1. TITLE PAGE

STUDY PROTOCOL

ATI001-103

Protocol Title	A Phase I/II Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects
Protocol Number:	ATI001-103
Phase:	Phase I/II
Date of Protocol:	Amendment 2: 30Oct2019 Amendment 1: 25Sep2017 Original: 04April2017
Sponsor:	Ziopharm Oncology, Inc. [redacted]
Medical Monitor:	[redacted]
Safety Reporting:	[redacted]

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ad-RTS-hIL-12	[redacted]
Ad-RTS-mIL-12	[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
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CRF	case report form
CRP	C-reactive protein
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
CYP450	cytochrome p450
DIPG	diffuse intrinsic pontine glioma
DLT	dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIAED	antiepileptic drugs
EMCV	encephalomyocarditis virus
ESP	Evaluable Safety Population
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
Gal4-EcR	Fusion protein between Gal4 DNA binding domain and ecdysone receptor ligand binding domain

Abbreviation or Specialist Term	Explanation
GalRE/P	Gal4 responsive promoter
GCP	Good Clinical Practice
hIL-12	human interleukin-12
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
INR	international normalized ratio
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
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
ORR	objective response rate
OS	overall survival
OSP	Overall Safety Population
PTT	partial thromboplastin time
PFS	progression -free survival
PI	Principal Investigator
PK	pharmacokinetic(s)
PKP	Pharmacokinetics Population
PO	oral(ly)
polyA	polyadenylation signal
PUbC	ubiquitin C promoter

Abbreviation or Specialist Term	Explanation
QD	once daily
rAd	recombinant adenovirus
RANO	Response Assessment for Neuro-Oncology
RBC	red blood cell
rhIL-12	recombinant human IL-12
RTS	[redacted]
RXR	retinoid X receptor
SAE	serious adverse event
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
Th1	T helper cell type 1
ULN	upper limit of normal
Vp	viral particles
VP16-RXR	fusion between VP16 transcriptional activation domain and a chimeric RXR
WBC	white blood cell

4. CLINICAL PROTOCOL SUMMARY

Title of Study:

A Phase I/II Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects

Protocol Number:

ATI001-103

Clinical Phase:

Phase I/II

Investigational Product:

Adenovirus-[redacted] (RTS)-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, which is activated in the presence of the orally (PO) administered 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 depends on the dose and frequency of veledimex administration, the expression of hIL-12 can be modulated and turned on and off by the veledimex dose and schedule.

Primary Objective:

- Phase I/II: To determine the safety and tolerability of intratumoral Ad-RTS-hIL-12 and varying veledimex doses administered PO in pediatric brain tumor subjects (supratentorial and/or DIPG)

Secondary Objectives:

- Phase I: To determine the recommended Phase II veledimex dose in pediatric brain tumor subjects when given with intratumoral Ad-RTS-hIL-12 (supratentorial and/or DIPG)
- Phase I/II: To determine the pharmacokinetics (PK) of veledimex in subjects treated with Ad-RTS-hIL-12 + veledimex (supratentorial and/or DIPG)
- Phase I: To determine the veledimex concentration ratio between the brain tumor and blood in subjects treated with Ad-RTS-hIL-12 + veledimex (Arm 1 only)
- [redacted]
- Phase I/II: To determine investigator assessment of response, including tumor objective response rate (ORR) and progression-free survival (PFS) of subjects treated with Ad-RTS-hIL-12 + veledimex (supratentorial and/or DIPG)
- Phase I/II: To determine overall survival (OS) of subjects treated with Ad-RTS-hIL-12 + veledimex (supratentorial and/or DIPG)

[redacted]

- [redacted]

Study Design:

This is a multicenter, open-label study, of Ad-RTS-hIL-12 administered by intratumoral injection and veledimex PO doses in pediatric brain tumor subjects, starting with phase I dose escalation cohorts. After the completion of a phase I dose escalation cohort in Arm 2, the SRC may elect to expand that cohort by up to 30 DIPG patients, which will be considered the Phase II component of the study. This study will investigate one fixed intratumoral Ad-RTS-hIL-12 dose [redacted] and escalating veledimex doses to determine the safe and tolerable Phase II pediatric dose based on the safety profiles observed in the presence of variable corticosteroid exposure. The study schema is outlined in Figure 4 (Arm 1) and Figure 5 (Arm 2).

This study is divided into three periods: the Screening Period, the Treatment Period, and the Follow-up Period (Initial and Long Term). After the informed consent form (ICF) or subject assent, as applicable, is signed, subjects will enter the Screening Period to assess eligibility. Eligible subjects will be stratified into one of two arms, according to diagnosis. Arm 1 is open to pediatric brain tumor subjects who are scheduled for a standard-of-care craniotomy and tumor resection, with the exclusion of subjects with diffuse intrinsic pontine glioma (DIPG). Arm 2 is open only to subjects with DIPG who are post prior standard focal radiotherapy (≥ 2 weeks and ≤ 10 weeks). Arm 1 subjects will receive one veledimex dose before the resection procedure. Samples (tumor, blood, and cerebrospinal fluid [CSF] [if available]) will be collected as described below. After Ad-RTS-hIL-12 intratumoral injection, Arm 1 subjects will continue administration of veledimex PO daily for 14 days, for a total of 15 doses of veledimex. Arm 2 subjects will receive a single Ad-RTS-hIL-12 [redacted]) dose by stereotactic injection and will receive veledimex PO daily for 14 days.

Arm 1: Pediatric brain tumor subjects scheduled for craniotomy and tumor resection (excluding DIPG)

Subjects with a clinical indication for tumor resection will receive veledimex 3 (± 2) hours before the craniotomy procedure, on an empty stomach (excluding other medications). At the time of tumor resection, brain tumor, blood, and CSF (if available) samples will be collected to determine the veledimex concentration ratio between brain tumor, blood, and CSF (if available).

Immediately after tumor resection, Ad-RTS-hIL-12 [redacted] will be administered by [redacted] injection into approximately two sites within the residual tumor for a total volume of 0.1 mL. The total amount delivered to each site will be recorded in the electronic case report form (eCRF). If less than the planned total injected volume is administered, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations. The day of Ad-RTS-hIL-12 administration is designated as Day 0. When available, an intra-operative magnetic resonance imaging (MRI) scan should be performed to guide the Ad-RTS-hIL-12 injection to areas of contrast-enhancing tumor tissue.

After the Ad-RTS-hIL-12 injection, veledimex will be administered PO once daily (QD) for 14 days. The first postresection veledimex dose is to be given on Day 1, preferably in the morning and within approximately 30 minutes of completion of a regular meal. There should be a minimum of 10 hours between veledimex doses. Subsequent veledimex doses (Days 2 to 14) are to be taken at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal.

Arm 2: Subjects with DIPG who will NOT undergo tumor resection

Subjects with DIPG who will not undergo tumor resection will receive Ad-RTS-hIL-12 by standard stereotactic surgery on Day 0. At the time of stereotactic surgery, prior to Ad-RTS-hIL-12 injection, brain tumor biopsy and blood samples will be collected.

Ad-RTS-hIL-12 [redacted] will be administered by stereotactic injection into the intratumoral site. The day of Ad-RTS-hIL-12 administration is designated as Day 0. The total amount delivered to each site will be recorded in the eCRF. If less than the planned total injected volume is administered, 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 PO QD for 14 days. The first veledimex dose is to be given on Day 1, preferably in the morning and within approximately 30 minutes of completion of a regular meal. Subsequent veledimex doses (Days 2 to 14) are to be taken QD and at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal. There should be a minimum of 10 hours between veledimex doses.

Cohorts:

Arm 1: This study has been modified to explore one veledimex dose in Arm 1: 10 mg.

Arm 2: This study is designed to explore two veledimex doses in Arm 2: 10 mg and 20 mg. Subject enrollment and veledimex dose escalation will proceed according to a standard 3+3 design. The first cohort will receive 10 mg veledimex followed by the second cohort receiving 20 mg veledimex.

Arm 1 and Arm 2 subjects may exhibit different safety and tolerability profiles. The 3+3 standard study design has been modified to independently evaluate the two arms separately.

The study arms and assigned doses will be divided into three cohorts as shown below:

Arm	Cohort	Procedure	Veledimex Dose[a] Assigned
1	1	Craniotomy	10 mg
2	3[b]	Stereotactic	10 mg
2	4	Stereotactic	20 mg

[a] Doses are BSA-adjusted doses
[b] Arm 1 Cohort 2 was removed in Protocol Amendment 2. The SRC reviewed the safety profile of Arm 1 Cohort 1 and determined it was appropriate to move forward with Arm 1, Cohort 2 and Arm 2, Cohort 1, however due to issues with enrollment of supratentorial patients, it was determined not to proceed with Cohort 2.
Note: After the completion of a phase I dose escalation cohort in Arm 2, the SRC may elect to expand that cohort by up to 30 DIPG patients, which will be considered the Phase II component of study.

Each cohort will consist of subjects ≤ 21 years-of-age who meet eligibility criteria.

Each subject in each dose escalation cohort will be monitored for 28 days after Ad-RTS-hIL-12 injection before additional subjects are enrolled in the same cohort. The evaluation period for DLT is 28 days after Ad-RTS-hIL-12 injection (Day 0 to Day 28).

Determination of safety and the recommendation to expand the current dose cohort, dose escalate, or discontinue the investigation, will occur after all dosed subjects in a cohort have been evaluated for at least 28 days after Ad-RTS-hIL-12 injection, as described in Section 7.3.

Number of Centers:

Approximately 3 to 5 centers

Number of Subjects (planned):

Approximately 45 subjects may be enrolled.

Study Population:

The eligible study population includes pediatric subjects with a) recurrent or refractory supratentorial brain tumors, not in direct continuity with the ventricular system, that are unresponsive to conventional treatment or for which there is no alternative curative therapy (Arm 1) and b) non-disseminated DIPG post prior standard focal radiotherapy and for which a biopsy has previously been obtained (access to results required; access to tissue preferred) (Arm 2).

Inclusion Criteria:

1. Male or female subjects ≤ 21 years-of-age with the demonstrated ability to swallow capsules whole and who are willing to provide access to previously obtained biopsy results
2. Provision of written informed consent and assent, when applicable, for tumor resection, stereotactic surgery, tumor biopsy, sample collection, and/or treatment with study drug prior to undergoing any study-specific procedures
3. **Arm 1**: Evidence of recurrent or progressive supratentorial tumor, which has shown a > 25% increase in bi-dimensional measurements by MRI or is refractory with significant neuro-deterioration that is not otherwise explained with no known curative therapy, not in direct continuity with the ventricular system (e.g., there is physical separation between the tumor and ventricle, the tumor does not open directly into the ventricular system).

   Arm 2: Clinical presentation of DIPG and compatible MRI with approximately 2/3 of the pons included and without evidence of dissemination. Subjects should be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (*i.e.*, dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m^2/day).
4. 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. Targeted agents, including small-molecular tyrosine kinase inhibitors: 2 weeks
   b. Other cytotoxic agents: 3 weeks
   c. Nitrosoureas: 6 weeks
   d. Monoclonal antibody immunotherapies (*e.g.*, PD-1, CTLA-4): 6 weeks
   e. Vaccine-based and/or viral therapy: 3 months
5. On a stable or decreasing dose of dexamethasone for the previous 7 days
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment

7. Have age-appropriate functional performance:
    a. Lansky score ≥ 40 (Appendix 1) or
    b. Karnofsky score > 50 (Appendix 2) or
    c. Eastern Cooperative Oncology Group (ECOG) score ≤ 2 (Appendix 3)
8. Have adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
    a. Hemoglobin ≥ 8 g/L
    b. Absolute lymphocyte count ≥ 500/mm^3
    c. Absolute neutrophil count ≥ 1000/mm^3
    d. Platelets ≥ 100,000/mm^3 (untransfused [> 5 days] without growth factors)
    e. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) for age
    f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN for age
    g. Total bilirubin < 1.5 x ULN for age
    h. International normalized ratio (INR) and activated thromboplastin time within normal institutional limits
9. Male and female subjects of childbearing potential must agree to use a highly reliable method of birth control (expected failure rate < 1% per year) from the Screening visit through 28 days after the last dose of study drug. Women of childbearing potential must have a negative pregnancy test at screening.

Exclusion Criteria:

1. Radiotherapy treatment prior to the first veledimex dose:
    a. Focal radiation ≤ 4 weeks
    b. Whole-brain radiation ≤ 6 weeks
    c. Cranio-spinal radiation ≤ 12 weeks

    Note: Subjects in Arm 2 (*i.e.*, with DIPG) must be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m^2/day) per Inclusion Criterion 3 above.
2. Subjects with clinically significant increased intracranial pressure (*e.g.*, impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
3. Subjects whose body surface area (BSA) would expose them to < 75% or > 125% of the target dose per the provided dosing table
4. Known immunosuppressive disease, autoimmune condition, and/or chronic viral infection (*e.g.*, human immunodeficiency virus [HIV], hepatitis)
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 (EIAEDs) within 7 days prior to the first dose of study drug. See Appendix 4 for prohibited and permitted antiepileptic drugs.
7. Other concurrent clinically active malignant disease, requiring treatment

8. Nursing or pregnant females
9. Prior exposure to veledimex
10. Use of medications that induce, inhibit, or are substrates of cytochrome p450 (CYP450) 3A4 within 7 days prior to veledimex dosing without consultation with the Medical Monitor
11. Use of heparin or acetylsalicylic acid (ASA) without consultation with the Medical Monitor
    a. The use of systemic heparinization, or any ASA containing medications, is prohibited during active dosing with veledimex. Prophylactic heparin SC, per institutional protocol, or heparin when used for maintaining patency of an access port of a PICC line is permitted.
12. Presence of any contraindication for a neurosurgical procedure
13. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator as agreed to by the Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol

Study Oversight for Safety Evaluation:

The first level of safety oversight will occur through the site Investigator in conjunction with the Medical Monitor. The site Investigator will communicate with the Medical Monitor during the active dosing period for all subjects on a daily basis regarding clinical status and laboratory values, prior to the patient receiving the daily dose of veledimex, and additionally as clinically indicated.

A formal Safety Review Committee (SRC), comprised of the study Investigators, the Medical Monitor, and other appropriate Sponsor representatives, will provide the overall safety oversight. Additional external medical and scientific experts may also be invited to participate in the reviews, as needed. A separate charter will outline the SRC activities. Briefly, the SRC will evaluate subject safety within each cohort. If no significant safety events occur with the first subject of each cohort, the second and third subjects will be enrolled and treated. If a significant safety event occurs with the first subject, the SRC will convene to evaluate the safety event(s) and to make a recommendation and decision on the enrollment of the second and third subjects in the same cohort.

