microenvironment supports the relevance of IL-12 as an important immunotherapeutic agent. Its ability to activate and recruit dendritic cells that facilitate the cross-priming of tumor antigen-specific T-cells, along with its influence on NK and $CD8^+$ T-cell cytotoxic activities and antigen-specific antitumor responses (Mosmann et al. 1989, Trinchieri 1995, Tsung et al. 1997, Mailliard et al. 2002) warrant further study in cancer therapy. Additionally, IL-12 has also been shown to stimulate the production of superoxides and nitric oxide and possess potent antiangiogenic activity through IFN-γ (Voest et al. 1995, Wigginton et al. 1996, Coughlin et al. 1998). The potent antitumor activity of IL-12 has been well documented in various cancer mouse models including melanoma, mammary carcinoma, sarcoma, and colon and renal carcinoma (Colombo et al. 2002). The potent nature of its biological activity and signaling complexity has also prompted the study of different delivery mechanism with a focus on intratumoral delivery and tumor microenvironment modulation.

Based on such data, human studies of IL-12 as an anticancer agent were initiated. The first of these studies was a Phase I dose escalation of intravenous (IV) administered recombinant human IL-12 in subjects with either melanoma or renal cell carcinoma. The study reported a transient complete response in melanoma and a partial response in renal cell carcinoma with significant toxicities. The Phase II trial observed similar toxicities, and two IL-12 related deaths prompted the Food and Drug Administration (FDA) to suspend the trial (Atkins et al 1997, Leonard et al 1997). Additional studies confirmed that systemic administration of recombinant IL-12 resulted in significant toxicity, limiting its potential for clinical development (Salem et al. 2006). These results prompted the investigation of alternative delivery routes focusing on locoregional administration either by subcutaneous injection or intratumoral delivery implementing IL-12 as a direct anticancer therapeutic or as an adjuvant to vaccination.

6.4. Adenoviral Vectors for Gene Therapy

6.4.1. Adenoviral Safety

Adenoviral vectors have been used extensively to deliver a variety of gene products to human subjects, including cancer subjects. Although adenoviral vectors are immunogenic, virtually all recipients have pre-existing humoral immunity to adenoviruses and they are generally considered a safe and well tolerated vehicle for gene delivery. Numerous studies have utilized adenoviral vectors to achieve intratumoral expression of a variety of genes. In a Phase I/II clinical trial of subjects with prostate cancer, direct intraprostatic injection of a replication-defective adenoviral vector encoding bacterial nitroreductase (dose levels 5 x 10^{10} -1 × 10^{12} viral particles [vp]) was well tolerated, with minimal adverse events (AEs) (Patel et al. 2009) . A Phase I study of subjects with oral leukoplakia implemented multiple intraepithelial injections of recombinant adenovirus (rAd)-p53 (1 x 10^{8} vp/cm^2) and demonstrated good tolerance of the vector, with no evidence of dose-limiting toxicity (DLTs) (Zhang et al. 2009) . In another Phase I/II study of subjects with chemoradiation-resistant advanced esophageal carcinoma, intratumoral injections of adenovirus vector containing p53 (Ad.5CMV-p53) were well tolerated at doses ranging from 10 x 10^{11} to 25 x 10^{11} vp, with no DLTs, and generally mild to moderate adverse events (AEs) (Shimada et al. 2006) . The most common AEs were fever (all 10 subjects), pain (30% of subjects), and hyperglycemia, which was attributed to the use of total parental nutrition (30% of subjects). Hypocalcemia was reported in two subjects (20%) and one subject each (10%) experienced activated partial thromboplastin time (aPTT) prolongation, abnormally high serum amylase, and abnormally high serum creatinine.

In a Phase I study of subjects with advanced pancreatic, colorectal, or primary liver tumors, intratumoral injection of an adenoviral vector encoding hIL-12 (Ad.IL-12) was well tolerated at doses of up to 3 × 10^{12} vp. Common AEs were similar to symptoms observed with gene delivery by other adenoviral vectors, including transient, mild to moderate fever, malaise, sweating, and lymphopenia (Sangro et al. 2004).

A recent randomized, open-label, Phase III study compared a regimen of surgical resection, adenovirus-mediated gene therapy (intraoperative perilesional sitimagene ceradenovec), intravenous ganciclovir, and standard of care interventions versus surgical resection plus standard of care interventions in 250 subjects with newly diagnosed high-grade glioma amenable to resection. Results showed that although the time to death or re-intervention was prolonged,

OS was not improved for the investigational regimen relative to the standard of care regimen (Westphal et al. 2013). This apparent difference may have been due to the composite primary endpoint and/or that while OS is a robust endpoint, there is no discussion of effect size and for recently-diagnosed tumors it might be less suitable to capture meaningful treatment effects for the initial stages of disease because of uncontrolled therapy at relapse (*ibid*). Nevertheless, the authors concluded that the treatment had an increased hazard ratio for the primary analysis with a positive overall benefit-risk ratio, with similar AEs (hemiparesis [often transient], hyponatremia, and seizures, but no cerebral hemorrhages nor hematomas), as compared with the standard-of-care regimen.

6.4.1.1. Safety of Intratumoral Injection of IL-12 Gene Vectors

In contrast with the systemic toxicity resulting from administration of recombinant IL-12 protein, local administration of IL-12 via injection of plasmid or adenoviral vectors containing the hIL-12 gene has proven to be well tolerated in subjects with various cancers, and therefore appears to provide an effective delivery method for this potent immunomodulatory cytokine. Several studies have investigated the safety of intratumoral expression of IL-12 in subjects with metastatic melanoma. A Phase I study investigated intratumoral expression of IL-12 together with the co-stimulatory molecule B7.1 via two separate canarypox virus viral vectors (ALVAC) in subjects with metastatic melanoma and reported mild to moderate injection site reactions, fever, chills, myalgia, and fatigue as AEs (Triozzi et al. 2005). However, all subjects also developed antibodies to ALVAC. Notably, serum IL-12 and IFN-γ levels were not increased after treatment. Another Phase I trial showed that delivery by electroporation of a plasmid containing IL-12 to tumors in subjects with metastatic melanoma resulted in minimal systemic toxicity, with transient pain after electroporation being the most common AE (Daud et al. 2008). Results from another Phase I study showed that intratumoral injection of DNA encoding hIL-12 in subjects with metastatic melanoma was well tolerated overall (Heinzerling et al. 2005). Eight of nine subjects experienced a transient response at the intratumoral injection site, and some subjects who had tumor responses also showed some increases in systemic in IL-12, interferon gamma-induced protein 10 (IP-10), and IFN-γ.

Localized production of IL-12 also has been reported as well tolerated in subjects with other malignancies. For example, a Phase I study in 17 subjects with metastatic pancreatic, colorectal, or primary liver cancer examined intratumoral injection of dendritic cells engineered to secrete IL-12 via a rAD vector (Mazzolini et al. 2005). In that study, the most common AEs were lymphopenia, fever, and malaise. Subjects also developed antibodies to the adenoviral capsid proteins. Intraperitoneal injection of a plasmid containing the hIL-12 gene in women with chemotherapy-resistant, recurrent, ovarian cancer also was found to be generally safe and well tolerated (Anwer et al. 2010). Low-grade fever and abdominal pain were the most common AEs. Plasmid DNA was not detected in the subjects' serum samples, and treatment-related increases in IFN-γ levels were observed in pleural fluid, but not in serum. Similar data were reported in a study of subjects with advanced pancreatic, colorectal, or primary liver malignancies who received intratumoral injections of adenoviral vectors encoding hIL-12 at doses ranging from 2.5×10^{10} to 3×10^{12} vp (Sangro et al. 2004). In that study, treatment was well tolerated and a maximum tolerated dose (MTD) was not reached. Transient lymphopenia was observed in 86% of subjects, and the severity was increased at higher vector doses. Transient, mild to moderate fever, sometimes accompanied by malaise and sweating, was observed in ~ 60% of subjects during the first 2 days after the injection. Five of the 21 subjects (24%) experienced nausea

[redacted]

[redacted]

[redacted]

6.5.3. Veledimex

Veledimex is a diacylhydrazine that is fully active at the RTS receptor. Drug product is formulated as a semi-solid containing veledimex as a dry powder and excipients. This formulation has been encapsulated in gelatin capsules for oral administration in clinical trials.

Nonclinical studies *in vitro* and *in vivo* demonstrate that veledimex interacts with the receptor component EcR of RTS to induce the activation of therapeutic gene transcription, leading to the production of transgene messenger RNA and, ultimately, protein (Anderson et al. 2000, Palli et al. 2003, Karzenowski et al. 2005).

6.5.4. Cemiplimab-rwlc

Cemiplimab-rwlc (Libtayo ®), is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD L1-mediated T cell inhibition. Cemiplimab-rwlc was isolated from Regeneron's VelocImmune™ human antibody mouse platform and contains a human light chain variable domain fused to human kappa constant domain and a heavy chain variable region in a human IgG4 Fc format. The IgG4 Fc domain contains a serine to proline mutation in the hinge region to promote dimer stabilization, designated IgG4P.

6.9. Summary of Safety

Please see the Investigator's Brochure for the most current safety information.

7. STUDY OBJECTIVES

7.1. Primary Objective

To determine the safety and efficacy of intratumoral [redacted] (Ad-RTS-hIL-12) and oral (PO) veledimex [redacted] in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively.

7.2. Secondary Objectives

- To determine the survival rates at 6, 12, 18 and 24 months
- To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months
- To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months
- To determine the tumor response rates at 6, 12, 18 and 24 months
- [redacted]

8. STUDY DESIGN

8.1. Overall Study Design

This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 ([redacted] and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively.

This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility [redacted]

Subjects will receive cemiplimab-rwlc on Day -7 (±3 days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection and Ad-RTS-hIL-12 [redacted] will be administered by freehand injection. Ad-RTS-hIL-12 will be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). The total amount delivered to each site will be recorded in the eCRF. If the total administered volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations.

After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing.

Subjects will receive a dose of cemiplimab-rwlc (350 mg) IV on Day 15 and every three weeks thereafter (Q3W) until documented progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the follow-up period. Delays in cemiplimab-rwlc dosing due to toxicities are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days.

A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor.

After the first six patients have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused to allow for additional safety follow-up and assessment. The SRC will review safety data after the 6th subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products.

8.2. Study Oversight for Safety Evaluation

Safety oversight will occur through the site investigator and medical monitor. A formal SRC, guided by the SRC charter, will include the study investigators, the medical monitor and other appropriate sponsor representatives and will provide overall safety oversight. Additional

external medical and scientific experts may also be invited to participate in the reviews as needed and appropriate and as decided by the SRC. If a significant safety event occurs, the SRC will convene to evaluate the safety event(s) and make a recommendation and decision on the enrollment and continued treatment of subjects.

9. SUBJECT SELECTION

Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.

9.1. Inclusion Criteria

1. Male or female subject ≥18 and ≤75 years of age
2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures
3. Histologically confirmed glioblastoma from archival tissue
4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy. Multifocal disease is allowed, but subjects must not have more than 5 enhancing lesions.
5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor)
   a. Nitrosoureas: 6 weeks
   b. Other cytotoxic agents: 4 weeks
   c. Antiangiogenic agents: 4 weeks
   d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks
   e. Vaccine-based or CAR-T therapy: 3 months
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment
7. Karnofsky Performance Status ≥70
8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
   a. Hemoglobin ≥9 g/L
   b. Lymphocytes >500/mm^3
   c. Absolute neutrophil count ≥1500/mm^3
   d. Platelets ≥100,000/mm^3
   e. Serum creatinine ≤1.5 x upper limit of normal (ULN)
   f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN.
   g. Total bilirubin <1.5 x ULN

h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) within normal institutional limits

9. Female of child bearing potential* and sexually active male subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Normal cardiac and pulmonary function as evidenced by a normal ECG with QTc ≤450 msec and peripheral oxygen saturation (SpO2) ≥ 92% on Room air by pulse oximetry

9.2. Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment with bevacizumab

[redacted]

3. Subjects receiving systemic corticosteroids for treatment of disease-related symptoms during the 4 weeks prior to Day -7
4. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
5. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

   NOTE:

   - Subjects with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For subjects with controlled HIV infection, monitoring will be performed per local standards.
   - Subjects with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Subjects with controlled infections must undergo periodic monitoring of HBV DNA. Subjects must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.

- Subjects who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

6. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively.
7. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed.
8. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer
9. Nursing or pregnant females
10. Prior exposure to veledimex
11. Use of an investigational product within prior 30 days.
12. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.
13. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor
14. Presence of any contraindication for a neurosurgical procedure
15. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of DVT may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor.
16. Unstable or clinically significant medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples include, but are not limited to, history of myocarditis or congestive heart failure (as defined by New York Heart Association Functional Class III or IV), unstable angina, serious uncontrolled cardiac arrythmia, myocardial infarction within 6 months of screening, active interstitial lung disease (ILD)/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids uncontrolled asthma, or colitis.

9.3. Subject Enrollment

Approximately 36 subjects may be enrolled.

9.4. Withdrawal of Subjects from Study Treatment and/or Study

The sponsor may terminate this study at any time. The investigator and/or the subject have the right to terminate the subject's participation in the study at any time. Efforts should be made to ask subjects who discontinue study drug to be available to complete the Follow-up assessments.

A subject may withdraw or be withdrawn from the study treatment prematurely for any of the following reasons:

- Principal Investigator (PI) determines further participation is not in the subject's best interest (e.g., subject experiences rapid clinical deterioration in the absence of confirmed disease progression)
- Subject has confirmed disease progression
- A subject must be withdrawn in the event of any of the following:
- Subject withdraws informed consent.
- Any treatment-related AEs that meet withdrawal criteria
- Substantial noncompliance with study requirements
- Subjects with a confirmed positive pregnancy test
- Any intercurrent illness that would, in the judgement of the investigator or sponsor's medical monitor, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy
- Subjects who did not receive any study drugs

- *NOTE: Any subject who wishes to withdraw from the study treatment may do so at any time but will be asked to be available for the safety, tumor response, and survival follow-up assessments.*

Every effort should be made to follow subjects who withdraw from study treatment for ongoing treatment-related AEs. Subjects who withdraw during the treatment period should continue to have study assessments as clinically indicated.

9.5. Replacement of Subjects

Subjects who withdraw from the study or do not receive each study drug may be replaced. All dosed subjects will be included in the overall safety assessment.

9.6. Premature Termination of Study or Study Site

The sponsor has the right to close the study at any time, although this should occur only after mutual consultation between the sponsor and the investigators. The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be informed of such action. Should the study or center be closed prematurely, all study materials (completed, partially completed, and blank electronic case report forms (eCRF), study medication, etc.) must be stored or disposed of according to the sponsor's instructions. Events that may trigger premature termination of the study or closure of a center include but are not limited to the following: new toxicity findings; decision to re-challenge patient who has experienced a Grade 4 event; interim analysis results; noncompliance with the protocol; changes in the development plans for the study drug; slow recruitment; and poor-quality data.

10. INVESTIGATIONAL PRODUCTS

Ad-RTS-hIL-12 and Veledimex is an investigational product has two components: the [redacted] (Ad-RTS-hIL-12) and veledimex (RTS activator ligand). [redacted] Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated (turned on and off) by the optimal veledimex dose and schedule.

Cemiplimab-rwlc is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kilounified atomic mass unit (kDa) based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The cemiplimab-rwlc heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody. Please refer to the Pharmacy Manual for additional information.

[redacted]

is provided in the Pharmacy Manual.

10.2. Preparation of Veledimex

Sponsor will provide veledimex capsules to be dispensed by the study site pharmacy to subjects for oral administration. Information regarding the veledimex is provided in the Pharmacy Manual.

10.3. Preparation of Cemiplimab-rwlc

Cemiplimab-rwlc will be supplied in single-dose vials. Information regarding the preparation of the cemiplimab-rwlc dose is provided in the Pharmacy Manual.

10.4. Handling and Storage

Study drugs must be stored in a restricted access area under the storage conditions indicated in the Investigator's Brochure or Pharmacy Manual. All necessary precautions while handling potentially toxic compounds must be strictly followed.

10.5. Monitoring of Subject Adherence and Managing Missed Doses

10.5.1. Veledimex

The first veledimex dose following Ad-RTS-hIL-12 injection is expected to be administered when the subject is at the clinical site, under careful medical supervision by the clinic staff to ensure that the subject does not have difficulty swallowing the capsules. Thereafter, subjects may be allowed to self-administer the remaining once daily doses as described. Subjects are to be instructed to take the appropriate number of capsules in the same way for each of the remaining treatment period days and may be reminded to do so by phone on non-visit days.

Subjects should NOT make up any missed doses.

Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the once daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff on Day 15, so that staff can properly assess dose compliance.

10.5.2. Cemiplimab-rwlc

The recommended dose of cemiplimab-rwlc is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks (Q3W) until confirmed disease progression or unacceptable toxicity.

10.6. Disposition of Unused Drug

All unused study drug should be destroyed at the study site in accordance with standard institutional practice and in accordance with United States Occupational Safety and Health Administration procedures, after full accountability has been documented. Any study drug destruction at study site must be documented and the records maintained in the investigator's study file.

10.7. Accountability and Dispensation

The investigator must maintain accurate records accounting for the receipt and dispensation of study drugs. The investigational materials are to be prescribed only by the investigator or the sub-investigators named on FDA Form 1572 and may only be dispensed by authorized personnel at the institution(s) listed therein. Under no circumstances will the PI allow the investigational drug(s) to be used for purposes or in subjects other than as directed by the protocol.

10.8. Treatment Plan

10.8.1. Cemiplimab-rwlc

On Day -7, Day 15, and approximately every 3 weeks thereafter subjects will receive cemiplimab-rwlc until confirmed disease progression or unacceptable toxicity.

10.8.2. Ad-RTS-hIL-12 + Veledimex

- Subjects will be given 20 mg of veledimex by mouth, when NPO (excluding other medications) 3 (± 2) hours before craniotomy (Day 0). The actual time of veledimex administration should be noted and recorded.
- Surgical planning will be performed on a diagnostic MRI acquired prior to the surgery as per standard of care.
- At the time of tumor resection, tumor, CSF (if available), and blood samples will be collected.
- Immediately after tumor resection, when available, an intraoperative MRI can be performed to identify contrast enhancing or T2/FLAIR hyper intense residual tumor. If intraoperative MRI is not available, the neurosurgeon will select sites for injection.
- [redacted].
- The day of Ad-RTS-hIL-12 administration is designated as Day 0. If Ad-RTS-hIL-12 injection is not performed, subject will not continue with post-resection veledimex dosing.
- After tumor resection and Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-resection veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning and within approximately 30 minutes of a regular meal.

Subjects should be carefully monitored for possible local reactions and/or hypersensitivity reactions, according to standard practice. Intracranial bleeding or other procedure-related events should be evaluated before the first veledimex dose is given post Ad-RTS-hIL-12 administration. Any changes in neurological status should be reported to the investigator immediately, either during hospitalization or once subject is discharged. Subjects should be instructed to call the study physician or study nurse if they develop any symptoms after they are released from the hospital.

NOTE: It is important that subjects are instructed to maintain adequate oral hydration while subjects are being administered veledimex. Study sites should monitor subjects for proper hydration and monitor blood pressure regularly. The incidence of low blood pressure to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

10.9. Stopping Rules

From Day -7 to 30 days after completion of Ad-RTS-hIL12 + veledimex dosing, if any subject experienced a death (other than death related to progressive disease); or if any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are

required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.

10.10. Dose Modifications and Dose Delays

Veledimex dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 2.

Table 2: Criteria for Dose Delay and Dose Reduction of veledimex

Adverse Reaction	Severity[2]	Veledimex Dosage Modifications[1]
Immediately life-threatening/ Potentially-Fatal Severe Adverse Reactions		
Any non-hematologic AE[3]	Grade 4 non-hematologic adverse event at least possibly related to study drug, that is considered by the treating physician to be immediately life-threatening, and results in emergent medical and/or surgical intervention	Discontinue
Other Severe Adverse Reactions		
Cytokine Release Syndrome	Grade 3 or higher (per the Ziopharm Working Definition of Cytokine Release Syndrome)	Withhold[4]
Any non-hematologic AE[3, 5] (except brain edema)	Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and persists at least 3 days	Withhold[4]
Cerebral edema[5]	Grade 3 or higher	Withhold[4,6]
Thrombocytopenia	Grade 3 or higher thrombocytopenia (< 50,000/mm^3) at least possibly related to study drug	Withhold[4]
Lymphopenia or other hematologic toxicity	Grade 4 or higher lymphopenia or other hematologic toxicity (except thrombocytopenia)	Withhold[4]
Increased transaminitis[8]	Grade 3 or higher increase in ALT or AST	Potentially Withhold[7]

1. These recommendations are for general guidance only. Treating physicians should manage patients according to their clinical judgement, as informed by institutional guidelines, best practices and these guideline recommendations.
2. Toxicity as graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.
3. Nausea and vomiting will not be considered in this category unless at least Grade 3 or 4 and refractory to antiemetics (i.e., defined as symptoms not mitigated by maximal medical support as directed by the Investigator (per institutional guidelines) in consultation with the Sponsor Clinical Medical Monitor).
4. Withhold the next and any successive doses of veledimex while the Grade 3 or 4 toxicity persists. Veledimex dosing may resume, after discussion with the Sponsor Clinical Medical Monitor, in subjects with rapid and substantial reversal of toxicity, either spontaneously or following appropriate medical treatment. The Sponsor Clinical Study Coordinator will be notified in advance of veledimex dosage modifications.
5. Seizures, headache, and cerebral edema are commonly observed in this population and will be recorded according to the grade of toxicity and therefore will not be considered in this category unless unresponsive to maximal medical support as directed by the Investigator (informed by institutional guidelines) and in consultation with the Sponsor Clinical Medical Monitor.
6. *Cerebral Edema Guideline Recommendations:* As a general guideline, mannitol (Osmitrol), corticosteroid treatment (i.e., dexamethasone or Decadron) and/or withholding the next dose(s) of veledimex short-term are considered for cerebral edema, CTCAE v5.0 Grade 3 (or for "moderate" severity descriptively). For Grade 4 cerebral edema, mannitol (Osmitrol), higher dose corticosteroids and/or longer-term withholding or discontinuation of veledimex are considered, especially if the edema is not sufficiently mitigated by urgent medical intervention. It is expected that the use of corticosteroids will vary between sites and among subjects, and therefore, the precise extent and dosage of steroids cannot be specified per protocol. The treating physician will decide as is safe and appropriate for the individual subject according to their clinical judgement as informed by the label and institutional guidelines and should consider the minimum steroid dose or the lowest amount that adequately and

rapidly controls the subject's signs and symptoms (refer to Rationale section below). Consideration also may be given to a limited number of doses of bevacizumab (Avastin) if (typically high-dose) corticosteroids are not in the best interests of the subject in the treating physician's clinical judgement and following consultation with the Medical Monitor. In the event of an immediately life-threatening event, the treating physician should consider surgical decompression.

7. *Rationale:* Cerebral edema may pre-exist experimental treatment to a variable extent and usually is associated with the underlying disease and/or increase following surgical procedures. The study treatment, particularly with combination therapy including an immune checkpoint inhibitor, also may possibly cause an increase in the severity of edema. Patients with glioblastoma receiving more than 4 mg dexamethasone qd were reported to have decreased overall survival, possibly due to immunosuppression (British J Cancer 2015:113, 232–241). Preliminary data presented at the Society for Neuro-Oncology 2018 Annual Meeting by Ziopharm Oncology also suggests that overall survival is decreased in 20 mg veledimex craniotomy cohort subjects (i.e., administered more than a 20 mg cumulative dosage of dexamethasone) during the initial treatment period (Days 0-14); the relative contributions of severity of the condition vs immunosuppression to the negative effect observed on overall survival are presently uncertain.
8. Withhold the next dose(s) of veledimex if the transaminitis is part of a constellation of findings consistent with Cytokine Release Syndrome (refer to Ziopharm Working Definition of Cytokine Release Syndrome). The treating physician may elect to follow the laboratory test trajectory and clinical status if an isolated transaminitis.

Cemiplimab-rwlc dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 3.

Table 3: Criteria for Dose Delay and Dose Reduction of cemiplimab-rwlc

Adverse Reaction	**Severity**	**Cemiplimab-rwlc Dosage Modifications**
Severe and Fatal Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold*
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold*
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN	Withhold*
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, 4	Withhold if clinically necessary*
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold*
	Grade 4	Permanently discontinue
Recurrent or persistent immune-mediated adverse events	• Recurrent Grades 3 or 4 • Grades 2 or 3 persistent for 12 weeks or longer after last cemiplimab-rwlc dose in spite of appropriate therapy • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last cemiplimab-rwlc dose	Permanently discontinue
Severe and Fatal Immune-Mediated Adverse Reactions		
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

AE = adverse event
*: Resume in patients with complete or partial resolution (Grade 0 to 1) after supraphysiologic dose of corticosteroids discontinued

10.11. Safety Monitoring and Adverse Effect Management

Each subject receiving cemiplimab-rwlc, Ad-RTS-hIL-12 or at least one dose of veledimex will be included in the Overall Safety Population (OSP). Parameters used in the safety analysis of all populations will include all laboratory tests, physical examination, imaging scans, and spontaneous reports of AEs reported by subjects. Each patient will be assessed according to the scheduled study procedures and any additional visits as a result of AEs. Cytokine release syndrome will be assessed per the Ziopharm Working Definition (Appendix 1). Other adverse events will be assessed according to the NCI CTCAE v5 criteria.

10.12. Severity Grading and Management of Local Reactions

Injection of agents into tissue carries a potential risk of local reactions that may be characterized as intense immunologic reaction at or near the injection site. Local reactions will be graded according to the NCI CTCAE v5 criteria.

As with all signs and symptoms, events should be recorded and graded as AEs according to NCI CTCAE v.5 criteria. Study stopping rules will not apply to a specific event if it is clearly unrelated to the study treatment.

10.13. Prophylactic Antipyretic and/or Analgesic Administration

The use of antipyretics and/or analgesics is allowed as a prophylactic measure perioperatively. Antipyretics and/or analgesics can be used anytime during study treatment, as indicated and required for patient safety and must be recorded as concomitant medications. Please refer to exclusion criteria for acute clinically significant and/or chronic infections.

NOTE: Since fever and other flu-like symptoms (e.g., chills, body aches, malaise, loss of appetite, etc.) are sometimes experienced following Ad-RTS-hIL-12 + veledimex, it is reasonable for subjects to be administered prophylactic antipyretic and/or analgesic medication prior to Ad-RTS-hIL-12 injection and during the first week after injection at the discretion of the treating physician. The incidence of pyrexia and flu-like symptoms to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

Please refer to Appendix 2 or the recommended regimen for the prophylactic administration of antipyretics and/or analgesics.

11. CONCOMITANT THERAPY

Information on concomitant medications, including all medications, blood products, vitamins, and other supplements, will be collected through the Screening, Treatment, through 90 days after the subject's last dose of any study drug.

Subjects experiencing brain tumor-related symptoms or edema should be treated with corticosteroids as per standard practice. The treating physician should consider the minimum starting steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher starting steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subjects' symptoms, as determined to be safe and appropriate by the treating physician

11.1. Permitted Medications

Subjects may receive standard treatments, including palliative and supportive care for any illness or symptom management during study treatment, including:

- Corticosteroids are permitted for brain tumor related- symptoms. The treating physician should consider the minimum steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subject's symptoms, as determined to be safe and appropriate by the treating physician. Physiologic replacement doses of corticosteroids are also permitted (NOTE: Intranasal corticosteroids are excluded due to rapid systemic absorption).
- Antidiarrheal therapy is permitted for study drug induced- diarrhea
- Antiemetics are permitted for study drug- induced- nausea and vomiting

NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

11.2. Prohibited Medications/Therapies

The following medications are prohibited during the study:

- Any other investigational agent or anticancer therapy (chemotherapy, radiotherapy, etc.) while receiving study treatment
- Palliative radiotherapy is not permitted while on study
- Enzyme inducing anti-epileptic drugs (EIAED) are listed in Appendix 3 and are NOT permitted.
- Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness

  NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

12. STUDY PROCEDURES

12.1. Written Informed Consent

The provided written ICF must be signed before any protocol specific procedures and assessments can be performed. A copy of the signed ICF will be given to the subject and a copy should be filed in the medical record. The original ICF should be kept on file with the study reports. Standard of care evaluations performed as part of the subject's routine treatment prior to signing the ICF can be used if they were conducted within the timeframe of the screening period. Refer to Section 12.3.2.1 and Section 17.8 for further information.

12.2. Subject Registration

Centralized registration of subjects will be completed according to a process defined by the sponsor. Eligible subjects are to be enrolled and assigned a unique study identification number before the planned cemiplimab-rwlc dose. Once assigned, a subject's identification number will not be reused.

12.3. Schedule of Assessments and Observations

Screening assessments must be performed within 30 days prior to the Ad-RTS-hIL-12 injection. Any screening tests, exams, or procedures outside of this range may be repeated at the investigator's discretion. All study visits must be completed as described in the protocol while subjects are taking veledimex capsules. Follow-up assessments are allowed a window of ± 7 days. Refer to Table 1 Schedule of Study Procedures for further information.

12.3.1. Study Tests, Exams, and Procedures

12.3.1.1. Demographics, Medical and Cancer History, and Concomitant Medications

Each subject's complete medical history will be documented during screening, including demographic information, relevant medical history, current primary cancer diagnosis, and prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries, and any associated residual toxicities). In addition, concomitant medications, including blood products, vitamins, and other supplements received during the screening period (28 days) prior to initiating study treatment will be recorded. Concomitant medications will continue to be collected through 90 days after the subject's last dose of any study drug.

12.3.1.2. Physical Examinations

A complete physical examination will also include a neurological examination.

12.3.1.3. Vital Signs, Height, and Weight

Vital signs will include blood pressure, pulse rate, temperature, and respiration rate. Subject's blood pressure should be monitored regularly, with hydration as needed to prevent hypotension for 72 hours after administration of Ad-RTS-hIL-12, as previously noted. Assessment of vital signs is required prior to injection of Ad-RTS-hIL-12, and prior to veledimex dosing. Height and weight will be measured and recorded according to Schedule of Study Procedures.

12.3.1.4. Karnofsky Performance Status

The Karnofsky Performance Status measures the ability of cancer subjects to perform ordinary tasks. Scores range from 0 to 100 with a higher score meaning that the patient is better able to carry out daily activities. The Karnofsky Performance Status is used to determine a patient's

prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial. Subjects must have a Karnofsky Performance Status score of ≥ 70 at the Screening Visit to be included in the study.

12.3.1.5. Pregnancy Testing

Females of childbearing potential will have a serum pregnancy test at the Screening Visit and a urine or serum pregnancy test on Day 0, with a negative pregnancy outcome prior to study drug initiation.

12.3.1.6. Monitoring of Adverse Events

Monitoring and recording of AEs and serious adverse events (SAEs) will be conducted throughout the study. Adverse events and SAEs that occur following the signing of the ICF through 90 days after the subject's last dose of any study drug- must be recorded on the AE eCRF.

Definitions, documentation, and reporting of AEs and SAEs are described in Section 14.

NOTE: Subjects should be instructed to maintain adequate oral hydration while being administered veledimex. Study sites must should monitor subjects for proper hydration and blood pressure should be monitored regularly. Prophylactic antipyretic medications may also be considered. The incidence of adverse events to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

12.3.1.7. Clinical Laboratory Assessments

The hematology panel comprises a complete blood count (CBC), including white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, mean corpuscular volume (MCV), and platelet count.

The serum chemistry panel comprises the following parameters: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, amylase, blood urea nitrogen (BUN), glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.

The coagulation panel includes activated partial thromboplastin time (aPTT) or partial prothrombin time (PTT) and prothrombin time (PT) or INR. The acute phase reactants include erythrocyte sedimentation rate (ESR) and CRP.

The urinalysis panel (dipstick) includes appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated.

12.3.1.8. MRI

Subjects should be able to undergo MRI scans with contrast agent at screening and during study participation. MRI scans should be available for collection upon sponsor request.

[redacted]

12.3.1.10. Electrocardiogram

A standard, single, 12-lead electrocardiogram (ECG) for evaluation of the QT/QTc interval will be performed.

12.3.2. Schedule of Assessments

The study design is outlined in Synopsis the sequence of assessments is provided in Synopsis Table 1.

12.3.2.1. Screening Period: Assessments

The screening exams, tests, and procedures must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex:

- Signed informed consent form
- Medical/cancer history
- Physical examination (including targeted neurological examination)
- Height and weight
- Vital signs including SpO_2
- ECG
- Karnofsky Performance Status
- History of prior treatments and any associated residual toxicity
- Medications taken during the 28 days prior to consent, in addition to those ongoing during screening
- Adverse events evaluation
- MRI
- Serum pregnancy test
- **Hematology Panel including**: complete blood count (CBC), white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, and platelet count
- **Serum Chemistry Panel including**: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, blood urea nitrogen (BUN), lipase, amylase, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.
- **Coagulation Panel including**: activated partial thromboplastin time (aPTT), international normalized ratio (INR) ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein).
- **Urinalysis Panel (dipstick) including**: appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated
- **Thyroid Panel**: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)

[redacted]

- Subject registration

12.3.2.2. Treatment Period: Day -7

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test (within 72 hours prior to cemiplimab-rwlc dosing)
- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel
- Confirm eligibility
- Cemiplimab-rwlc dose

12.3.2.3. Treatment Period: Day 0 (Ad-RTS-hIL-12 injection)

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel (All labs should be collected prior to the subject's pre-op dose of veledimex)
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- ECG
- Dose of veledimex 3 (± 2) hours prior to resection, on an empty stomach (excluding other medications) AND compliance diary. Intratumoral Ad-RTS-hIL-12 will be administered by freehand injection.
- [redacted]

12.3.2.4. Treatment Period: Day 1

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- Blood sample for immune function evaluation
- MRI scan: to be done within 24 hours (a +48hr window is allowed) of Ad-RTS-hIL-12 administration and to be used as the baseline MRI for tumor response assessment

- [redacted]

12.3.2.5. Treatment Period: Day 2

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel

12.3.2.6. Treatment Period: Day 3

- Once daily veledimex dose AND compliance diary (The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.)
- Physical Examination (including targeted neurological evaluation)
- Vital signs including SpO2
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- [redacted]
- ECG

12.3.2.7. Treatment Period: Days 4 through 6

- Once daily veledimex dose AND compliance diary
- Adverse events evaluation
- Concomitant medications

12.3.2.8. Treatment Period: Day 7

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO2
- Weight
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- ECG
- [redacted]

[redacted]

12.3.2.9. Treatment Period: Day 8-13

- Once daily veledimex dose AND compliance diary

12.3.2.10. Treatment Period: Day 14

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- Thyroid Panel
- ECG

[redacted]

12.3.2.11. Treatment Period: Day 15

- Cemiplimab-rwlc dose

12.3.2.12. Treatment Period: Day 22

- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel

12.3.2.13. Treatment Period: Day 28

- Urine or serum pregnancy test

[redacted]

12.3.2.14. Treatment Period: Day 36

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications

- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose
- [redacted]

12.3.2.15. Treatment Period: Day 57

- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Thyroid Panel
- Urinalysis Panel
- Cemiplimab-rwlc dose
- MRI
- [redacted]

12.3.2.16. Treatment Period: Every 3 weeks after Day 57

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO2
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel
- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose
- [redacted]

12.3.2.17. Treatment Period: Every 8 weeks after Day 57

- MRI scans
- Adverse events evaluation
- Concomitant medications
- Survival Status

12.3.2.18. Unscheduled Visits Collections

In the event of subject termination or an unscheduled visit for a drug-related AE, an unscheduled visit kit should be obtained for cytokines and immunological markers for CSF evaluation, if applicable.

At all visits, concomitant medications, adverse events, and survival status will be documented: Concomitant medications will be monitored and recorded throughout the study. Medications

received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.

Refer to Synopsis Table 1 for Schedule of Study Procedures.

13. TUMOR RESPONSE ASSESSMENTS

13.1. Tumor Response

The secondary time-to event endpoints of this study include Investigator assessment of PFS, and ORR.

Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). A baseline MRI should be performed within 24 hours (a + 48hr window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines attached in Appendix 4. MRI scans will be collected and stored at the study site and each subject will be evaluated for response by the study investigator. Subjects should be imaged throughout the study using the same method(s) as were used for the screening and baseline MRIs. Independent tumor response assessments, as well as posttreatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines.

Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, scans should be obtained and provided to the central imaging lab until disease progression is confirmed centrally.

Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bidimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

For 2 years, subjects without confirmed disease progression should continue to have tumor assessments every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation).

13.2. Tumor Response Evaluation and Pseudo-Progression

The interpretation of MRI findings in subjects with treated brain tumors has an inherent uncertainty that stems from the pseudo-progression phenomena. Pseudo-progression is a term used to describe the appearance of radiographic disease progression due to increase contrast enhancement on MRI without true tumor progression. The increase in contrast enhancement can be influenced by several parameters including differences in radiologic technique, the amount of contrast agent used, the timing of the contrast agent administration relative to the imaging, postsurgical changes, infarction, treatment related inflammation, seizure activity, sub-acute radiation effects, radiation necrosis, and corticosteroid use. Consideration of these factors by experts and clinical experience is likely to identify these subjects. In this study, the first tumor assessment MRI will be done on Day 57 (± 3 days). Imaging assessments will be performed using iRANO criteria.

13.3. Central Imaging Reads

An independent central imaging lab will review reported responses and progression events using iRANO criteria. An Imaging Charter will be developed to provide guidance and consistency.

14. SAFETY ASSESSMENTS

The safety population will include all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex.

14.1. Adverse Events and Definitions

14.1.1. Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether considered drug-related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure, and any worsening of a pre-existing condition regardless of causality to study drug. An AE is also known as an adverse experience.

14.1.2. Suspected Adverse Reaction

Any AE for which there is evidence to suggest a causal relationship (reasonable possibility) between the drug and the AE. A suspected adverse reaction implies less certainty about causality than an adverse reaction.

14.1.3. Adverse Reaction

Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

14.1.4. Unexpected Adverse Reaction

Any AE that is (a) not listed in the Reference Safety Information (RSI) of Investigator's Brochure, (b) not listed with the specificity and severity that is being observed, (c) not consistent with the risk information described in the general investigational plan or elsewhere in the current application (in the absence of an investigator brochure), and (d) listed as occurring with a class of drugs, but not specifically mentioned as occurring with the particular drug under investigation.

14.2. Evaluation of Adverse Events

Adverse events include:

- Suspected adverse drug reactions
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities when compared to baseline, in signs, symptoms, clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, extensions of symptoms, or apparently unrelated illnesses

The following considerations apply when identifying an AE:

- Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

- If a constellation of symptoms results in a confirmed diagnosis, the diagnosis (not the symptoms) should be recorded as the AE term.
- If a diagnosis cannot be established, the symptoms should be recorded as the AEs.
- If an ongoing symptom has been included in the medical history, an associated severity grade and frequency should also be documented so that a worsening in severity or frequency of a symptom can be readily identified as an AE.
- Progression of disease is not itself an AE unless the progression of disease is assessed by the investigator as related to the study treatments; however, the presenting sign or symptom of the disease progression should be documented as an AE (e.g., increase in pain). Death due to "progression of disease" within the SAE reporting period (from the signing of the ICF until 90 days after the last dose of any study treatments) should be reported as SAE.

Adverse events will be followed from the next study until resolution or to the end of the follow-up period. AEs that are drug-related should be followed until resolved or no resolution is expected.

14.3. Determination of Seriousness

14.3.1. Serious Adverse Event

An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death during the active study period or within 90 days following study drug administration. In addition, a reported death at any time post-study that is thought to be related to study drug administration.
- Life-threatening AE: An AE that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (i.e., this does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Permanent, persistent, or significant disability: A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization refers to admission of a subject into a hospital for at least a 24-hour stay. Hospitalizations for routine blood transfusions, hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, are not considered SAEs. Emergency room visits that do not result with admission are not considered as SAEs.
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth.
- Important medical event: Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent a life-threatening situation, hospitalization or death.

14.3.2. Non-Serious Adverse Event

An AE that does not fulfill the criteria for a SAE is classified as a non-serious AE.

14.4. Determination of Severity

The severity of AEs will be assessed according to the NCI CTCAE, Version 5. If an AE is not specifically defined in the NCI CTCAE, v5.0, the investigator will determine the severity of an AE based on the following general definitions recommended (National Cancer Institute 2017):

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuation of administration of the study drug.
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuation of administration or reducing the dose of the study drug.
- Life-threatening (Grade 4): The AE requires discontinuing administration of the study drug. The subject is at immediate risk of death.
- Death (Grade 5): The subject dies as a direct result of the complication or condition.

14.5. Determination of Causality

The investigator will use medical consideration to determine the potential relationship of the AE to the study drugs based on his/her clinical judgment. Assessment of causality will be based upon the following:

- Alternative possible causes of the AE, including the subject's underlying disease or comorbid conditions, other drugs, other host, and environmental factors
- The temporal sequence between the exposure to study drug and the AE
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or previously reported toxicity of the study drug or similar drugs
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

Relationship assessments that indicate "Not Related" to investigational product:

- None: The event is related to an etiology other than the investigational product (the alternative etiology must be documented in the study subject's medical record and/or SAE form).
- Unlikely or Remote: The event is unlikely to be related to the investigational product and likely to be related to factors other than investigational product.

Relationship assessments that indicate "Related" to investigational product:

- Possible: There is an association between the event and the administration of the investigational product and there is a plausible mechanism for the event to be related

to investigational product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

- Probable: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and causes other than the investigational product has been ruled out and/or the event re-appeared on re-exposure to the investigational product.

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. AEs may occur due to procedures required during the screening process (e.g., blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

- Protocol-related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol-related: The event is related to an etiology other than the study procedure (the alternative etiology must be documented in the study subject's medical record).

14.6. Documenting Adverse Events

All AEs, including SAEs, are to be accurately recorded on the Adverse Event page of the subject's eCRF from the time the subject signs the informed consent through 90 days after the subject's last dose of any study drug. Each event will be assessed for serious criteria, severity, and causality (Section 14.5). The date of onset, as well as the duration of the event will be recorded. In addition, treatments provided to the subject, actions taken with the study drugs, and the outcome of the AE will also be noted.

14.7. Reporting Serious Adverse Events (SAE), and Adverse Events of Special interest (AESI)

14.7.1. Time Frame for Reporting

All SAEs and AESIs must be reported to the sponsor or sponsor designee within 24 hours of awareness, regardless of initiation of new anticancer therapy including the following:

- Any SAE or AESI experienced by the subject from the signing of informed consent to 90 days after the last dose of any study drug, regardless of relationship to study drug.
- Any SAE or AESI that the investigator becomes aware of, and believes to be study drug-related, that occurs more than 90 days after the subject last received study drug.

All SAEs must be reported to the following fax line within 24 hours of awareness:

[redacted]

Additional data concerning the SAE (e.g., diagnostic test reports, hospital summaries, etc.) must be promptly reported (within 24 hours of receipt) to the sponsor or sponsor's designee, until resolution of the SAE. Should the FDA or National Regulatory Authorities require that the sponsor submit additional data on the event, the investigator will be asked to provide those data to the sponsor in a timely fashion.

14.7.2. Information to be Provided by the Investigator

Within 24 hours of becoming aware of the SAE or subject death, the investigator must notify the sponsor or designee and transmit information to the sponsor or designee. Information (initial and follow-up) should be provided on an electronic and/or paper SAE Report form signed and dated by the investigator. The SAE Report form and copies of source documents with subject identifiers redacted will be transmitted by fax. A hospital discharge summary should be provided if the subject was hospitalized. An SAE report will be considered final once all relevant information has been received and reviewed by the sponsor.

The SAE report form is provided in the investigator study files. Please refer to the investigator study files for instructions on how to complete these forms. The investigator will provide all the following information related to the event:

- Investigator identification
- Subject identification (e.g., subject number, initials, sex, age or date of birth)
- Information regarding study drug administration (e.g. start/stop date, dose, and frequency)
- Day of SAE occurrence documentation on SAE form
- Description of event
- Action taken with the study drugs in relation to the SAE
- Outcome of the SAE

In addition to the above information, the investigator must provide, for each event term, an assessment of:

- Severity/intensity
- Relationship to the study drug (causality assessment)

14.8. Sponsor and Investigator Responsibility for Reporting Adverse Events

All AEs and SAEs will be reported to regulatory authorities, IRBs/IECs, and investigators in accordance with all applicable global laws and regulations, including but not limited to 21 CFR 312.32. The investigator must submit all Safety Letters received from the sponsor to his/her

IRB/IEC per agreements and local requirements. The investigator must keep copies of all safety reports/letters, including correspondence with Ziopharm and the IRB/IEC, in the study file.

14.9. Follow-up Information for Adverse Events

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved, stabilized, returned to baseline, or is otherwise explained by the investigator.

14.9.1. Required Follow-up for Adverse Events

All treatment-emergent AEs-and SAEs will be collected through 90 days after the last dose of any study drug). All the AEs and SAEs should be followed up by the next study visit of the AE/SAE be aware of; all the related AEs and SAEs should be followed up until:

- The event resolves
- The event returns to baseline, if a baseline value is available
- The event stabilizes (following consultation and agreement by the Ziopharm Medical Monitor)
- The event can be attributed to factors other than the study drug or other than study procedure

14.10. Pregnancies

Subjects who become pregnant during the study should immediately discontinue participation in the study. The sponsor should be immediately notified.

An initial Pregnancy Report form, and a Pregnancy Outcome Form are to be completed by the investigator or designee. The Pregnancy Report form, and the completion guidelines will be provided in the investigator study files. Please refer to the investigator study files for details on how to complete these forms.

14.11. Overdose

Investigational product overdose of study subject, with or without associated AEs/SAEs, should be reported within 24 hours of awareness to sponsor ([redacted] All AEs or SAEs as a result of overdose should be reported as described previously in Section 14.6 and Section 14.7.

15. [redacted]

[redacted]

16. STATISTICAL METHODS

This is an uncontrolled single arm study to determine whether the intratumoral Adenovirus [redacted] (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) is effective based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma. Where applicable, estimates of OS and other surrogate endpoints will be compared with well-matched historical control data to determine whether the estimates obtained in this study will be viewed as promising to support further development of this experimental combination of treatments. All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

16.1. Populations for Analysis

- The safety population will comprise all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 or any doses of veledimex
- The per protocol population will comprise subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post Ad-RTS-hIL-12 dose of veledimex, at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation (i.e., subjects who have had minor protocol violation(s) that are deemed not to impact efficacy will be included in this analysis population.)
- [redacted]

16.2. Sample Size and Power Calculations

We plan to accrue up to 36 subjects to obtain approximately 25 subjects evaluable for efficacy. This patient population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS.

[redacted]

A sample size of up to 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19[redacted] In addition, a Toxicity boundary based on repeated significance testing provides for a guideline to seriously consider stopping the trial if the number of subjects experiencing unacceptable toxicity exceeds the proportions below assuming a 30% Toxicity rate is acceptable and 60% would be unacceptable:

Low boundary: 3/5 5/10 8/15 9/20 11/25

High boundary: 3/5 6/10 8/15 10/20 11/25

According to boundary conditions stated herein, a review will be performed after 5, 10, 15, 20 and 25 subjects reach Day 30. Serious consideration for stopping the clinical trial should be given if the number of subjects meeting the Stopping Rules criteria is determined to be greater than 3/5, 5/10, 8/15, 9/20, or 11/25, the values which form the lower boundary condition. For

clinical study purposes, the lower bound will always be crossed first triggering the decision rule. The Stopping Rules are defined in section 10.9. The toxicity boundaries assume an alpha=0.1 and beta=0.1 for a power of 90%.

The method for determination of the Toxicity boundary used the Toxbdry function in the Clinfun R package implementation of repeated significance testing methodology (Ivanova et al. 2005, Jennison and Turnbull 2000). The operating characteristics of the boundary conditions will be specified in a separate statistical analysis plan (SAP).

If the study continues to completion, a sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) approximately 10% standard error of the estimate assuming the binomial estimation method.

16.3. Endpoints

16.3.1. Primary Endpoint

The primary endpoint for evaluation of efficacy is:

- The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

The primary endpoint is to determine the safety and efficacy of intratumoral [redacted] (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma.

16.3.2. Secondary Endpoints

Secondary endpoints include:

- Overall survival rate will be determined at 6, 12, 18 and 24 months
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

16.4. Safety Evaluation

Safety will be evaluated in using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

Safety will be evaluated based on frequency and severity of adverse events (AEs), Serious adverse events (SAEs), laboratory abnormalities, electrocardiograms (ECGs), vital signs and physical/neurologic examination findings. The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5. The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug.

16.5. Efficacy Evaluation

- The primary analysis for efficacy is based on the per protocol population.
- Secondary analyses for all efficacy endpoints will be based on the Safety population.

The primary endpoint for evaluation of efficacy is:

- the estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to 24 months for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

Secondary endpoints include:

- The OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint.
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc will be determined based on the investigator assessment
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months will be determined based on an investigator assessment.
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

16.6. Analyses

16.6.1. Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include at least demographic features such as sex, age, and race, as well as disease-specific status and medical history.

Categorical data will be summarized using counts and percentages for a particular category. For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation, minimum, and maximum values will be presented.

16.6.2. Safety Analyses

The safety population will be used to perform safety evaluations for all safety variables.

Safety evaluations will be based on the incidence, intensity, and type of AEs and SAEs. Clinically significant changes in the subjects' physical examinations, vital signs, and ECG evaluations, and abnormal laboratory values will be captured as AEs. Safety will also be assessed based on medical history and prior/concomitant medications.

The safety evaluation period extends from the date the patient signs the ICF until 90 days after the last dose of study drug, unless the patient discontinues the trial due to one of the following reasons:

- Documented progression
- Symptomatic deterioration also denoted as symptomatic progression
- AEs that the investigator feels will subsequently make the subject noncompliant with the protocol planned Schedule of Study Procedures
- Loss to follow-up
- Noncompliance with the protocol
- Other reason not listed above

All treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by number and percent of subjects, and according to relationship to the study drugs, severity, and seriousness. Treatment-emergent is defined as any AE that occurs during or after administration of the first dose of study drug through the evaluation period for safety defined above, regardless of relationship to study drug; or any event that is present at baseline that worsens in intensity or is subsequently considered to be drug related by the investigator. Deaths, SAEs, and AEs resulting in study discontinuation will be listed.

Subjects who discontinue the trial as defined above will be followed for safety up to 90 days after discontinuation and until all safety events that have started during the safety evaluation period are classified as resolved or the end of the study is reached. After the conclusion of the safety evaluation period is triggered by a discontinuation event, the subject continues to be followed only for OS.

Listings of vital signs and physical examination data will be presented by visit.

16.6.3. Overall Survival

OS is defined as the duration of time from the first dose of study drug (Day -7) to the date of death or to the last follow-up contact date if the subject has not died, in which case the subject is censored if still alive up to 2 years from the first dose of study drug received.

16.6.4. Tumor Response Analyses

Investigator assessment of ORR and PFS will be determined according to iRANO criteria. A two-sided confidence interval will be computed for the ORR. PFS and OS will be estimated using the Kaplan-Meier method for appropriately-sized subject groups.

Following completion of the study, best response will be determined for each subject in accordance with iRANO guidelines and the ORR will be presented for all subjects. Where applicable, summary data of PFS, OS, and durability of response will be determined using Kaplan-Meier methodology; otherwise, a listing by-subject will display the data obtained. Two-sided confidence intervals will be computed for the ORR. Descriptive statistics will be performed for different patient populations.

16.6.5. Multi-Center Study

Tumor response and safety data will be presented over all study centers.

16.6.6. Adjustments for Covariates

No adjustments for covariates will be made.

16.6.7. Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

16.6.8. Procedures for Reporting Deviations to Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared prior to database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

17. STUDY MANAGEMENT

17.1. Electronic Case Report Forms and Source Documentation

For each subject, electronic case report forms (eCRFs) and corresponding source records will be maintained at each clinical site. The sponsor or designee will provide the study sites with secure access to and sufficient training on the electronic data capture (EDC) application, to permit site personnel to enter or correct information in the eCRFs for the subjects for whom they are responsible.

The eCRFs should be completed in a timely manner, and every effort should be made to have forms completed and up-to-date in anticipation of a visit by the sponsor's monitor. Specific instructions will be provided to the site. All requested information must be entered on the eCRF in the spaces provided. If an item is not available or is not applicable, it should be documented as such; do not leave a space blank.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Through the EDC application, the investigator must provide formal approval of all subject information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the subjects for whom he/she is responsible. The audit trail entry will show the user's identification information and the date and time of any corrections.

eCRF completion may be delegated to other study personnel; however, such delegation must be documented in writing. If, for any reason, certain data are lacking to complete an individual report form, the investigator will provide a written statement explaining the reasons for the lack of data.

Sponsor or designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

17.2. Good Clinical Practice

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and Ziopharm policies.

17.3. Sponsor Monitoring

After satisfactory receipt of all necessary regulatory paperwork, the sponsor's monitor will arrange that all study material be delivered to the study site at a mutually convenient time. A site initiation visit (SIV) by Ziopharm and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of study protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and study file maintenance.

Throughout the course of the study, the sponsor's monitor will make frequent contact with the investigator, and this will include telephone and/or onsite visits. During these visits, eCRFs will be reviewed for completeness and adherence to protocol. As part of the data audit, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the Medical Monitor. The monitor also will perform drug accountability checks and may

periodically request review of the investigator's study file to assure completeness of documentation in all respects of study conduct.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 17.5. The investigator or appointed delegate will receive the sponsor's representative during these onsite visits and will cooperate in providing the documents for inspection and responding to inquiries that may arise as part of this review. The investigator will also permit inspection of the study files by authorized representatives of the FDA.

17.4. Duration of the Study

The duration of this study from the time of initiating subject enrollment until the completion of survival follow-up is anticipated to be approximately 48 months, including 24 months for enrollment and 2 years of further follow-up.

The overall duration is expected to be up to 2 years for an individual subject, including the following:

- Screening period of up to 30 days prior to dosing with Ad-RTS-hIL-12 and veledimex
- Initial Study treatment period of 3 weeks (Days -7 through 14)
- Assessment of safety through the Follow-up Period
- Assessment of tumor response at Day 57 (± 3 days), and every 2 months thereafter until the occurrence of confirmed tumor progression
- Survival status through 2 years

In addition, subjects who discontinue or complete study treatment without objective evidence of disease progression should continue to be followed until confirmed disease progression has been documented. Subjects will be followed for survival status for 2 years after enrollment, except for death or loss to follow-up. The active study period refers to the study period from informed consent through the Initial Follow-up Period.

17.5. Records Retention

Records of drug disposition, eCRFs, and reports of the clinical trial must be maintained by the investigator for a period of at least 2 years following the date on which the test article is approved by FDA for marketing for the purposes that were investigated in the study. If no application is to be filed or if the application is not approved for such indication, the records must be stored for two additional years and then returned to Ziopharm. No records will be destroyed but will be indefinitely stored.

17.6. Institutional Review Board/ Independent Ethics Committee

This protocol and the study ICF must be reviewed and approved by the Institutional Biosafety Committee, where applicable, and IRB/IEC prior to the start of the study, and a copy of the approval letter supplied to Ziopharm. During the study, the investigator shall make timely and accurate reports to the IRB/IEC on study progress at intervals not exceeding 1 year, as well as satisfying any other local IRB/IEC reporting regulations. Copies of all reports to, and correspondence with, the IRB/IEC must be provided to Ziopharm. Further, within 3 months of

the completion or early termination of the study, a final report should be made to the IRB/IEC and Ziopharm by the investigator.

All protocol revisions must originate with and be documented by Ziopharm. If the requested revision is an amendment, the investigator must sign it. The FDA will be notified of all revisions by Ziopharm. The investigator must submit the amendment to his/her IRB/IEC for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to Ziopharm.

It is the investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review to Ziopharm representatives as part of the routine study monitoring process.

17.7. Confidentiality and HIPAA

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by Ziopharm, or its representatives, will be identified by subject number and study code.

The written ICF will also explain that, for data verification purposes, authorized representatives of Ziopharm, a regulatory authority (FDA), and/or the IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the subject's medical history.

The written ICF will be accompanied by or include a separate document incorporating United States Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which the subjects authorize the use and disclosure of their Protected Health Information.

17.8. Informed Consent

17.8.1. FDA Informed Consent Requirements

The investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the prospective subject prior to enrollment. The ICF should also indicate that, by signature, the prospective subject or, where appropriate, a legal guardian, permits access to relevant medical records by the sponsor and by representatives of the FDA. If a prospective subject does not understand English, an appropriate translation into his or her primary language must be made available. The investigator or designee will obtain written, informed, and witnessed consent. The prospective subject will have ample time and opportunity to ask questions. The prospective subject will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, the prospective subject will be asked if he/she is willing to sign and personally date a statement of informed consent. Only if the prospective subject voluntarily agrees to sign the informed consent statement and has done so, may he/she enroll into the study. A copy of his/her signed and dated informed consent will be provided to each prospective subject. The signed ICF is to remain in the investigator's file.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol that necessitates a change to the content of the subject's informed consent. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm continuation of his/her participation in the study by his/her

signature on the revised ICF, if applicable. Any written ICF and written information must receive IRB/IEC approval/favorable opinion in advance of use.

17.8.2. Subject Informed Consent Form

Ziopharm will provide a sample subject ICF for modification, as appropriate, by the investigator.

18. PROTOCOL APPROVAL PAGE

A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Except for a change intended to eliminate an immediate hazard to subjects, the study shall be conducted as described in the approved protocol. All deviations from the protocol will be documented in the eCRF. Any significant deviation or deviation related to dosing or safety evaluation will be reported to Ziopharm and documented in the eCRF.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Study Site Institution Name: _____

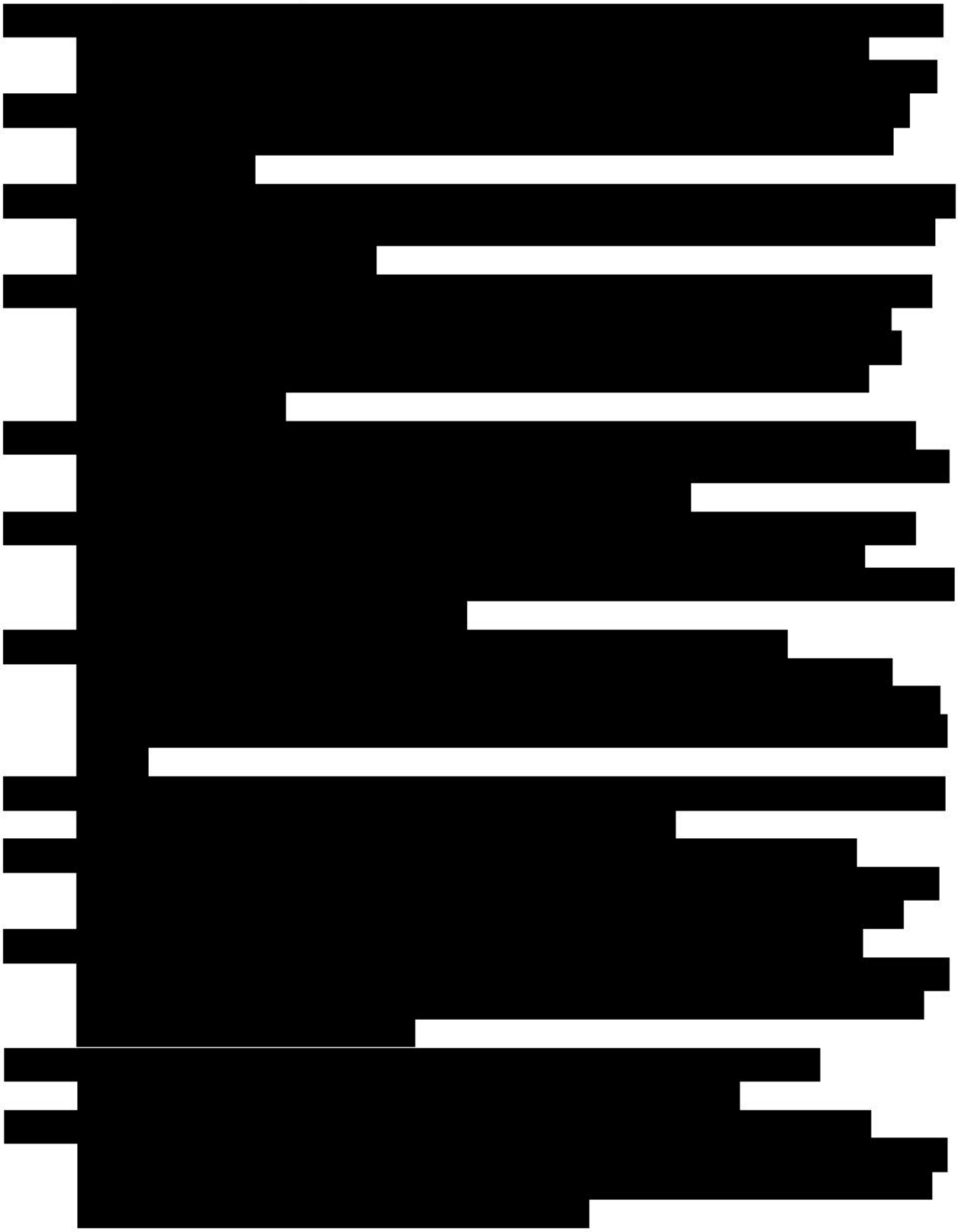
Principal Investigator

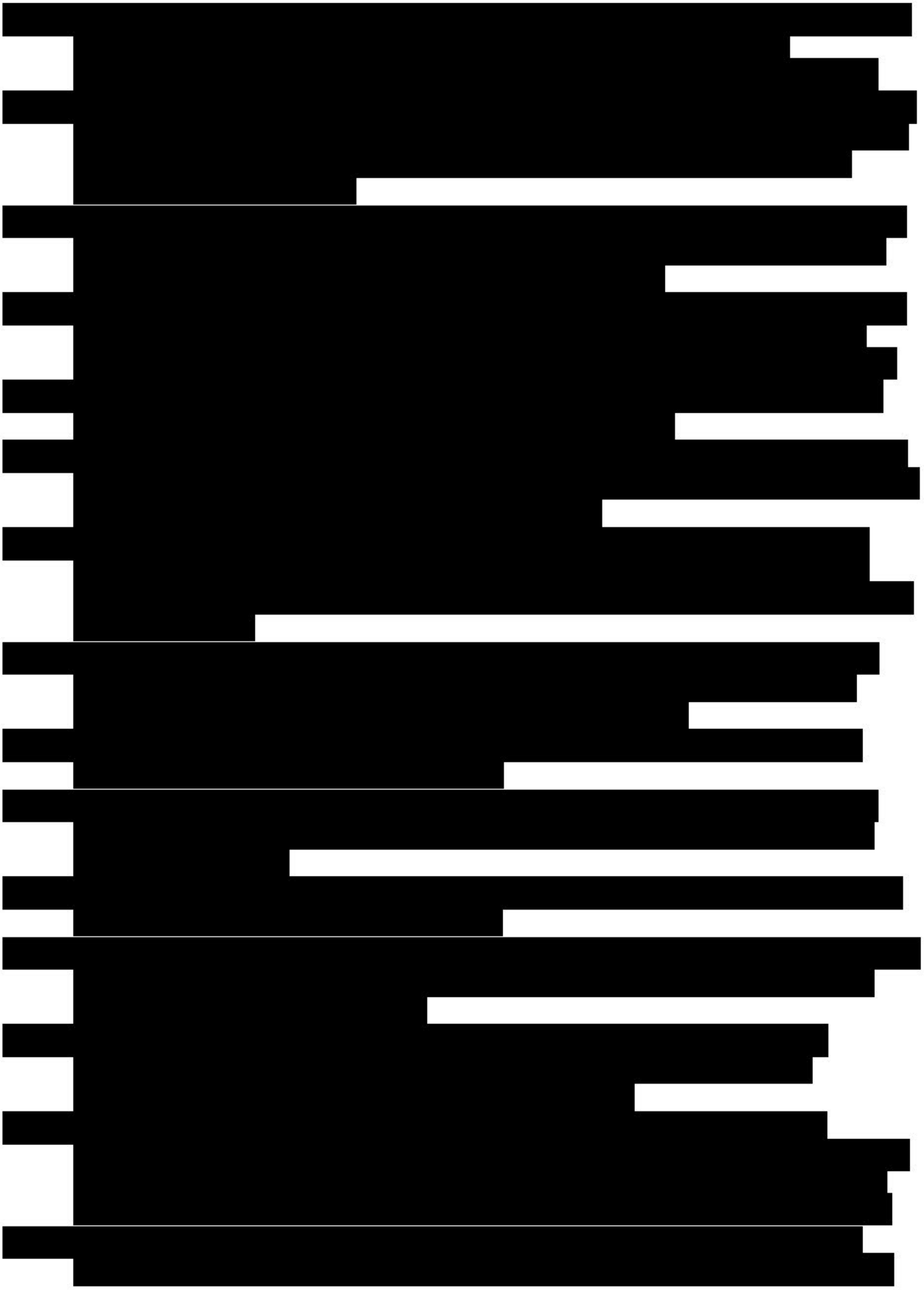
Print Name: _____

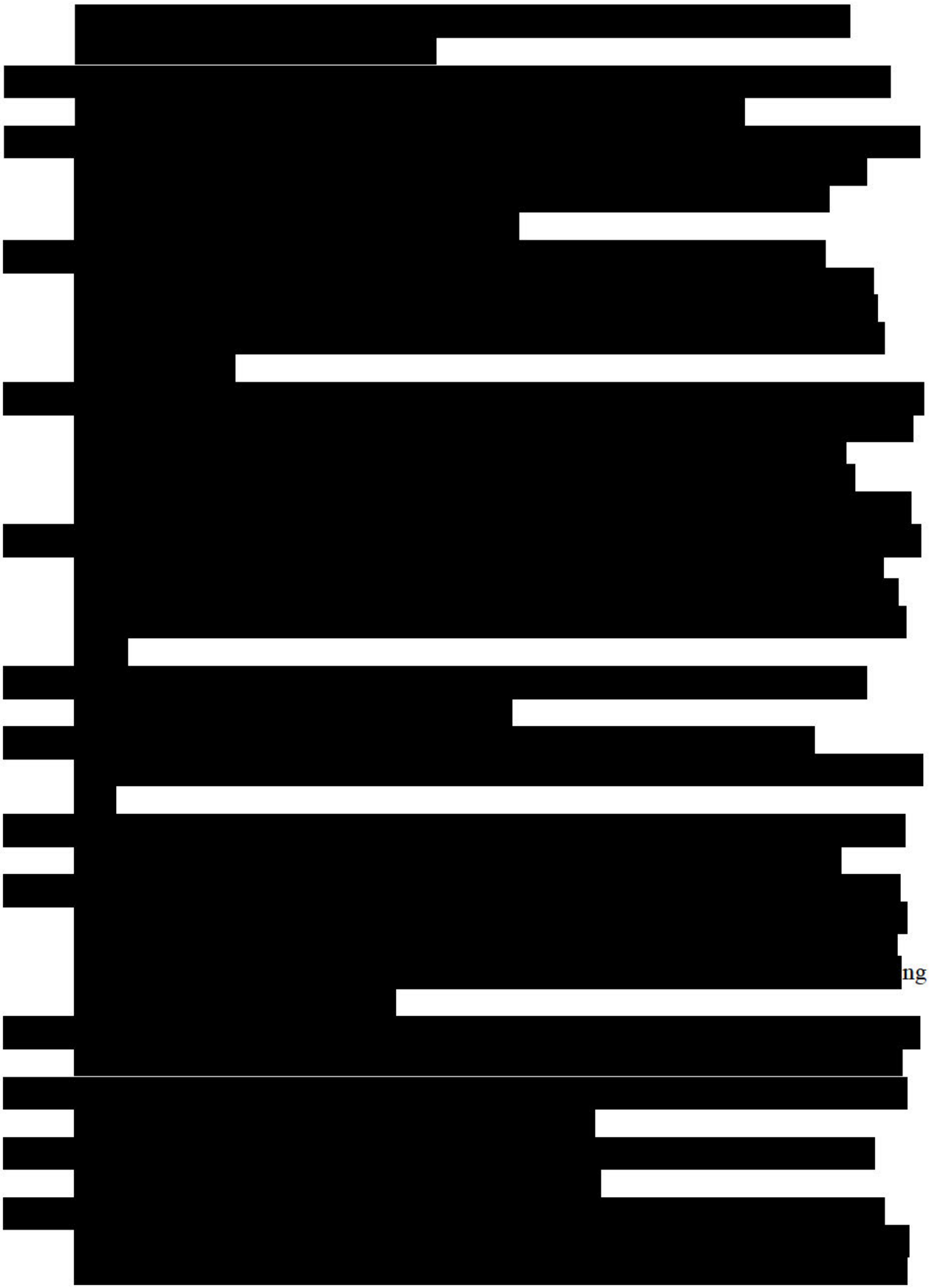
Signature: _____

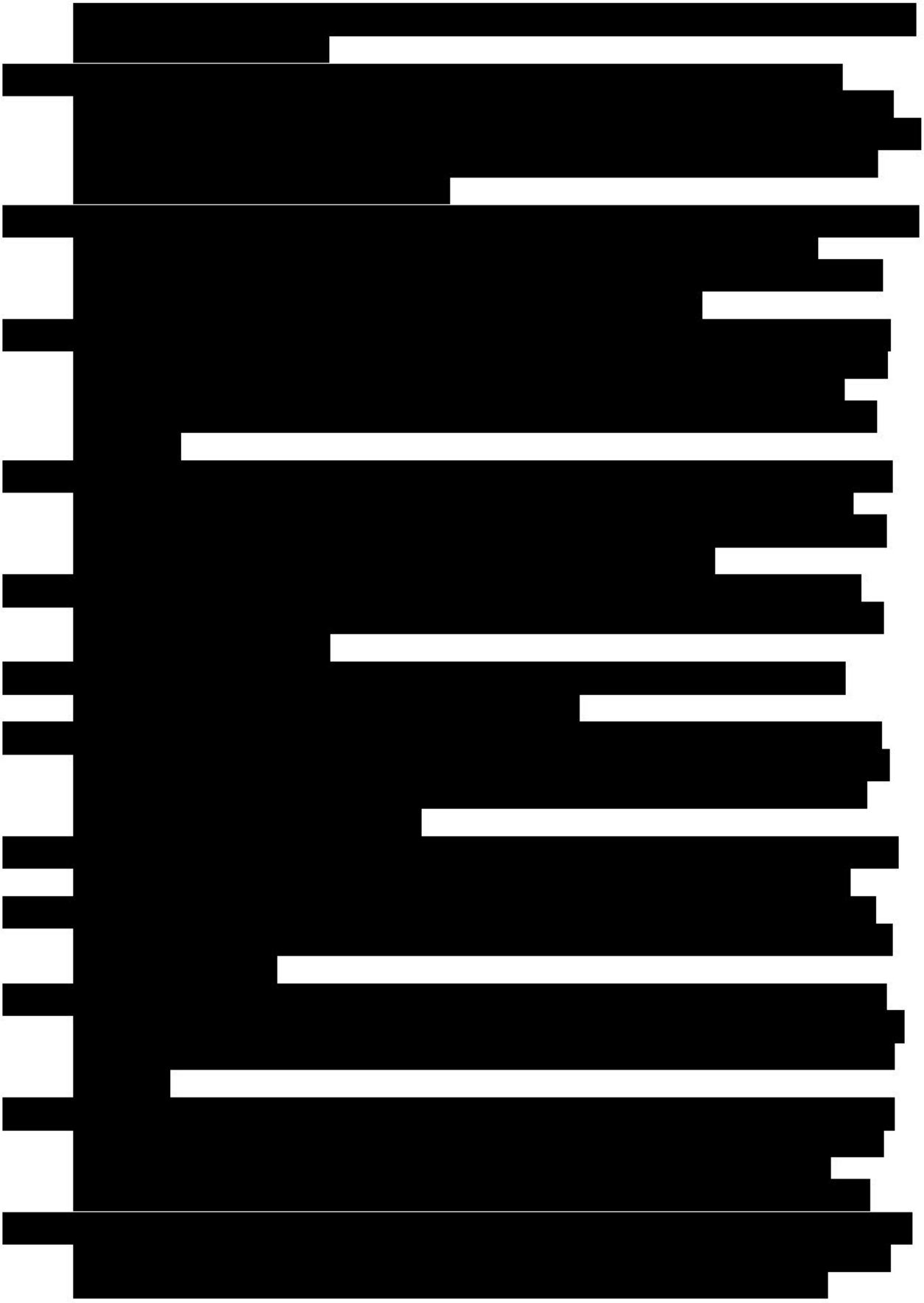
Date: _____

19. [redacted]









20. APPENDICES

APPENDIX 1. ZIOPHARM CYTOKINE RELEASE SYNDROME WORKING DEFINITION - AD-RTS-HIL-12 + VELEDIMEX (VERSION 3, 07 JANUARY 2019)

Cytokine release syndrome (CRS) is a multi-faceted immune disorder presenting clinically as a multi-system disorder. Elevated cytokine levels support the diagnosis of CRS in Ad-RTS-hIL-12 gene therapy study along with the grading criteria below:	
Grade 1	**Symptoms that are not life threatening and require symptomatic treatment only, e.g. (<u>any</u> of the following):** General: Influenza-like illness (flu-like symptoms): fever (temperature of 100°F [37.8°C] or greater) and fatigue, malaise, or myalgia Neurological: Grade 1 headache Grade 1 decreased level of consciousness (e.g. somnolence, drowsiness, lethargy, disorientation) GI: Grade 1 nausea or vomiting
Grade 2	**Symptoms that require and respond to moderate interventions and occurrence of <u>any</u> of the following:** **1. Hypotension responsive to fluids or single, low dose vasopressor** **2. Oxygen requirement < 40%** **3. Grade 3 transaminitis (ALT/AST), lymphopenia, or Grade 2 organ toxicities, e.g.:** Hematologic: Grade 2 neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 2 creatinine increase 4. **Other symptoms, e.g.:** General: Grade 3 fever Neurological: Grade 2 decreased level of consciousness (e.g., slow response to stimuli; limiting instrumental activities of daily living) Grade 2 or 3 headache GI: Grade 2 nausea or vomiting
Grade 3	**Symptoms that require and respond to aggressive interventions and occurrence of <u>any</u> of the following:** **1. Hypotension requiring high dose or multiple vasopressors** **2. Oxygen requirement ≥ 40%** **3. Grade 4 transaminitis (ALT/AST), lymphopenia, or Grade 3 organ toxicities, e.g.:** Hematologic: ≥Grade 3 febrile neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 3 creatinine increase Cardiac: Grade 3 arrhythmia, or acute heart failure Pulmonary: Grade 3 pulmonary edema, or dyspnea **4. Other symptoms, e.g.:** Neurological: Grade 3 decreased level of consciousness (e.g. difficult to arouse) Aseptic meningitis GI: Grade 3 nausea or vomiting
Grade 4	**Life-threatening symptoms and occurrence of any of the following:** **1. Requirement for ventilator support** **2. Grade 4 organ toxicities (excluding lymphopenia and asymptotic elevated transaminitis), e.g.:** Renal: Renal failure and dialysis indicated Cardiac: Cardiac arrest Pulmonary: Respiratory failure Neurological: Coma
Grade 5	**Death**

APPENDIX 2. RECOMMENDED REGIMEN FOR ANTIPYRETIC AND/OR ANALGESIC PROPHYLAXIS

Recombinant adenoviral vectors have the potential to elicit potent cellular and humoral immune responses. While the mechanism responsible for these effects is poorly understood, transient low-grade fevers are common after systemic rAD vector administration* and temperatures up to 104° F with chills and generalized malaise have been observed with treatment. Because low-grade fever is very likely to occur, prophylaxis with acetaminophen is strongly recommended.

Each site should follow its institutional protocol for the administration of acetaminophen. Acetaminophen is available without a prescription in 325 mg or 500 mg tablets. Common brand names of acetaminophen include Aspirin Free Anacin®, FeverAll®, Genapap®, Mapap®, NeoPAP®, Panadol®, Tempra®, and Tylenol®.

In general, fever can be adequately prophylaxed or treated with acetaminophen. If a fever occurs despite prophylactic medication or does not respond to usual doses of acetaminophen, then a combination of both acetaminophen and ibuprofen may be considered. Alternating doses of ibuprofen with acetaminophen may effectively control fever while preventing accidental overdose of acetaminophen. Acetaminophen is typically effective for controlling central fevers whereas ibuprofen is more potent as a peripheral analgesic/ anti-inflammatory medication. Ibuprofen is available without a prescription at a dosage of 200 mg and by prescription in 400, 600 or 800 mg tablets or capsules. Common brand names of ibuprofen include Advil®, ElixSure®, Ibuprom®, Ibutab®, Motrin® and Tab-Profen®.

Adverse events are uncommon although may be serious as some individuals are allergic to these medications. Additionally, overdoses of acetaminophen may cause liver failure. Therefore, subjects with liver disease and chronic alcohol users should avoid acetaminophen. Ibuprofen is excreted by the kidneys so should be avoided in patients with renal insufficiency, though most would be excluded from enrollment. High dose ibuprofen also may increase the risk of blood clots, stroke, heart attack, and gastrointestinal bleeding, and being a potent anti-inflammatory agent could reduce the efficacy of the investigational controlled IL-12 therapy.