Upon completion of each cohort, the SRC will meet to review the data collected to determine next steps as described in Section 7.3. Enrollment in Cohort 4 (with the 20 mg assigned veledimex dose) will not commence until the SRC has determined that dosing at the lower level, Cohort 3, did not result in DLTs that would preclude dose escalation.

In addition to recommending the opening of Arm 2 Cohort 3, or dose escalation to Cohort 4, the SRC may also determine if the study should proceed with the Phase II portion (an expansion of an Arm 2 cohort). In the event that the SRC determines that escalation and/or expansion is not warranted, a decision will be made about stopping the investigation. At the discretion of the SRC, the investigation may be continued at a lower dose. Dose escalation, cohort expansion, and de-escalation rules will be followed as defined in Section 7.3 and study stopping rules will be followed as defined in Section 7.10.

Study Drug Dose and Mode of Administration:

Ad-RTS-hIL-12:

Ad-RTS-hIL-12 will be administered by either [redacted] injection into residual tumor sites immediately after tumor resection (Arm 1) or by stereotactic injection into the intratumoral site (Arm 2).

Veledimex:

Veledimex will be administered PO. There should be a minimum of 10 hours between veledimex doses.

Arm 1 (Cohort 1) will receive veledimex 3 (± 2) hours before the planned craniotomy and will continue veledimex dosing after Ad-RTS-hIL-12 administration for an additional 14 days. Subsequent veledimex doses (Days 1 to 14) are to be taken QD and at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal.

Arm 2 (Cohorts 3 and 4) will receive veledimex only after Ad-RTS-hIL-12 administration for 14 days. The first veledimex dose is to be given on Day 1, preferably in the morning and within approximately 30 minutes of completion of a regular meal. Subsequent veledimex doses (Days 2 to 14) are to be taken QD and at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal.

Based on the planned Phase III dose (20 mg [approximately 10.6 mg/m^2]) in the adult population, this study will explore the following BSA-adjusted veledimex doses given after Ad-RTS-hIL-12 [redacted] administration. The starting dose in Cohort 1 will be 10 mg, which is approximately 5.3 mg/m^2. The actual administered dose will depend on the subject's BSA and available capsule sizes. Because veledimex is an oral agent and is supplied in fixed capsule sizes (5 mg and 20 mg), the actual administered dose is based on a subject's BSA and is bound by the rounding constraints set by 5 mg. The Sponsor developed a BSA-adjusted dosing algorithm designed to enable dosing within 25% of the target mg/m^2 dose.

If a subject's BSA would expose the subject to < 75% or > 125% of the target assigned dose, the actual administered dose will be modified to ensure that the target mg/m^2 dose is achieved. Minimum BSA restrictions for enrollment must be met in order for a subject to be appropriately dosed. Potential subjects whose BSAs do not have a correlated administered dose may be enrolled at the discretion of the Investigator and the Medical Monitor, but will not be considered in the assessment of the recommended Phase II pediatric dose. Dosing of these subjects can only commence once the cohort has been reviewed by the SRC and determined that the dosing at the specified level (10 mg or 20 mg) is appropriate for escalation or as the recommended Phase II pediatric dose. These subjects will be analyzed separately.

The dosing table illustrates this algorithm and captures the BSA-adjusted actual administered dose that subjects would receive at assigned dose levels based on a minimum capsule size of 5 mg.

Cohort	Target Dose (mg/m^2)	Min BSA (m^2)	Min BSA Target Dose (mg/m^2)	Percentage of Expected Dose (%)	Max BSA (m^2)	Max BSA Target Dose (mg/m^2)	Percentage of Expected Dose (%)	Actual Dose [a] (mg)
10 mg	5.3	0.5	10	189%	0.75	6.7	126%	5 mg[b]
10 mg	5.3	0.76	6.6	124%	1.26	4.0	75%	5 mg
10 mg	5.3	1.27	3.9	74%	1.5	3.3	63%	5 mg
10 mg	5.3	1.27	7.9	149%	1.5	6.7	126%	10 mg[b]
10 mg	5.3	1.51	6.6	125%	2.53	4.0	75%	10 mg
Cohort	Target Dose (mg)	Min BSA (m^2)	Min BSA Target Dose (mg)	Percentage of Expected Dose (%)	Max BSA (m^2)	Max BSA Target Dose (mg)	Percentage of Expected Dose (%)	Actual Dose [a] (mg)
20 mg	10.6	0.5	10	94%	0.63	7.9	75%	5 mg
20 mg	10.6	0.64	7.8	74%	0.75	6.7	63%	5 mg
20 mg	10.6	0.64	15.6	147%	0.75	13.3	126%	10 mg[b]
20 mg	10.6	0.76	13.2	124%	1.25	8.0	75%	10 mg
20 mg	10.6	1.26	11.9	112%	1.87	8.0	75%	15 mg
20 mg	10.6	1.88	10.6	100%	2.53	7.9	75%	20 mg

[a] The actual dose is ± 25% of the target dose.
[b] Subjects in this BSA range may be dosed, as above, at the discretion of the Investigator and the Medical Monitor.

Expansion Cohort(s) (Phase II Portion):

Expansion cohort(s) are prospectively planned in this study, in Arm 2, at the discretion of the SRC.

Each subject in each dose escalation cohort (3+3 standard design) will be monitored for 28 days before subsequent subjects are enrolled. The SRC will convene after the third and/or final subject in each cohort completes the 28-day DLT evaluation period and will make a recommendation regarding expanding the current cohort by up to 30 additional subjects (Phase II component), opening of the next cohort/dose escalating, dose de-escalating, or discontinuing the investigation.

If the SRC recommends expanding the current cohort, a 28-day review period may not be required between each patient. Based on the safety profile of the current cohort, the SRC will make a determination related to the waiting period.

The SRC will determine if/when the MTD is met and may recommend cohort expansion at that dose.

Dose escalation, cohort expansion, and de-escalation rules will be followed as defined in Section 7.3 and study stopping rules will be followed as defined in Section 7.10.

Dose Escalation/Cohort Expansion:

Each subject in each dose escalation cohort (3+3 standard design) will be monitored for 28 days before subsequent subjects are enrolled. The SRC will convene after the final subject in Cohort 1 completes the 28-day DLT evaluation period. The SRC will make a recommendation regarding:

- Opening enrollment of Cohort 3
- Discontinuing the investigation

The SRC will convene once the third and/or final subject in Cohort 3 completes the 28-day DLT evaluation period. The SRC will make a recommendation regarding:

- Expansion of Cohort 3 (Phase II portion)
- Opening enrollment of Cohort 4
- Discontinuing the investigation

The SRC will convene once the third and/or final subject in Cohort 4 completes the 28-day DLT evaluation period. Cohorts 1 and 3 will be reviewed independently by the SRC. The SRC will make a recommendation regarding:

- Expansion of Cohort 4 (Phase II portion)
- Discontinuing the investigation

In addition to recommending dose escalation, cohort expansion, or discontinuation of treatment, as noted above, the SRC may recommend dose de-escalation at any point based on safety review.

Dose De-Escalation:

If it is determined that dose escalation or cohort expansion should not proceed, dose de-escalation may be undertaken and the SRC will consider de-escalating the veledimex dose as follows:

- De-escalation by increments of 5 mg from the cohort in which two or more DLTs were observed (*e.g.*, 15 mg, de-escalated from 20 mg)

If there are two or more DLTs in the dose de-escalation cohort, the SRC will consider de-escalating the veledimex dose by an additional increment of 5 mg (*e.g.*, 5 mg down from 10 mg) or declaring a previously studied dose level the recommended Phase II pediatric dose.

Dose Schedule:

Ad-RTS-hIL-12: intratumoral [redacted] administered on Day 0 for all cohorts
Veledimex:

- Cohort 1: 10 mg veledimex (adjusted for BSA) QD on Days 0 to 14
- Cohort 3: 10 mg veledimex (adjusted for BSA) QD on Days 1 to 14
- Cohort 4: 20 mg veledimex (adjusted for BSA) QD on Days 1 to 14

Definition of DLT:

An event, occurring within the first 28 days (*i.e.*, Day 0 to Day 28) that meets at least one of the following conditions:

- Any local reaction that requires operative intervention and is felt to be attributable to study drug
- Any local reaction that has life-threatening consequences requiring urgent intervention or results in death and is felt to be attributable to study drug

- Any Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and lasts ≥ 3 days
- Nausea and vomiting will not be considered a DLT unless at least Grade 3 and refractory to antiemetics
- Grade 3 or higher thrombocytopenia (< 50,000/mm^3) at least possibly related to study drug
- Any Grade 4 hematologic toxicity (except thrombocytopenia) that is at least possibly related to study drug and lasts ≥ 5 days

Dose escalation may be stopped by the Medical Monitor before a DLT is observed, but where the observed toxicities indicate the strong likelihood of unacceptable toxicity at higher doses.

Note: Diagnostic brain tumor biopsy is not considered a DLT. Seizures, headaches, fatigue and cerebral or pontine edema are commonly observed in this population and will be recorded according to the grade of toxicity but will not be considered a DLT unless a relationship to study drug is deemed to be the main contributory factor. Transient neurological changes are expected in Arm 2 and will not be considered a DLT unless they last > 10 days.

Expansion cohorts will be allowed in Arm 2 if deemed appropriate by the SRC. If an expansion cohort is implemented, the veledimex dose may be delayed or reduced for individual subjects in the event of toxicity. If ≥ 33% of subjects in the expansion cohort experience DLTs, using the definition in the dose-escalation phase, additional subjects may be enrolled at the next lower dose tested in the dose-escalation phase or at an intermediate dose, as recommended by the SRC. All DLTs must be reported to the Sponsor within 24 hours of Investigator/site awareness.

Definition of Recommended Phase II Pediatric Dose:

The recommended Phase II pediatric veledimex dose will be determined from the Evaluable Safety Population (ESP), as defined below. The recommended Phase II pediatric dose is defined as the dose level below the dose in which ≥ 33% of subjects in the same cohort experience DLTs. If two DLTs occur in the same cohort, subject dosing will stop in the cohort experiencing the DLTs.

Safety Evaluation:

Safety will be evaluated in the Overall Safety Population (OSP) and the Evaluable Safety Population (ESP), as defined below, using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

In the DLT evaluation period (Day 0 to Day 28), if any subject experiences a local reaction that requires operative intervention and is felt to be attributable to study drug(s); any local reaction that has life-threatening consequences requiring urgent intervention or results in death and is felt to be attributable to study drug; or any Grade 4 hematologic toxicity, except thrombocytopenia, that is at least possibly related to study drug and lasts ≥ 5 days, enrollment of new subjects will be paused pending review by the SRC.

Safety assessments will be based on medical review of adverse event reports and the results of vital signs, physical and neurologic examinations, electrocardiograms (ECGs), clinical laboratory tests, and

monitoring of the frequency and severity of adverse events. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

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

The reporting period for safety data will be from the date of ICF or assent signature through the Initial Follow-Up Period (Day 56).

Evaluation at the Recommended Phase II Pediatric Veledimex Dose:

A decision to enroll additional subjects as part of an expansion cohort will be made by the SRC.

Criteria for Evaluation:

Tumor Response Assessments and Overall Survival:

The ESP will be evaluated for Investigator assessment of ORR, PFS, and OS. Response will be assessed using the baseline (Day 2 ± 24 hours) Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria used to characterize tumor response assessments. In the absence of a pediatric RANO criteria, adult response criteria will be used.

[redacted]

Pharmacokinetic Evaluations:

Veledimex PK parameters will be evaluated at each dose level in the dose escalation cohorts and in any expansion cohort(s).

Statistical Methods:

Analysis Populations:

This is an amendment to an ongoing study that has been previously described. For all practical purposes the connotation of the safety population for the planned safety analysis are subjects being denoted in defining the overall safety population (OSP) defined below to distinguish this group from the subgroup of subjects denoted as the evaluable safety population (ESP) who must receive Ad-RTS-hIL-12 and at least one dose of veledimex after injection.

This distinction provides for inclusion of both drug components (Ad-RTS-hIL-12 + veledimex) in order to evaluate dose escalation via the rule-based criteria fundamental to the 3+3 method. This means that during dose escalation if at least one of three Ad-RTS-hIL-12 treated subjects does not receive at least one dose of veledimex after injection, additional eligible subjects will be enrolled as applicable in order to achieve the samples size of three evaluable subjects to assist the SRC's evaluation when making a dose escalation or a dose de-escalation decision. Specifically,

- The OSP includes all subjects who received at least one dose of veledimex or Ad-RTS-hIL-12
- The ESP includes all subjects who received Ad-RTS-hIL-12 and at least one dose of veledimex after Ad-RTS-hIL-12 administration, and are BSA conformant
- The Pharmacokinetics Population (PKP) includes all subjects who received veledimex with sufficient timepoints

Safety Analysis:

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

The ESP will be used to make decisions regarding escalation to higher veledimex doses for Arm 2, the rule-based criteria of a 3 + 3 design, as previously described.

For the first (10 mg) veledimex dose cohorts in Arms 1 and 2 (*i.e.*, Cohorts 1 and 3, respectively), a minimum of three ESP subjects must be eligible for evaluation of safety. In addition, evaluation of any DLTs will be performed according to protocol-defined criteria.

Safety variables will be tabulated and presented by arm and by dose cohort. Exposure to study drug(s) and reasons for discontinuation of study treatment will be tabulated. All treatment-emergent adverse events (TEAEs) will be coded according to the System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). The TEAEs will be tabulated by the number and percent of subjects according to relationship to study drug(s), severity, and seriousness. Laboratory parameters will be summarized by visit. Vital signs and physical examination data will be listed by visit.

Tumor Response and Overall Survival Analyses

If an SRC committee decision results in enrolling subjects into an expansion cohort, the primary analysis for tumor response variables and OS will be performed on the ESP population. Secondary analyses will include all treated subjects as defined by the safety population denoted the OSP. The Investigator assessment of ORR and PFS will be determined for each cohort. The OS is defined as the duration of time from the first dose of study drug to the date of death or, for subjects who are still alive two years after first dose of study drug, subjects will be censored at the last follow-up contact date. A 2-sided confidence interval will be computed for the ORR. The PFS and OS will be analyzed using Kaplan-Meier methods. If an expansion cohort to treat up to 30 subjects is not performed, instead of a statistical analysis of data from very small sample sizes, listings of the investigator assessment of ORR and PFS by subjects will constructed on the subjects treated during the dose escalation phase.

[redacted] PK, [redacted]

Veledimex PK parameters will be determined based on blood (plasma) levels of veledimex using WinNonLin Phoenix 64. [redacted]

Sample Size Determination

The choice of the number of subjects was based on the standard 3 + 3 design, modified for independent evaluation of two subject arms that may exhibit different safety and tolerability profiles.