APPENDIX 3. PROHIBITED ENZYME-INDUCING AND NON-ENZYME-INDUCING ANTIEPILEPTIC DRUGS

Enzyme-inducing Antiepileptic Drugs	Non-Enzyme-inducing Antiepileptic Drugs
Cerebyx® (fosphenytoin)	Zarontin® (ethosuximide) ONFI® (clobazam)
Dilantin® (phenytoin)	
Gabitril® (tiagabine)	
Luminal®, Solfoton® (phenobarbital)	
Nembutal® (pentobarbital)	
Trileptal® (oxacarbazepine)	
Tegretol® (carbamazepine)	
Topamax® (topiramate)	

APPENDIX 4. IMMUNOTHERAPY RESPONSE ASSESSMENT IN NEURO-ONCOLOGY: A REPORT OF THE RANO WORKING GROUP

Immunotherapy Response Assessment in Neuro-Oncology: A Report of the RANO Working Group

TITLE PAGE

STUDY PROTOCOL

Protocol Title: A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Protocol Number: ATI001-204

Phase: II

Date of Protocol: Amendment 1: 09 May 2019
Original: 07 February 2019

Sponsor: Ziopharm Oncology, Inc.

[redacted]

[redacted]

[redacted]

1. CLINICAL PROTOCOL SYNOPSIS

Title	A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma
Protocol Number	ATI001-204
Clinical Phase	Phase II
Investigational Product(s)	Ad-RTS-hIL12 + veledimex:  Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of an RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated by veledimex dose and schedule. Cemiplimab-rwlc Cemiplimab-rwlc (Libtayo®) is a programmed death receptor-1(PD-1)-blocking antibody.
Research Hypothesis	Among subjects with recurrent or progressive glioblastoma, Ad-RTS-hIL-12 and veledimex in combination with cemiplimab-rwlc (Libtayo®) can be safely administered, show evidence of efficacy, and can induce signals of immune activity.
Study Objectives	**Primary Objectives** To determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively. **Secondary Objectives** • To determine the survival rates at 6, 12, 18 and 24 months • To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months

	• To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months • To determine the tumor response rates at 6, 12, 18 and 24 months [redacted]
Investigational Product(s)	Ad-RTS-hIL-12 + veledimex: Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand) Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of an RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be turned on and off by veledimex dose and schedule. Cemiplimab-rwlc Cemiplimab-rwlc (Libtayo®) is a programmed death receptor-1 (PD-1) blocking antibody.
Number of Centers	Approximately 10 centers
Number of Subjects	Approximately 30 subjects
Study Design	This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 [redacted] and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively, in the presence of variable systemic corticosteroid exposure. This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility. Subjects will receive cemiplimab-rwlc on Day -7 (±3days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection of Ad-RTS-hIL-12 and Ad-RTS-hIL-12 [redacted] will be administered by freehand injection. Ad-RTS-hIL-12 will

	be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). [redacted] The total amount of virus delivered to each site will be recorded in the electronic Case Report Form (eCRF). If the total administered (injected) volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations. After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing. Subjects will receive a dose of cemiplimab-rwlc (350 mg) on Day 15 and every three weeks thereafter (Q3W) until confirmed progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the safety follow-up period. Delays in cemiplimab-rwlc dosing due to toxicity are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days. A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor. After the first six subjects have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused. The SRC will review safety data after the 6th subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products. The primary endpoint for evaluation of safety is: • The safety profile The primary endpoint for evaluation of efficacy is: • Overall survival (OS) Secondary endpoints include: • Overall Survival rate at 6, 12, 18 and 24 months

	• PFS, and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months • Objective Response Rate at 6, 12, 18 and 24 months • To determine the tumor response rate at 6, 12, 18 and 24 months [redacted]
Dose & Schedule	**Ad-RTS-hIL-12:** intratumoral [redacted] administered on Day 0 **Veledimex**: 20 mg PO QD on Days 0 to 14 **Cemiplimab-rwlc**: 350 mg IV on Day -7, Day 15, and approximately every 3 weeks (Q3W) until confirmed progression (iRANO), unacceptable toxicity or subject withdrawal.
Therapy Duration	From administration of the first study drug (cemiplimab-rwlc) until the subject has confirmed progressive disease per iRANO, unacceptable toxicity, the subject withdraws consent, or the end of the follow-up period.
Eligible Population	The eligible study population includes adult subjects with recurrent or progressive glioblastoma for which there is no alternative curative therapy. **Eligibility Criteria** Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells. **Inclusion Criteria** 1. Male or female subject ≥18 and ≤75 years of age 2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures 3. Histologically confirmed glioblastoma from archival tissue 4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy. Multifocal disease is allowed. 5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic

	effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor) a. Nitrosoureas: 6 weeks b. Other cytotoxic agents: 4 weeks c. Antiangiogenic agents: 4 weeks d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks e. Vaccine-based or CAR-T therapy: 3 months 6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment 7. Karnofsky Performance Status ≥70 8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements: a. Hemoglobin ≥9 g/L b. Lymphocytes >500/mm^3 c. Absolute neutrophil count ≥1500/mm^3 d. Platelets ≥100,000/mm^3 e. Serum creatinine ≤1.5 x upper limit of normal (ULN) f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN g. Total bilirubin <1.5 x ULN h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) within normal institutional limits 9. Female of child bearing potential* and sexually active male subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation

initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrhoeic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Normal cardiac and pulmonary function as evidenced by a normal ECG with QTc ≤450 msec and peripheral oxygen saturation (SpO2) ≥92% on Room air by pulse oximetry

Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment of disease with bevacizumab **(NOTE: short use (< 4 doses) of bevacizumab for controlling edema is allowed)**
3. Subjects receiving systemic corticosteroids for treatment of disease-related symptoms during the 4 weeks prior to Day -7
4. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
5. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

NOTE:

- Subjects with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For

	Subjects with controlled HIV infection, monitoring will be performed per local standards. • Subjects with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Subjects with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug. • Subjects who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted. 6. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively. 7. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed. 8. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer 9. Nursing or pregnant females 10. Prior exposure to veledimex 11. Use of an investigational product within prior 30 days. 12. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells 13. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor

	14. Presence of any contraindication for a neurosurgical procedure 15. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of deep vein thrombosis (DVT) may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor. 16. Unstable or clinically significant medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples include, but are not limited to, a history of myocarditis or congestive heart failure (as defined by New York Heart Association Functional Class III or IV), unstable angina, serious uncontrolled cardiac arrythmia, myocardial infarction within 6 months of screening, active interstitial lung disease (ILD)/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids uncontrolled asthma, or colitis.
Stopping Rules	From Day -7 to 30 days after completion of Ad-RTS-hIL12 + veledimex dosing, if any subject experienced a death (other than death related to progressive disease); or if any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.
Statistical Methods	**Analysis Populations** • The safety population will be comprised of all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex

- The per protocol population will be comprised of subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post Ad-RTS-hIL-12 dose of veledimex, at least 1 post Ad-RTS-hIL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation (i.e., subjects who have had minor protocol violation(s) that are deemed not to impact efficacy will be included in this analysis population.)
- [redacted]

Safety Evaluation

Safety will be evaluated based on frequency and severity of adverse events (AEs), Serious adverse events (SAEs), laboratory abnormalities, electrocardiograms (ECGs), vital signs and physical/neurologic examination findings.
The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug.

Efficacy Evaluation

- The primary analysis for efficacy is based on the per protocol population.
- Secondary analyses for all efficacy endpoints will be based on the Safety population.

The primary endpoint for evaluation of efficacy is:

- The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to 2 years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

Secondary endpoints include:

- The OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

Tumor Response Assessments:

The Per Protocol Population will be evaluated for ORR, PFS, PSP, and OS. Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, efforts will be made to encourage obtaining additional to confirm disease progression.

- Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). A baseline MRI will be performed within 24 hours (a +48-hour window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines
- Independent tumor response assessments, as well as post-treatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines.

	• Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bi-dimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD). [redacted]
Sample Size Determination	We plan to accrue up to 30 subjects to obtain approximately 25 subjects evaluable for efficacy. This subject population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS at 12 weeks. A sample size of approximately 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19. Note: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that sufficient subjects have measurable disease for evaluation of overall response rate per iRANO criteria.

	In addition, a toxicity boundary based on repeated significance testing provides a guideline for stopping the trial if the number of subjects experiencing unacceptable toxicity exceeds the proportions below, assuming a 30% toxicity rate is acceptable and 60% would be unacceptable: Low boundary: 3/5 5/10 8/15 9/20 11/25 High boundary: 3/5 6/10 8/15 10/20 11/25 Note: A sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) a 10% standard error of the estimate assuming the binomial estimation method.
Study Duration	The duration of this study from the time of initiating subject screening until the completion of survival follow-up is anticipated to be approximately 36 months, including 12 months for enrollment and 24 months of follow-up. The start of study is defined as the date when the first subject is consented into the study and the study stop date is the date of the last subject's last visit.

Table 1: Schedule of Study Procedures

Activity	Screening	Treatment							
	Day -30 to -8*	**Day -7 ****	**Day 0[a]**	**Day 1**	**Day 2**	**Day 3**	**Day 4 to 6**	**Day 7**	**Day 8 to 13**
Informed consent	X								
Medical/Cancer history[d]	X								
Physical exam[e], including targeted neurological exam	X	X	X	X	X	X		X	
Karnofsky PS[f]	X	X	X						
Height (screen) and weight	X							X	
Vital signs[g]	X	X	X	X	X	X		X	
Adverse events[h]	CONTINUOUS								
Concomitant medications[h]	CONTINUOUS								
Survival status[i]	CONTINUOUS								
Pregnancy test[j]	X	X	X						
Hematology[k]	X	X	X[a]	X	X	X		X	
Coagulation[l]	X		X[a]	X		X		X	
Serum chemistry[m]	X	X	X[a]	X	X	X		X	
Urinalysis[n]	X	X	X[a]			X		X	
Thyroid panel[o]	X								
ECG[p]	X		X			X		X	
Confirm eligibility		X[q]							
Cemiplimab-rwlc dose[q]		X							
Ad-RTS-hIL-12			X[r,s]						
Veledimex dose and diary[v]			X[s, t]	X[s, t]	X	X[u]	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]					[redacted]			
MRI scans[z]	X[z]			X[z, aa]					
Tumor sample and CSF (if available)[bb]			X						
Neutralizing antibody status testing[cc]	X							X	

Table 1: Schedule of Study Procedures (continued)

Activity	Treatment							Long Term Follow-up
	Day 14	Day 15	Day 22	Day 28	Day 36 ±3 days	Day 57 ±3 days	Every 3 weeks[b] ±7days	Every 8 weeks[c] ±7days
Informed consent								
Medical/Cancer history[d]								
Physical exam[e], including targeted neurological exam	X				X		X	
Karnofsky PS[f]	X				X		X	
Height (screen) and weight	X				X			
Vital signs[g]	X				X		X	
Adverse events[h]	CONTINUOUS							
Concomitant medications[h]	CONTINUOUS							
Survival status[i]	CONTINUOUS							
Pregnancy test[j]				X	X		X	
Hematology[k]	X		X		X	X	X	
Coagulation[l]	X				X			
Serum chemistry[m]	X		X		X	X	X	
Urinalysis[n]	X		X			X	X	
Thyroid panel[o]	X				X	X	X	
ECG[p]	X				X		X	
Confirm eligibility								
Cemiplimab-rwlc dose[q]		X			X	X	X	
Ad-RTS-hIL-12								
Veledimex dose and diary	X[v]							
[redacted]	[redacted]			[redacted]				
[redacted]	[redacted]			[redacted]				
[redacted]	[redacted]			[redacted]				
MRI scans[z]						X[z]		X[z]
Tumor sample and CSF if (available)[bb]								
Neutralizing antibody status testing[cc]	X				X			

[*] Screening assessments must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex.
[**] Day -7 dosing with cemiplimab-rwlc may be performed within ± 3 days.
[a] The PI will review all results of laboratory tests drawn within 24 hours prior to surgery.
[b] Every 3 weeks from Day 57
[c] Every 8 weeks from Day 57 in addition to assessments performed every 3 weeks

[d] Medical history includes demographic information, relevant medical and surgical history. Cancer history includes current cancer diagnosis, prior treatment (regimen[s], doses, start and stop dates, and any associated residual toxicity), and best response for each regimen.
[e] A complete physical examination including a neurological exam and mental status is required at baseline and discharge from hospital. Targeted neurological exams thereafter.
[f] KPS is required at Screening, Day -7, Day 0, Day 14, Day 36 and every 3 weeks thereafter.
[g] Blood pressure, pulse, temperature, and respiration will be recorded. Pulse oximetry peripheral oxygen situation (SpO2) will be recorded at Screening, Day -7, Day 0, Day 3, Day 7, Day 14, Day 36 and every 3 weeks from Day 57. Blood pressure should be monitored closely, with hydration as needed to prevent hypotension after veledimex administration. Subjects must be instructed to maintain adequate oral hydration on and between veledimex dosing days; sites must closely monitor hydration status.
[h] Concomitant medications will be monitored and recorded throughout the study. Medications received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.
[i] Subjects will be followed to document start of new anticancer therapies and survival status for 2 years following administration of Ad-RTS-hIL-12.
[j] Serum pregnancy test at Screening for females of childbearing potential, must be within 72 hours prior to first dose of cemiplimab-rwlc; urine or serum pregnancy test on all other days.
[k] Hematology: Complete blood count, white blood count with differential, red blood cell count, red blood cell indices, hematocrit, hemoglobin, and platelet count. The Day 0 testing should be obtained prior to veledimex dosing.
[l] Coagulation: aPTT, INR, erythrocyte sedimentation rate and C-reactive protein. The Day 0 testing should be obtained prior to veledimex dosing.
[m] Serum Chemistry: AST, ALT, lactate dehydrogenase, alkaline phosphatase, lipase, amylase, creatinine, total bilirubin, total protein, albumin, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate. The Day 0 testing should be obtained prior to veledimex dosing.
[n] Urinalysis Panel (dipstick): appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals and cells may be done if indicated. The Day 0 testing should be obtained prior to veledimex dosing.
[o] Thyroid Panel: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)
[p] Standard 12-lead ECG; single measurement at each time point. The Day 0 testing should be obtained prior to veledimex dosing.
[q] Eligibility must be confirmed within 24 hours prior to dosing with cemiplimab-rwlc. In the event of toxicities likely related to cemiplimab-rwlc, the PI and the Medical Monitor will individualize the management of cemiplimab-rwlc dosing in general accordance with the Investigator's Brochure. Doses must be at least 21 days apart. Delays of up to 14 days are acceptable for toxicity, in consultation with the medical monitor.
[r] Ad-RTS-hIL-12 intratumoral injection should be administered by freehand injection. Subjects must be instructed to maintain adequate oral hydration during the Treatment Period; sites must closely monitor subjects' hydration status. Because of the potential for toxicity (e.g., fevers, chills, fatigue, and dehydration), administration of prophylactic antipyretics is recommended after injection of Ad-RTS-hIL-12.
[s] Each subject will be carefully monitored for any local reactions and/or hypersensitivity reactions following the AdRTS-hIL-12 injection and veledimex administration. Subjects should be instructed to call the clinical site if headache, hemiparesis, seizure, or other local reactions develop anytime and especially between study visits.
[t] The first post-resection veledimex dose will be given on the next day, designated as Day 1, under supervision of the clinical staff to ensure there are no difficulties swallowing the capsule. Subsequent veledimex doses are to be taken once daily, in the morning and within 30 minutes of a regular meal.
[u] The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.
[v] Study sites must assess compliance of veledimex dosing. Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time of the daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff for assessment of compliance.
[redacted]
[y] Optional assessment, as total blood volume for phlebotomy clinically permits
[z] Appropriate cancer staging procedures should be performed during screening. All imaging should be of diagnostic quality. The brain will be imaged using the same method(s) throughout the study. Measurable target lesions should be selected and measured per iRANO guidelines. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Additional tumor response assessments as well as a posttreatment diagnostic brain biopsy may be performed at the discretion of the Investigator as part of standard-of-care treatment, per current iRANO guidelines. MRI scans are required for all subjects, including those with unconfirmed disease progression, to ensure that more slowly declining tumor burden in response to therapy is noted. For 2 years, subjects without confirmed disease progression should continue to have tumor assessments every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation). MRI scans should be available for collection upon Sponsor request. If appropriate, in accordance with iRANO, subjects should continue to receive cemiplimab-rwlc until progression has been confirmed.
[aa] The MRI scan designated on Day 1 should be taken within 24 hours (a + 48hr window is allowed) of Ad-RTS-hIL-12 administration and is the baseline scan for tumor response assessments.
[bb] A tumor sample will be collected on Day 0 and also be collected at the time of progressive disease (per iRANO). The Day 0 tumor sample may be used for testing of IDH and methylation status. Archival tumor tissue, if available, should be submitted for analysis.
[cc] Neutralizing antibody status for Ad-RTS-hIL-12, it should be assessed at screening, Day7, Day 14 and Day 36.

2. TABLE OF CONTENTS

3. LIST OF TABLES

4. LIST OF FIGURES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ab	Antibody
Ad	Ad-RTS-hIL-12 or Ad-RTS-mIL-12, depending on context
Ad-RTS-hIL-12	Adenovirus RheoSwitch Therapeutic System® human interleukin-12
Ad-RTS-mIL-12	Adenovirus RheoSwitch Therapeutic System® mouse interleukin-12
ALVAC	Canarypox virus viral vectors
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
BBB	(Putative) blood-brain barrier
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
CHO	Chinese hamster ovary
CR	Complete response
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP3A4 or CYP450 3A4	Cytochrome P450 3A4
DIPG	Diffuse intrinsic pontine glioma
DP	Drug product
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report form
EIAED	Anti-epileptic drugs

Abbreviation or Specialist Term	Explanation
EMCV	Encephalomyocarditis virus
ESR	Erythrocyte sedimentation rate
FDA	U.S. Food and Drug Administration
Gal4-EcR	Fusion protein between Gal4 DNA binding domain and ecdysone receptor ligand binding domain
GalRE/P	Gal4 responsive promoter
GBM	Glioblastoma (multiforme)
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
hIL-12	Human interleukin-12
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-β	Interferon-beta
IFN-γ	Interferon-gamma
INR	International normalized ratio
IL-2	Interleukin-2
IL-12	Interleukin-12
IP-10	IFN-γ-induced protein 10
iRANO	Immunotherapy Response Assessment for Neuro-Oncology
IRB	Institutional Review Board
IV	Intravenous(ly)
IRES	internal ribosome entry site
IUD	Intrauterine device
KDa	kilo (K)- unified atomic mass units (Daltons or Da)
LDH	Lactate dehydrogenase
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

Abbreviation or Specialist Term	Explanation
NCI	National Cancer Institute
NK	Natural killer
NOS	Not otherwise specified
NPO	Nothing by mouth (literally, nil per os)
ORR	Objective response rate
OS	Overall survival
OSP	Overall Safety Population
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PKP	Pharmacokinetics Population
PO	Oral(ly)
polyA	polyadenylation signal
PR	Partial response
PSP	Pseudo-progression
PUbC	Ubiquitin C promoter
Q	Each/every (*quaque*), as in Q3W (every 3 weeks)
QD	Each day (*quaque die*)
rAd	Recombinant adenovirus
RANO	Response Assessment for Neuro-Oncology
RBC	Red blood cell
rhIL-12	Recombinant human IL-12
RTS	RheoSwitch Therapeutic System
RXR	Retinoid X receptor
SAE	Serious adverse event
SD	Stable disease
SpO_2	Saturation of peripheral oxygen
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
Th1	T-helper cell type 1
ULN	Upper limit of normal

Abbreviation or Specialist Term	Explanation
V	Veledimex
v	Version (followed by number)
vp	Viral particles
VP16-RXR	Fusion between VP16 transcriptional activation domain and a chimeric RXR
WBC	White blood cell

6. INTRODUCTION

6.1. Immunotherapy in Glioblastoma

The revised 2016 World Health Organization Classification of Tumors of the Central Nervous System makes use of molecular genetic findings in addition to histology to define tumor entities on the basis of combined phenotypic and genotypic features to generate "integrated diagnoses" (Louis et al. 2016). It has resulted in substantial restructuring of the diffuse gliomas, as compared with the 2007 CNS WHO Classification. In the revised classification the diffuse gliomas include the anaplastic astrocytomas (anaplastic astrocytoma, IDH-wildtype; anaplastic astrocytoma, IDH-mutant; and anaplastic astrocytoma, NOS [Not Otherwise Specified]) and anaplastic oligodendroglioma (with IDH-mutant and 1p/19q-codeleted subtypes) that are classified as WHO Grade III and the glioblastomas (glioblastoma, IDH-wildtype including giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma subtypes; glioblastoma, IDH-mutant; and glioblastoma, NOS) that are classified as WHO Grade IV. Of the WHO Grade III and Grade IV tumors, glioblastomas make up 60% to 70%, anaplastic astrocytomas 10% to 15%, and several other anaplastic subtypes the rest (Central Brain Tumor Registry).

Glioblastomas are by far the most frequent malignant glioma and are associated with a particularly aggressive course and dismal prognosis (Lieberman 2017). Standard of care treatment for glioblastomas is based on surgical resection with the intent to remove as much of the tumor as is feasible (Fernandes et al. 2017, Paolillo et al. 2018). Resection is then followed by radiotherapy and concomitant adjuvant temozolomide. However, such aggressive treatment is associated with only modest improvements in survival. Newly diagnosed glioblastoma subjects have a median overall survival (OS) of 12 to 15 months (Ahmed et al. 2014) and 2-year OS rate of up to 27% (Omuro et al. 2013), while OS in subjects that have failed TMZ and bevacizumab, or equivalent salvage chemotherapy, is reported as being as short as 3 to 5 months (Omuro et al., 2013; Iwamoto et al., 2009). To date, no salvage treatment has been validated by Phase III data for recurrent or progressive glioblastoma. For subjects with recurrent glioblastoma, the median OS is 6 to 7 months (Omuro et al. 2013), and median progression-free survival (PFS) is 2 to 3 months.

The lack of standard and validated salvage therapies has prompted the use of nitrosoureas, temozolomide rechallenge, bevacizumab, and other targeted agents that are unsatisfactory treatment options. This likely reflects the complexities of disease heterogeneity, and the treatment limitations of brain tumors given the low activity of antineoplastic agents, de novo or acquired drug resistance, the sensitivity of the brain to irreversible damage in response to treatment and the presence of the blood brain barrier (BBB), which maintains the brain as a privileged compartment. Surgical resection may be offered for subjects with recurrent disease, with the goal of alleviating mass effect, improving symptoms, and achieving cytoreduction. Surgical resection, however, is limited by the infiltrative nature of the disease and the lack of clear margins delimitating the tumor. Given the poor overall prognosis and lack of effective treatments, new therapeutic approaches for malignant gliomas are needed.

Immunotherapy for brain tumors is actively being investigated with an array of newer therapeutic modalities. Only about a third of glioblastomas have been reported to demonstrate a robust CD8+ cell population present within the tumor microenvironment (Heimberger et al. 2008), and these cells are anergic (i.e., not secreting interferon gamma [IFN-γ] or incapable of cytolytic activity). The immune infiltration in glioblastomas is highly variable and is likely driven by the genetic composition and mutational load of the tumor (Beier et al. 2012, Doucette et al. 2013). The anticipated specificity and efficiency of cytotoxic T-cells (CD8+), activated by local production of IL-12, is particularly attractive

and may both spare normal brain cells and minimize systemic toxicity. We have shown in an orthotopic mouse model that survival and tumor killing was greatly enhanced by combining a checkpoint inhibitor and Ad-RTS-mIL-12 + veledimex (Barrett et al. 2016b). Early clinical trials suggest that combining immunotherapeutic approaches with surgery, radiation, and chemotherapy may improve outcomes (Mitchell et al. 2008). Preliminary results from the CheckMate 143 (NCT 02017717) randomized clinical trial in first recurrence of glioblastoma, announced in a World Federation of Neuro-Oncology Societies (WFNOS) 2017 abstract, demonstrated a failure of nivolumab to prolong overall survival of patients with recurrent GBM, and this monotherapy arm of the trial was prematurely terminated (Filley et al 2017). However, an encouraging example of a *combination* immunotherapy approach to treating glioblastoma is a study of the safety and activity of nivolumab (human programmed death receptor-1 [PD-1] blocking antibody) in combination with ipilimumab (anti-cytotoxic T lymphocyte associated antigen 4 [CTLA-4] antibody) in patients with recurrent disease (Reardon et al. 2016). In this ongoing dose escalation study, combination therapy was tolerable, with 12-month overall survival (OS) ranging from 25% to 40%.

In Ziopharm's ongoing Phase I trial of intratumoral viral delivery of Ad-RTS-hIL-12 + veledimex to date 31 subjects have been orally dosed in 4 cohorts: 10 mg (n=6), 20 mg (n=7), 30 mg (n=4), 40 mg (n=6), and an expansion cohort of 20 mg (n=8). Results show that veledimex crossed the blood-brain-barrier, with approximately 40% of plasma levels detected in the brain tumor. Subjects in the 20 mg dose cohort (n=15) have better median OS (12.7 months) than in other cohorts.

Immune checkpoint inhibitors penetration across the blood-brain-barrier to the tumor tissue remains controversial, but the goal is to achieve maximum therapeutic effect while limiting systemic toxicity, especially when CD8+ cells have been mobilized to the tumor as we have documented following treatment with Ad-RTS-hIL-12 + veledimex.

6.2. Interleukin-12 and Cancer Immunotherapy

Interleukin-12 (IL-12) is a pro-inflammatory cytokine and has been recognized as a master regulator of cell mediated immunity in response to intracellular pathogens and neoplastic transformation. Structurally, IL-12 is a heterodimeric protein composed of p35 and p40 subunits covalently linked to form the biologically active IL-12 p70 molecule (Carra et al. 2000). The expression of the p40 subunit is tightly regulated and requires specific priming and amplification signals through complex combinatorial matching of Toll receptor agonists and specific cytokines, thus limiting the cell types that can produce native biologically active IL-12 to activated antigen-presenting cells, neutrophils, and macrophages (Trinchieri 2003). On a secondary level, IL-12 production can also be negatively regulated through various mechanisms including production of IL-10 and transforming growth factor β (TGFβ).

Initial studies identified that IL-12 was produced by innate immune cells in response to pathogens and that it led to the production of interferon gamma (IFN-γ) and tumor necrosis alpha (TNFα) by T and natural killer (NK) cells (Micallef et al.1996, Trinchieri 2003). When it was discovered that IL-12 could drive naïve T-helper cell differentiation to the inflammatory T-helper cell type 1 (Th1) phenotype (Hsieh et al. 1993), a role for IL-12 was established as a bridge between innate immune cells and the adaptive immune response through polarization of naïve CD4+ cells. More recent data demonstrate additional functional roles of IL-12 directly influencing CD8+ T-cell differentiation (Curtsinger et al. 2003, Kalinski et al. 1999) and the reactivation and survival of memory CD4+ T-cells (Yoo et al. 2002). This is particularly important in the context of the tumor microenvironment where high levels of IL-12 have been shown to repolarize antigen-experienced CD4+ T-cells back to the functional antitumor Th1 phenotype (Wesa et al. 2007).

Evidence that IL-12 is able to trigger innate and adaptive immunity and modulate the tumor microenvironment supports the relevance of IL-12 as an important immunotherapeutic agent. Its ability to activate and recruit dendritic cells that facilitate the cross-priming of tumor antigen-specific T-cells, along with its influence on NK and $CD8^+$ T-cell cytotoxic activities and antigen-specific antitumor responses (Mosmann et al. 1989, Trinchieri 1995, Tsung et al. 1997, Mailliard et al. 2002) warrant further study in cancer therapy. Additionally, IL-12 has also been shown to stimulate the production of superoxides and nitric oxide and possess potent antiangiogenic activity through IFN-γ (Voest et al. 1995, Wigginton et al. 1996, Coughlin et al. 1998). The potent antitumor activity of IL-12 has been well documented in various cancer mouse models including melanoma, mammary carcinoma, sarcoma, and colon and renal carcinoma (Colombo et al. 2002). The potent nature of its biological activity and signaling complexity has also prompted the study of different delivery mechanism with a focus on intratumoral delivery and tumor microenvironment modulation.

Based on such data, human studies of IL-12 as an anticancer agent were initiated. The first of these studies was a Phase I dose escalation of intravenous (IV) administered recombinant human IL-12 in subjects with either melanoma or renal cell carcinoma. The study reported a transient complete response in melanoma and a partial response in renal cell carcinoma with significant toxicities. The Phase II trial observed similar toxicities, and two IL-12 related deaths prompted the Food and Drug Administration (FDA) to suspend the trial (Atkins et al 1997, Leonard et al 1997). Additional studies confirmed that systemic administration of recombinant IL-12 resulted in significant toxicity, limiting its potential for clinical development (Salem et al. 2006). These results prompted the investigation of alternative delivery routes focusing on locoregional administration either by subcutaneous injection or intratumoral delivery implementing IL-12 as a direct anticancer therapeutic or as an adjuvant to vaccination.

6.3. Local IL-12 Delivery and Development of an Inducible IL-12 Immunotherapy

The potent effects of cytokines, particularly IL-12, as mediators of an anticancer immune response remain compelling. This is especially true since the advent of immunotherapies such as anti-CTLA-4 and anti-PD1 antibodies provide proof of concept that inhibiting immune checkpoints translates into clinical benefit. IL-12 biology including the level of activation, location of initial expression, immune effector function, and biologically active combination with other cytokines remain incompletely understood.

Several human studies that have implemented the local delivery of cytokines or chemotherapeutic agents have already shown that such an approach reduces systemic toxicity and produces signals of clinical benefit. One particularly relevant trial implemented a gene transfer strategy to express interferon beta (IFN-β) locally in glioma tumors, and thus achieved high intratumoral IFN-β expression without systemic toxicity. The IFN-β was constitutively expressed through a replication-defective serotype 5 adenoviral vector under the control of a cytomegalovirus promoter achieving transduction of both dividing and non-dividing cells. The investigators reported the approach proved feasible and well tolerated; however, although the IFN-β transduction was variable among subjects, it was associated with apoptosis (Chiocca et al. 2008).

In the current Phase I study, we are exploring a local treatment strategy for high-grade gliomas with the goal of extending the IL-12 therapeutic window and reducing its systemic toxicity. [redacted] The replication-incompetent Ad-RTS-hIL-12 vector is injected locally in the tumor lesion and

initiates hIL-12 transcription only in the presence of the promoter specific oral activator ligand, veledimex. With this system, the IL-12 expression level can be modulated by the dose and frequency of veledimex administration, making it feasible to lower or terminate IL-12 expression in the event of severe or unexpected toxicities.

6.4. Adenoviral Vectors for Gene Therapy

6.4.1. Adenoviral Safety

Adenoviral vectors have been used extensively to deliver a variety of gene products to human subjects, including cancer subjects. Although adenoviral vectors are immunogenic, virtually all recipients have pre-existing humoral immunity to adenoviruses and they are generally considered a safe and well tolerated vehicle for gene delivery. Numerous studies have utilized adenoviral vectors to achieve intratumoral expression of a variety of genes. In a Phase I/II clinical trial of subjects with prostate cancer, direct intraprostatic injection of a replication-defective adenoviral vector encoding bacterial nitroreductase (dose levels 5 x 10^{10} -1 × 10^{12} viral particles [vp]) was well tolerated, with minimal adverse events (AEs) (Patel et al. 2009) . A Phase I study of subjects with oral leukoplakia implemented multiple intraepithelial injections of recombinant adenovirus (rAd)-p53 (1 x 10^{8} vp/cm^2) and demonstrated good tolerance of the vector, with no evidence of dose-limiting toxicity (DLTs) (Zhang et al. 2009) . In another Phase I/II study of subjects with chemoradiation-resistant advanced esophageal carcinoma, intratumoral injections of adenovirus vector containing p53 (Ad.5CMV-p53) were well tolerated at doses ranging from 10 x 10^{11} to 25 x 10^{11} vp, with no DLTs, and generally mild to moderate adverse events (AEs) (Shimada et al. 2006) . The most common AEs were fever (all 10 subjects), pain (30% of subjects), and hyperglycemia, which was attributed to the use of total parental nutrition (30% of subjects). Hypocalcemia was reported in two subjects (20%) and one subject each (10%) experienced activated partial thromboplastin time (aPTT) prolongation, abnormally high serum amylase, and abnormally high serum creatinine.

In a Phase I study of subjects with advanced pancreatic, colorectal, or primary liver tumors, intratumoral injection of an adenoviral vector encoding hIL-12 (Ad.IL-12) was well tolerated at doses of up to 3 × 10^{12} vp. Common AEs were similar to symptoms observed with gene delivery by other adenoviral vectors, including transient, mild to moderate fever, malaise, sweating, and lymphopenia (Sangro et al. 2004).

A recent randomized, open-label, Phase III study compared a regimen of surgical resection, adenovirus-mediated gene therapy (intraoperative perilesional sitimagene ceradenovec), intravenous ganciclovir, and standard of care interventions versus surgical resection plus standard of care interventions in 250 subjects with newly diagnosed high-grade glioma amenable to resection. Results showed that although the time to death or re-intervention was prolonged, OS was not improved for the investigational regimen relative to the standard of care regimen (Westphal et al. 2013). This apparent difference may have been due to the composite primary endpoint and/or that while OS is a robust endpoint, there is no discussion of effect size and for recently-diagnosed tumors it might be less suitable to capture meaningful treatment effects for the initial stages of disease because of uncontrolled therapy at relapse (*ibid*). Nevertheless, the authors concluded that the treatment had an increased hazard ratio for the primary analysis with a positive overall benefit-risk ratio, with similar AEs (hemiparesis [often transient], hyponatremia, and seizures, but no cerebral hemorrhages nor hematomas), as compared with the standard-of-care regimen.

6.4.1.1. Safety of Intratumoral Injection of IL-12 Gene Vectors

In contrast with the systemic toxicity resulting from administration of recombinant IL-12 protein, local administration of IL-12 via injection of plasmid or adenoviral vectors containing the hIL-12 gene has proven to be well tolerated in subjects with various cancers, and therefore appears to provide an effective delivery method for this potent immunomodulatory cytokine. Several studies have investigated the safety of intratumoral expression of IL-12 in subjects with metastatic melanoma. A Phase I study investigated intratumoral expression of IL-12 together with the co-stimulatory molecule B7.1 via two separate canarypox virus viral vectors (ALVAC) in subjects with metastatic melanoma and reported mild to moderate injection site reactions, fever, chills, myalgia, and fatigue as AEs (Triozzi et al. 2005). However, all subjects also developed antibodies to ALVAC. Notably, serum IL-12 and IFN-γ levels were not increased after treatment. Another Phase I trial showed that delivery by electroporation of a plasmid containing IL-12 to tumors in subjects with metastatic melanoma resulted in minimal systemic toxicity, with transient pain after electroporation being the most common AE (Daud et al. 2008). Results from another Phase I study showed that intratumoral injection of DNA encoding hIL-12 in subjects with metastatic melanoma was well tolerated overall (Heinzerling et al. 2005). Eight of nine subjects experienced a transient response at the intratumoral injection site, and some subjects who had tumor responses also showed some increases in systemic in IL-12, interferon gamma-induced protein 10 (IP-10), and IFN-γ.

Localized production of IL-12 also has been reported as well tolerated in subjects with other malignancies. For example, a Phase I study in 17 subjects with metastatic pancreatic, colorectal, or primary liver cancer examined intratumoral injection of dendritic cells engineered to secrete IL-12 via a rAD vector (Mazzolini et al. 2005). In that study, the most common AEs were lymphopenia, fever, and malaise. Subjects also developed antibodies to the adenoviral capsid proteins. Intraperitoneal injection of a plasmid containing the hIL-12 gene in women with chemotherapy-resistant, recurrent, ovarian cancer also was found to be generally safe and well tolerated (Anwer et al. 2010). Low-grade fever and abdominal pain were the most common AEs. Plasmid DNA was not detected in the subjects' serum samples, and treatment-related increases in IFN-γ levels were observed in pleural fluid, but not in serum. Similar data were reported in a study of subjects with advanced pancreatic, colorectal, or primary liver malignancies who received intratumoral injections of adenoviral vectors encoding hIL-12 at doses ranging from 2.5×10^{10} to 3×10^{12} vp (Sangro et al. 2004). In that study, treatment was well tolerated and a maximum tolerated dose (MTD) was not reached. Transient lymphopenia was observed in 86% of subjects, and the severity was increased at higher vector doses. Transient, mild to moderate fever, sometimes accompanied by malaise and sweating, was observed in ~ 60% of subjects during the first 2 days after the injection. Five of the 21 subjects (24%) experienced nausea and/or vomiting on the day of the injection. No cumulative toxicity was observed. These events were deemed related to injection of the virus and not to transgene expression.

[redacted]

[redacted]

[redacted]

6.5.3. Veledimex

Veledimex is a diacylhydrazine that is fully active at the RTS receptor. Drug product is formulated as a semi-solid containing veledimex as a dry powder and excipients. This formulation has been encapsulated in gelatin capsules for oral administration in clinical trials.

[redacted]

6.5.4. Cemiplimab-rwlc

Cemiplimab-rwlc (Libtayo ®), is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD L1-mediated T cell inhibition. Cemiplimab-rwlc was isolated from Regeneron's VelocImmune™ human antibody mouse platform and contains a human light chain variable domain fused to human kappa constant domain and a heavy chain variable region in a human IgG4 Fc format. The IgG4 Fc domain contains a serine to proline mutation in the hinge region to promote dimer stabilization, designated IgG4P.

[redacted]

both species is 1:40 resulting in a human equivalent dose (HED) of 2.4 x 10^{12} vp or 2.4 x 10^{11} vp

[redacted]

6.9. Summary of Safety

Please see the Investigator's Brochure for the most current safety information.

[redacted]

7. STUDY OBJECTIVES

7.1. Primary Objective

To determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin 12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively.

7.2. Secondary Objectives

- To determine the survival rates at 6, 12, 18 and 24 months
- To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months
- To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months
- To determine the tumor response rates at 6, 12, 18 and 24 months
- [redacted]

8. STUDY DESIGN

8.1. Overall Study Design

This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 [redacted] and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively.

This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility. Subjects will receive cemiplimab-rwlc on Day -7 (±3 days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection and Ad-RTS-hIL-12 [redacted] will be administered by freehand injection. Ad-RTS-hIL-12 will be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). The total amount delivered to each site will be recorded in the eCRF. If the total administered volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations.

After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing.

Subjects will receive a dose of cemiplimab-rwlc (350 mg) IV on Day 15 and every three weeks thereafter (Q3W) until documented progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the follow-up period. Delays in cemiplimab-rwlc dosing due to toxicities are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days.

A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor.

After the first six patients have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused to allow for additional safety follow-up and assessment. The SRC will review safety data after the 6th subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products.

8.2. Study Oversight for Safety Evaluation

Safety oversight will occur through the site investigator and medical monitor. A formal SRC, guided by the SRC charter, will include the study investigators, the medical monitor and other appropriate sponsor representatives and will provide overall safety oversight. Additional external medical and scientific experts may also be invited to participate in the reviews as needed and appropriate and as decided by the SRC. If a significant safety event occurs, the SRC will convene to evaluate the safety event(s) and make a recommendation and decision on the enrollment and continued treatment of subjects.

9. SUBJECT SELECTION

Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.