Up to 45 subjects may be enrolled into this study, including 3 to 6 subjects per cohort, and the expansion cohort, if recommended by the SRC. Subjects who withdraw from the study during the DLT evaluation period (Day 0 to Day 28) for reasons other than toxicity or disease progression may be replaced.
Study Duration The duration of this study from the time of initiating subject screening until completion of survival follow-up is anticipated to be approximately 48 months, including 24 months for enrollment and 24 months for follow-up. The study start is defined as the date when the first subject is consented into the study; the study stop date is the date when all subjects in the survival follow-up portion of the study have died or reached the 24 month follow-up assessment for which the data captured indicate that the subject is still living.

Table 1: Schedule of Study Procedures

	Screening Period	Treatment Period								Initial Follow-up Period			Long Term Follow-up
Activity	Day -28 to -1	Day 0	Day 1	Day 2	Day 3	Day 4-6[gg]	Day 7	Day 8-13	Day 14	Day 15	Day 28 ± 7	Day 56 ±7	Every 8 weeks[cc] (± 1 week)
Clinical Assessments													
Informed Consent	X												
Medical/ Cancer History[a,]	X												
Physical Exam[c], including targeted neurological exam	X	X	X	X	X		X		X		X		
Lansky PS, Karnofsky, or ECOG[d]	X	X							X		X		
Height (only at Screen) and Weight	X	X					X		X		X		
Vital Signs[e]	X	X	X	X	X		X		X		X		
PI/MM Contact[ff]		X	X	X	X	X	X	X	X				
Patient Contact[dd]		X	X	X	X	X	X	X	X				
Adverse Events[f]	X →												
Concomitant Medications[b,f]	X →												X[g]
Survival Status[g]		X →											
Clinical Laboratory[u]													
Pregnancy Test[h]	X	X									X		
Hematology Panel[i]	X	X	X	X	X	X	X		X		X		
Coagulation Panel[j]	X	X			X		X		X				
Serum Chemistry Panel[k]	X	X	X	X	X[v]	X	X[v]		X[v]		X[v]		
Urinalysis Panel[l]	X	X							X				
ECG[m]	X	X			X				X				
Eligibility Review	X	X											
Registration[n]	X												

Table 1: Schedule of Study Procedures (Continued)

	Screening Period	Treatment Period								Initial Follow-up Period			Long Term Follow-up
Activity	Day -28 to -1	Day 0	Day 1	Day 2	Day 3	Day 4-6[gg]	Day 7	Day 8-13	Day 14	Day 15	Day 28 ± 7	Day 56 ±7	Every 8 weeks[cc] (± 1 week)
Study Drug Administration													
Ad-RTS-hIL-12		X[o,p]											
Veledimex Dose[p] Arm 1		X	X[q,v]	X	X[v]	X	X[v]	X	X[v]				
Veledimex Dose[p] Arm 2			X[q,v]	X	X[v]	X	X[v]	X	X[v]				
Veledimex Dose Compliance/ Subject Diary[r]			X	X	X	X	X	X	X				
PK[redacted]													
[redacted]													
Veledimex PK Blood Sample Arm 1[s, u]		X[t]	X	X					X	X			
Veledimex PK Blood Sample Arm 2[s, u]			X	X					X	X			
[redacted]		[redacted]			[redacted]		[redacted]		[redacted]		[redacted]		
[redacted]		[redacted]					[redacted]		[redacted]		[redacted]		
[redacted]	[redacted]			[redacted]					[redacted]		[redacted]	[redacted]	[redacted]
MRI Scans[w,x,ee]	X[w,x]		X[w,x,y]	X[w,x,y]					X[w]		X[w,x]	X[w,x]	X[w,x]
CT Scan			X[hh]										
Tumor Sample[u,z](Arm 1)		X											
Tumor Biopsy[u,z] (Arm 2)		X[aa]										X[bb]	
CSF Sample[z,z] (Arm 1 only)		X											

*All assessments should be performed prior to study drug administration, as applicable, unless otherwise stated.

[a] Medical history includes demographic information, medical history, and surgical history. Cancer history includes current cancer diagnosis, prior treatment (regimen[s], doses, start and stop dates, any associated residual toxicity, and best response for each regimen).
[b] Medications received in the period preceding consent (~28 days) in addition to those ongoing at screening will be captured in the CRF.
[c] A complete physical examination including a neurological exam and mental status is required at baseline; targeted neurological exams thereafter.
[d] Refer Appendices 1-3 for the published grading scores
[e] Blood pressure, pulse, temperature, and respiration will be recorded. 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 subjects' hydration status.
[f] Monitoring and recording of concomitant medications, adverse events (AEs), and serious adverse events (SAEs) will be conducted throughout the study. Concomitant medications given and AEs/SAEs considered related to study assessments that occur following signed informed consent form (ICF) or assent and prior to study drug dosing must be recorded in the CRF. Concomitant medications given and AEs/SAEs that occur after study drug dosing through the Initial Follow-up Period (*i.e.*, Day 56 visit) must be recorded in the CRF. AEs that are ongoing at the end of the Initial Follow-up Period and are considered drug related should be followed until resolution or no resolution is expected.
[g] Subjects will be followed to document other anticancer therapies and survival status for two years following administration of Ad-RTS-hIL-12.
[h] Females of childbearing potential will have a serum pregnancy test at the Screening Visit and a urine or serum pregnancy test on Day -1 or Day 0, with a negative test result required prior to first dose of study drug (either veledimex [Arm 1] or injection of Ad-RTS-hIL-12 [Arm 2]). Pregnancy tests will be repeated on Day 28.
[i] Hematology Panel (Screening, Days 0, 1, 2, 3, 5, 7, 14, and 28): complete blood count, white blood cell count with differential, red blood cell count, hematocrit, hemoglobin, ESR, and platelet count.
[j] Coagulation Panel: activated partial thromboplastin time (aPTT/PTT), international normalized ratio, erythrocyte sedimentation rate, and C-reactive protein.
[k] Serum Chemistry Panel (Screening, Days 0, 1, 2, 3, 5, 7, 14, and 28): aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, creatinine, total bilirubin, total protein, albumin, lipase, amylase, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate.
[l] 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 clinically indicated.
[m] Standard 12-lead ECG; single measurement at each time point. If ECG is normal at screening and subject has no cardiac risk factors, ECG does not need to be done after Day 0.
[n] Centralized registration of eligible subjects will be completed after all screening procedures have been completed, and the subject is deemed eligible by Investigator and Medical Monitor prior to first dose of study drug (either veledimex [Arm 1] or injection of Ad-RTS-hIL-12 [Arm 2]), according to a process defined by the Sponsor.
[o] Ad-RTS-hIL-12 intratumoral injection should be administered by [redacted] injection for Arm 1 subjects and intracranial stereotactic injection for Arm 2 subjects. 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.
[p] Each subject will be carefully monitored for any local reactions and/or hypersensitivity reactions following the Ad-RTS-hIL-12 injection and veledimex administration.
[q] The first postresection veledimex dose is to be given on Day 1, preferably with food. Subsequent veledimex doses are to be taken QD, in the morning and within approximately 30 minutes of completion of a regular meal. Dosing on Days 2 to 14 should be at approximately the same time of day (± 1 hours) as the Day 1 dosing.
[r] Study sites must determine compliance of veledimex dosing. Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the QD dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and reason for any missed doses. At the end of dosing, subject diary and study drug container(s) with any remaining capsules should be returned to the study staff, so that staff can properly assess dose compliance.

[s] The PK sampling is to be conducted in accordance with Table 2 for Arm 1 and Table 3 for Arm 2. In the event that blood volume to be drawn on a given study day would exceed the allowable amount, the Principal Investigator and Medical Monitor will discuss and determine the priority of testing to be completed to ensure patient safety.

[t] [redacted]

[u] [redacted] be of diagnostic quality. The brain is to be imaged using the same method(s) used throughout the study. Measurable target lesions should be selected and measured per iRANO criteria guidelines for adults, pending issuance of pediatric criteria. Repeat scans to confirm progression should be completed at 4 weeks and preferably again 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 providing standard-of-care treatment in accordance with current iRANO guidelines.

[x] The Day 28 (± 7 days) and Day 56 (± 7 days) 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 performed every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation). MRI scans and reports should be sent to the Sponsor per the Sponsor's defined process.

[y] The MRI scan designated on Day 2 has an allowable window of ± 24 hours and will be considered the baseline scan for tumor response assessments.

[z] Additional tumor, blood, and CSF (if available) samples to be collected, if available, as part of standard-of-care procedures. For example, additional CSF samples may be obtained at the time of MRI scans whenever sedation is clinically indicated or if an Ommaya reservoir is implanted.

[aa] The tumor sample on Day 0 should be collected prior to Ad-RTS-hIL-12 injection.

[bb] A tumor sample should be collected if there is a concern of pseudo-progression. The biopsy at Day 56 is strongly recommended. Patients should remain on-study for continued follow-up until confirmed progression per iRANO or the patient meets other withdrawal criteria.

[cc] Every 8 weeks from Day 56.

[dd] The patient should be contacted every day during the treatment period to discuss clinical status and updates on current/new adverse events. If the patient is discharged prior to Day 14, follow-up may occur via telephone. Successful contact and contact attempts will be documented in EDC.

[ee] CSF may be collected at time of the time of MRI scans such as if sedation is clinically indicated or if an Ommaya reservoir is implanted. Collection is optional.

[ff] The site Investigator will communicate with the Medical Monitor during the active dosing period for all subjects on a daily basis regarding clinical status and laboratory values, prior to the patient receiving their daily dose of veledimex, and additionally as clinically indicated.

[gg] Assessments to be performed on Day 4, Day 5, and Day 6.

[hh] To be collected as clinically indicated.

Table 2: Arm 1 Schedule of Veledimex Pharmacokinetic Sampling Times

Sample Number	Day 0	Day 1	Day 2	Day 14	Day 15
1	pre-dose[a]	pre-dose[a]	pre-dose[a]	pre-dose[a]	24 hours post Day 14 dose[b]
2	During resection	2 hours post-dose[b]	-	2 hours post-dose[b]	-
3	-	4 hours post-dose[b]	-	4 hours post-dose[b]	-
4	-	6 hours post-dose[b]	-	6 hours post-dose[b]	-

[a] ≤ 30 minutes prior to veledimex dose
[b] PK Collections: post-dose PK collections will have a ± 30-minute draw window

Table 3: Arm 2 Schedule of Veledimex Pharmacokinetic Sampling Times

Sample Number	Day 0	Day 1	Day 2	Day 14	Day 15
1	-	pre-dose[a]	pre-dose[a]	pre-dose[a]	24 hours post Day 14 dose[b]
2	-	2 hours post-dose[b]	-	2 hours post-dose[b]	-
3	-	4 hours post-dose[b]	-	4 hours post-dose[b]	-
4	-	6 hours post-dose[b]	-	6 hours post-dose[b]	-

[a] ≤ 30 minutes prior to veledimex dose
[b] PK Collections: post-dose PK collections will have a ± 30-minute draw window

5. INTRODUCTION

5.1. Disease Background

Pediatric central nervous system tumors are a heterogeneous group of tumors, with subtypes that possess distinctly different clinical courses (Johnson, Cullen et al. 2014). Pediatric glioblastoma is characterized by its aggressive clinical course and accounts for a significant amount of morbidity and mortality among children with brain tumors. According to the Central Brain Tumor Registry of the United States (CBTRUS), glioblastoma comprises approximately 2.9% of brain and central nervous system tumors in children 0 to 19 years old (Ostrom, Gittleman et al. 2016). Their 2-year survival rate is approximately 33%. Although the prognosis of glioblastoma is better in children than in adults, there are fewer therapies available for use in children. Currently only lomustine and temozolomide are labeled for pediatric use. Lomustine use in pediatrics is not based on adequate and well-controlled clinical studies (NextSource Biotechnology 2014). The safety and effectiveness of temozolomide in pediatric patients have not been established (Merck & Co. 2015). Nonetheless, the current standard-of-care is considered to be temozolomide and radiation therapy (Al-Saffar, Marshall et al. 2014).

The most common form of pediatric brainstem gliomas is diffuse intrinsic pontine glioma (DIPG), representing 75% to 85% of these tumors (Warrren 2012). The prognosis of children with DIPG is poor, with a 1-year overall survival (OS) of less than 45% (Cohen, Heideman et al. 2011). There are no effective treatments available for DIPG. Indeed, an open-label Phase II study in children with DIPG found no evidence that chemoradiotherapy with temozolomide followed by adjuvant temozolomide resulted in better event-free survival or OS than a historical control of radiation therapy (Cohen, Heideman et al. 2011). Other recent studies of pediatric subjects with DIPG generally report 2-year survival rates of < 10% (Warrren 2012). The current standard of care for DIPG is focal radiation therapy.

5.2. 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-12p70 molecule (Carra, Gerosa et al. 2000). IL-12 is produced by innate immune cells in response to pathogens, leading to the production of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha from T and natural killer (NK) cells (Micallef, Ohtsuki et al. 1996, Trinchieri 2003). The discovery that IL-12 can drive naïve T helper cell differentiation to the inflammatory T helper cell type 1 (Th1) phenotype (Hsieh, Macatonia et al. 1993) established IL-12 as a bridge between innate immune cells and the adaptive immune response through polarization of naïve cluster of differentiation (CD) CD4+ cells. IL-12 also directly influences CD8+ T cell differentiation (Kalinski, Hilkens et al. 1999, Curtsinger, Lins et al. 2003) and the reactivation and survival of memory CD4+ T cells (Yoo, Cho et al. 2002). This is particularly important in the context of the tumor microenvironment, where high levels of IL-12 repolarize antigen-experienced CD4+ T cells back to the functional antitumor Th1 phenotype (Wesa, Kalinski et al. 2007).

The first human study of IL-12 as an anticancer agent was a Phase I dose escalation of intravenously (IV) administered recombinant human IL-12 (rhIL-12) in subjects with either melanoma or renal cell carcinoma. There was 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 2 IL-12-related deaths prompted the Food and Drug Administration (FDA) to suspend the trial (Atkins, Robertson et al. 1997, Leonard, Sherman et al. 1997). Additional studies confirmed that systemic administration of recombinant IL-12 resulted in significant toxicity, limiting its potential for clinical development (Salem, Gillanders et al. 2006). These results prompted the investigation of local (intratumoral) delivery of IL-12 as a direct anticancer therapeutic or as an adjuvant to vaccination.

5.3. Adenoviral Vectors for Gene Therapy

5.3.1. Adenoviral Safety

Adenoviral vectors have been used extensively to deliver a variety of gene products to human subjects, including subjects with cancer. To date, numerous studies 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 5×10^{10} to 1×10^{12} viral particles [vp]) was well tolerated, with minimal adverse events (AEs) (Patel, Young et al. 2009). A Phase I study of subjects with oral leukoplakia implemented multiple intraepithelial injections of recombinant adenovirus (rAd) p53 (1×10^{8} vp/cm^2) and demonstrated good tolerance of the vector, with no evidence of dose limiting toxicity (DLTs) (Zhang, Li et al. 2009). 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 10×10^{11} to 25×10^{11} vp, with no DLTs, and generally mild to moderate AEs (Shimada, Matsubara et al. 2006). The most common AEs were fever (all 10 subjects [100%]), pain (30%), and hyperglycemia (30%), which was attributed to the use of total parental nutrition. Hypocalcemia was reported in 20% of subjects and 10% experienced activated partial thromboplastin time (aPTT) elongation, 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 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, Massolini et al. 2004).

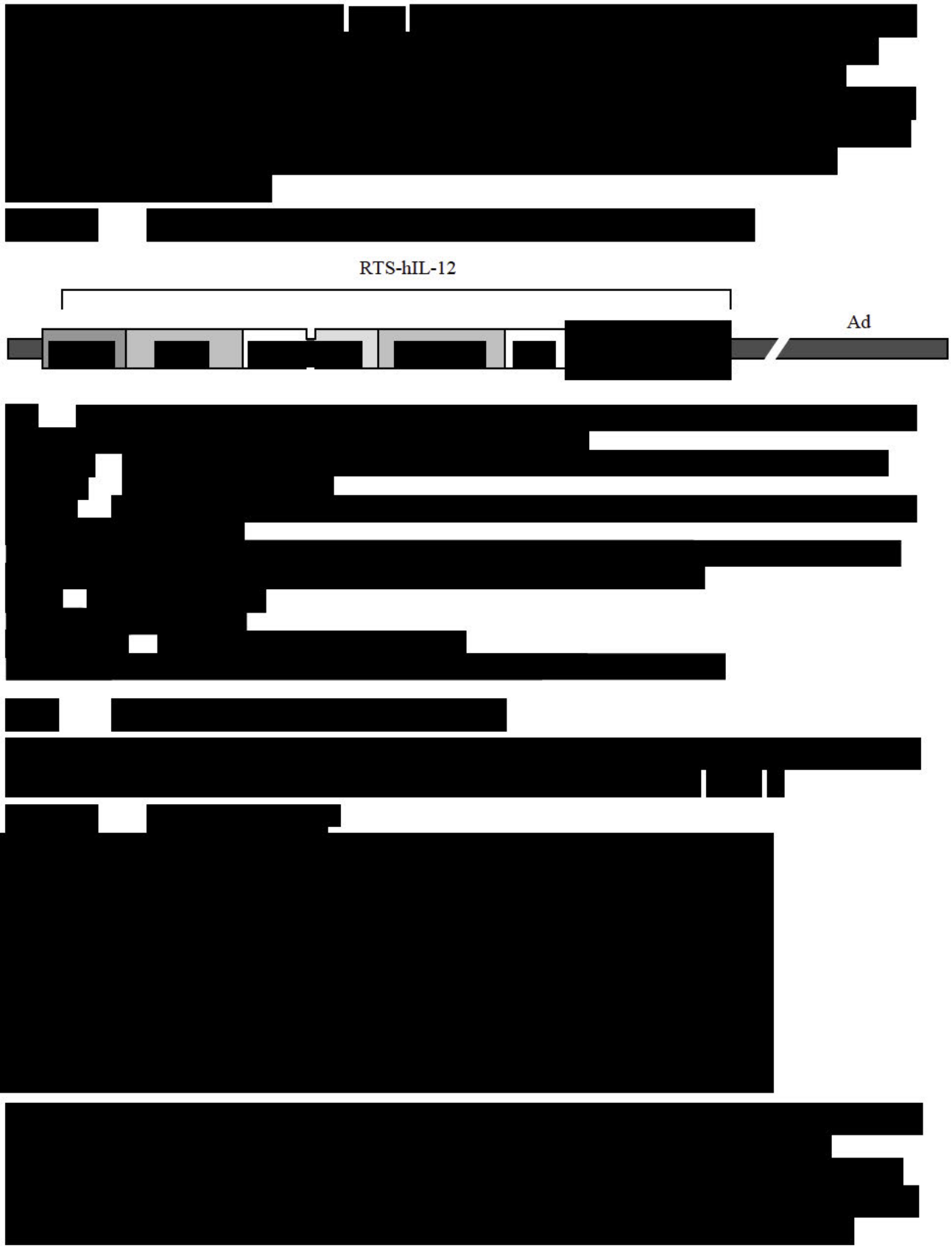
A recent randomized, open-label, Phase III study compared a regimen of surgical resection, adenovirus-mediated gene therapy (intraoperative perilesional sitimagene ceradenovec), IV ganciclovir, and standard-of-care interventions versus surgical resection plus standard-of-care interventions in 250 subjects with newly diagnosed high-grade glioma amenable to resection. Results showed that, although the time to death or re intervention was prolonged, overall survival (OS) was not improved relative to the standard-of-care regimen (Westphal, Yla-Herttuala et al. 2013). However, the authors concluded that the treatment had a positive risk benefit ratio, with similar AEs (hemiparesis [often transient], hyponatremia, and seizures) compared with the standard-of-care regimen.

5.3.2. 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 been 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 2 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, Allen 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, and with transient pain after electroporation being the most common AE (Daud, DeConti 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, Burg et al. 2005). Eight of 9 subjects experienced a transient response at the intratumoral injection site, and some subjects who had tumor responses also showed some increases in systemic IL-12, IFN-γ-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, Alfaro 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, Barnes 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, Massolini et al. 2004). In that study, 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 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]


RTS-hIL-12
Ad

[redacted]

5.4.3. 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 (PO) 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 ribonucleic acid and, ultimately, protein (Anderson, Haskell et al. 2000, Palli, Kapitskaya et al. 2003, Karzenowski, Potter et al. 2005).

[redacted]

[redacted]

Please refer to the current Investigator's Brochure for additional information regarding the nonclinical Ad-RTS-mIL-12 + veledimex program.

5.6. Study Rationale

Human brain cancers are infiltrated by T regulatory cells that preferentially accumulate in high grade tumors, which markedly suppresses the immune system (El Andaloussi and Lesniak 2006, Fecci, Mitchell et al. 2006, Jacobs, Idema et al. 2009, Jacobs, Idema et al. 2010). This, combined with the known ability of IL-12 to up-regulate immune responses (see Section 5.2), supports the hypothesis that the treatment of pediatric brain tumors has the potential to be improved through controlled local immunostimulation with IL-12.

[redacted] he starting dose in Cohort 1 will be 10 mg, which is approximately 5.3 mg/m^2. The actual dose administered will depend on the subject's BSA and available capsule size. Two dose levels of veledimex (10 mg, 20 mg) and one dose level of Ad-RTS-hIL-12 (2 x 10^{11} vp) will be assessed in pediatric subjects (≤ 21 years of ages with the documented ability to swallow).

Based on our animal modeling and our clinical experience with Ad-RTS-hIL-12 and veledimex, we expect a significant safety margin and tolerability profile. However, we will also implement

rigorous safety monitoring and will review safety data on an ongoing basis in addition to mandated SRC meetings.

5.7. Clinical Studies of Ad-RTS-hIL-12 and Veledimex in Malignancies

Four clinical studies with Ad-RTS-hIL-12 + veledimex have been conducted or are in progress in subjects with melanoma, breast cancer, and high-grade gliomas.

Please see the Investigator's Brochure for the most current information on these studies.

[redacted]

Please see the Investigator's Brochure for the most current information on these studies.

6. STUDY OBJECTIVES

6.1. Primary Objective

- Phase I/II: To determine the safety and tolerability of intratumoral Ad-RTS-hIL-12 and varying veledimex doses administered PO in pediatric brain tumor subjects (supratentiorial and/or DIPG)

6.2. Secondary Objectives

- Phase I: To determine the recommended Phase II veledimex dose in pediatric brain tumor subjects when given with intratumoral Ad-RTS-hIL-12 (supratentiorial and/or DIPG)
- Phase I/II: To determine the pharmacokinetics (PK) of veledimex in subjects treated with Ad-RTS-hIL-12 + veledimex (supratentiorial and/or DIPG)
- Phase I: To determine the veledimex concentration ratio between the brain tumor and blood in subjects treated with Ad-RTS-hIL-12 + veledimex (Arm 1 only)

[redacted]

- Phase I/II: To determine investigator assessment of response, including tumor ORR and PFS of subjects treated with Ad-RTS-hIL-12 + veledimex (supratentiorial and/or DIPG)
- Phase I/II: To determine OS of subjects treated with Ad-RTS-hIL-12 + veledimex (supratentiorial and/or DIPG)

6.3. [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, open-label study, of Ad-RTS-hIL-12 administered by intratumoral injection and veledimex administered PO in pediatric brain tumor subjects, starting with phase I dose escalation cohorts. After the completion of a phase I dose escalation cohort in Arm 2, the SRC may elect to expand that cohort by up to 30 DIPG patients, which will be considered the Phase II component of the study. This study will investigate one fixed intratumoral Ad-RTS-hIL-12 dose [redacted] and escalating veledimex doses to determine the safe and tolerable Phase II pediatric dose based on the safety profiles observed in the presence of variable corticosteroid exposure. The study schema is outlined in Figure 4 (Arm 1) and Figure 5 (Arm 2).

This study is divided into 3 periods: the Screening Period, the Treatment Period, and the Follow-up Period (Initial and Long Term). After the informed consent form (ICF) or subject assent, as applicable, is signed, subjects will enter the Screening Period to assess eligibility. Eligible subjects will be stratified into one of two arms, according to diagnosis. Arm 1 is open to pediatric brain tumor subjects who are scheduled for a standard-of-care craniotomy and tumor resection, with the exclusion of subjects with diffuse intrinsic pontine glioma (DIPG). Arm 2 is open to subjects with DIPG who are post prior standard focal radiotherapy (≥ 2 weeks and ≤ 10 weeks). Arm 1 subjects will receive one veledimex dose before the resection procedure. Samples (tumor, blood, and cerebrospinal fluid [CSF] [if available]) will be collected as described below. After Ad-RTS-hIL-12 intratumoral injection, Arm 1 subjects will continue administration of veledimex PO daily for 14 days for a total of 15 doses of veledimex. Arm 2 subjects will receive a single Ad-RTS-hIL-12 [redacted] dose by stereotactic injection and will receive veledimex PO daily for 14 days.

Figure 4: Study ATI001-103 Schema: Arm 1 (Cohort 1)

Arm 1: Pediatric brain tumor subjects scheduled for craniotomy and tumor resection (excluding DIPG)

Subjects with a clinical indication for tumor resection will receive veledimex 3 (± 2) hours before the craniotomy procedure, on an empty stomach (excluding other medications). At the time of tumor resection, brain tumor, blood, and CSF (if available) samples will be collected to determine the veledimex concentration ratio between brain tumor, blood, and CSF (if available).

Immediately after tumor resection, Ad-RTS-hIL-12 [redacted] will be administered by [redacted] injection into approximately two sites within the residual tumor for a total volume of 0.1 mL. The total amount delivered to each site will be recorded in the CRF. If less than the planned total injected volume is administered, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations. The day of Ad-RTS-hIL-12 administration is designated as Day 0. When available, an intra-operative magnetic resonance imaging (MRI) scan should be performed to guide the Ad-RTS-hIL-12 injection to areas of contrast-enhancing tumor tissue.

After the Ad-RTS-hIL-12 injection, veledimex will be administered PO QD for 14 days. The first postresection veledimex dose is to be given on Day 1, preferably in the morning and within approximately 30 minutes of completion of a regular meal. There should be a minimum of 10 hours between veledimex doses. Subsequent veledimex doses (Days 2 to 14) are to be taken at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal.

Arm 2: Subjects with DIPG who will NOT undergo tumor resection

Subjects with DIPG who will not undergo tumor resection will receive Ad-RTS-hIL-12 by standard stereotactic surgery on Day 0. At the time of stereotactic surgery, prior to Ad-RTS-hIL-12 injection, brain tumor biopsy and blood samples will be collected. Ad-RTS-hIL-12 [redacted] will be administered by stereotactic injection into the intratumoral site. The day of Ad-RTS-hIL-12 administration is designated as Day 0. The total amount delivered to each site will be recorded in the eCRF. If less than the planned total injected volume is administered, 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 PO QD for 14 days. The first veledimex dose is to be given on Day 1, preferably in the morning and within approximately 30 minutes of completion of a regular meal. Subsequent veledimex doses (Days 2 to 14) should be at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal. There should be a minimum of 10 hours between veledimex doses.

Cohorts

Arm 1: This study has been modified to explore one veledimex dose in Arm 1: 10 mg.

Arm 2: This study is designed to explore two veledimex doses in Arm 2: 10 mg and 20 mg. Subject enrollment and veledimex dose escalation will proceed according to a standard 3+3 design. The first cohort will receive 10 mg veledimex followed by the second cohort receiving 20 mg veledimex.

Arm 1 and Arm 2 subjects may exhibit different safety and tolerability profiles. The 3+3 standard study design has been modified to independently evaluate the two arms separately.

The study arms and assigned doses will be divided into 3 cohorts as shown below:

Table 4a: ATI001-103 Cohorts

Arm	Cohort	Indication	Procedure	Assigned Veledimex Dose[a]
1	1	Resectable pediatric brain tumor	Craniotomy	10 mg
2	3[b]	DIPG	Stereotactic	10 mg
2	4	DIPG	Stereotactic	20 mg

[a] Doses are BSA-adjusted doses
[b] Arm 1 Cohort 2 was removed in Protocol Amendment 2. The SRC reviewed the safety profile of Arm 1 Cohort 1 and determined it was appropriate to move forward with Arm 1, Cohort 2 and Arm 2, Cohort 1, however due to issues with enrollment of supratentorial patients, it was determined not to proceed with Cohort 2.
Note: After the completion of a phase I dose escalation cohort in Arm 2, the SRC may elect to expand that cohort by up to 30 DIPG patients, which will be considered the Phase II component of study.

Each cohort will consist of subjects ≤ 21 years-of-age who meet eligibility criteria.

Each subject in each dose escalation cohort will be monitored for 28 days after Ad-RTS-hIL-12 injection before additional subjects are enrolled in the same cohort. The evaluation period for DLT is 28 days after Ad-RTS-hIL-12 injection (Day 0 to Day 28).

Determination of safety and the recommendation to expand the current dose cohort, dose escalate, or discontinue the investigation, will occur after all dosed subjects in a cohort have been evaluated for at least 28 days after Ad-RTS-hIL-12 injection, as described in Section 7.3.