9.1. Inclusion Criteria

1. Male or female subject ≥18 and ≤75 years of age
2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures
3. Histologically confirmed glioblastoma from archival tissue
4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy. Multifocal disease is allowed.
5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor)
    a. Nitrosoureas: 6 weeks
    b. Other cytotoxic agents: 4 weeks
    c. Antiangiogenic agents: 4 weeks
    d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks
    e. Vaccine-based or CAR-T therapy: 3 months
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment
7. Karnofsky Performance Status ≥70
8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
    a. Hemoglobin ≥9 g/L
    b. Lymphocytes >500/mm^3
    c. Absolute neutrophil count ≥1500/mm^3
    d. Platelets ≥100,000/mm^3
    e. Serum creatinine ≤1.5 x upper limit of normal (ULN)
    f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN.
    g. Total bilirubin <1.5 x ULN
    h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) within normal institutional limits

9. Female of child bearing potential* and sexually active male subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Normal cardiac and pulmonary function as evidenced by a normal ECG with QTc ≤450 msec and peripheral oxygen saturation (SpO2) ≥ 92% on Room air by pulse oximetry

9.2. Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment with bevacizumab

   (NOTE: Brief use (< 4 doses) of bevacizumab for controlling edema is allowed)
3. Subjects receiving systemic corticosteroids for treatment of disease-related symptoms during the 4 weeks prior to Day -7
4. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
5. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

   NOTE:

   - Subjects with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For subjects with controlled HIV infection, monitoring will be performed per local standards.
   - Subjects with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Subjects with controlled infections must undergo periodic monitoring of HBV DNA. Subjects must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
   - Subjects who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

6. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively.
7. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed.
8. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer
9. Nursing or pregnant females
10. Prior exposure to veledimex
11. Use of an investigational product within prior 30 days.
12. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.
13. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor
14. Presence of any contraindication for a neurosurgical procedure
15. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of DVT may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor.
16. Unstable or clinically significant medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples include, but are not limited to, history of myocarditis or congestive heart failure (as defined by New York Heart Association Functional Class III or IV), unstable angina, serious uncontrolled cardiac arrythmia, myocardial infarction within 6 months of screening, active interstitial lung disease (ILD)/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids uncontrolled asthma, or colitis.

9.3. Subject Enrollment

Approximately 30 subjects may be enrolled.

9.4. Withdrawal of Subjects from Study Treatment and/or Study

The sponsor may terminate this study at any time. The investigator and/or the subject have the right to terminate the subject's participation in the study at any time. Efforts should be made to ask subjects who discontinue study drug to be available to complete the Follow-up assessments.

A subject may withdraw or be withdrawn from the study treatment prematurely for any of the following reasons:

- Principal Investigator (PI) determines further participation is not in the subject's best interest (e.g., subject experiences rapid clinical deterioration in the absence of confirmed disease progression)
- Subject has confirmed disease progression
- A subject must be withdrawn in the event of any of the following:
- Subject withdraws informed consent.
- Any treatment-related AEs that meet withdrawal criteria
- Substantial noncompliance with study requirements
- Subjects with a confirmed positive pregnancy test
- Any intercurrent illness that would, in the judgement of the investigator or sponsor's medical monitor, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy
- Subjects who did not receive any study drugs

- *NOTE: Any subject who wishes to withdraw from the study treatment may do so at any time but will be asked to be available for the safety, tumor response, and survival follow-up assessments.*

Every effort should be made to follow subjects who withdraw from study treatment for ongoing treatment-related AEs. Subjects who withdraw during the treatment period should continue to have study assessments as clinically indicated.

9.5. Replacement of Subjects

Subjects who withdraw from the study or do not receive each study drug may be replaced. All dosed subjects will be included in the overall safety assessment.

9.6. Premature Termination of Study or Study Site

The sponsor has the right to close the study at any time, although this should occur only after mutual consultation between the sponsor and the investigators. The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be informed of such action. Should the study or center be closed prematurely, all study materials (completed, partially completed, and blank electronic case report forms (eCRF), study medication, etc.) must be stored or disposed of according to the sponsor's instructions. Events that may trigger premature termination of the study or closure of a center include but are not limited to the following: new toxicity findings; decision to re-challenge patient who has experienced a Grade 4 event; interim analysis results; noncompliance with the protocol; changes in the development plans for the study drug; slow recruitment; and poor-quality data.

10. INVESTIGATIONAL PRODUCTS

Ad-RTS-hIL-12 and Veledimex is an investigational product has two components: the Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand). Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of the RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated (turned on and off) by the optimal veledimex dose and schedule.

Cemiplimab-rwlc is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kilounified atomic mass unit (kDa) based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The cemiplimab-rwlc heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody. Please refer to the Pharmacy Manual for additional information.

Antibody generation by VelocImmune® mice is carried out using standard techniques after immunization with PD-1. The genes encoding the heavy and light chains of cemiplimab-rwlc were introduced into Chinese Hamster Ovary (CHO) cells, and a stable expression cell line (Cell Line 1) was selected for the antibody. Later in development, a second stable expression cell line with higher titer (Cell Line 2) was developed for this antibody. For both cell lines, the expression of REGN2810 was regulated, such that the recombinant CHO cells were de-repressed to initiate antibody expression and secretion into the cell culture medium in production bioreactors. Antibody is harvested via filtration and purified through a series of preparative column chromatographic and filtration steps to generate drug substance. Drug substance is then formulated and sterile-filtered to produce the final drug product (DP).

10.1. Preparation of Ad-RTS-hIL-12

Ad-RTS-hIL-12 will be supplied as a sterile, single-use vial for injection. Each 0.1 mL contains [redacted] Ad-RTS-hIL-12. Information regarding the preparation of the Ad-RTS-hIL-12 dose is provided in the Pharmacy Manual.

10.2. Preparation of Veledimex

Sponsor will provide veledimex capsules to be dispensed by the study site pharmacy to subjects for oral administration. Information regarding the veledimex is provided in the Pharmacy Manual.

10.3. Preparation of Cemiplimab-rwlc

Cemiplimab-rwlc will be supplied in single-dose vials. Information regarding the preparation of the cemiplimab-rwlc dose is provided in the Pharmacy Manual.

10.4. Handling and Storage

Study drugs must be stored in a restricted access area under the storage conditions indicated in the Investigator's Brochure or Pharmacy Manual. All necessary precautions while handling potentially toxic compounds must be strictly followed.

10.5. Monitoring of Subject Adherence and Managing Missed Doses

10.5.1. Veledimex

The first veledimex dose following Ad-RTS-hIL-12 injection is expected to be administered when the subject is at the clinical site, under careful medical supervision by the clinic staff to ensure that the subject does not have difficulty swallowing the capsules. Thereafter, subjects may be allowed to self-administer the remaining once daily doses as described. Subjects are to be instructed to take the appropriate number of capsules in the same way for each of the remaining treatment period days and may be reminded to do so by phone on non-visit days.

Subjects should NOT make up any missed doses.

Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the once daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff on Day 15, so that staff can properly assess dose compliance.

10.5.2. Cemiplimab-rwlc

The recommended dose of cemiplimab-rwlc is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks (Q3W) until confirmed disease progression or unacceptable toxicity.

10.6. Disposition of Unused Drug

All unused study drug should be destroyed at the study site in accordance with standard institutional practice and in accordance with United States Occupational Safety and Health Administration procedures, after full accountability has been documented. Any study drug destruction at study site must be documented and the records maintained in the investigator's study file.

10.7. Accountability and Dispensation

The investigator must maintain accurate records accounting for the receipt and dispensation of study drugs. The investigational materials are to be prescribed only by the investigator or the sub-investigators named on FDA Form 1572 and may only be dispensed by authorized personnel at the institution(s) listed therein. Under no circumstances will the PI allow the investigational drug(s) to be used for purposes or in subjects other than as directed by the protocol.

10.8. Treatment Plan

10.8.1. Cemiplimab-rwlc

On Day -7, Day 15, and approximately every 3 weeks thereafter subjects will receive cemiplimab-rwlc until confirmed disease progression or unacceptable toxicity.

10.8.2. Ad-RTS-hIL-12 + Veledimex

- Subjects will be given 20 mg of veledimex by mouth, when NPO (excluding other medications) 3 (± 2) hours before craniotomy (Day 0). The actual time of veledimex administration should be noted and recorded.
- Surgical planning will be performed on a diagnostic MRI acquired prior to the surgery as per standard of care.
- At the time of tumor resection, tumor, CSF (if available), and blood samples will be collected.

- Immediately after tumor resection, when available, an intraoperative MRI can be performed to identify contrast enhancing or T2/FLAIR hyper intense residual tumor. If intraoperative MRI is not available, the neurosurgeon will select sites for injection.
- Subjects will receive Ad-RTS-hIL-12 [redacted] This will be administered by freehand injection into approximately two sites within the residual tumor for a total volume of 0.1 mL selected by the neurosurgeon. When available an intra-operative MRI can be performed to guide the Ad-RTS-hIL-12 injection to areas of contrast-enhancing tumor tissue.
- The day of Ad-RTS-hIL-12 administration is designated as Day 0. If Ad-RTS-hIL-12 injection is not performed, subject will not continue with post-resection veledimex dosing.
- After tumor resection and Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-resection veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning and within approximately 30 minutes of a regular meal.

Subjects should be carefully monitored for possible local reactions and/or hypersensitivity reactions, according to standard practice. Intracranial bleeding or other procedure-related events should be evaluated before the first veledimex dose is given post Ad-RTS-hIL-12 administration. Any changes in neurological status should be reported to the investigator immediately, either during hospitalization or once subject is discharged. Subjects should be instructed to call the study physician or study nurse if they develop any symptoms after they are released from the hospital.

NOTE: It is important that subjects are instructed to maintain adequate oral hydration while subjects are being administered veledimex. Study sites should monitor subjects for proper hydration and monitor blood pressure regularly. The incidence of low blood pressure to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

10.9. Stopping Rules

From Day -7 to 30 days after completion of Ad-RTS-hIL12 + veledimex dosing, if any subject experienced a death (other than death related to progressive disease); or if any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.

10.10. Dose Modifications and Dose Delays

Veledimex dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 2.

Table 2: Criteria for Dose Delay and Dose Reduction of veledimex

Adverse Reaction	Severity[2]	Veledimex Dosage Modifications[1]
Immediately life-threatening/ Potentially-Fatal Severe Adverse Reactions		
Any non-hematologic AE[3]	Grade 4 non-hematologic adverse event at least possibly related to study drug, that is considered by the treating physician to be immediately life-threatening, and results in emergent medical and/or surgical intervention	Discontinue
Other Severe Adverse Reactions		
Cytokine Release Syndrome	Grade 3 or higher (per the Ziopharm Working Definition of Cytokine Release Syndrome)	Withhold[4]
Any non-hematologic AE[3, 5] (except brain edema)	Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and persists at least 3 days	Withhold[4]
Cerebral edema[5]	Grade 3 or higher	Withhold[4,6]
Thrombocytopenia	Grade 3 or higher thrombocytopenia (< 50,000/mm^3) at least possibly related to study drug	Withhold[4]
Lymphopenia or other hematologic toxicity	Grade 4 or higher lymphopenia or other hematologic toxicity (except thrombocytopenia)	Withhold[4]
Increased transaminitis[8]	Grade 3 or higher increase in ALT or AST	Potentially Withhold[7]

1. These recommendations are for general guidance only. Treating physicians should manage patients according to their clinical judgement, as informed by institutional guidelines, best practices and these guideline recommendations.
2. Toxicity as graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.
3. Nausea and vomiting will not be considered in this category unless at least Grade 3 or 4 and refractory to antiemetics (i.e., defined as symptoms not mitigated by maximal medical support as directed by the Investigator (per institutional guidelines) in consultation with the Sponsor Clinical Medical Monitor).
4. Withhold the next and any successive doses of veledimex while the Grade 3 or 4 toxicity persists. Veledimex dosing may resume, after discussion with the Sponsor Clinical Medical Monitor, in subjects with rapid and substantial reversal of toxicity, either spontaneously or following appropriate medical treatment. The Sponsor Clinical Study Coordinator will be notified in advance of veledimex dosage modifications.
5. Seizures, headache, and cerebral edema are commonly observed in this population and will be recorded according to the grade of toxicity and therefore will not be considered in this category unless unresponsive to maximal medical support as directed by the Investigator (informed by institutional guidelines) and in consultation with the Sponsor Clinical Medical Monitor.
6. *Cerebral Edema Guideline Recommendations:* As a general guideline, mannitol (Osmitrol), corticosteroid treatment (i.e., dexamethasone or Decadron) and/or withholding the next dose(s) of veledimex short-term are considered for cerebral edema, CTCAE v5.0 Grade 3 (or for "moderate" severity descriptively). For Grade 4 cerebral edema, mannitol (Osmitrol), higher dose corticosteroids and/or longer-term withholding or discontinuation of veledimex are considered, especially if the edema is not sufficiently mitigated by urgent medical intervention. It is expected that the use of corticosteroids will vary between sites and among subjects, and therefore, the precise extent and dosage of steroids cannot be specified per protocol. The treating physician will decide as is safe and appropriate for the individual subject according to their clinical judgement as informed by the label and institutional guidelines and should consider the minimum steroid dose or the lowest amount that adequately and rapidly controls the subject's signs and symptoms (refer to Rationale section below). Consideration also may be given to a limited number of doses of bevacizumab (Avastin) if (typically high-dose) corticosteroids are not in the best interests of the subject in the treating physician's clinical judgement and following consultation with the Medical Monitor. In the event of an immediately life-threatening event, the treating physician should consider surgical decompression.
7. *Rationale:* Cerebral edema may pre-exist experimental treatment to a variable extent and usually is associated with the underlying disease and/or increase following surgical procedures. The study treatment, particularly with combination therapy including an immune checkpoint inhibitor, also may possibly cause an increase in the severity of edema. Patients with glioblastoma receiving more than 4 mg dexamethasone qd were reported to have decreased overall survival, possibly due to immunosuppression (British J Cancer 2015:113, 232–241). Preliminary data presented at the Society for Neuro-Oncology 2018 Annual Meeting by Ziopharm Oncology also suggests that overall survival is decreased in 20 mg veledimex craniotomy cohort subjects (i.e., administered more than a 20 mg cumulative dosage of dexamethasone) during the initial treatment period (Days 0-14); the relative contributions of severity of the condition vs immunosuppression to the negative effect observed on overall survival are presently uncertain.
8. Withhold the next dose(s) of veledimex if the transaminitis is part of a constellation of findings consistent with Cytokine Release Syndrome (refer to Ziopharm Working Definition of Cytokine Release Syndrome). The treating physician may elect to follow the laboratory test trajectory and clinical status if an isolated transaminitis.

Cemiplimab-rwlc dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 3.

Table 3: Criteria for Dose Delay and Dose Reduction of cemiplimab-rwlc

Adverse Reaction	Severity	Cemiplimab-rwlc Dosage Modifications
Severe and Fatal Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold*
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold*
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN	Withhold*
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, 4	Withhold if clinically necessary*
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold*
	Grade 4	Permanently discontinue
Recurrent or persistent immune-mediated adverse events	• Recurrent Grades 3 or 4 • Grades 2 or 3 persistent for 12 weeks or longer after last cemiplimab-rwlc dose in spite of appropriate therapy • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last cemiplimab-rwlc dose	Permanently discontinue
Severe and Fatal Immune-Mediated Adverse Reactions		
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

AE = adverse event
*: Resume in patients with complete or partial resolution (Grade 0 to 1) after supraphysiologic dose of corticosteroids discontinued

10.11. Safety Monitoring and Adverse Effect Management

Each subject receiving cemiplimab-rwlc, Ad-RTS-hIL-12 or at least one dose of veledimex will be included in the Overall Safety Population (OSP). Parameters used in the safety analysis of all populations will include all laboratory tests, physical examination, imaging scans, and spontaneous reports of AEs reported by subjects. Each patient will be assessed according to the scheduled study procedures and any additional visits as a result of AEs. Cytokine release syndrome will be assessed per the Ziopharm Working Definition (Appendix 1). Other adverse events will be assessed according to the NCI CTCAE v5 criteria.

10.12. Severity Grading and Management of Local Reactions

Injection of agents into tissue carries a potential risk of local reactions that may be characterized as intense immunologic reaction at or near the injection site. Local reactions will be graded according to the NCI CTCAE v5 criteria.

As with all signs and symptoms, events should be recorded and graded as AEs according to NCI CTCAE v.5 criteria. Study stopping rules will not apply to a specific event if it is clearly unrelated to the study treatment.

10.13. Prophylactic Antipyretic and/or Analgesic Administration

The use of antipyretics and/or analgesics is allowed as a prophylactic measure perioperatively. Antipyretics and/or analgesics can be used anytime during study treatment, as indicated and required for patient safety and must be recorded as concomitant medications. Please refer to exclusion criteria for acute clinically significant and/or chronic infections.

NOTE: Since fever and other flu-like symptoms (e.g., chills, body aches, malaise, loss of appetite, etc.) are sometimes experienced following Ad-RTS-hIL-12 + veledimex, it is reasonable for subjects to be administered prophylactic antipyretic and/or analgesic medication prior to Ad-RTS-hIL-12 injection and during the first week after injection at the discretion of the treating physician. The incidence of pyrexia and flu-like symptoms to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

Please refer to Appendix 2 or the recommended regimen for the prophylactic administration of antipyretics and/or analgesics.

11. CONCOMITANT THERAPY

Information on concomitant medications, including all medications, blood products, vitamins, and other supplements, will be collected through the Screening, Treatment, through 90 days after the subject's last dose of any study drug.

Subjects experiencing brain tumor-related symptoms or edema should be treated with corticosteroids as per standard practice. The treating physician should consider the minimum starting steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher starting steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subjects' symptoms, as determined to be safe and appropriate by the treating physician

11.1. Permitted Medications

Subjects may receive standard treatments, including palliative and supportive care for any illness or symptom management during study treatment, including:

- Corticosteroids are permitted for brain tumor related- symptoms. The treating physician should consider the minimum steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subject's symptoms, as determined to be safe and appropriate by the treating physician. Physiologic replacement doses of corticosteroids are also permitted (NOTE: Intranasal corticosteroids are excluded due to rapid systemic absorption).
- Antidiarrheal therapy is permitted for study drug induced- diarrhea
- Antiemetics are permitted for study drug- induced- nausea and vomiting

NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

11.2. Prohibited Medications/Therapies

The following medications are prohibited during the study:

- Any other investigational agent or anticancer therapy (chemotherapy, radiotherapy, etc.) while receiving study treatment
- Palliative radiotherapy is not permitted while on study
- Enzyme inducing anti-epileptic drugs (EIAED) are listed in Appendix 3 and are NOT permitted.
- Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness

NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

12. STUDY PROCEDURES

12.1. Written Informed Consent

The provided written ICF must be signed before any protocol specific procedures and assessments can be performed. A copy of the signed ICF will be given to the subject and a copy should be filed in the medical record. The original ICF should be kept on file with the study reports. Standard of care evaluations performed as part of the subject's routine treatment prior to signing the ICF can be used if they were conducted within the timeframe of the screening period. Refer to Section 12.3.2.1 and Section 17.8 for further information.

12.2. Subject Registration

Centralized registration of subjects will be completed according to a process defined by the sponsor. Eligible subjects are to be enrolled and assigned a unique study identification number before the planned cemiplimab-rwlc dose. Once assigned, a subject's identification number will not be reused.

12.3. Schedule of Assessments and Observations

Screening assessments must be performed within 30 days prior to the Ad-RTS-hIL-12 injection. Any screening tests, exams, or procedures outside of this range may be repeated at the investigator's discretion. All study visits must be completed as described in the protocol while subjects are taking veledimex capsules. Follow-up assessments are allowed a window of ± 7 days. Refer to Table 1 Schedule of Study Procedures for further information.

12.3.1. Study Tests, Exams, and Procedures

12.3.1.1. Demographics, Medical and Cancer History, and Concomitant Medications

Each subject's complete medical history will be documented during screening, including demographic information, relevant medical history, current primary cancer diagnosis, and prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries, and any associated residual toxicities). In addition, concomitant medications, including blood products, vitamins, and other supplements received during the screening period (28 days) prior to initiating study treatment will be recorded. Concomitant medications will continue to be collected through 90 days after the subject's last dose of any study drug.

12.3.1.2. Physical Examinations

A complete physical examination will also include a neurological examination.

12.3.1.3. Vital Signs, Height, and Weight

Vital signs will include blood pressure, pulse rate, temperature, and respiration rate. Subject's blood pressure should be monitored regularly, with hydration as needed to prevent hypotension for 72 hours after administration of Ad-RTS-hIL-12, as previously noted. Assessment of vital signs is required prior to injection of Ad-RTS-hIL-12, and prior to veledimex dosing. Height and weight will be measured and recorded according to Schedule of Study Procedures.

12.3.1.4. Karnofsky Performance Status

The Karnofsky Performance Status measures the ability of cancer subjects to perform ordinary tasks. Scores range from 0 to 100 with a higher score meaning that the patient is better able to carry out daily activities. The Karnofsky Performance Status is used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

Subjects must have a Karnofsky Performance Status score of ≥ 70 at the Screening Visit to be included in the study.

12.3.1.5. Pregnancy Testing

Females of childbearing potential will have a serum pregnancy test at the Screening Visit and a urine or serum pregnancy test on Day 0, with a negative pregnancy outcome prior to study drug initiation.

12.3.1.6. Monitoring of Adverse Events

Monitoring and recording of AEs and serious adverse events (SAEs) will be conducted throughout the study. Adverse events and SAEs that occur following the signing of the ICF through 90 days after the subject's last dose of any study drug- must be recorded on the AE eCRF.

Definitions, documentation, and reporting of AEs and SAEs are described in Section 13.

NOTE: Subjects should be instructed to maintain adequate oral hydration while being administered veledimex. Study sites must should monitor subjects for proper hydration and blood pressure should be monitored regularly. Prophylactic antipyretic medications may also be considered. The incidence of adverse events to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

12.3.1.7. Clinical Laboratory Assessments

The hematology panel comprises a complete blood count (CBC), including white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, mean corpuscular volume (MCV), and platelet count.

The serum chemistry panel comprises the following parameters: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, amylase, blood urea nitrogen (BUN), glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.

The coagulation panel includes activated partial thromboplastin time (aPTT) or partial prothrombin time (PTT) and prothrombin time (PT) or INR. The acute phase reactants include erythrocyte sedimentation rate (ESR) and CRP.

The urinalysis panel (dipstick) includes appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated.

12.3.1.8. MRI

Subjects should be able to undergo MRI scans with contrast agent at screening and during study participation. MRI scans should be available for collection upon sponsor request.

12.3.1.9. Viral Shedding Assessment

Urine, feces, saliva, buccal, and blood samples will be collected and tested for viral replication.

12.3.1.10. Electrocardiogram

A standard, single, 12-lead electrocardiogram (ECG) for evaluation of the QT/QTc interval will be performed.

12.3.2. Schedule of Assessments

The study design is outlined in Synopsis the sequence of assessments is provided in Synopsis Table 1.

12.3.2.1. Screening Period: Assessments

The screening exams, tests, and procedures must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex:

- Signed informed consent form
- Medical/cancer history
- Physical examination (including targeted neurological examination)
- Height and weight
- Vital signs including SpO_2
- ECG
- Karnofsky Performance Status
- History of prior treatments and any associated residual toxicity
- Medications taken during the 28 days prior to consent, in addition to those ongoing during screening
- Adverse events evaluation
- MRI
- Serum pregnancy test
- **Hematology Panel including**: complete blood count (CBC), white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, and platelet count
- **Serum Chemistry Panel including**: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, blood urea nitrogen (BUN), lipase, amylase, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.
- **Coagulation Panel including**: activated partial thromboplastin time (aPTT), international normalized ratio (INR) ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein).
- **Urinalysis Panel (dipstick) including**: appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated
- **Thyroid Panel**: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)
- Viral shedding assessment
- [redacted]
- Blood sample for immune function evaluation
- Subject registration

12.3.2.2. Treatment Period: Day -7

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test (within 72 hours prior to cemiplimab-rwlc dosing)
- Hematology Panel
- Serum Chemistry Panel

- Urinalysis Panel
- Confirm eligibility
- Cemiplimab-rwlc dose

12.3.2.3. Treatment Period: Day 0 (Ad-RTS-hIL-12 injection)

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel (All labs should be collected prior to the subject's pre-op dose of veledimex)
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- ECG
- Dose of veledimex 3 (± 2) hours prior to resection, on an empty stomach (excluding other medications) AND compliance diary. Intratumoral Ad-RTS-hIL-12 will be administered by freehand injection.
- [redacted]

12.3.2.4. Treatment Period: Day 1

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- [redacted]
- MRI scan: to be done within 24 hours (a +48hr window is allowed) of Ad-RTS-hIL-12 administration and to be used as the baseline MRI for tumor response assessment
- [redacted]

12.3.2.5. Treatment Period: Day 2

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel

12.3.2.6. Treatment Period: Day 3

- Once daily veledimex dose AND compliance diary (The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.)
- Physical Examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- [redacted]
- ECG

12.3.2.7. Treatment Period: Days 4 through 6

- Once daily veledimex dose AND compliance diary
- Adverse events evaluation
- Concomitant medications

12.3.2.8. Treatment Period: Day 7

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- ECG
- [redacted]

12.3.2.9. Treatment Period: Day 8-13

- Once daily veledimex dose AND compliance diary

12.3.2.10. Treatment Period: Day 14

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- Thyroid Panel
- ECG

[redacted]

12.3.2.11. Treatment Period: Day 15

- Cemiplimab-rwlc dose

12.3.2.12. Treatment Period: Day 22

- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel

12.3.2.13. Treatment Period: Day 28

- Urine or serum pregnancy test
- Blood sample for evaluation of serum cytokine profile
- Blood sample for immune function evaluation

[redacted]

12.3.2.14. Treatment Period: Day 36

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel

- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose
- [redacted]

12.3.2.15. Treatment Period: Day 57

- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Thyroid Panel
- Urinalysis Panel
- Cemiplimab-rwlc dose
- MRI

12.3.2.16. Treatment Period: Every 3 weeks after Day 57

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel
- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose

12.3.2.17. Treatment Period: Every 8 weeks after Day 57

- MRI scans
- Adverse events evaluation
- Concomitant medications
- Survival Status

12.3.2.18. Unscheduled Visits Collections

In the event of subject termination or an unscheduled visit for a drug-related AE, an unscheduled visit kit should be obtained for cytokines and immunological markers for CSF evaluation, if applicable.
At all visits, concomitant medications, adverse events, and survival status will be documented: Concomitant medications will be monitored and recorded throughout the study. Medications received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.

Refer to Synopsis Table 1 for Schedule of Study Procedures.

13. TUMOR RESPONSE ASSESSMENTS

13.1. Tumor Response

The secondary time-to event endpoints of this study include Investigator assessment of PFS, and ORR.

Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). A baseline MRI should be performed within 24 hours (a + 48hr window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines attached in Appendix 4. MRI scans will be collected and stored at the study site and each subject will be evaluated for response by the study investigator. Subjects should be imaged throughout the study using the same method(s) as were used for the screening and baseline MRIs. Independent tumor response assessments, as well as posttreatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines.

Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, scans should be obtained and provided to the central imaging lab until disease progression is confirmed centrally.

Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bidimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

For 2 years, subjects without confirmed disease progression should continue to have tumor assessments every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation).

13.2. Tumor Response Evaluation and Pseudo-Progression

The interpretation of MRI findings in subjects with treated brain tumors has an inherent uncertainty that stems from the pseudo-progression phenomena. Pseudo-progression is a term used to describe the appearance of radiographic disease progression due to increase contrast enhancement on MRI without true tumor progression. The increase in contrast enhancement can be influenced by several parameters including differences in radiologic technique, the amount of contrast agent used, the timing of the contrast agent administration relative to the imaging, postsurgical changes, infarction, treatment related inflammation, seizure activity, sub-acute radiation effects, radiation necrosis, and corticosteroid use. Consideration of these factors by experts and clinical experience is likely to identify these subjects. In this study, the first tumor assessment MRI will be done on Day 57 (± 3 days). Imaging assessments will be performed using iRANO criteria.

13.3. Central Imaging Reads

An independent central imaging lab will review reported responses and progression events using iRANO criteria. An Imaging Charter will be developed to provide guidance and consistency.

14. SAFETY ASSESSMENTS

The safety population will include all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex.

14.1. Adverse Events and Definitions

14.1.1. Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether considered drug-related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure, and any worsening of a pre-existing condition regardless of causality to study drug. An AE is also known as an adverse experience.

14.1.2. Suspected Adverse Reaction

Any AE for which there is evidence to suggest a causal relationship (reasonable possibility) between the drug and the AE. A suspected adverse reaction implies less certainty about causality than an adverse reaction.

14.1.3. Adverse Reaction

Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

14.1.4. Unexpected Adverse Reaction

Any AE that is (a) not listed in the Reference Safety Information (RSI) of Investigator's Brochure, (b) not listed with the specificity and severity that is being observed, (c) not consistent with the risk information described in the general investigational plan or elsewhere in the current application (in the absence of an investigator brochure), and (d) listed as occurring with a class of drugs, but not specifically mentioned as occurring with the particular drug under investigation.

14.2. Evaluation of Adverse Events

Adverse events include:

- Suspected adverse drug reactions
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities when compared to baseline, in signs, symptoms, clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, extensions of symptoms, or apparently unrelated illnesses

The following considerations apply when identifying an AE:

- Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

- If a constellation of symptoms results in a confirmed diagnosis, the diagnosis (not the symptoms) should be recorded as the AE term.
- If a diagnosis cannot be established, the symptoms should be recorded as the AEs.
- If an ongoing symptom has been included in the medical history, an associated severity grade and frequency should also be documented so that a worsening in severity or frequency of a symptom can be readily identified as an AE.
- Progression of disease is not itself an AE unless the progression of disease is assessed by the investigator as related to the study treatments; however, the presenting sign or symptom of the disease progression should be documented as an AE (e.g., increase in pain). Death due to "progression of disease" within the SAE reporting period (from the signing of the ICF until 90 days after the last dose of any study treatments) should be reported as SAE.

Adverse events will be followed from the next study until resolution or to the end of the follow-up period. AEs that are drug-related should be followed until resolved or no resolution is expected.

14.3. Determination of Seriousness

14.3.1. Serious Adverse Event

An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death during the active study period or within 90 days following study drug administration. In addition, a reported death at any time post-study that is thought to be related to study drug administration.
- Life-threatening AE: An AE that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (i.e., this does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Permanent, persistent, or significant disability: A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization refers to admission of a subject into a hospital for at least a 24-hour stay. Hospitalizations for routine blood transfusions, hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, are not considered SAEs. Emergency room visits that do not result with admission are not considered as SAEs.
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth.
- Important medical event: Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent a life-threatening situation, hospitalization or death.

14.3.2. Non-Serious Adverse Event

An AE that does not fulfill the criteria for a SAE is classified as a non-serious AE.

14.4. Determination of Severity

The severity of AEs will be assessed according to the NCI CTCAE, Version 5. If an AE is not specifically defined in the NCI CTCAE, v5.0, the investigator will determine the severity of an AE based on the following general definitions recommended (National Cancer Institute 2017):

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuation of administration of the study drug.
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuation of administration or reducing the dose of the study drug.
- Life-threatening (Grade 4): The AE requires discontinuing administration of the study drug. The subject is at immediate risk of death.
- Death (Grade 5): The subject dies as a direct result of the complication or condition.

14.5. Determination of Causality

The investigator will use medical consideration to determine the potential relationship of the AE to the study drugs based on his/her clinical judgment. Assessment of causality will be based upon the following:

- Alternative possible causes of the AE, including the subject's underlying disease or comorbid conditions, other drugs, other host, and environmental factors
- The temporal sequence between the exposure to study drug and the AE
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or previously reported toxicity of the study drug or similar drugs
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

Relationship assessments that indicate "Not Related" to investigational product:

- None: The event is related to an etiology other than the investigational product (the alternative etiology must be documented in the study subject's medical record and/or SAE form).
- Unlikely or Remote: The event is unlikely to be related to the investigational product and likely to be related to factors other than investigational product.

Relationship assessments that indicate "Related" to investigational product:

- Possible: There is an association between the event and the administration of the investigational product and there is a plausible mechanism for the event to be related to investigational product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

- Probable: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and causes other than the investigational product has been ruled out and/or the event re-appeared on re-exposure to the investigational product.

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. AEs may occur due to procedures required during the screening process (e.g., blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

- Protocol-related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol-related: The event is related to an etiology other than the study procedure (the alternative etiology must be documented in the study subject's medical record).

14.6. Documenting Adverse Events

All AEs, including SAEs, are to be accurately recorded on the Adverse Event page of the subject's eCRF from the time the subject signs the informed consent through 90 days after the subject's last dose of any study drug. Each event will be assessed for serious criteria, severity, and causality (Section 14.5). The date of onset, as well as the duration of the event will be recorded. In addition, treatments provided to the subject, actions taken with the study drugs, and the outcome of the AE will also be noted.

14.7. Reporting Serious Adverse Events (SAE), and Adverse Events of Special interest (AESI)

14.7.1. Time Frame for Reporting

All SAEs and AESIs must be reported to the sponsor or sponsor designee within 24 hours of awareness, regardless of initiation of new anticancer therapy including the following:

- Any SAE or AESI experienced by the subject from the signing of informed consent to 90 days after the last dose of any study drug, regardless of relationship to study drug.
- Any SAE or AESI that the investigator becomes aware of, and believes to be study drug-related, that occurs more than 90 days after the subject last received study drug.

All SAEs must be reported to the following fax line within 24 hours of awareness:

[redacted]

Additional data concerning the SAE (e.g., diagnostic test reports, hospital summaries, etc.) must be promptly reported (within 24 hours of receipt) to the sponsor or sponsor's designee, until resolution of the SAE. Should the FDA or National Regulatory Authorities require that the sponsor submit additional data on the event, the investigator will be asked to provide those data to the sponsor in a timely fashion.

14.7.2. Information to be Provided by the Investigator

Within 24 hours of becoming aware of the SAE or subject death, the investigator must notify the sponsor or designee and transmit information to the sponsor or designee. Information (initial and follow-up) should be provided on an electronic and/or paper SAE Report form signed and dated by the investigator. The SAE Report form and copies of source documents with subject identifiers redacted will be transmitted by fax. A hospital discharge summary should be provided if the subject was hospitalized. An SAE report will be considered final once all relevant information has been received and reviewed by the sponsor.

The SAE report form is provided in the investigator study files. Please refer to the investigator study files for instructions on how to complete these forms. The investigator will provide all the following information related to the event:

- Investigator identification
- Subject identification (e.g., subject number, initials, sex, age or date of birth)
- Information regarding study drug administration (e.g. start/stop date, dose, and frequency)
- Day of SAE occurrence documentation on SAE form
- Description of event
- Action taken with the study drugs in relation to the SAE
- Outcome of the SAE

In addition to the above information, the investigator must provide, for each event term, an assessment of:

- Severity/intensity
- Relationship to the study drug (causality assessment)

14.8. Sponsor and Investigator Responsibility for Reporting Adverse Events

All AEs and SAEs will be reported to regulatory authorities, IRBs/IECs, and investigators in accordance with all applicable global laws and regulations, including but not limited to 21 CFR 312.32. The investigator must submit all Safety Letters received from the sponsor to his/her IRB/IEC per agreements and local requirements. The investigator must keep copies of all safety reports/letters, including correspondence with Ziopharm and the IRB/IEC, in the study file.

14.9. Follow-up Information for Adverse Events

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved, stabilized, returned to baseline, or is otherwise explained by the investigator.

14.9.1. Required Follow-up for Adverse Events

All treatment-emergent AEs-and SAEs will be collected through 90 days after the last dose of any study drug). All the AEs and SAEs should be followed up by the next study visit of the AE/SAE be aware of; all the related AEs and SAEs should be followed up until:

- The event resolves
- The event returns to baseline, if a baseline value is available
- The event stabilizes (following consultation and agreement by the Ziopharm Medical Monitor)
- The event can be attributed to factors other than the study drug or other than study procedure

14.10. Pregnancies

Subjects who become pregnant during the study should immediately discontinue participation in the study. The sponsor should be immediately notified.

An initial Pregnancy Report form, and a Pregnancy Outcome Form are to be completed by the investigator or designee. The Pregnancy Report form, and the completion guidelines will be provided in the investigator study files. Please refer to the investigator study files for details on how to complete these forms.

14.11. Overdose

Investigational product overdose of study subject, with or without associated AEs/SAEs, should be reported within 24 hours of awareness to sponsor [redacted] All AEs or SAEs as a result of overdose should be reported as described previously in Section 14.6 and Section 14.7.

[redacted]

[redacted]

16. STATISTICAL METHODS

This is an uncontrolled single arm study to determine whether the intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) is effective based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma. Where applicable, estimates of OS and other surrogate endpoints will be compared with well-matched historical control data to determine whether the estimates obtained in this study will be viewed as promising to support further development of this experimental combination of treatments. All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

16.1. Populations for Analysis

- The safety population will comprise all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 or any doses of veledimex
- The per protocol population will comprise subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post Ad-RTS-hIL-12 dose of veledimex, at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation (i.e., subjects who have had minor protocol violation(s) that are deemed not to impact efficacy will be included in this analysis population.)
- The biomarker-evaluable population will comprise subjects who have adequate biomarker sample(s) at screening (baseline) and at least one follow-up assessment

16.2. Sample Size and Power Calculations

We plan to accrue up to 30 subjects to obtain approximately 25 subjects evaluable for efficacy. This patient population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS.
NOTE: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that sufficient subjects have measurable disease for evaluation of overall response rate per iRANO criteria.

A sample size of up to 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19. Note: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that sufficient subjects have measurable disease for evaluation of overall response rate per iRANO criteria. In addition, a Toxicity boundary based on repeated significance testing provides for a guideline to seriously consider stopping the trial if the number of subjects experiencing unacceptable toxicity exceeds the proportions below assuming a 30% Toxicity rate is acceptable and 60% would be unacceptable:

Low boundary: 3/5 5/10 8/15 9/20 11/25

High boundary: 3/5 6/10 8/15 10/20 11/25

The method for determination of the Toxicity boundary used the Toxbdry function in the Clinfun R package implementation of repeated significance testing methodology (Ivanova et al. 2005, Jennison and Turnbull 2000). The operating characteristics of the boundary conditions will be specified in a separate statistical analysis plan (SAP).

If the study continues to completion, a sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) approximately 10% standard error of the estimate assuming the binomial estimation method.

16.3. Endpoints

16.3.1. Primary Endpoint

The primary endpoint for evaluation of efficacy is:

- The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

The primary endpoint is to determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma.

16.3.2. Secondary Endpoints

Secondary endpoints include:

- Overall survival rate will be determined at 6, 12, 18 and 24 months
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

16.4. Safety Evaluation

Safety will be evaluated in using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

Safety will be evaluated based on frequency and severity of adverse events (AEs), Serious adverse events (SAEs), laboratory abnormalities, electrocardiograms (ECGs), vital signs and physical/neurologic examination findings. The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5. The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug.

16.5. Efficacy Evaluation

- The primary analysis for efficacy is based on the per protocol population.
- Secondary analyses for all efficacy endpoints will be based on the Safety population.

The primary endpoint for evaluation of efficacy is:

- the estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to 24 months for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

Secondary endpoints include:

- The OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint.
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc will be determined based on the investigator assessment
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months will be determined based on an investigator assessment.
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

16.6. Analyses

16.6.1. Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include at least demographic features such as sex, age, and race, as well as disease-specific status and medical history.

Categorical data will be summarized using counts and percentages for a particular category. For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation, minimum, and maximum values will be presented.

16.6.2. Safety Analyses

The safety population will be used to perform safety evaluations for all safety variables.

Safety evaluations will be based on the incidence, intensity, and type of AEs and SAEs. Clinically significant changes in the subjects' physical examinations, vital signs, and ECG evaluations, and abnormal laboratory values will be captured as AEs. Safety will also be assessed based on medical history and prior/concomitant medications.

The safety evaluation period extends from the date the patient signs the ICF until 90 days after the last dose of study drug, unless the patient discontinues the trial due to one of the following reasons:

- Documented progression
- Symptomatic deterioration also denoted as symptomatic progression
- AEs that the investigator feels will subsequently make the subject noncompliant with the protocol planned Schedule of Study Procedures
- Loss to follow-up
- Noncompliance with the protocol
- Other reason not listed above

All treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by number and percent of subjects, and according to relationship to the study drugs, severity, and seriousness. Treatment-emergent is defined as any AE that occurs during or after administration of the first dose of study drug through the evaluation period for safety defined above, regardless of relationship to study drug; or any event that is present at baseline that worsens in intensity or is subsequently considered to be drug related by the investigator. Deaths, SAEs, and AEs resulting in study discontinuation will be listed.

Subjects who discontinue the trial as defined above will be followed for safety up to 90 days after discontinuation and until all safety events that have started during the safety evaluation period are classified as resolved or the end of the study is reached. After the conclusion of the safety evaluation period is triggered by a discontinuation event, the subject continues to be followed only for OS.

Listings of vital signs and physical examination data will be presented by visit.

16.6.3. Overall Survival

OS is defined as the duration of time from the first dose of study drug to the date of death or to the last follow-up contact date if the subject has not died, in which case the subject is censored if still alive up to 2 years from the first dose of study drug received.

16.6.4. Tumor Response Analyses

Investigator assessment of ORR and PFS will be determined according to iRANO criteria. A two-sided confidence interval will be computed for the ORR. PFS and OS will be estimated using the Kaplan-Meier method for appropriately-sized subject groups.

Following completion of the study, best response will be determined for each subject in accordance with iRANO guidelines and the ORR will be presented for all subjects. Where applicable, summary data of PFS, OS, and durability of response will be determined using Kaplan-Meier methodology; otherwise, a listing by-subject will display the data obtained. Two-sided confidence intervals will be computed for the ORR. Descriptive statistics will be performed for different patient populations.

16.6.5. Multi-Center Study

Tumor response and safety data will be presented over all study centers.

16.6.6. Adjustments for Covariates

No adjustments for covariates will be made.

16.6.7. Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

16.6.8. Procedures for Reporting Deviations to Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared prior to database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

17. STUDY MANAGEMENT

17.1. Electronic Case Report Forms and Source Documentation

For each subject, electronic case report forms (eCRFs) and corresponding source records will be maintained at each clinical site. The sponsor or designee will provide the study sites with secure access to and sufficient training on the electronic data capture (EDC) application, to permit site personnel to enter or correct information in the eCRFs for the subjects for whom they are responsible.

The eCRFs should be completed in a timely manner, and every effort should be made to have forms completed and up-to-date in anticipation of a visit by the sponsor's monitor. Specific instructions will be provided to the site. All requested information must be entered on the eCRF in the spaces provided. If an item is not available or is not applicable, it should be documented as such; do not leave a space blank.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Through the EDC application, the investigator must provide formal approval of all subject information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the subjects for whom he/she is responsible. The audit trail entry will show the user's identification information and the date and time of any corrections.

eCRF completion may be delegated to other study personnel; however, such delegation must be documented in writing. If, for any reason, certain data are lacking to complete an individual report form, the investigator will provide a written statement explaining the reasons for the lack of data.

Sponsor or designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

17.2. Good Clinical Practice

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and Ziopharm policies.

17.3. Sponsor Monitoring

After satisfactory receipt of all necessary regulatory paperwork, the sponsor's monitor will arrange that all study material be delivered to the study site at a mutually convenient time. A site initiation visit (SIV) by Ziopharm and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of study protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and study file maintenance.

Throughout the course of the study, the sponsor's monitor will make frequent contact with the investigator, and this will include telephone and/or onsite visits. During these visits, eCRFs will be reviewed for completeness and adherence to protocol. As part of the data audit, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the Medical Monitor. The monitor also will perform drug accountability checks and may periodically request review of the investigator's study file to assure completeness of documentation in all respects of study conduct.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 17.5. The investigator or appointed delegate will receive the sponsor's representative during these onsite visits and will cooperate in providing the documents for inspection and responding to inquiries that may arise as part of this review. The investigator will also permit inspection of the study files by authorized representatives of the FDA.

17.4. Duration of the Study

The duration of this study from the time of initiating subject enrollment until the completion of survival follow-up is anticipated to be approximately 48 months, including 24 months for enrollment and 2 years of further follow-up.

The overall duration is expected to be up to 2 years for an individual subject, including the following:

- Screening period of up to 30 days prior to dosing with Ad-RTS-hIL-12 and veledimex
- Initial Study treatment period of 3 weeks (Days -7 through 14)
- Assessment of safety through the Follow-up Period
- Assessment of tumor response at Day 57 (± 3 days), and every 2 months thereafter until the occurrence of confirmed tumor progression
- Survival status through 2 years

In addition, subjects who discontinue or complete study treatment without objective evidence of disease progression should continue to be followed until confirmed disease progression has been documented. Subjects will be followed for survival status for 2 years after enrollment, except for death or loss to follow-up. The active study period refers to the study period from informed consent through the Initial Follow-up Period.

17.5. Records Retention

Records of drug disposition, eCRFs, and reports of the clinical trial must be maintained by the investigator for a period of at least 2 years following the date on which the test article is approved by FDA for marketing for the purposes that were investigated in the study. If no application is to be filed or if the application is not approved for such indication, the records must be stored for two additional years and then returned to Ziopharm. No records will be destroyed but will be indefinitely stored.

17.6. Institutional Review Board/ Independent Ethics Committee

This protocol and the study ICF must be reviewed and approved by the Institutional Biosafety Committee, where applicable, and IRB/IEC prior to the start of the study, and a copy of the approval letter supplied to Ziopharm. During the study, the investigator shall make timely and accurate reports to the IRB/IEC on study progress at intervals not exceeding 1 year, as well as satisfying any other local IRB/IEC reporting regulations. Copies of all reports to, and correspondence with, the IRB/IEC must be provided to Ziopharm. Further, within 3 months of the completion or early termination of the study, a final report should be made to the IRB/IEC and Ziopharm by the investigator.

All protocol revisions must originate with and be documented by Ziopharm. If the requested revision is an amendment, the investigator must sign it. The FDA will be notified of all revisions by Ziopharm. The investigator must submit the amendment to his/her IRB/IEC for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to Ziopharm.

It is the investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review to Ziopharm representatives as part of the routine study monitoring process.

17.7. Confidentiality and HIPAA

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by Ziopharm, or its representatives, will be identified by subject number and study code.

The written ICF will also explain that, for data verification purposes, authorized representatives of Ziopharm, a regulatory authority (FDA), and/or the IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the subject's medical history.

The written ICF will be accompanied by or include a separate document incorporating United States Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which the subjects authorize the use and disclosure of their Protected Health Information.

17.8. Informed Consent

17.8.1. FDA Informed Consent Requirements

The investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the prospective subject prior to enrollment. The ICF should also indicate that, by signature, the prospective subject or, where appropriate, a legal guardian, permits access to relevant medical records by the sponsor and by representatives of the FDA. If a prospective subject does not understand English, an appropriate translation into his or her primary language must be made available. The investigator or designee will obtain written, informed, and witnessed consent. The prospective subject will have ample time and opportunity to ask questions. The prospective subject will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, the prospective subject will be asked if he/she is willing to sign and personally date a statement of informed consent. Only if the prospective subject voluntarily agrees to sign the informed consent statement and has done so, may he/she enroll into the study. A copy of his/her signed and dated informed consent will be provided to each prospective subject. The signed ICF is to remain in the investigator's file.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol that necessitates a change to the content of the subject's informed consent. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm continuation of his/her participation in the study by his/her signature on the revised ICF, if applicable. Any written ICF and written information must receive IRB/IEC approval/favorable opinion in advance of use.

17.8.2. Subject Informed Consent Form

Ziopharm will provide a sample subject ICF for modification, as appropriate, by the investigator.

18. PROTOCOL APPROVAL PAGE

A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Except for a change intended to eliminate an immediate hazard to subjects, the study shall be conducted as described in the approved protocol. All deviations from the protocol will be documented in the eCRF. Any significant deviation or deviation related to dosing or safety evaluation will be reported to Ziopharm and documented in the eCRF.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

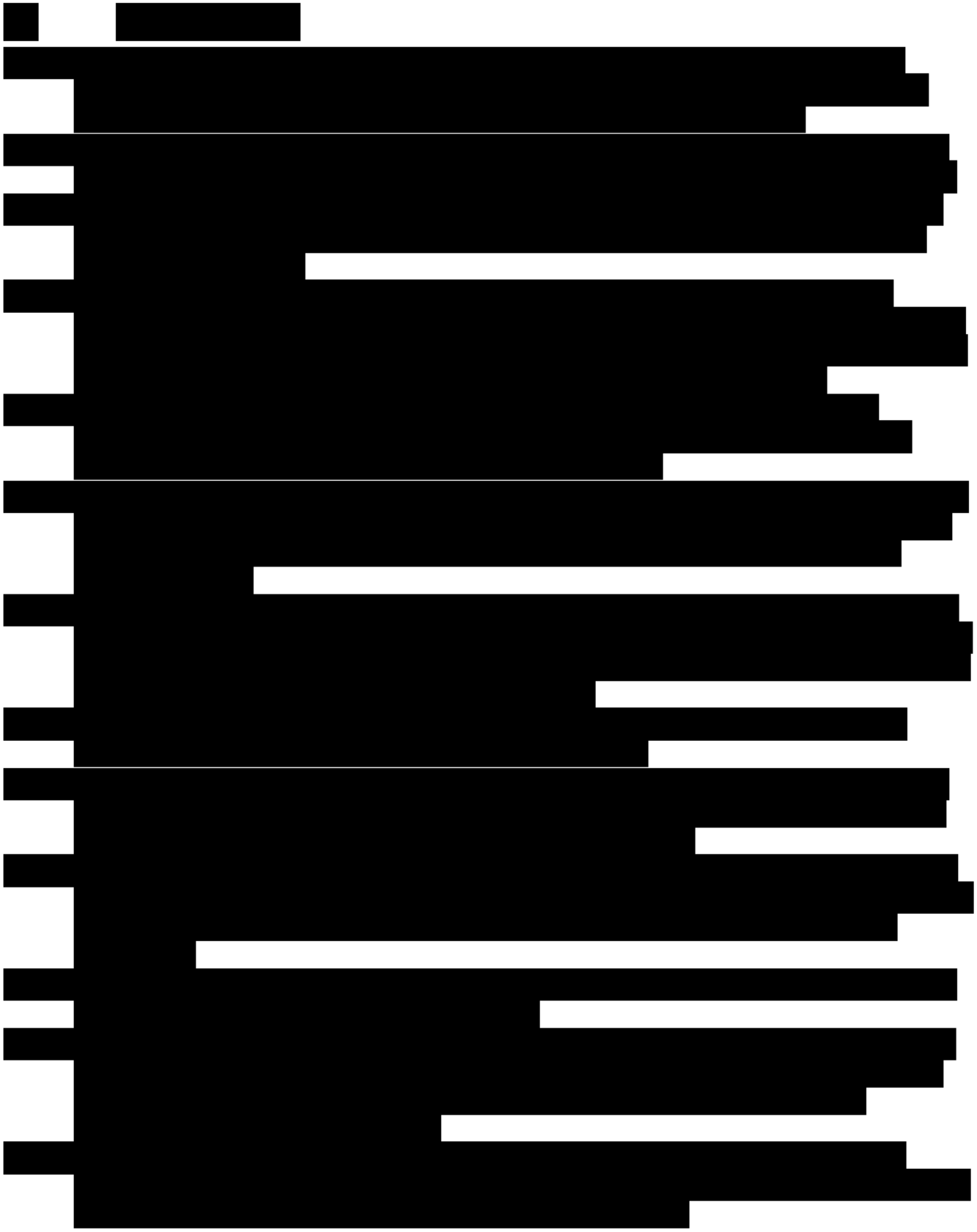
Study Site Institution Name: _____

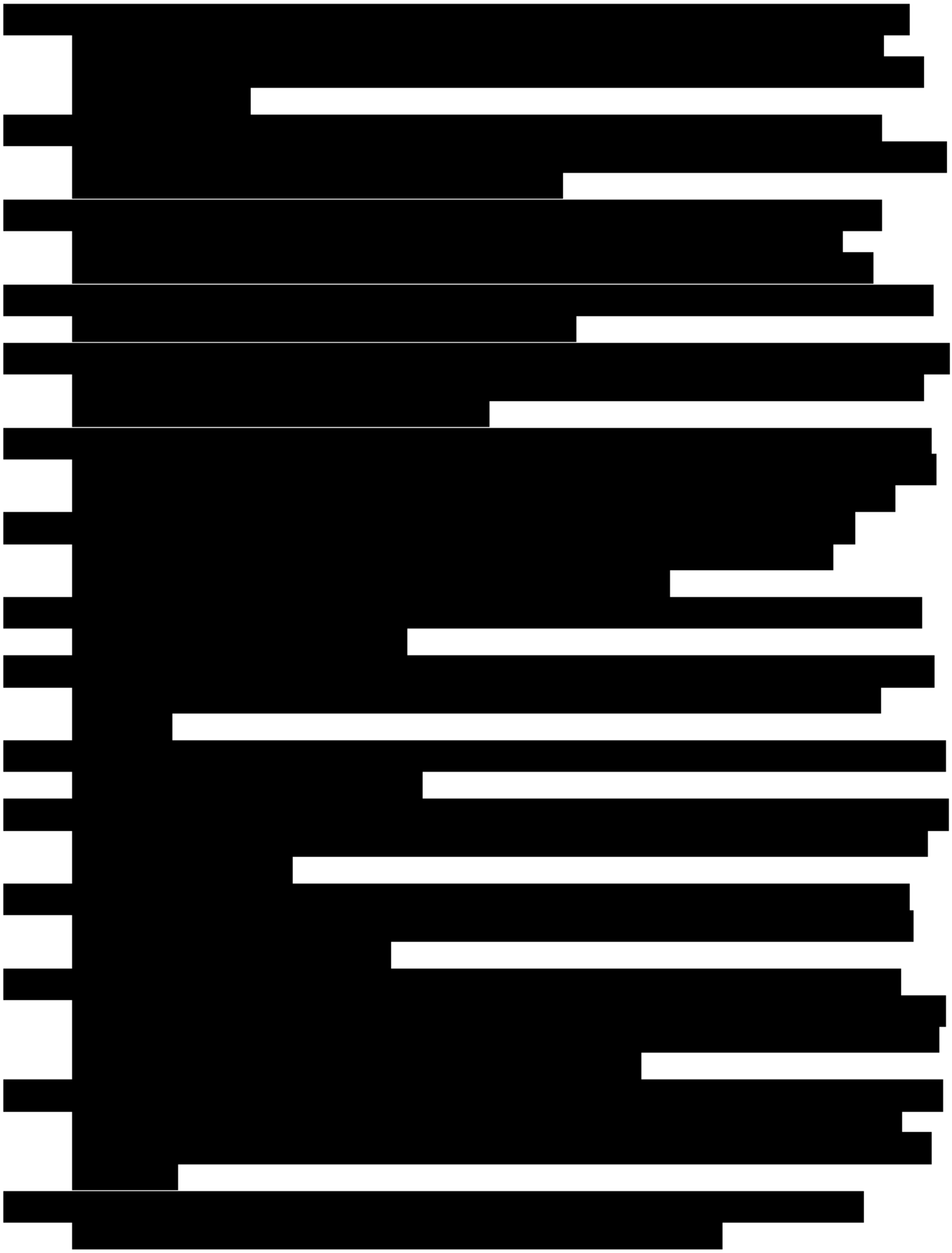
Principal Investigator

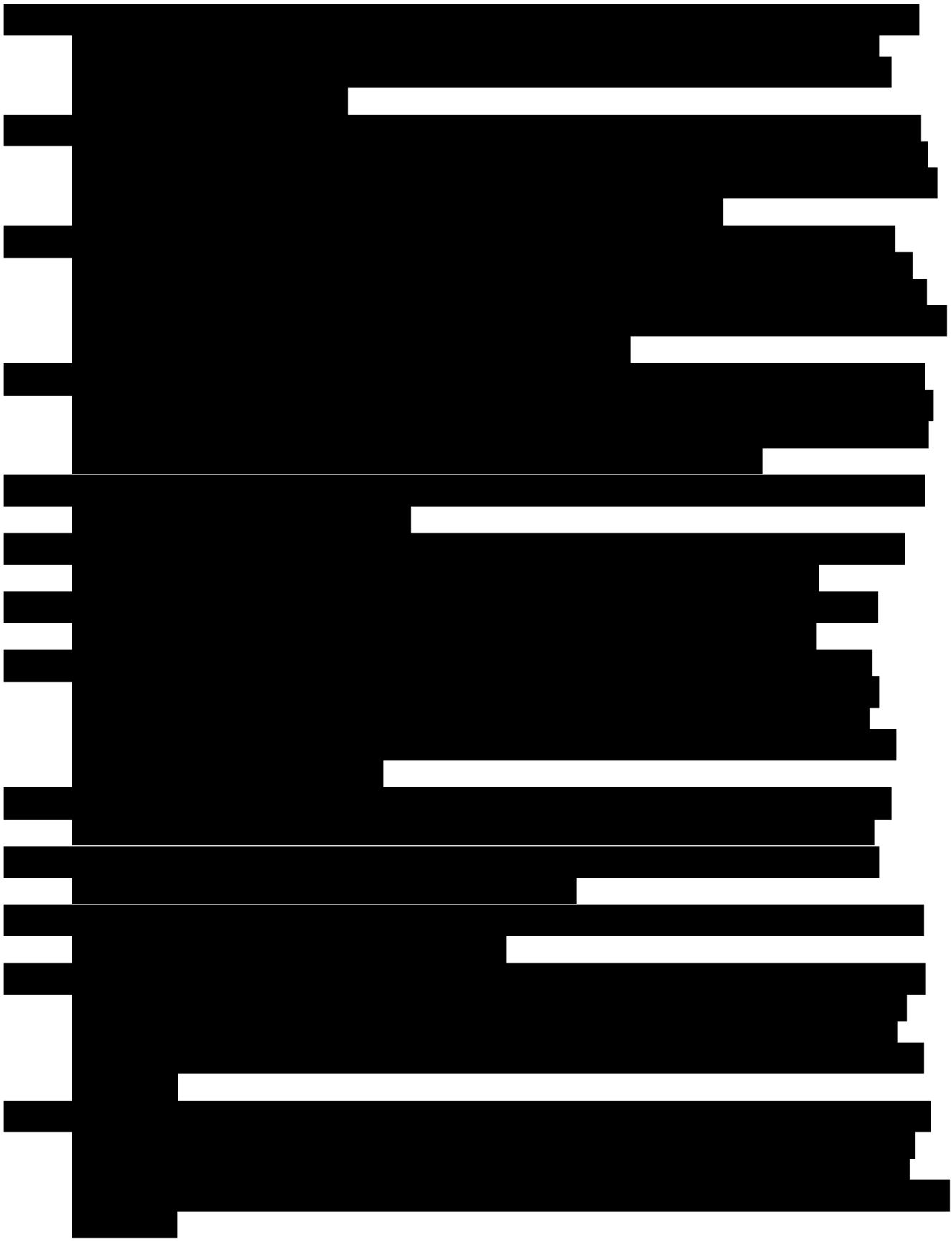
Print Name: _____

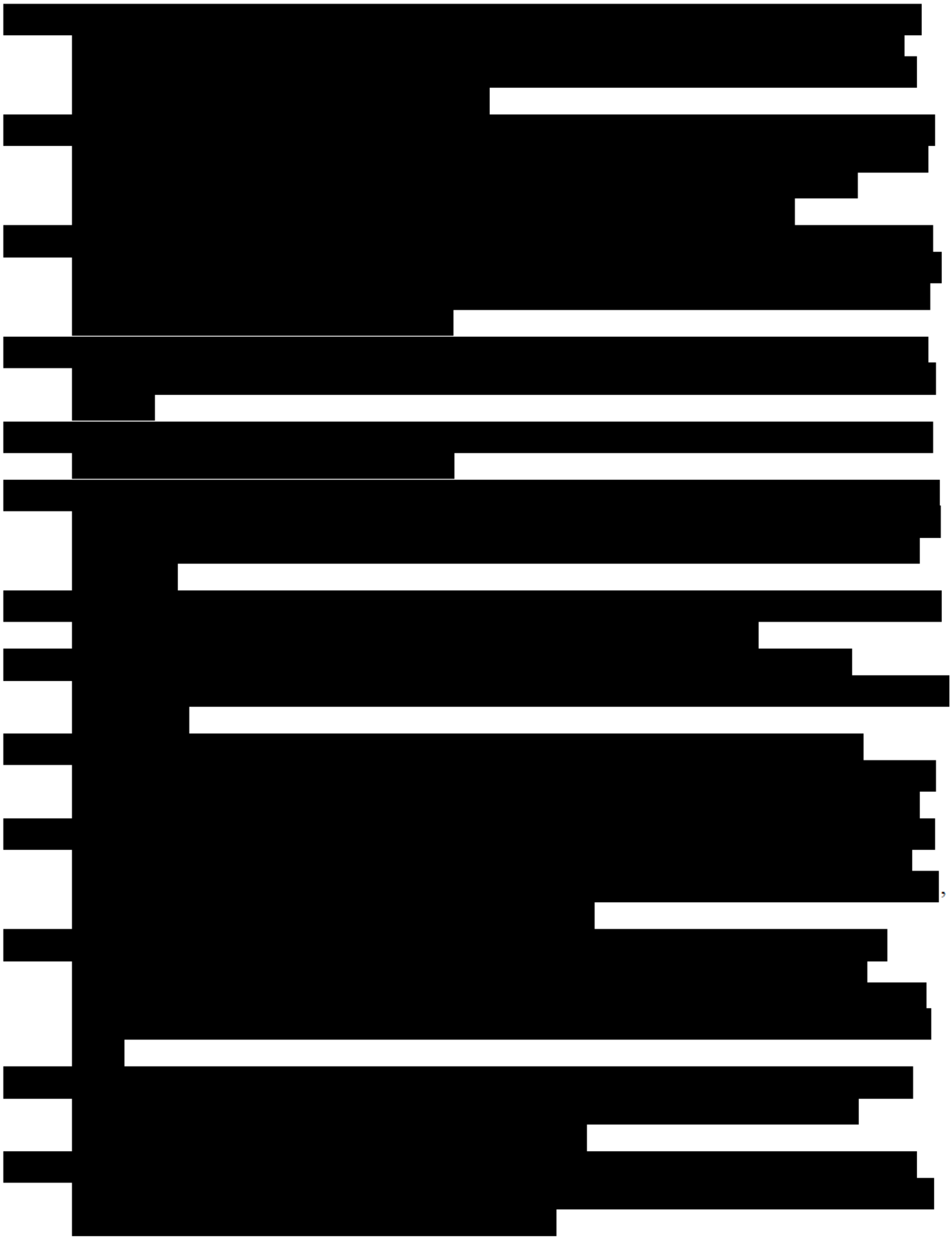
Signature: _____

Date: _____









20. APPENDICES

APPENDIX 1. ZIOPHARM CYTOKINE RELEASE SYNDROME WORKING DEFINITION - AD-RTS-HIL-12 + VELEDIMEX (VERSION 3, 07 JANUARY 2019)

Cytokine release syndrome (CRS) is a multi-faceted immune disorder presenting clinically as a multi-system disorder. Elevated cytokine levels support the diagnosis of CRS in Ad-RTS-hIL-12 gene therapy study along with the grading criteria below:	
Grade 1	**Symptoms that are not life threatening and require symptomatic treatment only, e.g. (<u>any</u> of the following):** General: Influenza-like illness (flu-like symptoms): fever (temperature of 100°F [37.8°C] or greater) and fatigue, malaise, or myalgia Neurological: Grade 1 headache Grade 1 decreased level of consciousness (e.g. somnolence, drowsiness, lethargy, disorientation) GI: Grade 1 nausea or vomiting
Grade 2	**Symptoms that require and respond to moderate interventions and occurrence of <u>any</u> of the following:** **1. Hypotension responsive to fluids or single, low dose vasopressor** **2. Oxygen requirement < 40%** **3. Grade 3 transaminitis (ALT/AST), lymphopenia, or Grade 2 organ toxicities, e.g.:** Hematologic: Grade 2 neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 2 creatinine increase 4. **Other symptoms, e.g.:** General: Grade 3 fever Neurological: Grade 2 decreased level of consciousness (e.g., slow response to stimuli; limiting instrumental activities of daily living) Grade 2 or 3 headache GI: Grade 2 nausea or vomiting
Grade 3	**Symptoms that require and respond to aggressive interventions and occurrence of <u>any</u> of the following:** **1. Hypotension requiring high dose or multiple vasopressors** **2. Oxygen requirement ≥ 40%** **3. Grade 4 transaminitis (ALT/AST), lymphopenia, or Grade 3 organ toxicities, e.g.:** Hematologic: ≥Grade 3 febrile neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 3 creatinine increase Cardiac: Grade 3 arrhythmia, or acute heart failure Pulmonary: Grade 3 pulmonary edema, or dyspnea **4. Other symptoms, e.g.:** Neurological: Grade 3 decreased level of consciousness (e.g. difficult to arouse) Aseptic meningitis GI: Grade 3 nausea or vomiting
Grade 4	**Life-threatening symptoms and occurrence of any of the following:** **1. Requirement for ventilator support** **2. Grade 4 organ toxicities (excluding lymphopenia and asymptotic elevated transaminitis), e.g.:** Renal: Renal failure and dialysis indicated Cardiac: Cardiac arrest Pulmonary: Respiratory failure Neurological: Coma
Grade 5	**Death**

APPENDIX 2. RECOMMENDED REGIMEN FOR ANTIPYRETIC AND/OR ANALGESIC PROPHYLAXIS

Recombinant adenoviral vectors have the potential to elicit potent cellular and humoral immune responses. While the mechanism responsible for these effects is poorly understood, transient low-grade fevers are common after systemic rAD vector administration* and temperatures up to 104° F with chills and generalized malaise have been observed with treatment. Because low-grade fever is very likely to occur, prophylaxis with acetaminophen is strongly recommended.

Each site should follow its institutional protocol for the administration of acetaminophen. Acetaminophen is available without a prescription in 325 mg or 500 mg tablets. Common brand names of acetaminophen include Aspirin Free Anacin®, FeverAll®, Genapap®, Mapap®, NeoPAP®, Panadol®, Tempra®, and Tylenol®.

In general, fever can be adequately prophylaxed or treated with acetaminophen. If a fever occurs despite prophylactic medication or does not respond to usual doses of acetaminophen, then a combination of both acetaminophen and ibuprofen may be considered. Alternating doses of ibuprofen with acetaminophen may effectively control fever while preventing accidental overdose of acetaminophen. Acetaminophen is typically effective for controlling central fevers whereas ibuprofen is more potent as a peripheral analgesic/ anti-inflammatory medication. Ibuprofen is available without a prescription at a dosage of 200 mg and by prescription in 400, 600 or 800 mg tablets or capsules. Common brand names of ibuprofen include Advil®, ElixSure®, Ibuprom®, Ibutab®, Motrin® and Tab-Profen®.

Adverse events are uncommon although may be serious as some individuals are allergic to these medications. Additionally, overdoses of acetaminophen may cause liver failure. Therefore, subjects with liver disease and chronic alcohol users should avoid acetaminophen. Ibuprofen is excreted by the kidneys so should be avoided in patients with renal insufficiency, though most would be excluded from enrollment. High dose ibuprofen also may increase the risk of blood clots, stroke, heart attack, and gastrointestinal bleeding, and being a potent anti-inflammatory agent could reduce the efficacy of the investigational controlled IL-12 therapy.

APPENDIX 3. PROHIBITED ENZYME-INDUCING AND NON-ENZYME-INDUCING ANTIEPILEPTIC DRUGS

Enzyme-inducing Antiepileptic Drugs	Non-Enzyme-inducing Antiepileptic Drugs
Cerebyx® (fosphenytoin)	Zarontin® (ethosuximide) ONFI® (clobazam)
Dilantin® (phenytoin)	
Gabitril® (tiagabine)	
Luminal®, Solfoton® (phenobarbital)	
Nembutal® (pentobarbital)	
Trileptal® (oxacarbazepine)	
Tegretol® (carbamazepine)	
Topamax® (topiramate)	

APPENDIX 4. IMMUNOTHERAPY RESPONSE ASSESSMENT IN NEURO-ONCOLOGY: A REPORT OF THE RANO WORKING GROUP

Immunotherapy Response Assessment in Neuro-Oncology: A Report of the RANO Working Group

TITLE PAGE

STUDY PROTOCOL

Protocol Title: A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Protocol Number: ATI001-204

Phase: II

Date of Protocol: Original: 07 February 2019

Sponsor: Ziopharm Oncology, Inc.

[redacted]

1. CLINICAL PROTOCOL SYNOPSIS

Title	A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma
Protocol Number	ATI001-204
Clinical Phase	Phase II
Investigational Product(s)	Ad-RTS-hIL12 + veledimex: Adenovirus RheoSwitch Therapeutic System® human interleukin 12 (Ad-RTS-hIL-12) and veledimex (RTS® activator ligand) Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of an RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated by veledimex dose and schedule. Cemiplimab-rwlc Cemiplimab-rwlc (Libtayo®) is a programmed death receptor-1(PD-1)-blocking antibody.
Research Hypothesis	Among subjects with recurrent or progressive glioblastoma, Ad-RTS-hIL-12 and veledimex in combination with cemiplimab-rwlc (Libtayo®) can be safely administered, show evidence of efficacy, and can induce signals of immune activity.
Study Objectives	**Primary Objectives** To determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively. **Secondary Objectives** • To determine the survival rates at 6, 12, 18 and 24 months • To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months

	• To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months • To determine the tumor response rates at 6, 12, 18 and 24 months [redacted]
Investigational Product(s)	Ad-RTS-hIL-12 + veledimex: Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand) Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of an RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be turned on and off by veledimex dose and schedule. Cemiplimab-rwlc Cemiplimab-rwlc (Libtayo®) is a programmed death receptor-1 (PD-1) blocking antibody.
Number of Centers	Approximately 10 centers
Number of Subjects	Approximately 30 subjects
Study Design	This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 ([redacted] viral particles [vp]) and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively, in the presence of variable systemic corticosteroid exposure. This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility. Subjects will receive cemiplimab-rwlc on Day -7 (±3days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection of Ad-RTS-hIL-12 and Ad-RTS-hIL-12 (2×10^{11} vp) will be administered by freehand injection. Ad-RTS-hIL-12 will

	be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). Note: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that a sufficient number of subjects have measurable disease for evaluation of overall response rate by immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria. The total amount of virus delivered to each site will be recorded in the electronic Case Report Form (eCRF). If the total administered (injected) volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations. After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing. Subjects will receive a dose of cemiplimab-rwlc (350 mg) on Day 15 and every three weeks thereafter (Q3W) until confirmed progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the safety follow-up period. Delays in cemiplimab-rwlc dosing due to toxicity are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days. A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor. After the first six subjects have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused. The SRC will review safety data after the 6th subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products. The primary endpoint for evaluation of safety is: • The safety profile The primary endpoint for evaluation of efficacy is: • Overall survival (OS) Secondary endpoints include: • Overall Survival rate at 6, 12, 18 and 24 months

	• PFS, and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months • Objective Response Rate at 6, 12, 18 and 24 months • To determine the tumor response rate at 6, 12, 18 and 24 months [redacted]
Dose & Schedule	**Ad-RTS-hIL-12:** intratumoral [redacted] vp administered on Day 0 **Veledimex**: 20 mg PO QD on Days 0 to 14 **Cemiplimab-rwlc**: 350 mg IV on Day -7, Day 15, and approximately every 3 weeks (Q3W) until confirmed progression (iRANO), unacceptable toxicity or subject withdrawal.
Therapy Duration	From administration of the first study drug (cemiplimab-rwlc) until the subject has confirmed progressive disease per iRANO, unacceptable toxicity, the subject withdraws consent, or the end of the follow-up period.
Eligible Population	The eligible study population includes adult subjects with recurrent or progressive glioblastoma for which there is no alternative curative therapy. **Eligibility Criteria** Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells. **Inclusion Criteria** 1. Male or female subject ≥18 and ≤75 years of age 2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures 3. Histologically confirmed glioblastoma from archival tissue 4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy. Multi-focal disease is allowed. 5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic

	effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor) a. Nitrosoureas: 6 weeks b. Other cytotoxic agents: 4 weeks c. Antiangiogenic agents: 4 weeks d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks e. Vaccine-based or CAR-T therapy: 3 months 6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment 7. Karnofsky Performance Status ≥70 8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements: a. Hemoglobin ≥9 g/L b. Lymphocytes >500/mm^3 c. Absolute neutrophil count ≥1500/mm^3 d. Platelets ≥100,000/mm^3 e. Serum creatinine ≤1.5 x upper limit of normal (ULN) f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN g. Total bilirubin <1.5 x ULN h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) within normal institutional limits 9. Female of child bearing potential* and sexually active male subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;

intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrhoeic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Normal cardiac and pulmonary function as evidenced by a normal ECG and peripheral oxygen saturation (SpO2) ≥90% by pulse oximetry

Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment of disease with bevacizumab **(NOTE: short use (< 4 doses) of bevacizumab for controlling edema is allowed)**
3. Subjects receiving systemic corticosteroids for treatment of disease-related symptoms during the 4 weeks prior to Day -7
4. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
5. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

NOTE:

- Subjects with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For Subjects with controlled HIV infection, monitoring will be performed per local standards.

	• Subjects with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Subjects with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug. • Subjects who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted. 6. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively. 7. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed. 8. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer 9. Nursing or pregnant females 10. Prior exposure to veledimex 11. Use of an investigational product within prior 30 days. 12. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells. 13. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor 14. Presence of any contraindication for a neurosurgical procedure 15. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day

	-7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of deep vein thrombosis (DVT) may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor. 16. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples may include, but are not limited to, colitis, unstable angina, congestive heart failure, myocardial infarction within 2 months of screening, and ongoing maintenance therapy for life-threatening ventricular arrhythmia or uncontrolled asthma.
Stopping Rules	If any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.
Statistical Methods	**Analysis Populations** • The safety population will be comprised of all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex • The per protocol population will be comprised of subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post Ad-RTS-hIL-12 dose of veledimex, at least 1 post Ad-RTS-hIL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation (i.e., subjects who have had minor protocol violation(s) that are deemed not to impact efficacy will be included in this analysis population.)

	• The biomarker-evaluable population will comprise subjects who have adequate biomarker sample(s) at screening (baseline) and at least one follow-up assessment **Safety Evaluation** Safety will be evaluated based on frequency and severity of adverse events (AEs), Serious adverse events (SAEs), laboratory abnormalities, electrocardiograms (ECGs), vital signs and physical/neurologic examination findings. The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5. The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug. **Efficacy Evaluation** • The primary analysis for efficacy is based on the per protocol population. • Secondary analyses for all efficacy endpoints will be based on the Safety population. The primary endpoint for evaluation of efficacy is: • The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects. • The per protocol population will be followed from the first date of treatment up to 2 years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP). Secondary endpoints include: • The OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint • PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc • ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months

- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

Tumor Response Assessments:

The Per Protocol Population will be evaluated for ORR, PFS, PSP, and OS. Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, efforts will be made to encourage obtaining additional to confirm disease progression.

- Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). A baseline MRI will be performed within 24 hours (a +48-hour window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines
- Independent tumor response assessments, as well as post-treatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines.
- Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bi-dimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

[redacted]

	
Sample Size Determination	We plan to accrue up to 30 subjects to obtain approximately 25 subjects evaluable for efficacy. This subject population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS at 12 weeks. A sample size of approximately 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19. Note: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that sufficient subjects have measurable disease for evaluation of overall response rate per iRANO criteria. In addition, a toxicity boundary based on repeated significance testing provides a guideline for stopping the trial if the number of subjects experiencing unacceptable toxicity exceeds the proportions below, assuming a 30% toxicity rate is acceptable and 60% would be unacceptable: Low boundary: 3/5 5/10 8/15 9/20 11/25 High boundary: 3/5 6/10 8/15 10/20 11/25

	Note: A sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) a 10% standard error of the estimate assuming the binomial estimation method.
Study Duration	The duration of this study from the time of initiating subject screening until the completion of survival follow-up is anticipated to be approximately 36 months, including 12 months for enrollment and 24 months of follow-up. The start of study is defined as the date when the first subject is consented into the study and the study stop date is the date of the last subject's last visit.