The starting dose in Cohort 1 will be 10 mg, which is approximately 5.3 mg/m^2. The actual administered dose will depend on the subject's BSA and available capsule sizes (Table 4b). Because veledimex is an PO agent and is supplied in a fixed capsule size (5 mg and 20 mg), the actual administered dose is based on a subject's BSA and is bound by the rounding constraints set by 5 mg. The Sponsor developed a BSA-adjusted dosing algorithm designed to enable dosing within 25% of the target dose in mg/m^2.

If a subject's BSA would expose the subject to < 75% or > 125% of the target assigned dose, the actual administered dose will be modified to ensure that the target dose in mg/m^2 is achieved. Minimum BSA restrictions for enrollment must be met in order for a subject to be appropriately dosed. Potential subjects whose BSAs do not have a correlated administered dose may be enrolled at the discretion of the Investigator and the Medical Monitor but will not be considered in the assessment of the recommended Phase II pediatric dose. Dosing of these subjects can only commence once the cohort has been reviewed by the SRC and determined that the dosing at the specified level (10 mg or 20 mg) is appropriate for escalation or as the recommended Phase II pediatric dose. These subjects will be analyzed separately.

The dosing table (Table 4b) illustrates this algorithm and captures the BSA adjusted-actual administered dose that subjects would receive at assigned dose levels based on a minimum capsule size of 5 mg.

Table 4b: Veledimex Dosing Table

Cohort	Target Dose (mg)	Min BSA (m^2)	Min BSA Target Dose (mg)	Percentage of Expected Dose (%)	Max BSA (m^2)	Max BSA Target Dose (mg)	Percentage of Expected Dose (%)	Actual Dose [a] (mg)
10 mg	5.3	0.5	10	189	0.75	6.7	126	5[b]
10 mg	5.3	0.76	6.6	124	1.26	4.0	75	5
10 mg	5.3	1.27	3.9	74	1.5	3.3	63	5
10 mg	5.3	1.27	7.9	149%	1.5	6.7	126%	10 mg[b]
10 mg	5.3	1.51	6.6	125%	2.53	4.0	75%	10 mg
Cohort	**Target Dose (mg)**	**Min BSA (m^2)**	**Min BSA Target Dose (mg)**	**Percentage of Expected Dose (%)**	**Max BSA (m^2)**	**Max BSA Target Dose (mg)**	**Percentage of Expected Dose (%)**	**Actual Dose [a] (mg)**
20 mg	10.6	0.5	10	94%	0.63	7.9	75%	5 mg
20 mg	10.6	0.64	7.8	74%	0.75	6.7	63%	5 mg
20 mg	10.6	0.64	15.6	147%	0.75	13.3	126%	10 mg[b]
20 mg	10.6	0.76	13.2	124%	1.25	8.0	75%	10 mg
20 mg	10.6	1.26	11.9	112%	1.87	8.0	75%	15 mg
20 mg	10.6	1.88	10.6	100%	2.53	7.9	75%	20 mg

[a] The actual dose is ± 25% of the target dose.
[b] Subjects in this BSA range may be dosed at the discretion of the Investigator and the Medical Monitor

7.2. Study Oversight for Safety Evaluation

The first level of safety oversight will occur through the site Investigator in conjunction with the Medical Monitor. The site Investigator will communicate with the Medical Monitor during the active dosing period for all subjects on a daily basis regarding clinical status and laboratory values, prior to the patient receiving their daily dose of veledimex, and additionally as clinically indicated.

A formal Safety Review Committee (SRC), comprised of the study Investigators, the Medical Monitor, and other appropriate Sponsor representatives, will provide the overall safety oversight. Additional external medical and scientific experts may also be invited to participate in the reviews, as needed. A separate charter will outline the SRC activities. Briefly, the SRC will evaluate subject safety within each cohort. If no significant safety events occur with the first subject of each cohort, the second and third subjects will be enrolled and treated. If a significant safety event occurs with the first subject, the SRC will convene to evaluate the safety event(s) and to make a recommendation and decision on the enrollment of the second and third subjects in the same cohort.

Upon completion of each cohort, the SRC will meet to review the data collected to determine next steps as described in Section 7.3. Enrollment in Cohort 4, with the 20 mg assigned

veledimex dose will not commence until the SRC has determined that dosing at the lower level, Cohort 3, did not result in DLTs that would preclude dose escalation.

In addition to recommending the opening of Arm 2 Cohort 3, or dose escalation to Cohort 4, the SRC may also determine if the study should proceed with the Phase II portion (an expansion of an Arm 2 cohort). In the event that the SRC determines that escalation and/or expansion is not warranted, a decision will be made about stopping the investigation. At the discretion of the SRC, the investigation may be continued at a lower dose.

Dose escalation, cohort expansion, and de-escalation rules will be followed as defined in Section 7.3 and study stopping rules will be followed as defined in Section 7.10.

7.3. Dose Escalation, Cohort Expansion, and De-Escalation Decision Rules

Expansion cohort(s) are prospectively planned in this study, in Arm 2, at the discretion of the SRC.

Each subject in each dose escalation cohort (3+3 standard design) will be monitored for 28 days before subsequent subjects are enrolled. The SRC will convene after the third and/or final subject in each cohort completes the 28-day DLT evaluation period and will make a recommendation regarding expanding the current cohort by up to 30 additional subjects (phase II component), opening of the next cohort/dose escalating, dose de-escalating, or discontinuing the investigation.

If the SRC recommends expanding the current cohort, a 28-day review period may not be required between each patient. Based on the safety profile of the current cohort, the SRC will make a determination related to the waiting period.

The SRC will determine if/when the MTD is met and may recommend cohort expansion at that dose.

Study stopping rules will be followed as defined in Section 7.10.

Dose Escalation/Cohort Expansion

Each subject in each dose escalation cohort (3+3 standard design) will be monitored for 28 days before subsequent subjects are enrolled. The SRC will convene after the final subject in Cohort 1 completes the 28-day DLT evaluation period. The SRC will make a recommendation regarding:

- Opening enrollment of Cohort 3
- Discontinuing the investigation

If the SRC recommends opening enrollment in Cohort 3, each subject will be monitored for 28 days before subsequent subjects are enrolled in the same cohort. The SRC will convene once the third and/or final subjects (*i.e.*. subject 3 of 3 or 6 of 6) in Cohort 3 complete the 28-day DLT evaluation period. The SRC will make a recommendation regarding:

- Expansion of Cohort 3 (Phase II portion)
- Opening enrollment of Cohort 4
- Discontinuing the investigation

If the SRC recommends enrollment of Cohort 4, each subject will be monitored for 28 days before subsequent subjects are enrolled in the same cohort. The SRC will convene once the third and/or final subject (*i.e.*, subject 3 of 3 or 6 of 6) in Cohort 4 complete the 28-day DLT evaluation period. The SRC will make a recommendation regarding:

- Expansion of Cohort 4 (Phase II portion)
- Discontinuing the investigation

In addition to recommending dose escalation, cohort expansion, or discontinuation of treatment, as noted above, the SRC may recommend dose de-escalation at any point based on safety review.

Dose De-Escalation

If it is determined that dose escalation or cohort expansion should not proceed, dose de-escalation may be undertaken and the SRC will consider de-escalating the veledimex dose as follows:

- De-escalation by increments of 5 mg from the cohort in which 2 or more DLTs were observed (*e.g.*, 15 mg, de-escalated from 20 mg)
- If there are 2 or more DLTs in the dose de-escalation cohort, the SRC will consider stopping enrollment at that dose and de-escalating the veledimex dose by an additional increment of 5 mg (*e.g.*, 5 mg down from 10 mg) or declaring a previously studied dose level the recommended Phase II pediatric dose

If no DLTs occur among the three subjects in Cohort 1, dosing may proceed to the next cohort, Cohort 3, after the SRC provides their recommendation to proceed (Table 5). In any cohort, if one DLT occurs among the three subjects, three additional subjects will be enrolled. If one or more of the three additional subjects experience a DLT, dosing will stop. The SRC will then convene to evaluate safety, determine if the recommended Phase II dose has been reached per Section 7.5 , and will decide whether to stop treatment or de-escalate veledimex dosing. The SRC may also seek an *ad hoc* safety evaluation and recommendation by external experts as needed.

Table 5: Dose Escalation and De-Escalation Decision Rules

Subjects with DLTs (Any Dose Level)	**Decision Rule**	**Subject Count**
None of the first 3 subjects OR ≤ 1 subject (in the case of a 6-patient cohort) experiences a DLT	Expand current dose level cohort or enroll the next higher dose level cohort (after SRC recommendation).	3 or 6
1 of the first 3 subjects experiences a DLT	Enroll at least 3 more subjects in this dose level cohort. If none of the 3 additional subjects experiences a DLT, expand current dose level cohort or proceed to the next planned dose level cohort (after SRC recommendation).	6

Table 5: Dose Escalation and De-Escalation Decision Rules (Continued)

Subjects with DLTs (Any Dose Level)	Decision Rule	Subject Count
2 or more subjects in a cohort experience a DLT	If 2 subjects experience a DLT, then **STOP** dose escalation in the cohort experiencing the DLTs and do the following: • The SRC will conduct a safety review to evaluate safety and determine whether the cohort experiencing the 2 DLTs has met the definition of the recommended Phase II pediatric veledimex dose (Section 7.5). Based upon this review, the SRC will make a recommendation that the cohort either continue at the existing dose, at a lower dose level, or other measures to be undertaken including discontinuation of treatment. If it has been determined that escalation or cohort expansion should not proceed, dose de-escalation may be undertaken and the SRC will consider de-escalating the veledimex dose as follows: o De-escalation by increments of 5 mg from the cohort in which 2 or more DLTs were observed (e.g., 15 mg down from 20 mg). • If there are 2 of more DLTs in the dose de-escalation cohort, the SRC will consider de-escalating the veledimex dose by additional increments of 5 mg (*e.g.*, 5 mg down from 10 mg) or declaring a previously studied dose level the recommended Phase II pediatric dose.	2 to 6

After completion of a cohort, if it has been determined that the recommended Phase II pediatric dose has not been reached, escalation to the next cohort will proceed once recommended and authorized by the SRC.

7.4. Dose-Limiting Toxicity

An event, occurring within the first 28 days (*i.e.*, Day 0 to Day 28) that meets at least one of the following conditions:

- Any local reaction that requires operative intervention and is felt to be attributable to study drug
- Any local reaction that has life-threatening consequences requiring urgent intervention or results in death and is felt to be attributable to study drug
- Any Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and lasts ≥ 3 days
- Nausea and vomiting will not be considered a DLT unless at least Grade 3 or 4 and refractory to antiemetics (i.e, defined as symptoms unrelieved by maximal medical support as directed by the PI (per institutional guidelines) in consultation with the medical monitor).
- Grade 3 or higher thrombocytopenia (< 50,000/mm^3) at least possibly related to study drug

- Any Grade 4 or higher hematologic toxicity (except thrombocytopenia) that is at least possibly related to study drug and lasts ≥ 5 days

Dose escalation may be stopped by the Medical Monitor before a DLT is observed, but where the observed toxicities indicate the strong likelihood of unacceptable toxicity at higher doses.

Note: Diagnostic brain tumor biopsy is not considered a DLT. Seizures, headaches, and cerebral or pontine edema are commonly observed in this population and will be recorded according to the grade of toxicity but will not be considered a DLT unless a relationship to study drug is deemed to be the main contributory factor. Transient neurological changes are expected in Arm 2 and will not be considered a DLT unless they last > 10 days.

Expansion cohorts will be allowed in Arm 2 if deemed appropriate by the SRC. If an expansion cohort is implemented, the veledimex dose may be delayed or reduced for individual subjects in the event of toxicity. If ≥ 33% of subjects in the expansion cohort experience DLTs, using the definition in the dose-escalation phase, additional subjects may be enrolled at the next lower dose tested in the dose-escalation phase or at an intermediate dose, as recommended by the SRC. All DLTs should be reported to the Sponsor within 24 hours of Investigator/site awareness.

7.5. Recommended Phase II Pediatric Veledimex Dose and Corticosteroid Exposure

The recommended Phase II pediatric veledimex dose will be determined using the Evaluable Safety Population (ESP). The recommended pediatric Phase II dose is defined as the dose level below the dose in which ≥ 33% of subjects in the same cohort experience DLTs. If 2 DLTs occur in the same cohort, dose escalation will stop in the cohort experiencing the DLTs. A decision to enroll additional subjects in an expansion cohort will be made by the SRC.

The recommended pediatric Phase II dose in this study will be determined in the context of variable corticosteroid exposure and will be reported as such. Investigational treatment requires that steroid use be allowed to manage brain tumor related symptoms or edema, especially after tumor resection. It is expected that the use and dose of corticosteroids will vary among trial sites and among subjects, and therefore, the extent and dose of steroids is not specified in this protocol. The treating physician should consider the minimum starting steroid dose for study subjects, if determined that it is safe and appropriate for that individual subject. 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.

7.6. Dose Modification and Dose Delays

Treatment dose delays and dose reductions for individual subjects will be allowed in the event of toxicities, according to the criteria shown in Table 6. If a drug-related Grade 3 or higher AE occurs (excluding nausea and/or vomiting in subjects who did not receive optimal treatment with anti-emetics), the Investigator in conjunction with the Sponsor's Medical Monitor will decide whether the subject will remain on the study. The withheld doses will not be made up; the subject may be allowed to complete dosing according to the remaining schedule.

As mentioned in Section 7.4, fatigue, seizures, headaches, and cerebral or pontine edema are commonly observed in this population and will be recorded according to grade of toxicity, but

will not be considered a DLT unless a relationship to study drug is deemed to be the main contributory factor. If ≥ 33% of subjects experience DLTs, the SRC will convene to determine the course of action. The Medical Monitor or Investigators may request a meeting of the SRC at other times, as deemed clinically indicated.

Table 6: Criteria for Dose Delay and Dose Reduction

Event	Course of Action
Any local injection reaction that requires operative intervention	Hold study drug and contact the Medical Monitor for instructions on resuming dosing
Any local injection reaction that has life-threatening consequences requiring urgent intervention or results in death	Hold study drug and contact the Medical Monitor for instruction on resuming dosing
Any drug-related Grade 3 or higher AE[a]	Hold study drug and contact the Medical Monitor for instruction on resuming dosing

[a] Excluding nausea and/or vomiting in subjects who did not receive optimal treatment with anti-emetics

7.7. Safety Monitoring and Adverse Effect Management

Safety will be evaluated in the Overall Safety Population (OSP) and the Evaluable Safety Population (ESP) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Safety assessments will be based on medical review of adverse event reports and the results of vital signs, physical and neurologic examinations, electrocardiograms (ECGs), clinical laboratory tests, and monitoring of the frequency and severity of adverse events. In addition, urine, fecal, saliva, buccal, and blood samples will be collected and tested for viral replication.