Table 1: Schedule of Study Procedures

Activity	Screening	Treatment							
	Day -30 to -8*	Day -7 **	Day 0[a]	Day 1	Day 2	Day 3	Day 4 to 6	Day 7	Day 8 to 13
Informed consent	X								
Medical/Cancer history[d]	X								
Physical exam[e], including targeted neurological exam	X	X	X	X	X	X		X	
Karnofsky PS[f]	X	X	X						
Height (screen) and weight	X							X	
Vital signs[g]	X	X	X	X	X	X		X	
Adverse events[h]	CONTINUOUS								
Concomitant medications[h]	CONTINUOUS								
Survival status[i]	CONTINUOUS								
Pregnancy test[j]	X	X	X						
Hematology[k]	X	X	X[a]	X	X	X		X	
Coagulation[l]	X		X[a]	X		X		X	
Serum chemistry[m]	X	X	X[a]	X	X	X		X	
Urinalysis[n]	X	X	X[a]			X		X	
Thyroid panel[o]	X								
ECG[p]	X		X			X		X	
Confirm eligibility		X[q]							
Cemiplimab-rwlc dose[q]		X							
Ad-RTS-hIL-12			X[r,s]						
Veledimex dose and diary[v]			X[s, t]	X[s, t]	X	X[u]	X	X	X
Cytokine profile blood sample[x]	X		X[w]	X		X		X	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]					[redacted]			
MRI scans[z]	X[z]			X[z, aa]					
Tumor sample[aa]			X						
Neutralizing antibody status testing[bb]	X							X	

Table 1: Schedule of Study Procedures (continued)

Activity	Treatment							Long Term Follow-up
	Day 14	Day 15	Day 22	Day 28	Day 36 ±3 days	Day 57 ±3 days	Every 3 weeks[b] ±7days	Every 8 weeks[c] ±7days
Informed consent								
Medical/Cancer history[d]								
Physical exam[e], including targeted neurological exam	X				X		X	
Karnofsky PS[f]	X				X		X	
Height (screen) and weight	X				X			
Vital signs[g]	X				X		X	
Adverse events[h]	CONTINUOUS							
Concomitant medications[h]	CONTINUOUS							
Survival status[i]	CONTINUOUS							
Pregnancy test[j]				X			X	
Hematology[k]	X		X		X	X	X	
Coagulation[l]	X				X			
Serum chemistry[m]	X		X		X	X	X	
Urinalysis[n]	X		X			X	X	
Thyroid panel[o]	X				X	X	X	
ECG[p]	X				X		X	
Confirm eligibility								
Cemiplimab-rwlc dose[q]		X			X	X	X	
Ad-RTS-hIL-12								
Veledimex dose and diary	X[v]							
Cytokine profile blood sample[x]	X			X				
[redacted]	[redacted]			[redacted]				
[redacted]	[redacted]			[redacted]				
MRI scans[z]						X[z]		X[z]
Tumor sample[bb]								
Neutralizing antibody status testing[cc]	X				X			

[*] Screening assessments must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex.
[**] Day -7 dosing with cemiplimab-rwlc may be performed within ± 3 days.
[a] The PI will review all results of laboratory tests drawn within 24 hours prior to surgery.
[b] Every 3 weeks from Day 57

[c] Every 8 weeks from Day 57 in addition to assessments performed every 3 weeks
[d] Medical history includes demographic information, relevant medical and surgical history. Cancer history includes current cancer diagnosis, prior treatment (regimen[s], doses, start and stop dates, and any associated residual toxicity), and best response for each regimen.
[e] A complete physical examination including a neurological exam and mental status is required at baseline and discharge from hospital. Targeted neurological exams thereafter.
[f] KPS is required at Screening, Day -7, Day 0, Day 14, Day 36 and every 3 weeks thereafter.
[g] Blood pressure, pulse, temperature, and respiration will be recorded. Pulse oximetry peripheral oxygen situation (SpO2) will be recorded at Screening, Day -7, Day 0, Day 3, Day 7, Day 14, Day 36 and every 3 weeks from Day 57. Blood pressure should be monitored closely, with hydration as needed to prevent hypotension after veledimex administration. Subjects must be instructed to maintain adequate oral hydration on and between veledimex dosing days; sites must closely monitor hydration status.
[h] Concomitant medications will be monitored and recorded throughout the study. Medications received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.
[i] Subjects will be followed to document start of new anticancer therapies and survival status for 2 years following administration of Ad-RTS-hIL-12.
[j] Serum pregnancy test at Screening for females of childbearing potential, must be within 72 hours prior to first dose of cemiplimab-rwlc; urine or serum pregnancy test on all other days.
[k] Hematology: Complete blood count, white blood count with differential, red blood cell count, red blood cell indices, hematocrit, hemoglobin, and platelet count. The Day 0 testing should be obtained prior to veledimex dosing.
[l] Coagulation: aPTT, INR, erythrocyte sedimentation rate and C-reactive protein. The Day 0 testing should be obtained prior to veledimex dosing.
[m] Serum Chemistry: AST, ALT, lactate dehydrogenase, alkaline phosphatase, lipase, amylase, creatinine, total bilirubin, total protein, albumin, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate. The Day 0 testing should be obtained prior to veledimex dosing.
[n] Urinalysis Panel (dipstick): appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals and cells may be done if indicated. The Day 0 testing should be obtained prior to veledimex dosing.
[o] Thyroid Panel: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)
[p] Standard 12-lead ECG; single measurement at each time point. The Day 0 testing should be obtained prior to veledimex dosing.
[q] Eligibility must be confirmed within 24 hours prior to dosing with cemiplimab-rwlc. In the event of toxicities likely related to cemiplimab-rwlc, the PI and the Medical Monitor will individualize the management of cemiplimab-rwlc dosing in general accordance with the Investigator's Brochure. Doses must be at least 21 days apart. Delays of up to 14 days are acceptable for toxicity, in consultation with the medical monitor.
[r] Ad-RTS-hIL-12 intratumoral injection should be administered by freehand injection. Subjects must be instructed to maintain adequate oral hydration during the Treatment Period; sites must closely monitor subjects' hydration status. Because of the potential for toxicity (e.g., fevers, chills, fatigue, and dehydration), administration of prophylactic antipyretics is recommended after injection of Ad-RTS-hIL-12.
[s] Each subject will be carefully monitored for any local reactions and/or hypersensitivity reactions following the Ad-RTS-hIL-12 injection and veledimex administration. Subjects should be instructed to call the clinical site if headache, hemiparesis, seizure, or other local reactions develop anytime and especially between study visits.
[t] The first post-resection veledimex dose will be given on the next day, designated as Day 1, under supervision of the clinical staff to ensure there are no difficulties swallowing the capsule. Subsequent veledimex doses are to be taken once daily, in the morning and within 30 minutes of a regular meal.
[u] The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.
[v] Study sites must assess compliance of veledimex dosing. Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time of the daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff for assessment of compliance.
[redacted]
[y] Optional assessment, as total blood volume for phlebotomy clinically permits
[z] Appropriate cancer staging procedures should be performed during screening. All imaging should be of diagnostic quality. The brain will be imaged using the same method(s) throughout the study. Measurable target lesions should be selected and measured per iRANO guidelines. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Additional tumor response assessments as well as a posttreatment diagnostic brain biopsy may be performed at the discretion of the Investigator as part of standard-of-care treatment, per current iRANO guidelines. MRI scans are required for all subjects, including those with unconfirmed disease progression, to ensure that more slowly declining tumor burden in response to therapy is noted. For 2 years, subjects without confirmed disease progression should continue to have tumor assessments every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation). MRI scans should be available for collection upon Sponsor request. If appropriate, in accordance with iRANO, subjects should continue to receive cemiplimab until progression has been confirmed.
[aa] The MRI scan designated on Day 1 should be taken within 24 hours (a + 48hr window is allowed) of Ad-RTS-hIL-12 administration and is the baseline scan for tumor response assessments.
[bb] A tumor sample will be collected on Day 0 and also be collected at the time of progressive disease (per iRANO). The Day 0 tumor sample may be used for testing of IDH and methylation status. Archival tumor tissue, if available, should be submitted for analysis.
[cc] Neutralizing antibody status for Ad-RTS-hIL-12, it should be assessed at screening, Day7, Day 14 and Day 36.

2. TABLE OF CONTENTS

3. LIST OF TABLES

4. LIST OF FIGURES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ab	Antibody
Ad	Ad-RTS-hIL-12 or Ad-RTS-mIL-12, depending on context
Ad-RTS-hIL-12	Adenovirus RheoSwitch Therapeutic System® human interleukin-12
Ad-RTS-mIL-12	Adenovirus RheoSwitch Therapeutic System® mouse interleukin-12
ALVAC	Canarypox virus viral vectors
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
BBB	(Putative) blood-brain barrier
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
CHO	Chinese hamster ovary
CR	Complete response
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP3A4 or CYP450 3A4	Cytochrome P450 3A4
DIPG	Diffuse intrinsic pontine glioma
DP	Drug product
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report form
EIAED	Anti-epileptic drugs

Abbreviation or Specialist Term	Explanation
EMCV	Encephalomyocarditis virus
ESR	Erythrocyte sedimentation rate
FDA	U.S. Food and Drug Administration
Gal4-EcR	Fusion protein between Gal4 DNA binding domain and ecdysone receptor ligand binding domain
GalRE/P	Gal4 responsive promoter
GBM	Glioblastoma (multiforme)
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
hIL-12	Human interleukin-12
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-β	Interferon-beta
IFN-γ	Interferon-gamma
INR	International normalized ratio
IL-2	Interleukin-2
IL-12	Interleukin-12
IP-10	IFN-γ-induced protein 10
iRANO	Immunotherapy Response Assessment for Neuro-Oncology
IRB	Institutional Review Board
IV	Intravenous(ly)
IRES	internal ribosome entry site
IUD	Intrauterine device
KDa	kilo (K)- unified atomic mass units (Daltons or Da)
LDH	Lactate dehydrogenase
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

Abbreviation or Specialist Term	Explanation
NCI	National Cancer Institute
NK	Natural killer
NOS	Not otherwise specified
NPO	Nothing by mouth (literally, nil per os)
ORR	Objective response rate
OS	Overall survival
OSP	Overall Safety Population
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PKP	Pharmacokinetics Population
PO	Oral(ly)
polyA	polyadenylation signal
PR	Partial response
PSP	Pseudo-progression
PUbC	Ubiquitin C promoter
Q	Each/every (*quaque*), as in Q3W (every 3 weeks)
QD	Each day (*quaque die*)
rAd	Recombinant adenovirus
RANO	Response Assessment for Neuro-Oncology
RBC	Red blood cell
rhIL-12	Recombinant human IL-12
RTS	RheoSwitch Therapeutic System
RXR	Retinoid X receptor
SAE	Serious adverse event
SD	Stable disease
SpO_2	Saturation of peripheral oxygen
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
Th1	T-helper cell type 1
ULN	Upper limit of normal

Abbreviation or Specialist Term	Explanation
V	Veledimex
v	Version (followed by number)
vp	Viral particles
VP16-RXR	Fusion between VP16 transcriptional activation domain and a chimeric RXR
WBC	White blood cell

6. INTRODUCTION

6.1. Immunotherapy in Glioblastoma

The revised 2016 World Health Organization Classification of Tumors of the Central Nervous System makes use of molecular genetic findings in addition to histology to define tumor entities on the basis of combined phenotypic and genotypic features to generate "integrated diagnoses" (Louis et al. 2016). It has resulted in substantial restructuring of the diffuse gliomas, as compared with the 2007 CNS WHO Classification. In the revised classification the diffuse gliomas include the anaplastic astrocytomas (anaplastic astrocytoma, IDH-wildtype; anaplastic astrocytoma, IDH-mutant; and anaplastic astrocytoma, NOS [Not Otherwise Specified]) and anaplastic oligodendroglioma (with IDH-mutant and 1p/19q-codeleted subtypes) that are classified as WHO Grade III and the glioblastomas (glioblastoma, IDH-wildtype including giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma subtypes; glioblastoma, IDH-mutant; and glioblastoma, NOS) that are classified as WHO Grade IV. Of the WHO Grade III and Grade IV tumors, glioblastomas make up 60% to 70%, anaplastic astrocytomas 10% to 15%, and several other anaplastic subtypes the rest (Central Brain Tumor Registry).

Glioblastomas are by far the most frequent malignant glioma and are associated with a particularly aggressive course and dismal prognosis (Lieberman 2017). Standard of care treatment for glioblastomas is based on surgical resection with the intent to remove as much of the tumor as is feasible (Fernandes et al. 2017, Paolillo et al. 2018). Resection is then followed by radiotherapy and concomitant adjuvant temozolomide. However, such aggressive treatment is associated with only modest improvements in survival. Newly diagnosed glioblastoma subjects have a median overall survival (OS) of 12 to 15 months (Ahmed et al. 2014) and 2-year OS rate of up to 27% (Omuro et al. 2013), while OS in subjects that have failed TMZ and bevacizumab, or equivalent salvage chemotherapy, is reported as being as short as 3 to 5 months (Omuro et al., 2013; Iwamoto et al., 2009). To date, no salvage treatment has been validated by Phase III data for recurrent or progressive glioblastoma. For subjects with recurrent glioblastoma, the median OS is 6 to 7 months (Omuro et al. 2013), and median progression-free survival (PFS) is 2 to 3 months.

The lack of standard and validated salvage therapies has prompted the use of nitrosoureas, temozolomide rechallenge, bevacizumab, and other targeted agents that are unsatisfactory treatment options. This likely reflects the complexities of disease heterogeneity, and the treatment limitations of brain tumors given the low activity of antineoplastic agents, de novo or acquired drug resistance, the sensitivity of the brain to irreversible damage in response to treatment and the presence of the blood brain barrier (BBB), which maintains the brain as a privileged compartment. Surgical resection may be offered for subjects with recurrent disease, with the goal of alleviating mass effect, improving symptoms, and achieving cytoreduction. Surgical resection, however, is limited by the infiltrative nature of the disease and the lack of clear margins delimitating the tumor. Given the poor overall prognosis and lack of effective treatments, new therapeutic approaches for malignant gliomas are needed.

Immunotherapy for brain tumors is actively being investigated with an array of newer therapeutic modalities. Only about a third of glioblastomas have been reported to demonstrate a robust CD8+ cell population present within the tumor microenvironment (Heimberger et al. 2008), and these cells are anergic (i.e., not secreting interferon gamma [IFN-γ] or incapable of cytolytic activity). The immune infiltration in glioblastomas is highly variable and is likely driven by the genetic composition and mutational load of the tumor (Beier et al. 2012, Doucette et al. 2013). The anticipated specificity and efficiency of cytotoxic T-cells (CD8+), activated by local production of IL-12, is particularly attractive

and may both spare normal brain cells and minimize systemic toxicity. We have shown in an orthotopic mouse model that survival and tumor killing was greatly enhanced by combining a checkpoint inhibitor and Ad-RTS-mIL-12 + veledimex (Barrett et al. 2016b). Early clinical trials suggest that combining immunotherapeutic approaches with surgery, radiation, and chemotherapy may improve outcomes (Mitchell et al. 2008). Preliminary results from the CheckMate 143 (NCT 02017717) randomized clinical trial in first recurrence of glioblastoma, announced in a World Federation of Neuro-Oncology Societies (WFNOS) 2017 abstract, demonstrated a failure of nivolumab to prolong overall survival of patients with recurrent GBM, and this monotherapy arm of the trial was prematurely terminated (Filley et al 2017). However, an encouraging example of a *combination* immunotherapy approach to treating glioblastoma is a study of the safety and activity of nivolumab (human programmed death receptor-1 [PD-1] blocking antibody) in combination with ipilimumab (anti-cytotoxic T lymphocyte associated antigen 4 [CTLA-4] antibody) in patients with recurrent disease (Reardon et al. 2016). In this ongoing dose escalation study, combination therapy was tolerable, with 12-month overall survival (OS) ranging from 25% to 40%.

In Ziopharm's ongoing Phase I trial of intratumoral viral delivery of Ad-RTS-hIL-12 + veledimex to date 31 subjects have been orally dosed in 4 cohorts: 10 mg (n=6), 20 mg (n=7), 30 mg (n=4), 40 mg (n=6), and an expansion cohort of 20 mg (n=8). Results show that veledimex crossed the blood-brain-barrier, with approximately 40% of plasma levels detected in the brain tumor. Subjects in the 20 mg dose cohort (n=15) have better median OS (12.7 months) than in other cohorts.

Immune checkpoint inhibitors penetration across the blood-brain-barrier to the tumor tissue remains controversial, but the goal is to achieve maximum therapeutic effect while limiting systemic toxicity, especially when CD8+ cells have been mobilized to the tumor as we have documented following treatment with Ad-RTS-hIL-12 + veledimex.

6.2. Interleukin-12 and Cancer Immunotherapy

Interleukin-12 (IL-12) is a pro-inflammatory cytokine and has been recognized as a master regulator of cell mediated immunity in response to intracellular pathogens and neoplastic transformation. Structurally, IL-12 is a heterodimeric protein composed of p35 and p40 subunits covalently linked to form the biologically active IL-12 p70 molecule (Carra et al. 2000). The expression of the p40 subunit is tightly regulated and requires specific priming and amplification signals through complex combinatorial matching of Toll receptor agonists and specific cytokines, thus limiting the cell types that can produce native biologically active IL-12 to activated antigen-presenting cells, neutrophils, and macrophages (Trinchieri 2003). On a secondary level, IL-12 production can also be negatively regulated through various mechanisms including production of IL-10 and transforming growth factor β (TGFβ).

Initial studies identified that IL-12 was produced by innate immune cells in response to pathogens and that it led to the production of interferon gamma (IFN-γ) and tumor necrosis alpha (TNFα) by T and natural killer (NK) cells (Micallef et al.1996, Trinchieri 2003). When it was discovered that IL-12 could drive naïve T-helper cell differentiation to the inflammatory T-helper cell type 1 (Th1) phenotype (Hsieh et al. 1993), a role for IL-12 was established as a bridge between innate immune cells and the adaptive immune response through polarization of naïve CD4+ cells. More recent data demonstrate additional functional roles of IL-12 directly influencing CD8+ T-cell differentiation (Curtsinger et al. 2003, Kalinski et al. 1999) and the reactivation and survival of memory CD4+ T-cells (Yoo et al. 2002). This is particularly important in the context of the tumor microenvironment where high levels of IL-12 have been shown to repolarize antigen-experienced CD4+ T-cells back to the functional antitumor Th1 phenotype (Wesa et al. 2007).

Evidence that IL-12 is able to trigger innate and adaptive immunity and modulate the tumor microenvironment supports the relevance of IL-12 as an important immunotherapeutic agent. Its ability to activate and recruit dendritic cells that facilitate the cross-priming of tumor antigen-specific T-cells, along with its influence on NK and $CD8^+$ T-cell cytotoxic activities and antigen-specific antitumor responses (Mosmann et al. 1989, Trinchieri 1995, Tsung et al. 1997, Mailliard et al. 2002) warrant further study in cancer therapy. Additionally, IL-12 has also been shown to stimulate the production of superoxides and nitric oxide and possess potent antiangiogenic activity through IFN-γ (Voest et al. 1995, Wigginton et al. 1996, Coughlin et al. 1998). The potent antitumor activity of IL-12 has been well documented in various cancer mouse models including melanoma, mammary carcinoma, sarcoma, and colon and renal carcinoma (Colombo et al. 2002). The potent nature of its biological activity and signaling complexity has also prompted the study of different delivery mechanism with a focus on intratumoral delivery and tumor microenvironment modulation.

Based on such data, human studies of IL-12 as an anticancer agent were initiated. The first of these studies was a Phase I dose escalation of intravenous (IV) administered recombinant human IL-12 in subjects with either melanoma or renal cell carcinoma. The study reported a transient complete response in melanoma and a partial response in renal cell carcinoma with significant toxicities. The Phase II trial observed similar toxicities, and two IL-12 related deaths prompted the Food and Drug Administration (FDA) to suspend the trial (Atkins et al 1997, Leonard et al 1997). Additional studies confirmed that systemic administration of recombinant IL-12 resulted in significant toxicity, limiting its potential for clinical development (Salem et al. 2006). These results prompted the investigation of alternative delivery routes focusing on locoregional administration either by subcutaneous injection or intratumoral delivery implementing IL-12 as a direct anticancer therapeutic or as an adjuvant to vaccination.

6.3. Local IL-12 Delivery and Development of an Inducible IL-12 Immunotherapy

The potent effects of cytokines, particularly IL-12, as mediators of an anticancer immune response remain compelling. This is especially true since the advent of immunotherapies such as anti-CTLA-4 and anti-PD1 antibodies provide proof of concept that inhibiting immune checkpoints translates into clinical benefit. IL-12 biology including the level of activation, location of initial expression, immune effector function, and biologically active combination with other cytokines remain incompletely understood.

Several human studies that have implemented the local delivery of cytokines or chemotherapeutic agents have already shown that such an approach reduces systemic toxicity and produces signals of clinical benefit. One particularly relevant trial implemented a gene transfer strategy to express interferon beta (IFN-β) locally in glioma tumors, and thus achieved high intratumoral IFN-β expression without systemic toxicity. The IFN-β was constitutively expressed through a replication-defective serotype 5 adenoviral vector under the control of a cytomegalovirus promoter achieving transduction of both dividing and non-dividing cells. The investigators reported the approach proved feasible and well tolerated; however, although the IFN-β transduction was variable among subjects, it was associated with apoptosis (Chiocca et al. 2008).

In the current Phase I study, we are exploring a local treatment strategy for high-grade gliomas with the goal of extending the IL-12 therapeutic window and reducing its systemic toxicity. [redacted] The replication-incompetent Ad-RTS-hIL-12 vector is injected locally in the tumor lesion and

initiates hIL-12 transcription only in the presence of the promoter specific oral activator ligand, veledimex. With this system, the IL-12 expression level can be modulated by the dose and frequency of veledimex administration, making it feasible to lower or terminate IL-12 expression in the event of severe or unexpected toxicities.

6.4. Adenoviral Vectors for Gene Therapy

6.4.1. Adenoviral Safety

Adenoviral vectors have been used extensively to deliver a variety of gene products to human subjects, including cancer subjects. Although adenoviral vectors are immunogenic, virtually all recipients have pre-existing humoral immunity to adenoviruses and they are generally considered a safe and well tolerated vehicle for gene delivery. Numerous studies have utilized adenoviral vectors to achieve intratumoral expression of a variety of genes. In a Phase I/II clinical trial of subjects with prostate cancer, direct intraprostatic injection of a replication-defective adenoviral vector encoding bacterial nitroreductase (dose levels 5 x 10^{10} -1 × 10^{12} viral particles [vp]) was well tolerated, with minimal adverse events (AEs) (Patel et al. 2009) . A Phase I study of subjects with oral leukoplakia implemented multiple intraepithelial injections of recombinant adenovirus (rAd)-p53 (1 x 10^{8} vp/cm^2) and demonstrated good tolerance of the vector, with no evidence of dose-limiting toxicity (DLTs) (Zhang et al. 2009) . In another Phase I/II study of subjects with chemoradiation-resistant advanced esophageal carcinoma, intratumoral injections of adenovirus vector containing p53 (Ad.5CMV-p53) were well tolerated at doses ranging from 10 x 10^{11} to 25 x 10^{11} vp, with no DLTs, and generally mild to moderate adverse events (AEs) (Shimada et al. 2006) . The most common AEs were fever (all 10 subjects), pain (30% of subjects), and hyperglycemia, which was attributed to the use of total parental nutrition (30% of subjects). Hypocalcemia was reported in two subjects (20%) and one subject each (10%) experienced activated partial thromboplastin time (aPTT) prolongation, abnormally high serum amylase, and abnormally high serum creatinine.

In a Phase I study of subjects with advanced pancreatic, colorectal, or primary liver tumors, intratumoral injection of an adenoviral vector encoding hIL-12 (Ad.IL-12) was well tolerated at doses of up to 3 × 10^{12} vp. Common AEs were similar to symptoms observed with gene delivery by other adenoviral vectors, including transient, mild to moderate fever, malaise, sweating, and lymphopenia (Sangro et al. 2004).

A recent randomized, open-label, Phase III study compared a regimen of surgical resection, adenovirus-mediated gene therapy (intraoperative perilesional sitimagene ceradenovec), intravenous ganciclovir, and standard of care interventions versus surgical resection plus standard of care interventions in 250 subjects with newly diagnosed high-grade glioma amenable to resection. Results showed that although the time to death or re-intervention was prolonged, OS was not improved for the investigational regimen relative to the standard of care regimen (Westphal et al. 2013). This apparent difference may have been due to the composite primary endpoint and/or that while OS is a robust endpoint, there is no discussion of effect size and for recently-diagnosed tumors it might be less suitable to capture meaningful treatment effects for the initial stages of disease because of uncontrolled therapy at relapse (*ibid*). Nevertheless, the authors concluded that the treatment had an increased hazard ratio for the primary analysis with a positive overall benefit-risk ratio, with similar AEs (hemiparesis [often transient], hyponatremia, and seizures, but no cerebral hemorrhages nor hematomas), as compared with the standard-of-care regimen.

6.4.1.1. Safety of Intratumoral Injection of IL-12 Gene Vectors

In contrast with the systemic toxicity resulting from administration of recombinant IL-12 protein, local administration of IL-12 via injection of plasmid or adenoviral vectors containing the hIL-12 gene has proven to be well tolerated in subjects with various cancers, and therefore appears to provide an effective delivery method for this potent immunomodulatory cytokine. Several studies have investigated the safety of intratumoral expression of IL-12 in subjects with metastatic melanoma. A Phase I study investigated intratumoral expression of IL-12 together with the co-stimulatory molecule B7.1 via two separate canarypox virus viral vectors (ALVAC) in subjects with metastatic melanoma and reported mild to moderate injection site reactions, fever, chills, myalgia, and fatigue as AEs (Triozzi et al. 2005). However, all subjects also developed antibodies to ALVAC. Notably, serum IL-12 and IFN-γ levels were not increased after treatment. Another Phase I trial showed that delivery by electroporation of a plasmid containing IL-12 to tumors in subjects with metastatic melanoma resulted in minimal systemic toxicity, with transient pain after electroporation being the most common AE (Daud et al. 2008). Results from another Phase I study showed that intratumoral injection of DNA encoding hIL-12 in subjects with metastatic melanoma was well tolerated overall (Heinzerling et al. 2005). Eight of nine subjects experienced a transient response at the intratumoral injection site, and some subjects who had tumor responses also showed some increases in systemic in IL-12, interferon gamma-induced protein 10 (IP-10), and IFN-γ.

Localized production of IL-12 also has been reported as well tolerated in subjects with other malignancies. For example, a Phase I study in 17 subjects with metastatic pancreatic, colorectal, or primary liver cancer examined intratumoral injection of dendritic cells engineered to secrete IL-12 via a rAD vector (Mazzolini et al. 2005). In that study, the most common AEs were lymphopenia, fever, and malaise. Subjects also developed antibodies to the adenoviral capsid proteins. Intraperitoneal injection of a plasmid containing the hIL-12 gene in women with chemotherapy-resistant, recurrent, ovarian cancer also was found to be generally safe and well tolerated (Anwer et al. 2010). Low-grade fever and abdominal pain were the most common AEs. Plasmid DNA was not detected in the subjects' serum samples, and treatment-related increases in IFN-γ levels were observed in pleural fluid, but not in serum. Similar data were reported in a study of subjects with advanced pancreatic, colorectal, or primary liver malignancies who received intratumoral injections of adenoviral vectors encoding hIL-12 at doses ranging from 2.5×10^{10} to 3×10^{12} vp (Sangro et al. 2004). In that study, treatment was well tolerated and a maximum tolerated dose (MTD) was not reached. Transient lymphopenia was observed in 86% of subjects, and the severity was increased at higher vector doses. Transient, mild to moderate fever, sometimes accompanied by malaise and sweating, was observed in ~ 60% of subjects during the first 2 days after the injection. Five of the 21 subjects (24%) experienced nausea and/or vomiting on the day of the injection. No cumulative toxicity was observed. These events were deemed related to injection of the virus and not to transgene expression.

6.5. Ad-RTS-hIL-12 Gene Therapy Components

[redacted]

6.5.2. Ad-RTS-hIL-12

The Ad-RTS-hIL-12 (previously referred to as INXN-2001) replication-incompetent adenovirus engineered for this study implements the hIL-12 transgene under the RTS-regulated promoter (Figure 3), as described by Anderson et al (Anderson et al. 2000). Cells transduced with Ad-RTS-hIL-12 will produce hIL-12 protein when in the presence of the RTS specific activator ligand, veledimex. Because the level of transgene expression is dependent on the concentration of veledimex, hIL-12 production can be modulated by the dose and frequency of veledimex administration. Potential and unexpected IL-12-related AEs may, therefore, be addressed at least by dose reduction or termination of veledimex administration, if necessary.

[redacted]

[redacted]

[redacted]

6.5.3. Veledimex

Veledimex is a diacylhydrazine that is fully active at the RTS receptor. Drug product is formulated as a semi-solid containing veledimex as a dry powder and excipients. This formulation has been encapsulated in gelatin capsules for oral administration in clinical trials.

Nonclinical studies *in vitro* and *in vivo* demonstrate that veledimex interacts with the receptor component EcR of RTS to induce the activation of therapeutic gene transcription, leading to the production of transgene messenger RNA and, ultimately, protein (Anderson et al. 2000, Palli et al. 2003, Karzenowski et al. 2005).

6.5.4. Cemiplimab-rwlc

Cemiplimab-rwlc (Libtayo ®), is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD L1-mediated T cell inhibition. Cemiplimab-rwlc was isolated from Regeneron's VelocImmune™ human antibody mouse platform and contains a human light chain variable domain fused to human kappa constant domain and a heavy chain variable region in a human IgG4 Fc format. The IgG4 Fc domain contains a serine to proline mutation in the hinge region to promote dimer stabilization, designated IgG4P.

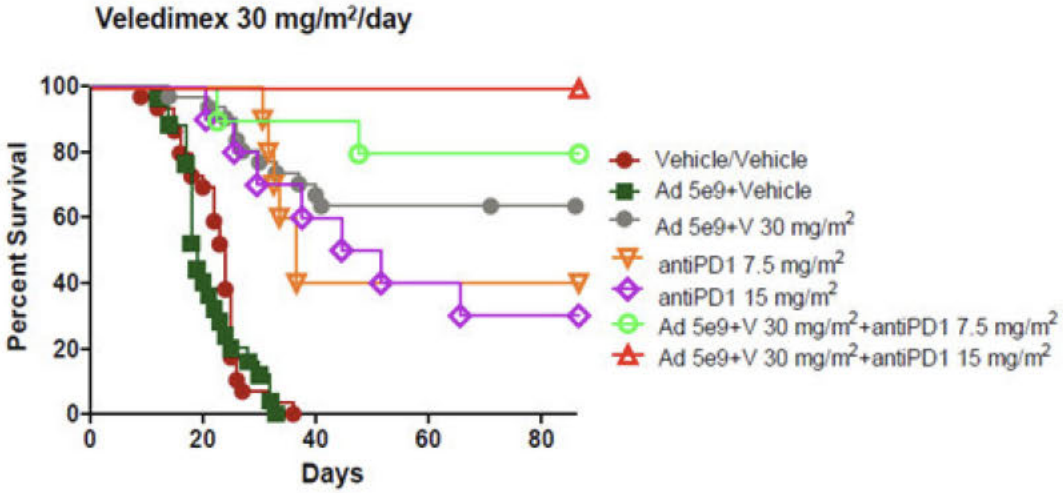
6.6. Nonclinical Data in the GL-261 Glioma Mouse Model

6.6.1. Ad-RTS-hIL-12 and Veledimex in Combination With a PD-1 Inhibitor

The utility of immunotherapy in the treatment of glioma may be improved through combination therapies that enhance cytotoxic immune-activation while concomitantly reducing immunosuppression, including the combination of local IL-12 administration and blockade of PD-1. In the orthotopic mouse model, we assessed the effects of adenovirus RheoSwitch Therapeutic System® mouse IL-12 (Ad-RTS-mIL-12) + veledimex alone, Ad-RTS-mIL-12 5 x 10^9 vp + veledimex 10 mg to 30 mg/m^2/day for 14 days or in combination with the anti-PD-1-specific monoclonal antibody RMP1-14 (antiPD-1, 7.5 and 15.0 mg/m^2 for 4/day for 5 days intraperitoneal) (Barrett et al. 2016a).

All mice without treatment succumbed to disease progression by Day 35 (Figure 4). Eighty days after immunotherapy, 70% to 80% of mice that received Ad-RTS-mIL-12 + veledimex monotherapy survived, 30% to 40% of mice that received anti-PD-1 monotherapy survived, and 100% of mice that received the combination of Ad-RTS-mIL-12 + veledimex 30 mg/m^2 + anti-PD-1 15.0 mg/m^2 survived.

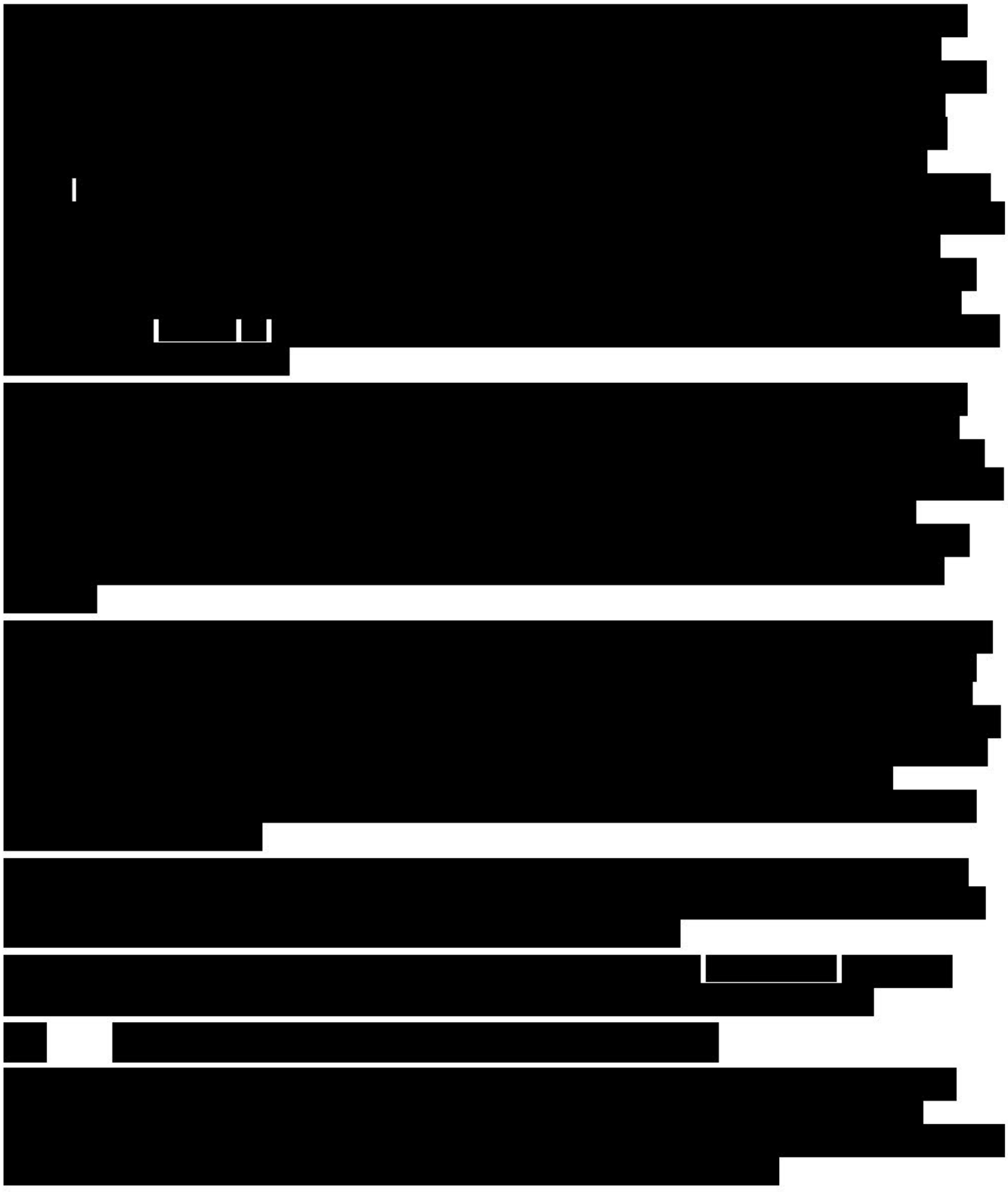
Figure 4: Overall Survival in GL-261 Mice Treated With Ad-RTS-mIL-12 + Veledimex Plus Anti-PD-1



There was also an increase in tumor IL-12 (100 pg/mg), which was 15 times greater than that of plasma peak 5 days after Ad-RTS-mIL-12 + veledimex. Furthermore, the combination of Ad-RTS-mIL-12 + veledimex + anti-PD-1 produced sustained peak IL-12 levels in tumor, which was associated with a 100% to 150% increase of activated T cells in the spleen, compared with the minimal changes observed with either immunotherapy alone.

In addition, there was an additive reduction in regulatory T cells (FOXP3) compared with either monotherapy. In summary, we demonstrated that controlled local immunostimulation with IL-12 combined with inhibition of PD-1 is an attractive approach for the treatment of glioma.

[redacted]



7. STUDY OBJECTIVES

7.1. Primary Objective

To determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin 12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the safety profile observed for drug safety and on an estimate of Overall Survival (OS) for efficacy, respectively.

7.2. Secondary Objectives

- To determine the survival rates at 6, 12, 18 and 24 months
- To determine the progression free survival (PFS), and rate of pseudo-progression (PSP) at 6, 12, 18 and 24 months
- To determine the Investigator's assessment of response, including tumor objective response rate (ORR) at 6, 12, 18 and 24 months
- To determine the tumor response rates at 6, 12, 18 and 24 months
- [redacted]

8. STUDY DESIGN

8.1. Overall Study Design

This is a multicenter Phase II study of an intratumoral injection of Ad-RTS-hIL-12 ([redacted] and veledimex (20 mg) administered PO in combination with cemiplimab-rwlc (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma. This study will determine the safety and efficacy of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc, based on the safety profile observed and overall survival, respectively.

This study includes a Screening Period, Treatment Period, and Survival Follow-up. After the informed consent form (ICF) is signed, subjects will enter the Screening Period to be assessed for eligibility. Subjects will receive cemiplimab-rwlc on Day -7 (±3 days). On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection and Ad-RTS-hIL-12 (2×10^{11} vp) will be administered by freehand injection. Ad-RTS-hIL-12 will be delivered intratumorally or at the margin of the tumor for a total volume of 0.1 mL following resection (subtotal or gross total). The total amount delivered to each site will be recorded in the eCRF. If the total administered volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations.

After the Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post craniotomy veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning. Dosing on Days 2-14 should be at approximately the same time of day (+/- 1 hours) as the Day 1 dosing.

Subjects will receive a dose of cemiplimab-rwlc (350 mg) IV on Day 15 and every three weeks thereafter (Q3W) until documented progression by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria, unacceptable toxicity, subject withdrawal or completing the follow-up period. Delays in cemiplimab-rwlc dosing due to toxicities are allowed at the discretion of the Principal Investigator in consultation with the Medical Monitor, for up to 14 days.

A formal Safety Review Committee (SRC) will be comprised of the study Investigators and the Medical Monitor.

After the first six patients have been enrolled and administered Ad-RTS-hIL-12 and veledimex in combination with at least one post Ad-RTS-hIL-12 dose of cemiplimab-rwlc, enrollment will be paused to allow for additional safety follow-up and assessment. The SRC will review safety data after the 6^{th} subject has reached Day 28 and decide if enrollment should occur at the same dose and schedule of the investigational products.

8.2. Study Oversight for Safety Evaluation

Safety oversight will occur through the site investigator and medical monitor. A formal SRC, guided by the SRC charter, will include the study investigators, the medical monitor and other appropriate sponsor representatives and will provide overall safety oversight. Additional external medical and scientific experts may also be invited to participate in the reviews as needed and appropriate and as decided by the SRC. If a significant safety event occurs, the SRC will convene to evaluate the safety event(s) and make a recommendation and decision on the enrollment and continued treatment of subjects.

9. SUBJECT SELECTION

Subjects with supratentorial glioblastoma who have not previously been treated with inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.

9.1. Inclusion Criteria

1. Male or female subject ≥18 and ≤75 years of age
2. Provision of written informed consent for tumor resection (subtotal allowed), tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study-specific procedures
3. Histologically confirmed glioblastoma from archival tissue
4. Evidence of tumor recurrence/progression by magnetic resonance imaging (MRI) according to Response Assessment in Neuro-Oncology (RANO) criteria after standard initial therapy
5. Previous standard-of-care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor)
   a. Nitrosoureas: 6 weeks
   b. Other cytotoxic agents: 4 weeks
   c. Antiangiogenic agents: 4 weeks
   d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks
   e. Vaccine-based or CAR-T therapy: 3 months
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment
7. Karnofsky Performance Status ≥70
8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
   f. Hemoglobin ≥9 g/L
   g. Lymphocytes >500/mm^3
   h. Absolute neutrophil count ≥1500/mm^3
   i. Platelets ≥100,000/mm^3
   j. Serum creatinine ≤1.5 x upper limit of normal (ULN)
   k. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN.
   l. Total bilirubin <1.5 x ULN
   m. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) within normal institutional limits

9. Clinically stable on a consistent or decreasing dose of dexamethasone or equivalent of less than or equal to 2 mg per day for at least 7 days prior to Day -7 (i.e., Day -14)
10. Male and female subjects must agree to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 4 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

* Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

9.2. Exclusion Criteria

1. Radiotherapy treatment within 4 weeks of starting veledimex
2. Prior treatment with bevacizumab

   (NOTE: Brief use (< 4 doses) of bevacizumab for controlling edema is allowed)
3. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
4. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

   NOTE:

   - Patients with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
   - Patients with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
   - Patients who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

5. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively.
6. Use of enzyme-inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed.
7. Other concurrent clinically active malignant disease, requiring treatment, except for non-melanoma cancers of the skin or carcinoma in situ of the cervix or non-metastatic prostate cancer
8. Nursing or pregnant females
9. Prior exposure to veledimex
10. Prior exposure to inhibitors of immuno-checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) or other agents specifically targeting T cells.
11. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 prior to veledimex dosing without consultation with the Medical Monitor
12. Presence of any contraindication for a neurosurgical procedure
13. Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness. Prophylactic subcutaneous heparin per institutional protocol for prevention of DVT may be allowed based on discussion with the Medical Monitor. Concomitant medications should continue to be reviewed in consultation with the Medical Monitor.
14. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator or Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples may include, but are not limited to, colitis, unstable angina, congestive heart failure, myocardial infarction within 2 months of screening, and ongoing maintenance therapy for life-threatening ventricular arrhythmia or uncontrolled asthma.

9.3. Subject Enrollment

Approximately 30 subjects may be enrolled.

9.4. Withdrawal of Subjects from Study Treatment and/or Study

The sponsor may terminate this study at any time. The investigator and/or the subject have the right to terminate the subject's participation in the study at any time. Efforts should be made to ask subjects who discontinue study drug to be available to complete the Follow-up assessments.

A subject may withdraw or be withdrawn from the study treatment prematurely for any of the following reasons:

- Principal Investigator (PI) determines further participation is not in the subject's best interest (e.g., subject experiences rapid clinical deterioration in the absence of confirmed disease progression)
- Subject has confirmed disease progression

A subject must be withdrawn in the event of any of the following:

- Subject withdraws informed consent.
- Any treatment-related AEs that meet withdrawal criteria
- Substantial noncompliance with study requirements
- Subjects with a confirmed positive pregnancy test
- Any intercurrent illness that would, in the judgement of the investigator or sponsor's medical monitor, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy
- Subjects who did not receive any study drugs

- *NOTE: Any subject who wishes to withdraw from the study treatment may do so at any time but will be asked to be available for the safety, tumor response, and survival follow-up assessments.*

Every effort should be made to follow subjects who withdraw from study treatment for ongoing treatment-related AEs. Subjects who withdraw during the treatment period should continue to have study assessments as clinically indicated.

9.5. Replacement of Subjects

Subjects who withdraw from the study or do not receive each study drug may be replaced. All dosed subjects will be included in the overall safety assessment.

9.6. Premature Termination of Study or Study Site

The sponsor has the right to close the study at any time, although this should occur only after mutual consultation between the sponsor and the investigators. The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be informed of such action. Should the study or center be closed prematurely, all study materials (completed, partially completed, and blank electronic case report forms (eCRF), study medication, etc.) must be stored or disposed of according to the sponsor's instructions. Events that may trigger premature termination of the study or closure of a center include but are not limited to the following: new toxicity findings; decision to re-challenge patient who has experienced a Grade 4 event; interim analysis results; noncompliance with the protocol; changes in the development plans for the study drug; slow recruitment; and poor-quality data.

10. INVESTIGATIONAL PRODUCTS

Ad-RTS-hIL-12 and Veledimex is an investigational product has two components: the Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand). Ad-RTS-hIL-12 is a replication-incompetent adenoviral vector containing the hIL-12 gene under the control of the RTS inducible promoter activated in the presence of the activator ligand, veledimex. Veledimex is a small molecule RTS specific transcription factor that stabilizes the RTS promoter components and allows transcription of the hIL-12 target gene. Since target gene expression is dependent on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated (turned on and off) by the optimal veledimex dose and schedule.

Cemiplimab-rwlc is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kilounified atomic mass unit (kDa) based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The cemiplimab-rwlc heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody. Please refer to the Pharmacy Manual for additional information.

Antibody generation by VelocImmune® mice is carried out using standard techniques after immunization with PD-1. The genes encoding the heavy and light chains of cemiplimab-rwlc were introduced into Chinese Hamster Ovary (CHO) cells, and a stable expression cell line (Cell Line 1) was selected for the antibody. Later in development, a second stable expression cell line with higher titer (Cell Line 2) was developed for this antibody. For both cell lines, the expression of REGN2810 was regulated, such that the recombinant CHO cells were de-repressed to initiate antibody expression and secretion into the cell culture medium in production bioreactors. Antibody is harvested via filtration and purified through a series of preparative column chromatographic and filtration steps to generate drug substance. Drug substance is then formulated and sterile-filtered to produce the final drug product (DP).

10.1. Preparation of Ad-RTS-hIL-12

Ad-RTS-hIL-12 will be supplied as a sterile, single-use vial for injection. Each 0.1 mL contains [redacted] Ad-RTS-hIL-12. Information regarding the preparation of the Ad-RTS-hIL-12 dose is provided in the Pharmacy Manual.

10.2. Preparation of Veledimex

Sponsor will provide veledimex capsules to be dispensed by the study site pharmacy to subjects for oral administration. Information regarding the veledimex is provided in the Pharmacy Manual.

10.3. Preparation of Cemiplimab-rwlc

Cemiplimab-rwlc will be supplied in single-dose vials. Information regarding the preparation of the cemiplimab-rwlc dose is provided in the Pharmacy Manual.

10.4. Handling and Storage

Study drugs must be stored in a restricted access area under the storage conditions indicated in the Investigator's Brochure or Pharmacy Manual. All necessary precautions while handling potentially toxic compounds must be strictly followed.

10.5. Monitoring of Subject Adherence and Managing Missed Doses

10.5.1. Veledimex

The first veledimex dose following Ad-RTS-hIL-12 injection is expected to be administered when the subject is at the clinical site, under careful medical supervision by the clinic staff to ensure that the subject does not have difficulty swallowing the capsules. Thereafter, subjects may be allowed to self-administer the remaining once daily doses as described. Subjects are to be instructed to take the appropriate number of capsules in the same way for each of the remaining treatment period days and may be reminded to do so by phone on non-visit days.

Subjects should NOT make up any missed doses.

Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the once daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff on Day 15, so that staff can properly assess dose compliance.

10.5.2. Cemiplimab-rwlc

The recommended dose of cemiplimab-rwlc is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks (Q3W) until confirmed disease progression or unacceptable toxicity.

10.6. Disposition of Unused Drug

All unused study drug should be destroyed at the study site in accordance with standard institutional practice and in accordance with United States Occupational Safety and Health Administration procedures, after full accountability has been documented. Any study drug destruction at study site must be documented and the records maintained in the investigator's study file.

10.7. Accountability and Dispensation

The investigator must maintain accurate records accounting for the receipt and dispensation of study drugs. The investigational materials are to be prescribed only by the investigator or the sub-investigators named on FDA Form 1572 and may only be dispensed by authorized personnel at the institution(s) listed therein. Under no circumstances will the PI allow the investigational drug(s) to be used for purposes or in subjects other than as directed by the protocol.

10.8. Treatment Plan

10.8.1. Cemiplimab-rwlc

On Day -7, Day 15, and approximately every 3 weeks thereafter subjects will receive cemiplimab-rwlc until confirmed disease progression or unacceptable toxicity.

10.8.2. Ad-RTS-hIL-12 + Veledimex

- Subjects will be given a cohort-specific dose of veledimex by mouth, when NPO (excluding other medications) 3 (± 2) hours before craniotomy (Day 0). The actual time of veledimex administration should be noted and recorded.
- Surgical planning will be performed on a diagnostic MRI acquired prior to the surgery as per standard of care.
- At the time of tumor resection, tumor, CSF (if available), and blood samples will be collected.

- Immediately after tumor resection, when available, an intraoperative MRI can be performed to identify contrast enhancing or T2/FLAIR hyper intense residual tumor. If intraoperative MRI is not available, the neurosurgeon will select sites for injection.
- Subjects will receive Ad-RTS-hIL-12 [redacted] This will be administered by freehand injection into approximately two sites within the residual tumor for a total volume of 0.1 mL selected by the neurosurgeon. When available an intra-operative MRI can be performed to guide the Ad-RTS-hIL-12 injection to areas of contrast-enhancing tumor tissue.
- The day of Ad-RTS-hIL-12 administration is designated as Day 0. If Ad-RTS-hIL-12 injection is not performed, subject will not continue with post-resection veledimex dosing.
- After tumor resection and Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-resection veledimex dose is to be given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning and within approximately 30 minutes of a regular meal.

Subjects should be carefully monitored for possible local reactions and/or hypersensitivity reactions, according to standard practice. Intracranial bleeding or other procedure-related events should be evaluated before the first veledimex dose is given post Ad-RTS-hIL-12 administration. Any changes in neurological status should be reported to the investigator immediately, either during hospitalization or once subject is discharged. Subjects should be instructed to call the study physician or study nurse if they develop any symptoms after they are released from the hospital.

NOTE: It is important that subjects are instructed to maintain adequate oral hydration while subjects are being administered veledimex. Study sites should monitor subjects for proper hydration and monitor blood pressure regularly. The incidence of low blood pressure to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

10.9. Stopping Rules

If any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or results in death; requires major operative intervention; or is a related grade 4 hematologic toxicity that persists for 5 days: then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee. The SRC will recommend if changes to the enrollment of additional subjects are required, including, but not limited to, potentially modifying the dose and schedule of veledimex, to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study.

10.10. Dose Modifications and Dose Delays

Veledimex dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 2.

Table 2: Criteria for Dose Delay and Dose Reduction of veledimex

Adverse Reaction	Severity[2]	Veledimex Dosage Modifications[1]
Immediately life-threatening/ Potentially-Fatal Severe Adverse Reactions		
Any non-hematologic AE[3]	Grade 4 non-hematologic adverse event at least possibly related to study drug, that is considered by the treating physician to be immediately life-threatening, and results in emergent medical and/or surgical intervention	Discontinue
Other Severe Adverse Reactions		
Cytokine Release Syndrome	Grade 3 or higher (per the Ziopharm Working Definition of Cytokine Release Syndrome)	Withhold[4]
Any non-hematologic AE[3, 5] (except brain edema)	Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and persists at least 3 days	Withhold[4]
Cerebral edema[5]	Grade 3 or higher	Withhold[4,6]
Thrombocytopenia	Grade 3 or higher thrombocytopenia (< 50,000/mm^3) at least possibly related to study drug	Withhold[4]
Lymphopenia or other hematologic toxicity	Grade 4 or higher lymphopenia or other hematologic toxicity (except thrombocytopenia)	Withhold[4]
Increased transaminitis[8]	Grade 3 or higher increase in ALT or AST	Potentially Withhold[7]

1. These recommendations are for general guidance only. Treating physicians should manage patients according to their clinical judgement, as informed by institutional guidelines, best practices and these guideline recommendations.
2. Toxicity as graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.
3. Nausea and vomiting will not be considered in this category unless at least Grade 3 or 4 and refractory to antiemetics (i.e., defined as symptoms not mitigated by maximal medical support as directed by the Investigator (per institutional guidelines) in consultation with the Sponsor Clinical Medical Monitor).
4. Withhold the next and any successive doses of veledimex while the Grade 3 or 4 toxicity persists. Veledimex dosing may resume, after discussion with the Sponsor Clinical Medical Monitor, in subjects with rapid and substantial reversal of toxicity, either spontaneously or following appropriate medical treatment. The Sponsor Clinical Study Coordinator will be notified in advance of veledimex dosage modifications.
5. Seizures, headache, and cerebral edema are commonly observed in this population and will be recorded according to the grade of toxicity and therefore will not be considered in this category unless unresponsive to maximal medical support as directed by the Investigator (informed by institutional guidelines) and in consultation with the Sponsor Clinical Medical Monitor.
6. *Cerebral Edema Guideline Recommendations:* As a general guideline, mannitol (Osmitrol), corticosteroid treatment (i.e., dexamethasone or Decadron) and/or withholding the next dose(s) of veledimex short-term are considered for cerebral edema, CTCAE v5.0 Grade 3 (or for "moderate" severity descriptively). For Grade 4 cerebral edema, mannitol (Osmitrol), higher dose corticosteroids and/or longer-term withholding or discontinuation of veledimex are considered, especially if the edema is not sufficiently mitigated by urgent medical intervention. It is expected that the use of corticosteroids will vary between sites and among subjects, and therefore, the precise extent and dosage of steroids cannot be specified per protocol. The treating physician will decide as is safe and appropriate for the individual subject according to their clinical judgement as informed by the label and institutional guidelines and should consider the minimum steroid dose or the lowest amount that adequately and rapidly controls the subject's signs and symptoms (refer to Rationale section below). Consideration also may be given to a limited number of doses of bevacizumab (Avastin) if (typically high-dose) corticosteroids are not in the best interests of the subject in the treating physician's clinical judgement and following consultation with the Medical Monitor. In the event of an immediately life-threatening event, the treating physician should consider surgical decompression.
7. *Rationale:* Cerebral edema may pre-exist experimental treatment to a variable extent and usually is associated with the underlying disease and/or increase following surgical procedures. The study treatment, particularly with combination therapy including an immune checkpoint inhibitor, also may possibly cause an increase in the severity of edema. Patients with glioblastoma receiving more than 4 mg dexamethasone qd were reported to have decreased overall survival, possibly due to immunosuppression (British J Cancer 2015:113, 232–241). Preliminary data presented at the Society for Neuro-Oncology 2018 Annual Meeting by Ziopharm Oncology also suggests that overall survival is decreased in 20 mg veledimex craniotomy cohort subjects (i.e., administered more than a 20 mg cumulative dosage of dexamethasone) during the initial treatment period (Days 0-14); the relative contributions of severity of the condition vs immunosuppression to the negative effect observed on overall survival are presently uncertain.
8. Withhold the next dose(s) of veledimex if the transaminitis is part of a constellation of findings consistent with Cytokine Release Syndrome (refer to Ziopharm Working Definition of Cytokine Release Syndrome). The treating physician may elect to follow the laboratory test trajectory and clinical status if an isolated transaminitis.

Cemiplimab-rwlc dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria shown in Table 3.

Table 3: Criteria for Dose Delay and Dose Reduction of cemiplimab-rwlc

Adverse Reaction	Severity	Cemiplimab-rwlc Dosage Modifications
Severe and Fatal Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold*
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold*
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN	Withhold*
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, 4	Withhold if clinically necessary*
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold*
	Grade 4	Permanently discontinue
Recurrent or persistent immune-mediated adverse events	• Recurrent Grades 3 or 4 • Grades 2 or 3 persistent for 12 weeks or longer after last cemiplimab-rwlc dose in spite of appropriate therapy • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last cemiplimab-rwlc dose	Permanently discontinue
Severe and Fatal Immune-Mediated Adverse Reactions		
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinued

AE = adverse event
*: Resume in patients with complete or partial resolution (Grade 0 to 1) after supraphysiologic dose of corticosteroids discontinued

10.11. Safety Monitoring and Adverse Effect Management

Each subject receiving cemiplimab-rwlc, Ad-RTS-hIL-12 or at least one dose of veledimex will be included in the Overall Safety Population (OSP). Parameters used in the safety analysis of all populations will include all laboratory tests, physical examination, imaging scans, and spontaneous reports of AEs reported by subjects. Each patient will be assessed according to the scheduled study procedures and any additional visits as a result of AEs. Cytokine release syndrome will be assessed per the Ziopharm Working Definition (Appendix 1). Other adverse events will be assessed according to the NCI CTCAE v5 criteria.

10.12. Severity Grading and Management of Local Reactions

Injection of agents into tissue carries a potential risk of local reactions that may be characterized as intense immunologic reaction at or near the injection site. Local reactions will be graded according to the NCI CTCAE v5 criteria.

As with all signs and symptoms, events should be recorded and graded as AEs according to NCI CTCAE v.5 criteria. Study stopping rules will not apply to a specific event if it is clearly unrelated to the study treatment.

10.13. Prophylactic Antipyretic and/or Analgesic Administration

The use of antipyretics and/or analgesics is allowed as a prophylactic measure perioperatively. Antipyretics and/or analgesics can be used anytime during study treatment, as indicated and required for patient safety and must be recorded as concomitant medications. Please refer to exclusion criteria for acute clinically significant and/or chronic infections.

NOTE: Since fever and other flu-like symptoms (e.g., chills, body aches, malaise, loss of appetite, etc.) are sometimes experienced following Ad-RTS-hIL-12 + veledimex, it is reasonable for subjects to be administered prophylactic antipyretic and/or analgesic medication prior to Ad-RTS-hIL-12 injection and during the first week after injection at the discretion of the treating physician. The incidence of pyrexia and flu-like symptoms to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

Please refer to Appendix 2 or the recommended regimen for the prophylactic administration of antipyretics and/or analgesics.

11. CONCOMITANT THERAPY

Information on concomitant medications, including all medications, blood products, vitamins, and other supplements, will be collected through the Screening, Treatment, through 90 days after the subject's last dose of any study drug.

Subjects experiencing brain tumor-related symptoms or edema should be treated with corticosteroids as per standard practice. The treating physician should consider the minimum starting steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher starting steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subjects' symptoms, as determined to be safe and appropriate by the treating physician

11.1. Permitted Medications

Subjects may receive standard treatments, including palliative and supportive care for any illness or symptom management during study treatment, including:

- Corticosteroids are permitted for brain tumor related- symptoms. The treating physician should consider the minimum steroid dose for study subjects, if determined that it is safe and appropriate for that individual patient. For study subjects who require a higher steroid dose, efforts should be made to taper steroids to the lowest amount that controls the subject's symptoms, as determined to be safe and appropriate by the treating physician. Physiologic replacement doses of corticosteroids are also permitted (NOTE: Intranasal corticosteroids are excluded due to rapid systemic absorption).
- Antidiarrheal therapy is permitted for study drug induced- diarrhea
- Antiemetics are permitted for study drug- induced- nausea and vomiting

NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

11.2. Prohibited Medications/Therapies

The following medications are prohibited during the study:

- Any other investigational agent or anticancer therapy (chemotherapy, radiotherapy, etc.) while receiving study treatment
- Palliative radiotherapy is not permitted while on study
- Enzyme inducing anti-epileptic drugs (EIAED) are listed in Appendix 3 and are NOT permitted.
- Use of heparin or other anti-coagulation therapy, or acetylsalicylic acid (ASA), or anti-platelet drug within Day -7 to Day 21 should not be used unless necessary to treat a life-threatening illness

NOTE: Care should be given when prescribing medications to avoid the use of drugs that are classified as CYP450 3A4 inducers, inhibitors, or substrates due to interactions with the study drug, unless needed for urgent intervention. All medications should be recorded in the case report form as indicated in the completion guidelines.

12. STUDY PROCEDURES

12.1. Written Informed Consent

The provided written ICF must be signed before any protocol specific procedures and assessments can be performed. A copy of the signed ICF will be given to the subject and a copy should be filed in the medical record. The original ICF should be kept on file with the study reports. Standard of care evaluations performed as part of the subject's routine treatment prior to signing the ICF can be used if they were conducted within the timeframe of the screening period. Refer to Section 12.3.2.1 and Section 17.8 for further information.

12.2. Subject Registration

Centralized registration of subjects will be completed according to a process defined by the sponsor. Eligible subjects are to be enrolled and assigned a unique study identification number before the planned cemiplimab-rwlc dose. Once assigned, a subject's identification number will not be reused.

12.3. Schedule of Assessments and Observations

Screening assessments must be performed within 30 days prior to the Ad-RTS-hIL-12 injection. Any screening tests, exams, or procedures outside of this range may be repeated at the investigator's discretion. All study visits must be completed as described in the protocol while subjects are taking veledimex capsules. Follow-up assessments are allowed a window of ± 7 days. Refer to Table 1 Schedule of Study Procedures for further information.

12.3.1. Study Tests, Exams, and Procedures

12.3.1.1. Demographics, Medical and Cancer History, and Concomitant Medications

Each subject's complete medical history will be documented during screening, including demographic information, relevant medical history, current primary cancer diagnosis, and prior cancer treatments (chemo- and immunotherapies, radiation therapy, surgeries, and any associated residual toxicities). In addition, concomitant medications, including blood products, vitamins, and other supplements received during the screening period (28 days) prior to initiating study treatment will be recorded. Concomitant medications will continue to be collected through 90 days after the subject's last dose of any study drug.

12.3.1.2. Physical Examinations

A complete physical examination will also include a neurological examination.

12.3.1.3. Vital Signs, Height, and Weight

Vital signs will include blood pressure, pulse rate, temperature, and respiration rate. Subject's blood pressure should be monitored regularly, with hydration as needed to prevent hypotension for 72 hours after administration of Ad-RTS-hIL-12, as previously noted. Assessment of vital signs is required prior to injection of Ad-RTS-hIL-12, and prior to veledimex dosing. Height and weight will be measured and recorded according to Schedule of Study Procedures.

12.3.1.4. Karnofsky Performance Status

The Karnofsky Performance Status measures the ability of cancer subjects to perform ordinary tasks. Scores range from 0 to 100 with a higher score meaning that the patient is better able to carry out daily activities. The Karnofsky Performance Status is used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

Subjects must have a Karnofsky Performance Status score of ≥ 70 at the Screening Visit to be included in the study.

12.3.1.5. Pregnancy Testing

Females of childbearing potential will have a serum pregnancy test at the Screening Visit and a urine or serum pregnancy test on Day 0, with a negative pregnancy outcome prior to study drug initiation.

12.3.1.6. Monitoring of Adverse Events

Monitoring and recording of AEs and serious adverse events (SAEs) will be conducted throughout the study. Adverse events and SAEs that occur following the signing of the ICF through 90 days after the subject's last dose of any study drug- must be recorded on the AE eCRF.

Definitions, documentation, and reporting of AEs and SAEs are described in Section 13.

NOTE: Subjects should be instructed to maintain adequate oral hydration while being administered veledimex. Study sites must should monitor subjects for proper hydration and blood pressure should be monitored regularly. Prophylactic antipyretic medications may also be considered. The incidence of adverse events to date has been lower in glioblastoma subjects as compared with breast cancer or melanoma subjects, likely because a lower dose of veledimex is used in glioblastoma.

12.3.1.7. Clinical Laboratory Assessments

The hematology panel comprises a complete blood count (CBC), including white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, mean corpuscular volume (MCV), and platelet count.

The serum chemistry panel comprises the following parameters: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, amylase, blood urea nitrogen (BUN), glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.

The coagulation panel includes activated partial thromboplastin time (aPTT) or partial prothrombin time (PTT) and prothrombin time (PT) or INR. The acute phase reactants include erythrocyte sedimentation rate (ESR) and CRP.

The urinalysis panel (dipstick) includes appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated.

12.3.1.8. MRI

Subjects should be able to undergo MRI scans with contrast agent at screening and during study participation. MRI scans should be available for collection upon sponsor request.

12.3.1.9. Viral Shedding Assessment

Urine, feces, saliva, buccal, and blood samples will be collected and tested for viral replication.

12.3.1.10. Electrocardiogram

A standard, single, 12-lead electrocardiogram (ECG) for evaluation of the QT/QTc interval will be performed.

12.3.2. Schedule of Assessments

The study design is outlined in Synopsis the sequence of assessments is provided in Synopsis Table 1.

12.3.2.1. Screening Period: Assessments

The screening exams, tests, and procedures must be conducted within 30 days prior to dosing with Ad-RTS-hIL-12 + veledimex:

- Signed informed consent form
- Medical/cancer history
- Physical examination (including targeted neurological examination)
- Height and weight
- Vital signs including SpO_2
- ECG
- Karnofsky Performance Status
- History of prior treatments and any associated residual toxicity
- Medications taken during the 28 days prior to consent, in addition to those ongoing during screening
- Adverse events evaluation
- MRI
- Serum pregnancy test
- **Hematology Panel including**: complete blood count (CBC), white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, and platelet count
- **Serum Chemistry Panel including**: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatinine, total bilirubin, total protein, albumin, blood urea nitrogen (BUN), lipase, amylase, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.
- **Coagulation Panel including**: activated partial thromboplastin time (aPTT), international normalized ratio (INR) ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein).
- **Urinalysis Panel (dipstick) including**: appearance, pH, specific gravity, glucose, protein/albumin, presence of blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals, and cells may be done if clinically indicated
- **Thyroid Panel**: free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)
- Viral shedding assessment
- Ad-RTS-hIL-12 neutralizing antibodies sample
- Serum sample for evaluation of cytokine profile
- Blood sample for immune function evaluation
- Subject registration

12.3.2.2. Treatment Period: Day -7

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test (within 72 hours prior to cemiplimab-rwlc dosing)
- Hematology Panel
- Serum Chemistry Panel

- Urinalysis Panel
- Confirm eligibility
- Cemiplimab-rwlc dose

12.3.2.3. Treatment Period: Day 0 (Ad-RTS-hIL-12 injection)

- Physical examination (including neurological examination)
- Karnofsky Performance Status
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel (All labs should be collected prior to the subject's pre-op dose of veledimex)
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- ECG
- Dose of veledimex 3 (± 2) hours prior to resection, on an empty stomach (excluding other medications) AND compliance diary. Intratumoral Ad-RTS-hIL-12 will be administered by freehand injection.
- Serum sample for evaluation of cytokine profile
- Blood sample for immune function evaluation
- Tumor and CSF (if available), will be collected at time of resection

12.3.2.4. Treatment Period: Day 1

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- Blood sample for immune function evaluation
- MRI scan: to be done within 24 hours (a +48hr window is allowed) of Ad-RTS-hIL-12 administration and to be used as the baseline MRI for tumor response assessment
- Serum sample for evaluation of cytokine profile

12.3.2.5. Treatment Period: Day 2

- Once daily veledimex AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel

12.3.2.6. Treatment Period: Day 3

- Once daily veledimex dose AND compliance diary (The Day 3 dose should be held until Day 3 labs have been reviewed. Subjects should not be dosed unless lymphocyte counts, platelet counts, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased. Medical monitor consultation is then advised.)
- Physical Examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Coagulation Panel
- Serum Chemistry Panel
- Urinalysis Panel
- Viral shedding assessment from urine, feces, saliva, buccal and blood samples
- Blood sample for evaluation of serum cytokine profile
- Blood sample for immune function evaluation
- ECG

12.3.2.7. Treatment Period: Days 4 through 6

- Once daily veledimex dose AND compliance diary
- Adverse events evaluation
- Concomitant medications

12.3.2.8. Treatment Period: Day 7

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- ECG
- Blood sample for evaluation of serum cytokine profile
- Blood sample for immune function evaluation
- Serum samples for evaluation of neutralizing antibodies

12.3.2.9. Treatment Period: Day 8-13

- Once daily veledimex dose AND compliance diary

12.3.2.10. Treatment Period: Day 14

- Once daily veledimex dose AND compliance diary
- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel
- Urinalysis Panel
- Thyroid Panel
- ECG
- Blood sample for evaluation of serum cytokine profile
- Blood sample for immune function evaluation
- Ad-RTS-hIL-12 neutralizing antibodies sample
- Viral shedding assessment from urine, feces, saliva, buccal and blood (as blood volume permits) samples

12.3.2.11. Treatment Period: Day 15

- Cemiplimab-rwlc dose

12.3.2.12. Treatment Period: Day 22

- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel

12.3.2.13. Treatment Period: Day 28

- Urine or serum pregnancy test
- Blood sample for evaluation of serum cytokine profile
- Blood sample for immune function evaluation
- Viral shedding assessment from urine, feces, saliva, buccal and blood (as blood volume permits) samples

12.3.2.14. Treatment Period: Day 36

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Weight
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Coagulation Panel

- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose
- Ad-RTS-hIL-12 neutralizing antibodies sample

12.3.2.15. Treatment Period: Day 57

- Adverse events evaluation
- Concomitant medications
- Hematology Panel
- Serum Chemistry Panel
- Thyroid Panel
- Urinalysis Panel
- Cemiplimab-rwlc dose
- MRI

12.3.2.16. Treatment Period: Every 3 weeks after Day 57

- Physical examination (including targeted neurological evaluation)
- Vital signs including SpO_2
- Karnofsky Performance Status
- Adverse events evaluation
- Concomitant medications
- Urine or serum pregnancy test
- Hematology Panel
- Serum Chemistry Panel
- Urinalysis Panel
- Thyroid Panel
- ECG
- Cemiplimab-rwlc dose

12.3.2.17. Treatment Period: Every 8 weeks after Day 57

- MRI scans
- Adverse events evaluation
- Concomitant medications
- Survival Status

12.3.2.18. Unscheduled Visits Collections

In the event of subject termination or an unscheduled visit for a drug-related AE, an unscheduled visit kit should be obtained for cytokines and immunological markers for CSF evaluation, if applicable.
At all visits, concomitant medications, adverse events, and survival status will be documented: Concomitant medications will be monitored and recorded throughout the study. Medications received in the period preceding consent (~28 days), in addition to those ongoing at screening, will be captured in the eCRF. Non-serious events from ICF signature until administration of first study drug that are not study related will be reported as medical history. Concomitant medications and AEs/SAEs must be recorded in the eCRF through 90 days after the last dose of any study drug. Ongoing drug-related AEs should be followed until resolution unless none is expected. New anti-cancer medications should be captured through completion of survival follow-up.

Refer to Synopsis Table 1 for Schedule of Study Procedures.

13. TUMOR RESPONSE ASSESSMENTS

13.1. Tumor Response

The secondary time-to event endpoints of this study include Investigator assessment of PFS, and ORR.

Tumor response will be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). A baseline MRI should be performed within 24 hours (a + 48hr window is allowed) of Ad-RTS-hIL-12 administration. The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines attached in Appendix 4. MRI scans will be collected and stored at the study site and each subject will be evaluated for response by the study investigator. Subjects should be imaged throughout the study using the same method(s) as were used for the screening and baseline MRIs. Independent tumor response assessments, as well as posttreatment tumor biopsies, may occur as available and at the discretion of the investigator. A repeat scan to confirm progression should be completed at 12 weeks (per iRANO) after first documentation of progression. Consideration should be given to performing a diagnostic brain biopsy, which should be performed in accordance with the current iRANO guidelines.

Tumor response will be assessed both locally and at an independent central imaging lab using the iRANO criteria. Copies of all scans will be provided to the independent central imaging lab for determination of tumor response. Final progression determinations will be made by the independent central imaging lab. Every effort should be made to continue study therapy until disease progression is confirmed per iRANO criteria. In the instance that a subject is withdrawn from study treatment due to investigator determined progression, scans should be obtained and provided to the central imaging lab until disease progression is confirmed centrally.

Response is defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bidimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

Tumor response assessments will occur at 8 weeks (Day 57 ± 3 days), and every 8 weeks thereafter for all subjects, including those who may have experienced a dose delay or missed a dose, until the occurrence of confirmed tumor progression, initiation of alternative therapy, or one year, whichever occurs first.

13.2. Tumor Response Evaluation and Pseudo-Progression

The interpretation of MRI findings in subjects with treated brain tumors has an inherent uncertainty that stems from the pseudo-progression phenomena. Pseudo-progression is a term used to describe the appearance of radiographic disease progression due to increase contrast enhancement on MRI without true tumor progression. The increase in contrast enhancement can be influenced by several parameters including differences in radiologic technique, the amount of contrast agent used, the timing of the contrast agent administration relative to the imaging, postsurgical changes, infarction, treatment related inflammation, seizure activity, sub-acute radiation effects, radiation necrosis, and corticosteroid use. Consideration of these factors by experts and clinical experience is likely to identify these subjects. In this study, the first tumor assessment MRI will be done on Day 57 (± 3 days). Imaging assessments will be performed using iRANO criteria.

13.3. Central Imaging Reads

An independent central imaging lab will review reported responses and progression events using iRANO criteria. An Imaging Charter will be developed to provide guidance and consistency.

14. SAFETY ASSESSMENTS

The safety population will include all subjects who have received at least one dose of any of the investigational agents: cemiplimab-rwlc, Ad-RTS-hIL-12 or veledimex.

14.1. Adverse Events and Definitions

14.1.1. Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether considered drug-related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure, and any worsening of a pre-existing condition regardless of causality to study drug. An AE is also known as an adverse experience.

14.1.2. Suspected Adverse Reaction

Any AE for which there is evidence to suggest a causal relationship (reasonable possibility) between the drug and the AE. A suspected adverse reaction implies less certainty about causality than an adverse reaction.

14.1.3. Adverse Reaction

Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

14.1.4. Unexpected Adverse Reaction

Any AE that is (a) not listed in the Reference Safety Information (RSI) of Investigator's Brochure, (b) not listed with the specificity and severity that is being observed, (c) not consistent with the risk information described in the general investigational plan or elsewhere in the current application (in the absence of an investigator brochure), and (d) listed as occurring with a class of drugs, but not specifically mentioned as occurring with the particular drug under investigation.

14.2. Evaluation of Adverse Events

Adverse events include:

- Suspected adverse drug reactions
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities when compared to baseline, in signs, symptoms, clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, extensions of symptoms, or apparently unrelated illnesses

The following considerations apply when identifying an AE:

- Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

- If a constellation of symptoms results in a confirmed diagnosis, the diagnosis (not the symptoms) should be recorded as the AE term.
- If a diagnosis cannot be established, the symptoms should be recorded as the AEs.
- If an ongoing symptom has been included in the medical history, an associated severity grade and frequency should also be documented so that a worsening in severity or frequency of a symptom can be readily identified as an AE.
- Progression of disease is not itself an AE unless the progression of disease is assessed by the investigator as related to the study treatments; however, the presenting sign or symptom of the disease progression should be documented as an AE (e.g., increase in pain). Death due to "progression of disease" within the SAE reporting period (from the signing of the ICF until 90 days after the last dose of any study treatments) should be reported as SAE.

Adverse events will be followed from the next study until resolution or to the end of the follow-up period. AEs that are drug-related should be followed until resolved or no resolution is expected.

14.3. Determination of Seriousness

14.3.1. Serious Adverse Event

An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death during the active study period or within 90 days following study drug administration. In addition, a reported death at any time post-study that is thought to be related to study drug administration.
- Life-threatening AE: An AE that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (i.e., this does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Permanent, persistent, or significant disability: A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization refers to admission of a subject into a hospital for at least a 24-hour stay. Hospitalizations for routine blood transfusions, hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, are not considered SAEs. Emergency room visits that do not result with admission are not considered as SAEs.
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth.
- Important medical event: Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent a life-threatening situation, hospitalization or death.

14.3.2. Non-Serious Adverse Event

An AE that does not fulfill the criteria for a SAE is classified as a non-serious AE.

14.4. Determination of Severity

The severity of AEs will be assessed according to the NCI CTCAE, Version 5. If an AE is not specifically defined in the NCI CTCAE, v5.0, the investigator will determine the severity of an AE based on the following general definitions recommended (National Cancer Institute 2017):

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuation of administration of the study drug.
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuation of administration or reducing the dose of the study drug.
- Life-threatening (Grade 4): The AE requires discontinuing administration of the study drug. The subject is at immediate risk of death.
- Death (Grade 5): The subject dies as a direct result of the complication or condition.

14.5. Determination of Causality

The investigator will use medical consideration to determine the potential relationship of the AE to the study drugs based on his/her clinical judgment. Assessment of causality will be based upon the following:

- Alternative possible causes of the AE, including the subject's underlying disease or comorbid conditions, other drugs, other host, and environmental factors
- The temporal sequence between the exposure to study drug and the AE
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or previously reported toxicity of the study drug or similar drugs
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

Relationship assessments that indicate "Not Related" to investigational product:

- None: The event is related to an etiology other than the investigational product (the alternative etiology must be documented in the study subject's medical record and/or SAE form).
- Unlikely or Remote: The event is unlikely to be related to the investigational product and likely to be related to factors other than investigational product.

Relationship assessments that indicate "Related" to investigational product:

- Possible: There is an association between the event and the administration of the investigational product and there is a plausible mechanism for the event to be related to investigational product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

- Probable: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product and causes other than the investigational product has been ruled out and/or the event re-appeared on re-exposure to the investigational product.

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. AEs may occur due to procedures required during the screening process (e.g., blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

- Protocol-related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol-related: The event is related to an etiology other than the study procedure (the alternative etiology must be documented in the study subject's medical record).

14.6. Documenting Adverse Events

All AEs, including SAEs, are to be accurately recorded on the Adverse Event page of the subject's eCRF from the time the subject signs the informed consent through 90 days after the subject's last dose of any study drug. Each event will be assessed for serious criteria, severity, and causality (Section 14.5). The date of onset, as well as the duration of the event will be recorded. In addition, treatments provided to the subject, actions taken with the study drugs, and the outcome of the AE will also be noted.

14.7. Reporting Serious Adverse Events (SAE), and Adverse Events of Special interest (AESI)

14.7.1. Time Frame for Reporting

All SAEs and AESIs must be reported to the sponsor or sponsor designee within 24 hours of awareness, regardless of initiation of new anticancer therapy including the following:

- Any SAE or AESI experienced by the subject from the signing of informed consent to 90 days after the last dose of any study drug, regardless of relationship to study drug.
- Any SAE or AESI that the investigator becomes aware of, and believes to be study drug-related, that occurs more than 90 days after the subject last received study drug.

All SAEs must be reported to the following fax line within 24 hours of awareness:

[redacted]

Additional data concerning the SAE (e.g., diagnostic test reports, hospital summaries, etc.) must be promptly reported (within 24 hours of receipt) to the sponsor or sponsor's designee, until resolution of the SAE. Should the FDA or National Regulatory Authorities require that the sponsor submit additional data on the event, the investigator will be asked to provide those data to the sponsor in a timely fashion.

14.7.2. Information to be Provided by the Investigator

Within 24 hours of becoming aware of the SAE or subject death, the investigator must notify the sponsor or designee and transmit information to the sponsor or designee. Information (initial and follow-up) should be provided on an electronic and/or paper SAE Report form signed and dated by the investigator. The SAE Report form and copies of source documents with subject identifiers redacted will be transmitted by fax. A hospital discharge summary should be provided if the subject was hospitalized. An SAE report will be considered final once all relevant information has been received and reviewed by the sponsor.