7.8. 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 v5.0 criteria. Study stopping rules will not apply to a specific event if it is clearly unrelated to study drug administration.

7.9. 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 subject safety and must be recorded as concomitant medications. Please refer to exclusion criteria for acute clinically significant and/or chronic infections.

Note: Because flu-like symptoms (*e.g.*, fever, headache, chills, dehydration, *etc*.) are commonly experienced following adenoviral vector administration, it is strongly recommended that subjects be treated with prophylactic antipyretic and/or analgesic medication prior to Ad-RTS-hIL-12 injection and during the first week after injection.

Please refer to Appendix 5 for the recommended regimen for the prophylactic administration of antipyretics and/or analgesics.

7.10. Study Stopping Rules

In the DLT evaluation period (Day 0 to Day 28), if any subject experiences a local reaction that requires operative intervention and is felt to be attributable to study drug; any local reaction that has life-threatening consequences requiring urgent intervention or results in death and is felt to be attributable to study drug; or any Grade 4 hematologic toxicity, except thrombocytopenia, that is at least possibly related to study drug and lasts ≥ 5 days, enrollment of new subjects will be paused pending review by the SRC.

In the event that there are other subjects actively being dosed in the cohort, the treating site's Principal Investigator (PI) and the Medical Monitor will discuss the relationship to study drug and determine whether or not to convene an urgent SRC meeting to make a decision to continue active dosing in ongoing subjects.

The SRC will make a decision to the enrollment of additional subjects at the relevant veledimex dose level, to expand the current dose level cohort, to de-escalate veledimex dosing at the relevant dose level, or to amend the protocol prior to enrollment of additional subjects, or to discontinue enrollment in the study. In the event that a decision is made to de-escalate dosing, the SRC will evaluate the appropriateness of dosing at a previously evaluated lower dose or exploring an intermediate dose level.

For any subject death within 30 days of study therapy, enrollment will be held pending review of the event by the SRC. Active dosing in ongoing subjects will continue at the discretion of the treating site's PI and the Medical Monitor pending the SRC review.

7.11. Principal Investigator

The Principal Investigator (PI) for study reporting purposes will be determined by the time of database lock. The PI will be chosen based on his or her contributions to the study design and/or analysis.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

The eligible study population includes pediatric subjects with a) recurrent or refractory supratentorial brain tumors, not in direct continuity with the ventricular system, that are unresponsive to conventional treatment or for which there is no alternative curative therapy (Arm 1) and b) non-disseminated DIPG post prior standard focal radiotherapy and for which a biopsy has previously been obtained (access to results required; access to tissue preferred) (Arm 2).

Inclusion Criteria:

1. Male or female subjects ≤ 21 years-of-age with the demonstrated ability to swallow capsules whole and who are willing to provide access to previously obtained biopsy results
2. Provision of written informed consent and assent, when applicable, for tumor resection, stereotactic surgery, tumor biopsy, sample collection, and/or treatment with study drug prior to undergoing any study-specific procedures
3. **Arm 1**: Evidence of recurrent or progressive supratentorial tumor, which has shown a > 25% increase in bi-dimensional measurements by MRI or is refractory with significant neuro-deterioration that is not otherwise explained with no known curative therapy, not in direct continuity with the ventricular system (e.g., there is physical separation between the tumor and ventricle, the tumor does not open directly into the ventricular system).

   Arm 2: Clinical presentation of DIPG and compatible MRI with approximately 2/3 of the pons included and without evidence of dissemination. Subjects should be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (*i.e.*, dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m2/day).
4. 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. Targeted agents, including small-molecular tyrosine kinase inhibitors: 2 weeks
   b. Other cytotoxic agents: 3 weeks
   c. Nitrosoureas: 6 weeks
   d. Monoclonal antibody immunotherapies (*e.g.*, PD-1, CTLA-4): 6 weeks
   e. Vaccine-based and/or viral therapy: 3 months
5. On a stable or decreasing dose of dexamethasone for the previous 7 days
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment
7. Have age-appropriate functional performance:
   a. Lansky score ≥ 40 (Appendix 1) or
   b. Karnofsky score > 50 (Appendix 2) or
   c. Eastern Cooperative Oncology Group (ECOG) score ≤ 2 (Appendix 3)

8. Have adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
    a. Hemoglobin ≥ 8 g/L
    b. Absolute lymphocyte count ≥ 500/mm^3
    c. Absolute neutrophil count ≥ 1000/mm^3
    d. Platelets ≥ 100,000/mm^3 (untransfused [> 5 days] without growth factors)
    e. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) for age
    f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN for age
    g. Total bilirubin < 1.5 x ULN for age
    h. International normalized ratio (INR) and activated thromboplastin time within normal institutional limits
9. Male and female subjects of childbearing potential must agree to use a highly reliable method of birth control (expected failure rate < 1% per year) from the Screening Visit through 28 days after the last dose of study drug. Women of childbearing potential must have a negative pregnancy test at screening.

8.2. Exclusion Criteria

1. Radiotherapy treatment prior to the first veledimex dose:
    a. Focal radiation ≤ 4 weeks
    b. Whole-brain radiation ≤ 6 weeks
    c. Cranio-spinal radiation ≤ 12 weeks

    Note: Subjects in Arm 2 (*i.e.*, with DIPG) must be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m^2/day) per Inclusion Criterion 3 above.
2. Subjects with clinically significant increased intracranial pressure (*e.g.*, impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
3. Subjects whose body surface area (BSA) would expose them to < 75% or > 125% of the target dose per the provided dosing table
4. Known immunosuppressive disease, autoimmune condition, and/or chronic viral infection (*e.g.*, human immunodeficiency virus [HIV], hepatitis)
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 (EIAEDs) within 7 days prior to the first dose of study drug. See Appendix 4 for prohibited and permitted antiepileptic drugs.
7. Other concurrent clinically active malignant disease, requiring treatment
8. Nursing or pregnant females
9. Prior exposure to veledimex

10. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 within 7 days prior to veledimex dosing without consultation with the Medical Monitor
11. Use of heparin or acetylsalicylic acid (ASA) without consultation with the Medical Monitor
    a. The use of systemic heparinization, or any ASA containing medications, is prohibited during active dosing with veledimex. Prophylactic s.c. heparin, per institutional protocol, or heparin used for maintaining patency of an access port of PICC line is permitted.
12. Presence of any contraindication for a neurosurgical procedure
13. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator in conjunction with the Medical Monitor, jeopardize the safety of a subject and/or their compliance with the protocol

8.3. Subject Enrollment

Approximately 45 subjects may be enrolled into the study.

8.4. Subject Withdrawal Criteria

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** discontinue study treatment prematurely for any of the following reasons:

- The Investigator determines further participation is not in 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** discontinue study treatment in the event of any of the following:

- Subject request to end study treatment
- Any treatment-related AE(s) that meet withdrawal criteria
- Substantial noncompliance with study requirements
- 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

A subject **MUST** be withdrawn from the study in the event of any of the following:

- Withdrawal of informed consent for the study
- Ad-RTS-hIL-12 injection was not injected

Every effort should be made to follow subjects who withdraw from study treatment for ongoing treatment-related AEs until resolved, no resolution is expected, or the study has ended.

8.5. Replacement of Subjects

Subjects who withdraw from the study during the DLT evaluation period (Day 0 to Day 28) for reasons other than toxicity or disease progression may be replaced.

8.6. 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 CRFs, 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; a center's decision to re-challenge subject 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.

9. INVESTIGATIONAL PRODUCT

9.1. Preparation of Ad-RTS-hIL-12

Ad-RTS-hIL-12 will be supplied in single-dose vials. Information regarding the preparation of the Ad-RTS-hIL-12 dose is provided in the Pharmacy Manual.

9.2. Preparation of Veledimex

The Sponsor will provide veledimex capsules to be dispensed by the study site pharmacy to subjects for PO administration.

9.3. Handling and Storage

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

9.4. Treatment Compliance

The first veledimex dose is expected to be administered when the subject is at the clinical site, under careful 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 veledimex 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 they 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 of the daily dose, the time the subject ate breakfast, the number of capsules taken, whether the 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 or before Day 15, so that staff can properly assess dose compliance.

9.5. Disposition of Unused Drug

All unused Ad-RTS-hIL-12 and veledimex should be destroyed at the study site in accordance with standard institutional practice and in accordance with the United States Occupational Safety and Health Administration procedures, after full accountability has been documented. Any study drug destruction at the study site must be documented and records maintained in the Investigator's study file.

9.6. Accountability and Dispensation

The Investigator must maintain accurate records accounting for the receipt and dispensation of study drug. 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. TREATMENT ADMINISTRATION

10.1. Ad-RTS-hIL-12 Dosage and Administration Procedures

- In Arm 1, subjects will be given a cohort-specific dose of veledimex PO, on an empty stomach (excluding other medications) 3 (± 2) hours before craniotomy. 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.
- On Day 0, at the time of tumor resection (Arm 1) or tumor biopsy (Arm 2), tumor and blood samples will be collected per the Schedule of Assessments.
- Immediately after tumor resection (Arm 1) or tumor biopsy (Arm 2), when available, an intraoperative MRI can be performed to identify contrast-enhancing or T2/FLAIR hyper-intense residual tumor. The intra-operative MRI can be used to guide the Ad-RTS-hIL-12 injection into areas of contrast-enhancing tumor tissue. If intraoperative MRI is not available, the neurosurgeon will select sites for injection.
- Subjects will receive Ad-RTS-hIL-12 [redacted] for a total volume of 0.1 mL. Arm 1 subjects will receive Ad-RTS-hIL-12 by [redacted] injection into approximately two sites within the residual tumor. Arm 2 subjects will receive Ad-RTS-hIL-12 by stereotactic injection into the intratumoral site.
- The day of Ad-RTS-hIL-12 administration is designated as Day 0.

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 the subject is discharged. Subjects should be instructed to call the study physician or study nurse of they develop any symptoms after they are released from the hospital.

Maintaining adequate hydration is crucial. It is important that subjects be instructed repeatedly to maintain adequate oral hydration throughout the active veledimex dosing period; study sites must closely monitor the subject's hydration status. Blood pressure should be monitored regularly.

Administration of prophylactic antipyretics is strongly recommended during the first week after Ad-RTS-hIL-12 injection.

10.2. Veledimex Administration and Timing

In Arm 1, the first veledimex dose will be taken before administration of Ad-RTS-hIL-12 (3 hours ± 2 hours) on Day 0 on an empty stomach (excluding other medications), before craniotomy and tumor resection. After the initial dose of veledimex, subjects will continue QD veledimex for an additional 14 days. Subjects in Arm 1 will receive up to a total of 15 veledimex doses.

In Arm 2, the first veledimex dose will be taken the day after administration of Ad-RTS-hIL-12 (*i.e.*, on Day 1). After the initial dose of veledimex, subjects will continue QD veledimex for an additional 13 days. Subjects in Arm 2 will receive up to a total of 14 veledimex doses.

In both study Arms, veledimex doses (Days 2 to 14) are to be taken QD and at approximately the same time of day (± 1 hour) as the Day 1 dosing and within approximately 30 minutes of completion of a regular meal. There should be a minimum of 10 hours between veledimex doses.

All veledimex doses will be recorded and safety monitored. If Ad-RTS-hIL-12 injection is not performed, subjects will not receive subsequent veledimex dosing.

11. CONCOMITANT THERAPY

Information on concomitant medications, including all medications, blood products, vitamins, and other supplements, will be collected from Screening through the Initial Follow-Up Period (Day 56). Subjects will be followed to document other anticancer therapies for two years following administration of Ad-RTS-hIL-12 (Day 0).

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 the individual subject. 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.
- Antidiarrheal therapy is permitted
- Anti-emetics are permitted for nausea and vomiting

11.2. Prohibited Medications

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 antiepileptic drugs (EIAEDs) are listed in Appendix 4 and are NOT permitted.
- CYP450 3A4 inducers, inhibitors, or substrates (including vitamins and/or herbal supplements) are prohibited prior to the first dose of veledimex until after the last dose of veledimex. Consultation with the Medical Monitor is required.
- Vitamins and/or herbal supplements are not recommended prior to the first dose of veledimex and until after the last dose of veledimex due to potential drug-drug interactions. Consultation with the Medical Monitor is required.

12. STUDY PROCEDURES

12.1. Written Informed Consent

The written ICF or assent form, as applicable, must be signed before any protocol-specific procedures and assessments can be performed. A copy of the signed ICF or assent form, as applicable, will be given to the subject and a copy should be filed in the medical record. The original ICF or assent form 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 or assent form can be used if they were conducted within the timeframe of the Screening Period. Refer to 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 will be enrolled and assigned a unique study identification number before the planned intratumoral Ad-RTS-hIL-12 injection. Once assigned, a subject's identification number will not be reused.

12.3. Schedule of Procedures and Observations

Screening assessments must be performed within 28 days prior to Ad-RTS-hIL-12 injection. All study visits must be completed as described in the protocol while subjects are taking veledimex capsules. Initial follow-up period and long-term follow-up period assessments are allowed a window of ± 7 days.

12.3.1. Study Tests, Exams, and Procedures

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 the Initial Follow up Period (Day 56). Subjects will be followed to document other anticancer therapies for two years following administration of Ad-RTS-hIL-12 (Day 0).

Physical Examinations

A complete physical examination, which includes a neurological examination will be completed and documented per the Schedule of Study Procedures (Table 1).

Vital Signs, Height, and Weight

Vital signs will include blood pressure, pulse rate, temperature, and respiration rate. Subject's blood pressure is to be monitored closely, with hydration as needed to prevent hypotension for 72 hours after administration of Ad-RTS-hIL-12. 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 the Schedule of Study Procedures (Table 1).

Lansky, Karnofsky, and ECOG Performance Status

The Lansky Performance Status measures the ability of subjects < 16 years-of-age with cancer to perform ordinary tasks; the Karnofsky scale is applicable to subjects ≥ 16 years-of-age. Scores for both assessments range from 0 to 100, with a higher score meaning that the subject is better able to carry out daily activities. The ECOG score is also used to describe a subject's functional status or decide if a subject can be enrolled in the clinical trial. The ECOG scale ranges from 0 to 5, with 0 indicating that a subject is fully active and a score of 5 indicating death.

These scales are used to determine prognosis, measure changes in a subject's ability to function, or decide if a subject can be enrolled in the clinical trial. Subjects must have a Lansky Performance Status score of ≥ 40 (Appendix 1), a Karnofsky Performance Status score of > 50 (Appendix 2), or an ECOG score of ≤ 2 to be included in the study (Appendix 3). Lansky, Karnofsky, or ECOG Performance testing will be conducted according to the Schedule of Study Procedures (Table 1).