The SAE report form is provided in the investigator study files. Please refer to the investigator study files for instructions on how to complete these forms. The investigator will provide all the following information related to the event:

- Investigator identification
- Subject identification (e.g., subject number, initials, sex, age or date of birth)
- Information regarding study drug administration (e.g. start/stop date, dose, and frequency)
- Day of SAE occurrence documentation on SAE form
- Description of event
- Action taken with the study drugs in relation to the SAE
- Outcome of the SAE

In addition to the above information, the investigator must provide, for each event term, an assessment of:

- Severity/intensity
- Relationship to the study drug (causality assessment)

14.8. Sponsor and Investigator Responsibility for Reporting Adverse Events

All AEs and SAEs will be reported to regulatory authorities, IRBs/IECs, and investigators in accordance with all applicable global laws and regulations. The investigator must submit all Safety Letters received from the sponsor to his/her IRB/IEC per agreements and local requirements. The investigator must keep copies of all safety reports/letters, including correspondence with Ziopharm and the IRB/IEC, in the study file.

14.9. Follow-up Information for Adverse Events

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved, stabilized, returned to baseline, or is otherwise explained by the investigator.

14.9.1. Required Follow-up for Adverse Events

All treatment-emergent AEs-and SAEs will be collected through 90 days after the last dose of any study drug). All the AEs and SAEs should be followed up by the next study visit of the AE/SAE be aware of; all the related AEs and SAEs should be followed up until:

- The event resolves
- The event returns to baseline, if a baseline value is available
- The event stabilizes (following consultation and agreement by the Ziopharm Medical Monitor)
- The event can be attributed to factors other than the study drug or other than study procedure

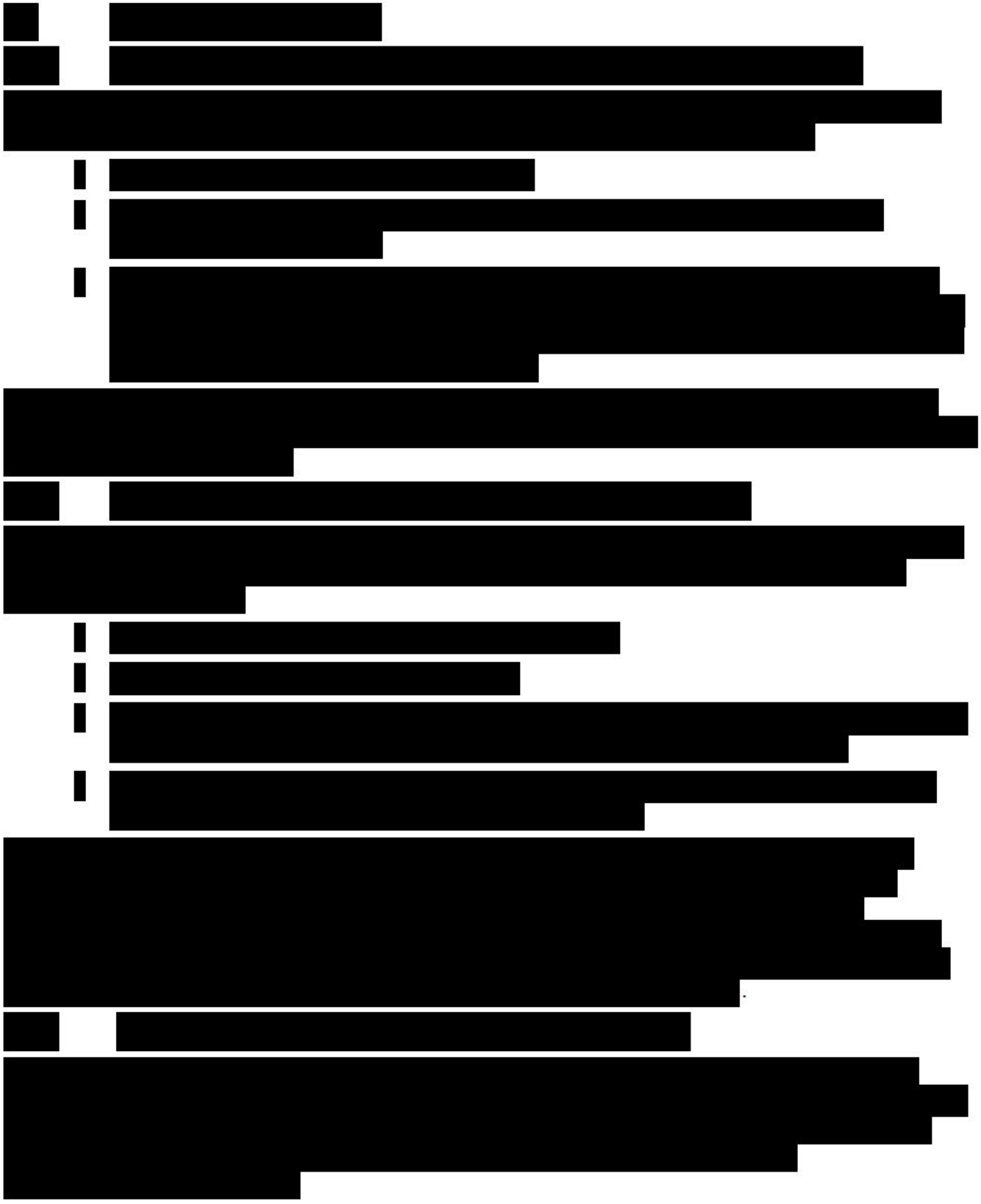
14.10. Pregnancies

Subjects who become pregnant during the study should immediately discontinue participation in the study. The sponsor should be immediately notified.

An initial Pregnancy Report form, and a Pregnancy Outcome Form are to be completed by the investigator or designee. The Pregnancy Report form, and the completion guidelines will be provided in the investigator study files. Please refer to the investigator study files for details on how to complete these forms.

14.11. Overdose

Investigational product overdose of study subject, with or without associated AEs/SAEs, should be reported within 24 hours of awareness to sponsor [redacted] All AEs or SAEs as a result of overdose should be reported as described previously in Section 14.6 and Section 14.7.



[redacted]

16. STATISTICAL METHODS

This is an uncontrolled single arm study to determine whether the intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) is effective based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma. Where applicable, estimates of OS and other surrogate endpoints will be compared with well-matched historical control data to determine whether the estimates obtained in this study will be viewed as promising to support further development of this experimental combination of treatments. All populations for analyses and the types of analyses to be performed will be defined in more detail in the statistical analysis plan (SAP).

16.1. Populations for Analysis

- The safety population will comprise all subjects who have received any of the investigational agents: cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 or any doses of veledimex
- The per protocol population will comprise subjects who have received Day -7 of cemiplimab-rwlc, the injection of Ad-RTS-hIL-12 with at least one post IL-12 dose of veledimex, at least one post IL-12 dose of cemiplimab-rwlc (e.g., Day 15), and who have not had a major protocol violation
- The biomarker-evaluable population will comprise subjects who have adequate biomarker sample(s) at screening (baseline) and at least one follow-up assessment

16.2. Sample Size and Power Calculations

We plan to accrue up to 30 subjects to obtain approximately 25 subjects evaluable for efficacy. This patient population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS.
NOTE: a minimum of 20 subjects undergoing subtotal resection will be required to ensure that sufficient subjects have measurable disease for evaluation of overall response rate per iRANO criteria.

A sample size of up to 30, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19. In addition, a Toxicity boundary based on repeated significance testing provides for a guideline to seriously consider stopping the trial if the number of subjects experiencing a grade 3 or grade 4 toxicity exceeds the proportions below assuming a 30% Toxicity rate is acceptable and 60% would be unacceptable:

Low boundary: 3/5 5/10 8/15 9/20 11/25

High boundary: 3/5 6/10 8/15 10/20 11/25

The method for determination of the Toxicity boundary used the Toxbdry function in the Clinfun R package implementation of repeated significance testing methodology (Ivanova et al. 2005, Jennison and Turnbull 2000). The operating characteristics of the boundary conditions will be specified in a separate statistical analysis plan (SAP).

If the study continues to completion, a sample size of 25 to 30 subjects provides for an estimate of OS at a point in time with (at most) approximately 10% standard error of the estimate assuming the binomial estimation method.

16.3. Endpoints

16.3.1. Primary Endpoint

The primary endpoint for evaluation of efficacy is:

- The estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to years for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

The primary endpoint is to determine the safety and efficacy of intratumoral Adenovirus RheoSwitch Therapeutic System® (RTS) human interleukin-12 (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab-rwlc (Libtayo®) based on the estimate of Overall Survival (OS) when treating subjects with recurrent or progressive glioblastoma.

16.3.2. Secondary Endpoints

Secondary endpoints include:

- Overall survival rate will be determined at 6, 12, 18 and 24 months
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months
- [redacted]

16.4. Safety Evaluation

Safety will be evaluated in using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

Safety assessments will be based on medical review of AE reports and the results of vital signs, physical and neurologic examinations, electrocardiograms (ECGs), clinical laboratory tests, and monitoring the frequency and severity of AEs. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

The reporting period of safety data will be from the date of ICF signature through 90 days after the last dose of any study drug.

16.5. Efficacy Evaluation

- The primary analysis for efficacy is based on the per protocol population.
- Secondary analyses for all efficacy endpoints will be based on the Safety population.

The primary endpoint for evaluation of efficacy is:

- the estimate of the OS which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects.
- The per protocol population will be followed from the first date of treatment up to 24 months for overall survival. Estimates of the single arm hazard rate will be determined and compared with historical control estimates

Secondary endpoints include:

- In addition, the OS rate will be determined for 6, 12, 18 and 24 months using a binomial estimate of subjects surviving for at least the amount of time established by the cutpoint.
- PFS, and rate of pseudo-progression (PSP) of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc will be determined based on the investigator assessment
- ORR of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab-rwlc at 6, 12, 18 and 24 months will be determined based on an investigator assessment.

16.6. Analyses

16.6.1. Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include at least demographic features such as sex, age, and race, as well as disease-specific status and medical history.

Categorical data will be summarized using counts and percentages for a particular category. For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation, minimum, and maximum values will be presented.

16.6.2. Safety Analyses

The safety population will be used to perform safety evaluations for all safety variables.

Safety evaluations will be based on the incidence, intensity, and type of AEs and SAEs. Clinically significant changes in the subjects' physical examinations, vital signs, and ECG evaluations, and abnormal laboratory values will be captured as AEs. Safety will also be assessed based on medical history and prior/concomitant medications.

The safety evaluation period extends from the date the patient signs the ICF until 90 days after the last dose of study drug, unless the patient discontinues the trial due to one of the following reasons:

- Documented progression
- Symptomatic deterioration also denoted as symptomatic progression
- AEs that the investigator feels will subsequently make the subject noncompliant with the protocol planned Schedule of Study Procedures
- Loss to follow-up
- Noncompliance with the protocol
- Other reason not listed above

All treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by number and percent of subjects, and according to relationship to the study drugs, severity, and seriousness. Treatment-emergent is defined as any AE that occurs during or after administration of the first dose of study drug through the evaluation period for safety defined above, regardless of relationship to study drug; or any event that is present at baseline that worsens in intensity or is subsequently considered to be drug related by the investigator. Deaths, SAEs, and AEs resulting in study discontinuation will be listed.

Subjects who discontinue the trial as defined above will be followed for safety up to 90 days after discontinuation and until all safety events that have started during the safety evaluation period are classified as resolved or the end of the study is reached. After the conclusion of the safety evaluation period is triggered by a discontinuation event, the subject continues to be followed only for OS.

Listings of vital signs and physical examination data will be presented by visit.

16.6.3. Overall Survival

OS is defined as the duration of time from the first dose of study drug to the date of death or to the last follow-up contact date if the subject has not died, in which case the subject is censored if still alive up to 2 years from the first dose of study drug received.

16.6.4. Tumor Response Analyses

Investigator assessment of ORR and PFS will be determined according to iRANO criteria. A two-sided confidence interval will be computed for the ORR. PFS and OS will be estimated using the Kaplan-Meier method for appropriately-sized subject groups.

Following completion of the study, best response will be determined for each subject in accordance with iRANO guidelines and the ORR will be presented for all subjects. Where applicable, summary data of PFS, OS, and durability of response will be determined using Kaplan-Meier methodology; otherwise, a listing by-subject will display the data obtained. Two-sided confidence intervals will be computed for the ORR. Descriptive statistics will be performed for different patient populations.

16.6.5. Multi-Center Study

Tumor response and safety data will be presented over all study centers.

16.6.6. Adjustments for Covariates

No adjustments for covariates will be made.

16.6.7. Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

16.6.8. Procedures for Reporting Deviations to Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared prior to database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

17. STUDY MANAGEMENT

17.1. Electronic Case Report Forms and Source Documentation

For each subject, electronic case report forms (eCRFs) and corresponding source records will be maintained at each clinical site. The sponsor or designee will provide the study sites with secure access to and sufficient training on the electronic data capture (EDC) application, to permit site personnel to enter or correct information in the eCRFs for the subjects for whom they are responsible.

The eCRFs should be completed in a timely manner, and every effort should be made to have forms completed and up-to-date in anticipation of a visit by the sponsor's monitor. Specific instructions will be provided to the site. All requested information must be entered on the eCRF in the spaces provided. If an item is not available or is not applicable, it should be documented as such; do not leave a space blank.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Through the EDC application, the investigator must provide formal approval of all subject information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the subjects for whom he/she is responsible. The audit trail entry will show the user's identification information and the date and time of any corrections.

eCRF completion may be delegated to other study personnel; however, such delegation must be documented in writing. If, for any reason, certain data are lacking to complete an individual report form, the investigator will provide a written statement explaining the reasons for the lack of data.

Sponsor or designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

17.2. Good Clinical Practice

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and Ziopharm policies.

17.3. Sponsor Monitoring

After satisfactory receipt of all necessary regulatory paperwork, the sponsor's monitor will arrange that all study material be delivered to the study site at a mutually convenient time. A site initiation visit (SIV) by Ziopharm and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of study protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and study file maintenance.

Throughout the course of the study, the sponsor's monitor will make frequent contact with the investigator, and this will include telephone and/or onsite visits. During these visits, eCRFs will be reviewed for completeness and adherence to protocol. As part of the data audit, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the Medical Monitor. The monitor also will perform drug accountability checks and may periodically request review of the investigator's study file to assure completeness of documentation in all respects of study conduct.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 17.5. The investigator or appointed delegate will receive the sponsor's representative during these onsite visits and will cooperate in providing the documents for inspection and responding to inquiries that may arise as part of this review. The investigator will also permit inspection of the study files by authorized representatives of the FDA.

17.4. Duration of the Study

The duration of this study from the time of initiating subject enrollment until the completion of survival follow-up is anticipated to be approximately 48 months, including 24 months for enrollment and 2 years of further follow-up.

The overall duration is expected to be up to 2 years for an individual subject, including the following:

- Screening period of up to 30 days prior to dosing with Ad-RTS-hIL-12 and veledimex
- Initial Study treatment period of 3 weeks (Days -7 through 14)
- Assessment of safety through the Follow-up Period
- Assessment of tumor response at Day 57 (± 3 days), and every 2 months thereafter until the occurrence of confirmed tumor progression
- Survival status through 2 years

In addition, subjects who discontinue or complete study treatment without objective evidence of disease progression should continue to be followed until confirmed disease progression has been documented. Subjects will be followed for survival status for 2 years after enrollment, except for death or loss to follow-up. The active study period refers to the study period from informed consent through the Initial Follow-up Period.

17.5. Records Retention

Records of drug disposition, eCRFs, and reports of the clinical trial must be maintained by the investigator for a period of at least 2 years following the date on which the test article is approved by FDA for marketing for the purposes that were investigated in the study. If no application is to be filed or if the application is not approved for such indication, the records must be stored for two additional years and then returned to Ziopharm. No records will be destroyed but will be indefinitely stored.

17.6. Institutional Review Board/ Independent Ethics Committee

This protocol and the study ICF must be reviewed and approved by the Institutional Biosafety Committee, where applicable, and IRB/IEC prior to the start of the study, and a copy of the approval letter supplied to Ziopharm. During the study, the investigator shall make timely and accurate reports to the IRB/IEC on study progress at intervals not exceeding 1 year, as well as satisfying any other local IRB/IEC reporting regulations. Copies of all reports to, and correspondence with, the IRB/IEC must be provided to Ziopharm. Further, within 3 months of the completion or early termination of the study, a final report should be made to the IRB/IEC and Ziopharm by the investigator.

All protocol revisions must originate with and be documented by Ziopharm. If the requested revision is an amendment, the investigator must sign it. The FDA will be notified of all revisions by Ziopharm. The investigator must submit the amendment to his/her IRB/IEC for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to Ziopharm.

It is the investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review to Ziopharm representatives as part of the routine study monitoring process.

17.7. Confidentiality and HIPAA

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by Ziopharm, or its representatives, will be identified by subject number and study code.

The written ICF will also explain that, for data verification purposes, authorized representatives of Ziopharm, a regulatory authority (FDA), and/or the IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the subject's medical history.

The written ICF will be accompanied by or include a separate document incorporating United States Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which the subjects authorize the use and disclosure of their Protected Health Information.

17.8. Informed Consent

17.8.1. FDA Informed Consent Requirements

The investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the prospective subject prior to enrollment. The ICF should also indicate that, by signature, the prospective subject or, where appropriate, a legal guardian, permits access to relevant medical records by the sponsor and by representatives of the FDA. If a prospective subject does not understand English, an appropriate translation into his or her primary language must be made available. The investigator or designee will obtain written, informed, and witnessed consent. The prospective subject will have ample time and opportunity to ask questions. The prospective subject will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, the prospective subject will be asked if he/she is willing to sign and personally date a statement of informed consent. Only if the prospective subject voluntarily agrees to sign the informed consent statement and has done so, may he/she enroll into the study. A copy of his/her signed and dated informed consent will be provided to each prospective subject. The signed ICF is to remain in the investigator's file.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or if there is an amendment to the protocol that necessitates a change to the content of the subject's informed consent. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm continuation of his/her participation in the study by his/her signature on the revised ICF, if applicable. Any written ICF and written information must receive IRB/IEC approval/favorable opinion in advance of use.

17.8.2. Subject Informed Consent Form

Ziopharm will provide a sample subject ICF for modification, as appropriate, by the investigator.

18. PROTOCOL APPROVAL PAGE

A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab-rwlc (Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma

Except for a change intended to eliminate an immediate hazard to subjects, the study shall be conducted as described in the approved protocol. All deviations from the protocol will be documented in the eCRF. Any significant deviation or deviation related to dosing or safety evaluation will be reported to Ziopharm and documented in the eCRF.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

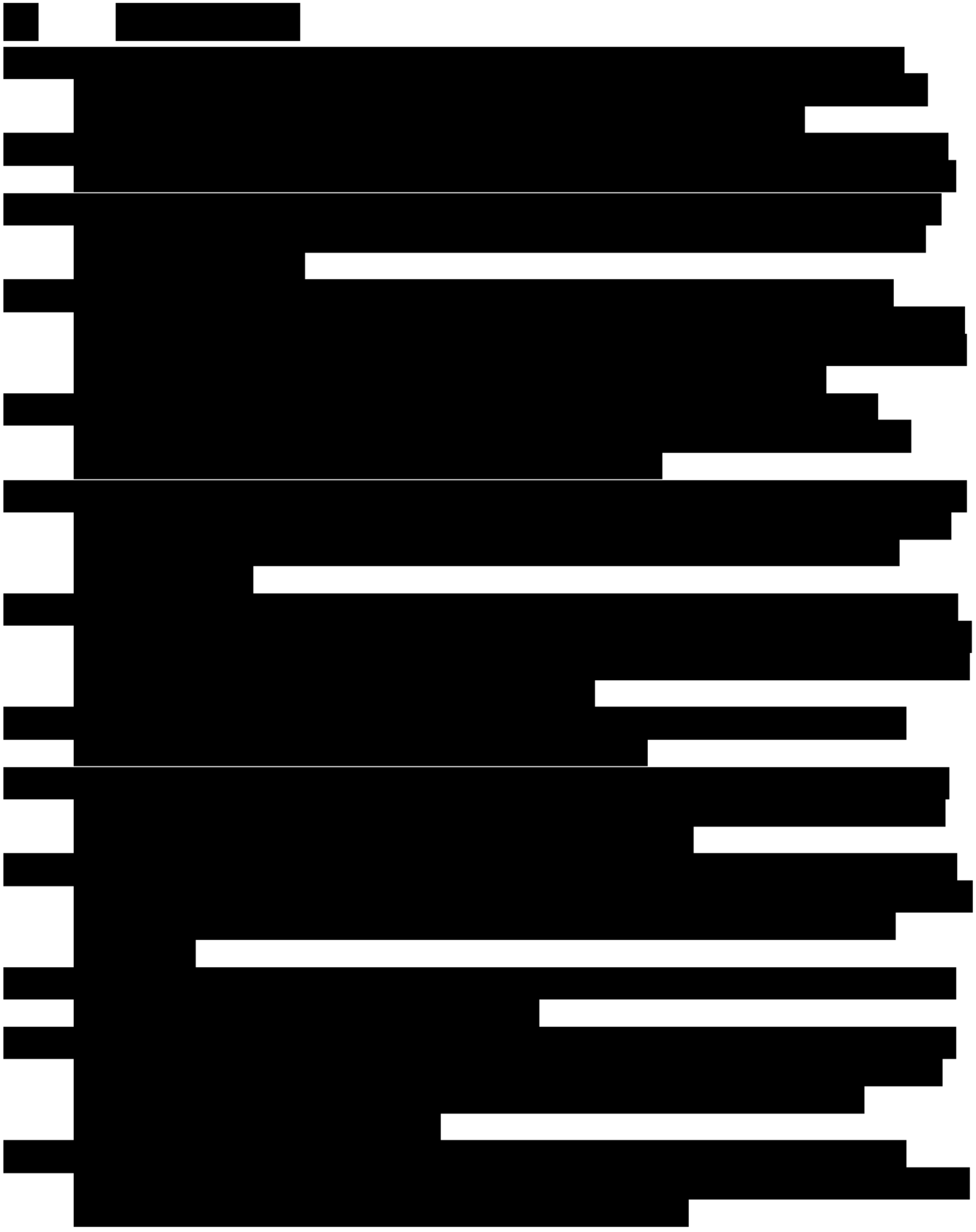
Study Site Institution Name: _____

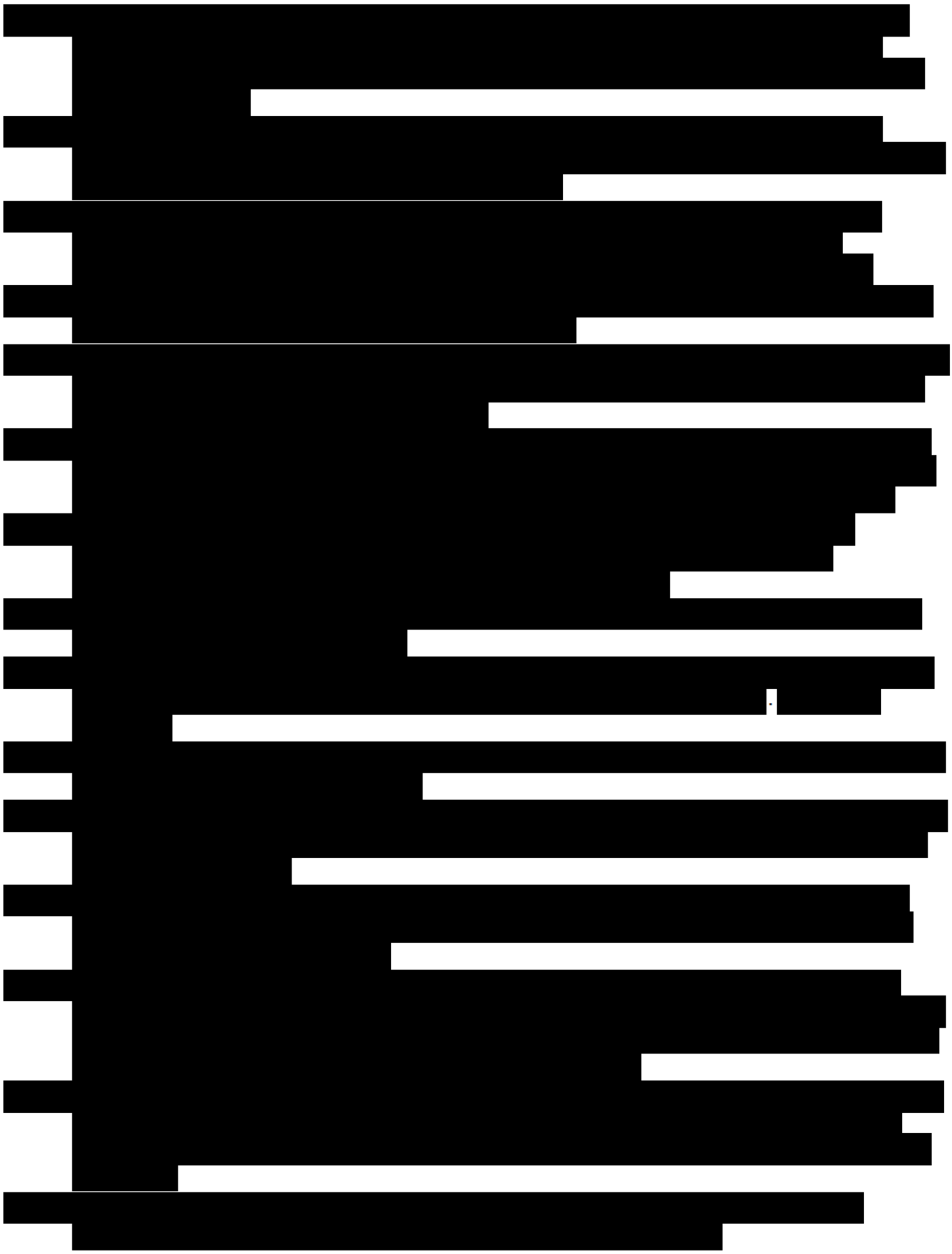
Principal Investigator

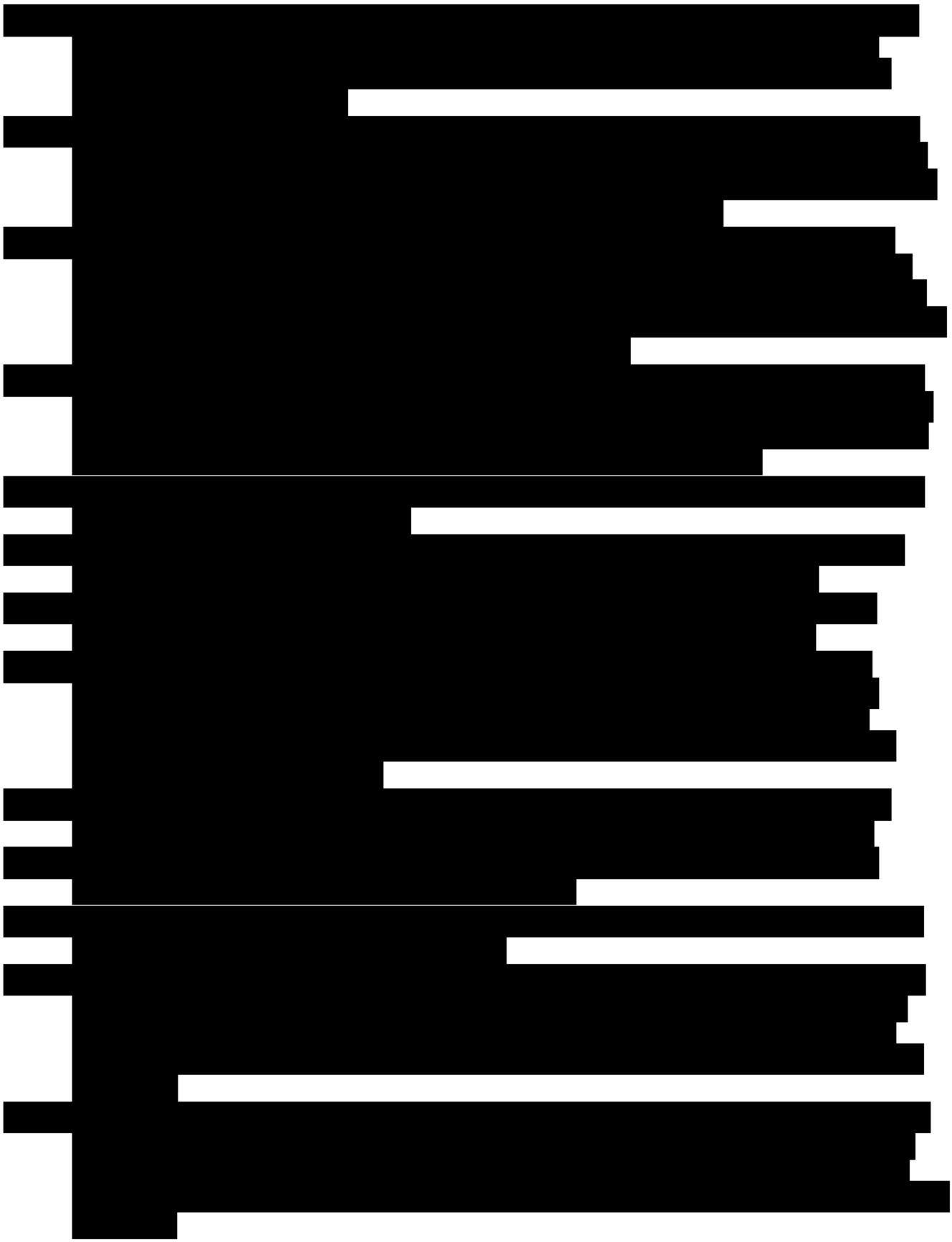
Print Name: _____

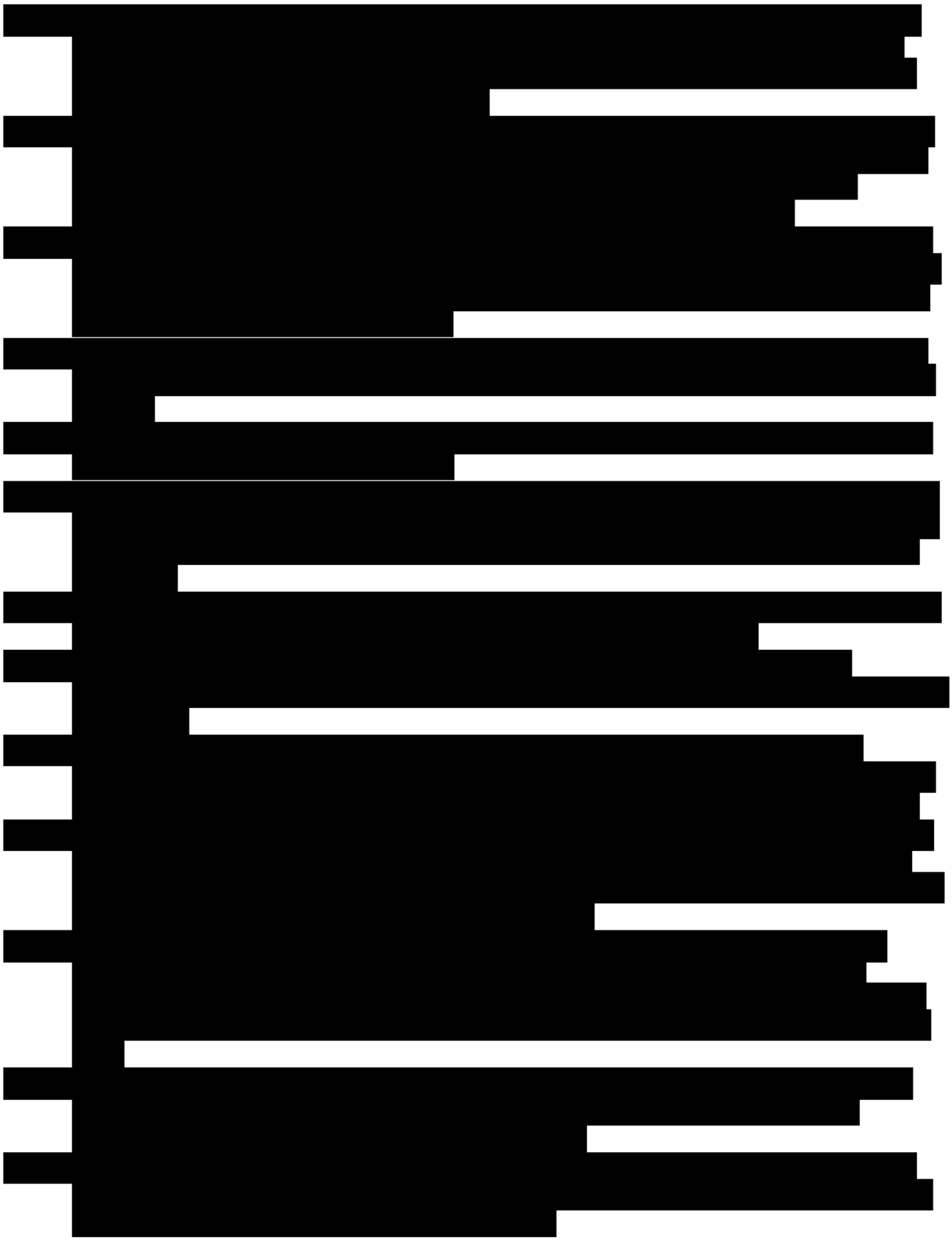
Signature: _____

Date: _____









20. APPENDICES

APPENDIX 1. ZIOPHARM CYTOKINE RELEASE SYNDROME WORKING DEFINITION - AD-RTS-HIL-12 + VELEDIMEX (VERSION 3, 07 JANUARY 2019)

Cytokine release syndrome (CRS) is a multi-faceted immune disorder presenting clinically as a multi-system disorder. Elevated cytokine levels support the diagnosis of CRS in Ad-RTS-hIL-12 gene therapy study along with the grading criteria below:	
Grade 1	**Symptoms that are not life threatening and require symptomatic treatment only, e.g. (<u>any</u> of the following):** General: Influenza-like illness (flu-like symptoms): fever (temperature of 100°F [37.8°C] or greater) and fatigue, malaise, or myalgia Neurological: Grade 1 headache Grade 1 decreased level of consciousness (e.g. somnolence, drowsiness, lethargy, disorientation) GI: Grade 1 nausea or vomiting
Grade 2	**Symptoms that require and respond to moderate interventions and occurrence of <u>any</u> of the following:** **1. Hypotension responsive to fluids or single, low dose vasopressor** **2. Oxygen requirement < 40%** **3. Grade 3 transaminitis (ALT/AST), lymphopenia, or Grade 2 organ toxicities, e.g.:** Hematologic: Grade 2 neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 2 creatinine increase 4. **Other symptoms, e.g.:** General: Grade 3 fever Neurological: Grade 2 decreased level of consciousness (e.g., slow response to stimuli; limiting instrumental activities of daily living) Grade 2 or 3 headache GI: Grade 2 nausea or vomiting
Grade 3	**Symptoms that require and respond to aggressive interventions and occurrence of <u>any</u> of the following:** **1. Hypotension requiring high dose or multiple vasopressors** **2. Oxygen requirement ≥ 40%** **3. Grade 4 transaminitis (ALT/AST), lymphopenia, or Grade 3 organ toxicities, e.g.:** Hematologic: ≥Grade 3 febrile neutropenia, or platelets decrease/thrombocytopenia Renal: Grade 3 creatinine increase Cardiac: Grade 3 arrhythmia, or acute heart failure Pulmonary: Grade 3 pulmonary edema, or dyspnea **4. Other symptoms, e.g.:** Neurological: Grade 3 decreased level of consciousness (e.g. difficult to arouse) Aseptic meningitis GI: Grade 3 nausea or vomiting
Grade 4	**Life-threatening symptoms and occurrence of any of the following:** **1. Requirement for ventilator support** **2. Grade 4 organ toxicities (excluding lymphopenia and asymptotic elevated transaminitis), e.g.:** Renal: Renal failure and dialysis indicated Cardiac: Cardiac arrest Pulmonary: Respiratory failure Neurological: Coma
Grade 5	**Death**

APPENDIX 2. RECOMMENDED REGIMEN FOR ANTIPYRETIC AND/OR ANALGESIC PROPHYLAXIS

Recombinant adenoviral vectors have the potential to elicit potent cellular and humoral immune responses. While the mechanism responsible for these effects is poorly understood, transient low-grade fevers are common after systemic rAD vector administration* and temperatures up to 104° F with chills and generalized malaise have been observed with treatment. Because low-grade fever is very likely to occur, prophylaxis with acetaminophen is strongly recommended.

Each site should follow its institutional protocol for the administration of acetaminophen. Acetaminophen is available without a prescription in 325 mg or 500 mg tablets. Common brand names of acetaminophen include Aspirin Free Anacin®, FeverAll®, Genapap®, Mapap®, NeoPAP®, Panadol®, Tempra®, and Tylenol®.

In general, fever can be adequately prophylaxed or treated with acetaminophen. If a fever occurs despite prophylactic medication or does not respond to usual doses of acetaminophen, then a combination of both acetaminophen and ibuprofen may be considered. Alternating doses of ibuprofen with acetaminophen may effectively control fever while preventing accidental overdose of acetaminophen. Acetaminophen is typically effective for controlling central fevers whereas ibuprofen is more potent as a peripheral analgesic/ anti-inflammatory medication. Ibuprofen is available without a prescription at a dosage of 200 mg and by prescription in 400, 600 or 800 mg tablets or capsules. Common brand names of ibuprofen include Advil®, ElixSure®, Ibuprom®, Ibutab®, Motrin® and Tab-Profen®.

Adverse events are uncommon although may be serious as some individuals are allergic to these medications. Additionally, overdoses of acetaminophen may cause liver failure. Therefore, subjects with liver disease and chronic alcohol users should avoid acetaminophen. Ibuprofen is excreted by the kidneys so should be avoided in patients with renal insufficiency, though most would be excluded from enrollment. High dose ibuprofen also may increase the risk of blood clots, stroke, heart attack, and gastrointestinal bleeding, and being a potent anti-inflammatory agent could reduce the efficacy of the investigational controlled IL-12 therapy.

APPENDIX 3. PROHIBITED ENZYME-INDUCING AND NON-ENZYME-INDUCING ANTIEPILEPTIC DRUGS

Enzyme-inducing Antiepileptic Drugs	Non-Enzyme-inducing Antiepileptic Drugs
Cerebyx® (fosphenytoin)	Zarontin® (ethosuximide) ONFI® (clobazam)
Dilantin® (phenytoin)	
Gabitril® (tiagabine)	
Luminal®, Solfoton® (phenobarbital)	
Nembutal® (pentobarbital)	
Trileptal® (oxacarbazepine)	
Tegretol® (carbamazepine)	
Topamax® (topiramate)	

APPENDIX 4. IMMUNOTHERAPY RESPONSE ASSESSMENT IN NEURO-ONCOLOGY: A REPORT OF THE RANO WORKING GROUP

Immunotherapy Response Assessment in Neuro-Oncology: A Report of the RANO Working Group