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 after signing of the ICF or assent and through the Initial Follow-up Period (Day 56) must be recorded on the AE CRF. AEs that are ongoing at the end of the Initial Follow-up Period and are considered drug related should be followed until resolution or no resolution is expected.

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

Maintaining adequate hydration is crucial. It is important that subjects be instructed repeatedly to maintain adequate oral hydration throughout the active veledimex dosing period; study sites must closely monitor the subject's hydration status. Blood pressure should be monitored regularly.

Administration of prophylactic antipyretics is strongly recommended during the first week following Ad-RTS-hIL-12 injection.

Clinical Laboratory Assessments

All laboratory assessments should be collected prior to study drug administration, as applicable, unless otherwise stated.

In the event that the blood volume to be drawn on a given study day would exceed the allowable amount, the Principal Investigator and the Medical Monitor will discuss and determine the priority of testing to be completed to ensure patient safety.

The hematology panel comprises a complete blood count (CBC), including white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, erythrocyte sedimentation rate (ESR), and platelet count.

The coagulation panel includes: aPTT/PTT and INR.

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

The urinalysis panel (dipstick) includes: 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 clinically indicated.

Pregnancy Testing

Females of childbearing potential will have a serum pregnancy test at Screening and a urine or serum pregnancy test on Day -1 or Day 0, with a negative test result required prior to the first dose of study drug (either veledimex [Arm 1] or injection of Ad-RTS-hIL-12 [Arm 2]). Pregnancy tests will be repeated on Day 28.

MRI

Subjects should be able to undergo MRI scans with a contrast agent at Screening and during study participation. MRI scans should be sent to the Sponsor per the Sponsor's defined process.

Electrocardiogram

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

12.3.2. Screening

The screening exams, tests, and procedures that must be done within 28 days of Ad-RTS-hIL-12 injection are:

- Signed ICF and assent form, as applicable
- Medical/cancer history, including prior treatments
- Physical examination (including targeted neurological examination)
- Lansky Performance Status, Karnofsky Performance Status, or ECOG status
- Height and weight
- Vital signs
- AEs
- Concomitant medications, including medications taken within 28 days of Ad-RTS-hIL-12 injection
- Serum pregnancy test for females of childbearing potential
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin, ESR, and platelet count
- **Coagulation Panel including:** aPTT/PTT and INR
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate
- **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

- ECG
- Eligibility review
- Subject registration
- [redacted]
- MRI scan for surgical planning
- [redacted]
- [redacted]

12.3.3. Treatment Period – Days 0-14

- All assessments should be performed pre-dose, as applicable, unless otherwise stated.
- The site Investigator will communicate with the Medical Monitor during the active dosing period for all subjects on a daily basis regarding clinical status and laboratory values, prior to the patient receiving their daily dose of veledimex, and additionally as clinically indicated.
- Patient contact required daily to discuss clinical status and updates on current/new adverse events. If the patient is discharged prior to Day 14, follow-up may occur via telephone. Successful contact and contact attempts will be documented in EDC.
- Subjects should be instructed to remain in close proximity to the clinical site from Day 0-14.

12.3.4. Treatment Period Day 0 (Ad-RTS-hIL-12 + Veledimex Administration)

- Physical examination (including targeted neurological examination)
- Lansky Performance Status, Karnofsky Performance Status, or ECOG status
- Weight
- Vital signs
- AEs
- Concomitant medications, including medications taken within 28 days of Ad-RTS-hIL-12 injection
- Survival status
- Urine or serum pregnancy test for females of childbearing potential (may be replaced with testing on Day -1)
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count, and ESR, (may be replaced with testing on Day -1)

- **Coagulation Panel including:** aPTT/PTT and INR, (may be replaced with testing on Day -1)
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate (may be replaced with testing on Day -1)
- **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 (may be replaced with testing on Day -1)
- ECG (may be replaced with testing on Day -1)
- Confirm eligibility
- Arm 1: blood samples for veledimex PK pre-dose and at time of resection (see Table 2)
- [redacted]
- [redacted]
- Arm 1: a cohort-specific-veledimex dose 3 (± 2) hours prior to resection, on an empty stomach (excluding other medications)
- Arm 1: intratumoral Ad-RTS-hIL-12 administered by [redacted] injection
- Arm 1: tumor sample and CSF (if available) will be collected at time of resection
- Arm 2: intratumoral Ad-RTS-hIL-12 administered by stereotactic injection into the intratumoral site
- [redacted]
- Patient contact to discuss clinical status and updates on current/new adverse events
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.5. Treatment Period Day 1

- Physical examination (including targeted neurological examination)
- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin, ESR, and platelet count

- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary
- [redacted]
- Blood sample for veledimex PK (Arm 1: Table 2; Arm 2: Table 3)
- CT scan, as clinically indicated
- Patient contact to discuss clinical status and updates on current/new adverse events
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.6. Treatment Period Day 2

- Physical examination (including targeted neurological examination)
- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin, and platelet count and ESR
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary
- Blood sample for veledimex PK (Arm 1: Table 2; Arm 2: Table 3)
- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration
- MRI scan (a window of ± 24 hours is allowed). CSF may be collected at time of MRI via Ommaya reservoir. Collection is optional.
- [redacted]

12.3.7. Treatment Period Day 3

- Physical examination (including targeted neurological examination)

- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin, and platelet count, and ESR.
- **Coagulation Panel including:** aPTT/PTT and INR,
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate
- ECG
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary

[redacted]

- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.8. Treatment Period Days 4-6 (to occur Day 4, Day 5, and Day 6)

- AEs
- Concomitant medications
- Survival status
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin, and platelet count, and ESR.
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate

[redacted]

- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.9. Treatment Period Day 7

- Physical examination (including targeted neurological examination)
- Weight
- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count, ESR
- **Coagulation Panel including:** aPTT/PTT and INR,
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary
- [redacted]
- [redacted]
- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.10. Treatment Period Days 8-13

- AEs
- Concomitant medications
- Survival status
- For all subjects, a cohort-specific veledimex dose
- Complete veledimex dose diary
- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration

12.3.11. Treatment Period Day 14

- Physical examination (including targeted neurological examination)
- Lansky Performance Status, Karnofsky Performance Status, or ECOG status

- Weight
- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count, and ESR
- **Coagulation Panel including:** aPTT/PTT and INR
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, CRP, and bicarbonate
- **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
- ECG
- For all subjects, a cohort-specific veledimex doseComplete veledimex dose diary
- [redacted]
- Blood sample for veledimex PK (Arm 1: Table 2; Arm 2: Table 3)
- [redacted]
- [redacted]
- MRI scan. CSF may be collected at time of MRI via Ommaya reservoir. Collection is optional.
- Patient contact to discuss clinical status and updates on current/new adverse events.
- PI/MM contact regarding clinical status and laboratory values, prior to veledimex administration
- [redacted]

12.3.12. Initial Follow-Up Period Day 15

- AEs
- Concomitant medications
- Survival status
- Blood sample for veledimex PK (Arm 1: Table 2; Arm 2: Table 3)

12.3.13. Initial Follow-Up Period Day 28 (± 7 days)

- Physical examination (including targeted neurological examination)
- Lansky Performance Status, Karnofsky Performance Status, or ECOG status
- Weight
- Vital signs
- AEs
- Concomitant medications
- Survival status
- **Hematology Panel including:** CBC, including WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count, and ESR
- **Serum Chemistry Panel including:** AST, ALT, LDH, ALP, lipase, amylase, creatinine, total bilirubin, total protein, albumin, BUN, glucose, sodium, potassium, chloride, calcium, phosphorus, and bicarbonate
- Urine or serum pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- [redacted]
- MRI scan. CSF may be collected at time of MRI via Ommaya reservoir. Collection is optional.
- [redacted]

12.3.14. Initial Follow-Up Period Day 56 (± 7 days)

- AEs
- Concomitant medications
- Survival status
- MRI scan. CSF may be collected at time of MRI via Ommaya reservoir. Collection is optional.
- **Arm 2**: A tumor sample should be collected once there is a concern of pseudo-progression. The biopsy at Day 56 is strongly recommended. Patients should remain on-study for continued follow-up until confirmed progression per iRANO or the patient meets other withdrawal criteria.
- [redacted]

12.3.15. Long-Term Follow-Up (every 8 weeks ± 1 week)

- Concomitant medications (subjects will be followed to document start of new anticancer treatments and survival status for two years following administration of Ad-RTS-hIL-12, [Day 0])
- MRI scan. CSF may be collected at time of MRI via Ommaya reservoir. Collection is optional.

[redacted]

12.3.16. Unscheduled Visit Collections

In the event of subject termination or an unscheduled visit for a drug-related AE, an unscheduled visit kit should be obtained [redacted] for CSF evaluation, if applicable.

[redacted]

- A tumor sample should be collected if there is a concern of pseudo-progression. The biopsy at Day 56 is strongly recommended. Patients should remain on-study for continued follow-up until confirmed progression per iRANO or the patient meets other withdrawal criteria.
- CSF may be collected at time of the time of MRI scans such as if sedation is clinically indicated or if an Ommaya reservoir is implanted. Collection is optional.

13. TUMOR RESPONSE ASSESSMENTS

13.1. Tumor Response

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

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 on Day 2 (a window of ± 24 hours is allowed). The Ad-RTS-hIL-12-injected lesion and/or other measurable brain lesions will be measured according to the iRANO criteria guidelines for adults, pending issuance of pediatric criteria (Okada, Weller et al. 2015) (see Appendix 6). MRI scans will be collected and stored at the study site and each subject will be evaluated for response by the study Investigator. MRI scans and reports should be sent to the Sponsor per the Sponsor's defined process. 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 tumor sample should be collected if there is a concern of pseudo-progression. The biopsy at Day 56 is strongly recommended. Repeat scans to confirm progression should be completed at 4 weeks and preferably again at 12 weeks (per iRANO) after first documentation of progression, if within 6 months of starting investigational therapy. 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 bidimensional tumor size as per iRANO criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease.

Tumor response assessments will occur at Day 14, at 4 weeks (Day 28 ± 7 days), at 8 weeks (Day 56 ± 7 days), and every 8 weeks (± 7 days) 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 two years following administration of Ad-RTS-hIL-12 (Day 0), 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, treated 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, pseudo-progression is unlikely to impact the duration of Ad-RTS-hIL-12 + veledimex therapy since the veledimex treatment period lasts 14 (Arm 2) to 15 (Arm 1) days. Imaging assessments

will be performed using iRANO criteria. A tumor sample should be collected once there is a concern for pseudo-progression as noted above. The biopsy at Day 56 is strongly recommended. Patients should remain on-study for continued follow-up until confirmed progression per iRANO or the patient meets other withdrawal criteria.

14. ASSESSMENT OF SAFETY

Safety will be evaluated in the Overall Safety Population (OSP) and the Evaluable Safety Population (ESP) using CTCAE v5.0.

The OSP includes all subjects who received at least 1 dose of veledimex or Ad-RTS-hIL-12.

The ESP includes all subjects who received Ad-RTS-hIL-12 and at least one dose of veledimex after Ad-RTS-hIL-12 administration, and are BSA conformant.

14.1. Adverse Events and Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign including an abnormal laboratory finding, symptom, 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.

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 a lesser degree of certainty about causality than an adverse reaction.

Adverse Reaction

Any AE caused by the use of 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.

Unexpected Adverse Reaction

Any AE that is (a) not listed as an adverse drug reaction in the 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.
- In the event that 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; however, the presenting sign or symptom of the disease progression should be documented as an AE (*e.g.*, increase in pain). However, if a subject experiences progression of disease that results in death, "progression of disease" should be reported as an SAE if, by medical opinion, the term best describes the cause of death.

Adverse events will be recorded from the time of consent and followed through the initial follow-up period (Day 56). AEs that are ongoing at Day 56 and considered 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 30 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. Important medical events also include:
  - New cancer: Occurrence or diagnosis of a new cancer during the trial is considered an SAE (this does not pertain to metastasis of current disease);
  - Any AE associated with an overdose of the study drug: An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the Investigator per protocol.

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, v.5.0. If the AE is not defined in the NCI CTCAE, v.5.0, the Investigator will determine the severity of an AE based on the following definitions:

- 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 drug 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, 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 study drug:

- **Unrelated**: The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study subject's medical record and/or SAE form).
- **Unlikely related**: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

Relationship assessments that indicate "Related" to study drug:

- **Possibly related**: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
- **Probably related**: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.
- **Related**: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out and/or the event re-appeared on re-exposure to the study drug.

For any untoward medical occurrence that starts before administration of study drug, only those that are assessed by the Investigator as protocol related should be reported to the Sponsor as an adverse event. If deemed unrelated to a study-specific procedure, the event should be added to the Medical History eCRF.

The following guidelines should be used by Investigators to assess the relationship of an untoward medical occurrence 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 electronic CRF from the time the subject signs the ICF or assent form through the initial follow-up period (Day 56). AEs that are ongoing at the end of the Initial Follow-up Period and are considered drug related should be followed until resolution or no resolution is expected.

Each event will be assessed for serious criteria, severity, and causality. 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 drug, and the outcome of the AE will also be noted.

14.7. Reporting Dose-Limiting Toxicities and Serious Adverse Events

Time Frame for Reporting

All DLTs and SAEs 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 death or SAE experienced by the subject from the signing of informed consent through the initial follow-up period (Day 56), regardless of relationship to study drug.
- Any death or SAE that the Investigator becomes aware of, and believes to be study drug related, that occurs beyond Day 56.

[redacted]

Questions or assistance with completing forms can be directed to Ziopharm Oncology, Drug Safety and Pharmacovigilance: [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 other National Regulatory Authority 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.

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 a 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. A 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. A DLT specific form will be used to report DLTs and is also provided in the Investigator files. Please refer to the Investigator study files for instructions on how to complete these forms. The Investigator will provide all of the following information related to the event:

- Investigator identification
- Subject identification (*e.g.*, subject number, initials, sex, and age or date of birth)

- Information regarding study drug administration (*e.g.*, start/stop date, dose, and frequency)
- Day of SAE or DLT occurrence documentation on SAE or DLT report forms
- Description of event
- Action taken with the study drug in relation to the SAE or DLT
- Outcome of the SAE or DLT

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 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 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

Safety data will be reported from the time of consent, as applicable, through the initial follow-up period (Day 56). Ongoing drug-related AEs should be followed until resolution unless none is expected.

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

Study drug overdose of a subject, with or without associated AEs/SAEs, should be reported within 24 hours of awareness to the Sponsor (Ziopharm Oncology, Drug Safety and Pharmacovigilance, [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. PHARMACODYNAMIC, PHARMACOKINETIC, AND IMMUNOLOGIC ASSESSMENTS

15.1. Veledimex Pharmacokinetic Assessments

In the event that the blood volume to be drawn on a given study day would exceed the allowable amount, the Principal Investigator and Medical Monitor will discuss and determine the priority of testing to be completed to ensure patient safety.

Veledimex PK assessments will occur for all subjects during study treatment and any expansion cohorts. Whole blood samples will be collected at the time points specified in the Schedule of Veledimex Pharmacokinetic Sampling Times for Arm 1 (Table 2) and Arm 2 (Table 3). Veledimex plasma concentrations will be determined using a fully validated liquid chromatography mass spectrometry assay.

16. STATISTICAL METHODS

This study is designed as a multicenter Phase I/II dose escalation study in pediatric subjects with brain tumors. Enrollment in Arm 1 Cohort 1 is open to subjects except those with DIPG; enrollment in Arm 2 (*i.e.*, Cohorts 3 and 4) is open to subjects with DIPG only. Cohorts will be enrolled according to a standard 3 + 3 design (see Section 7.1).

The primary analysis will be performed after all subjects complete the Initial Follow-up Period (Day 56). Additional analyses will be performed to determine ORR, PFS, and OS. The final analysis will be performed when the last subject completes two years of follow-up.

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.

16.1. Populations for Analysis

This is an amendment to an ongoing study that has been previously described. For all practical purposes the connotation of the safety population for the planned safety analysis are subjects being denoted in defining the overall safety population (OSP) defined below to distinguish this group from the subgroup of subjects denoted as the evaluable safety population (ESP) who must receive Ad-RTS-hIL-12 and at least one dose of veledimex after injection.

This distinction provides for inclusion of both drug components (Ad-RTS-hIL-12+ veledimex) in order to evaluate dose escalation via the rule-based criteria fundamental to the 3+3 method. This means that during dose escalation if at least one of three Ad-RTS-hIL-12 treated subjects does not receive at least one dose of veledimex, additional eligible subjects will be enrolled as applicable in order to achieve the samples size of three evaluable subjects to assist the SRC's evaluation when making a dose escalation or a dose de-escalation decision. Specifically,

- The OSP will be used to perform safety evaluations for all subjects who have received at least one dose of veledimex or Ad-RTS-hIL-12.
- The ESP will include subjects who received Ad-RTS-hIL-12 and at least one dose of their cohort specific-dose of veledimex after Ad-RTS-hIL-12 administration and are BSA conformant. The ESP will be used to make decisions regarding escalation to higher veledimex doses for Arms 1 and 2 separately, based on a standard 3 + 3 design, as described in Section 7.3.
- The Pharmacokinetics Population (PKP) for veledimex includes all subjects who receive veledimex with sufficient PK timepoints.

Up to 30 evaluable subjects in the Phase II expansion cohort may be enrolled to provide time to OS estimation. This subgroup will include subjects treated with both Ad-RTS-hIL-12 and at least one dose of veledimex as defined by the ESP and other evaluability criteria described in the Statistical Analysis Plan.

16.2. Sample Size and Power Calculations

- The sample size chosen was based on clinical considerations.

- For Cohorts 1 and 3, treated at 10 mg, the 3+3 rule-based dose escalation criteria will be applied to provide an independent algorithmic safety assessment to either dose escalate from 10 to 20 mg or to consider de-escalation, as applicable. The SRC will incorporate the findings in combination with other clinical factors to make the final recommendation pertaining to dose escalation from 10 mg to 20 mg or de-escalation from 10 mg to 5 mg.
- For Cohort 4, treated at 20 mg, the 3+3 rule-based dose escalation criteria will be applied to provide an independent algorithmic safety assessment to either confirm that 20 mg dosing is safe or to potentially de-escalate to a 15 mg dose for further evaluation based on the SRC recommendation.

After the dose escalation/de-escalation portion of the study Phase II dose will be determined for both pediatric disease populations:

- recurrent or refractory supratentorial brain tumor pediatric population
- DIPG pediatric population

At the discretion of the SRC, up to 30 evaluable DIPG subjects may be enrolled in the Phase II expansion cohort, which will support time to OS estimation. The projection of this sample size is based on clinical considerations as well as numbers to obtain sufficient preliminary assessments of overall response. Additional details will be provided in the Statistical Analysis Plan.

16.3. Endpoints

16.3.1. Primary Endpoint

- The primary endpoint is the assessment of safety and tolerability of Ad-RTS-hIL12, administered by intratumoral injection plus veledimex administered PO, as determined by the AE rate and the occurrence of DLTs analyzed specifically for each cohort.

16.3.2. Secondary Endpoints

- Determination of the recommended Phase II pediatric veledimex dose when given with intratumoral Ad-RTS-hIL-12 [redacted]
- Veledimex PK estimates
- The ratio of the concentration of veledimex in the brain tumor and the blood [redacted]
- Investigator assessment of response, including ORR and PFS
- OS

[redacted]

16.4. Analyses

16.4.1. Baseline Demographics and 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 based on non-missing values. For continuous variables, the mean, median, standard deviation, minimum, and maximum values will be presented. Data will be summarized by dose cohort and according to the defined populations for analysis.

16.4.2. Safety Analyses

For the first veledimex dose cohorts in Arms 1 and 2 (*i.e.*, Cohorts 1 and 3, respectively), a minimum of three ESP subjects must be eligible for evaluation of safety. In addition, evaluation of any DLTs will be performed according to protocol-defined criteria. Safety variables will be tabulated and presented by arm and by dose cohort.

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, 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 subject signs the ICF or assent form, as applicable, through the Initial Follow-up Period (Day 56), unless the subject discontinues from active follow-up due to one of the following reasons:

- Symptomatic deterioration also denoted symptomatic progression
- Loss to follow up
- Noncompliance with the protocol
- Other reason not listed above

Exposure to study drug(s) and reasons for discontinuation of study treatment will be tabulated. All treatment emergent- AEs (TEAEs) will be coded according to the System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). The TEAEs will be tabulated by number and percent of subjects according to relationship to the study drug(s), severity, and seriousness. A TEAE 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.

After the conclusion of the safety evaluation period is triggered by a discontinuation event, the subject continues to be followed only for OS.

Laboratory parameters will be summarized by visit. Listings of vital signs and physical examination data will be listed by visit.

16.4.3. Tumor Response and Overall Survival Analyses

Tumor response analysis will be performed on the ESP. The Investigator assessment of ORR and PFS will be determined for each cohort according to the baseline (Day 2 ± 24 hours) assessment, with tumor response characterized by iRANO (Okada, Weller et al. 2015) criteria for adults, pending issuance of pediatric criteria. The OS is defined as the duration of time from the first dose of study drug to the date of death or, for subjects who are still alive two years after first dose of study drug, subjects will be censored at the last follow-up contact date. A 2-sided confidence interval will be computed for the ORR. The PFS and OS will be analyzed using Kaplan-Meier methods.

16.4.4. [redacted], PK, and [redacted]

Veledimex PK parameters will be determined based on blood (plasma) levels of veledimex using [redacted] here possible, descriptive statistics of the PK parameters will be provided; individual subject veledimex concentrations, actual sampling times, and PK parameters will be listed. [redacted]

16.4.5. Multi-Center Study

Tumor response and safety data will be presented for each dose cohort pooled over all study centers.

16.4.6. Adjustments for Covariates

No adjustments for covariates will be made.

16.4.7. 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.

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 and sufficient training on the electronic data capture (EDC) application to permit site personnel to enter and/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 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 eCRFs. 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 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.

The 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. Study 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. An initiation visit 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 and 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, which 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 monitor. The monitor also will perform drug accountability checks and 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 regulatory authorities.

17.4. Duration of the Study

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

The overall duration is expected to be up to 2 years and 28 days for an individual subject, including the following:

- Screening period of up 28 days
- Study treatment period of up to 15 days
- 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 per iRANO has been documented. Subjects will be followed for survival status for two years after Ad-RTS-hIL-12 injection. The active study period refers to the study period from informed consent through the Survival 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 two 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 and assent form 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. As part of the review of the study, the IRB/IEC will be provided the protocol, the Investigator Brochure, and informed consent documents, including age appropriate assent forms per each institution's standards in order to determine that the study meets the requirements of 21 CFR 312.50, Subpart D. During the course of the study, the Investigator shall make timely and accurate reports to the IRB/IEC on study

progress at intervals not exceeding one 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 three 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 HIPPAA

The ICF and assent form 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 ICF and assent form will also explain that, for data verification purposes, authorized representatives of Ziopharm, a regulatory authority (*e.g.*, 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 ICF and assent form 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 and assent form 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. If the prospective subject voluntarily agrees to and signs the informed consent statement, he/she may enroll into the study. A copy of his/her signed and dated informed consent will be provided to each prospective subject. The signed ICF and assent form are to remain in the Investigator's file.

The ICF, assent form, 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 or assent form, if applicable. Any written ICF, assent form, 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 and assent form for modification, as appropriate, by the Investigator.

17.9. Audits and Inspections

Authorized representatives of Ziopharm, a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Ziopharm audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact Ziopharm immediately if contacted by a regulatory agency about an inspection.

18. PROTOCOL APPROVAL

A Phase I/II Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects

With the exception of 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 approved protocol will be documented. Any significant deviation or deviation related to dosing or safety evaluation will be reported to Ziopharm.

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: _____

19. [redacted]

[redacted]

20. APPENDICES

APPENDIX 1. LANSKY PERFORMANCE STATUS

Lansky Performance Status Scale Definitions Rating Criteria	
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Lansky et al, 1987

APPENDIX 2. KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Status Scale Definitions Rating (%) Criteria		
Able to carry on normal activity and work; no special care needed.	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs of symptoms of disease
	80	Normal activity with efforts; some signs of symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of ≥ or hospital care; diseases may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active support treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993, 109.

APPENDIX 3. ECOG PERFORMANCE STATUS

ECOG Performance Status Scale Definitions Rating Criteria	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken et al, 1982

APPENDIX 4. PROHIBITED AND PERMITTED ANTIEPILEPTIC DRUGS

Prohibited Enzyme-Inducing Antiepileptic Drugs	Permitted Antiepileptic Drugs
Dilantin® (phenytoin)	Depakote®, Depakene® (valproic acid)
Felbatol® (felbamate)	Gabitril® (tigabine)
Mysoline® (primidone)	Keppra® (levetircetam)
Solfoton®, Luminal® (phenobarbital)	Lamictal® (lamotrigine)
Tegretol® (carbamazepine)	Neurontin® (gabapentin)
Trileptal (oxcarbazepine)	Topamax® (topiramate)

APPENDIX 5. 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 recombinant adenovirus vector administration and temperatures up to 40°C or 104° F with chills and generalized malaise have been observed with treatment. Because low grade fever is very likely to occur during study treatment, anti-pyretic medication is recommended at the situation.

Acetaminophen and ibuprofen are commonly used anti-pyretic medication for pediatric patients. Both are available without a prescription. Current evidence suggests that there is no substantial difference in the safety and effectiveness of acetaminophen and ibuprofen in the care of a generally healthy child with fever. Severe side-effects of acetaminophen and ibuprofen are rare, over doses of acetaminophen may cause liver failure. Patients with liver disease should avoid using acetaminophen. Nephrotoxicity of ibuprofen were reported in children with dehydration. Therefore, precaution should be taken for using ibuprofen in patients with dehydration or kidney diseases. Some people may be allergic to the medications.

Alternating doses of ibuprofen and acetaminophen will also effectively control fever and prevent accidental overdose. Although some reports indicated that combination of both may result in a lower body temperature for a greater period of time, However, there is a lack of proven efficacy and safety evidence of the combination ibuprofen and/or acetaminophen should be taken in accordance with the package label.

APPENDIX 6. 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

PROTOCOL AMENDMENT SUMMARY

Protocol Title:	A Phase I Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects
Protocol Number:	ATI001-103
Study Drug:	Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand)
Date of Protocol:	Amendment 1: 25September2017 Original: 04April2017

NOTE TO INVESTIGATORS

Amendment 1 dated 25 September 2017 will be used to conduct the study in place of any preceding version of this protocol. ZIOPHARM Oncology will implement this version as of 25 September 2017. This protocol should be submitted to your IRB promptly.

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AMENDMENT 1

ATI001-103

1. Summary and Rationale for Changes

ZIOPHARM is amending the clinical protocol for the ATI001-103 study, "A Phase I Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects" to provide updated guidance to the investigator based on discussions with FDA, and updated SAE reporting process and to administrative edits for internal consistency purposes.

2. Tabular Summary of Revisions Implemented in the Amended Protocol

Updates due to FDA request:

Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
Study Design	~~The first subject~~ Each subject in each cohort will be monitored for 2~~1~~8 days after Ad-RTS-hIL-12 injection before additional subjects are enrolled in the same cohort. The evaluation period for DLT is 28 days after Ad-RTS-hIL-12 injection (Day 0 to Day 28).	[redacted]
Inclusion Criteria 3	Arm 1: Evidence of recurrent or progressive supratentorial tumor, which has shown a > 25% increase in bi-dimensional measurements by MRI or is refractory with significant neuro-deterioration that is not otherwise explained with no known curative therapy, not in direct continuity with the ventricular system (e.g., there is physical separation between the tumor and ventricule, the tumor does not open directly into the ventricular system).	[redacted]
Inclusion Criteria 8	Have adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements: a. Hemoglobin ≥ 8 g/L b. Absolute lymphocyte count ≥ 500/mm^3 c. Absolute neutrophil count ≥ 1000/mm^3 d. Platelets ≥ 100,000/mm^3 (untransfused [> 5 days] without growth factors) e. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) for age f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤~~5~~ 2.5 x ULN for age g. Total bilirubin < 1.5 x ULN for age	[redacted]

Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
	h. International normalized ratio (INR) and activated thromboplastin time within normal institutional limits	
Study Drug Dose and Mode of Administration	If a subject's BSA would expose the subject to < 75% or > 125% of the target assigned dose, the actual administered dose will be modified to ensure that the target mg/m^2 dose is achieved. Minimum BSA restrictions for enrollment must be met in order for a subject to be appropriately dosed. Potential subjects whose BSAs do not have a correlated administered dose may be enrolled at the discretion of the Investigator and the Medical Monitor, but will not be considered in the assessment of the recommended pediatric Phase II dose. Dosing of these subjects can only commence once the cohort has been reviewed by the SRC and determined that the dosing at the specified level (10 mg or 20 mg) is appropriate for escalation or as the recommended Phase 2 pediatric dose. These subjects will be analyzed separately.	[redacted]
Definition of DLT	• Any Grade 3 or higher non-hematologic adverse event that is at least possibly related to study drug and lasts ≥ 3~~5~~ days • ~~If judged appropriate by the SRC, certain DLTs that would otherwise preclude dose escalation (eg, observed in the presence of a prohibited CYP450 3A4 medication) may not limit the ability to escalate to the next dose.~~	[redacted]
7.1 Overall Study Design	Table 4 was updated to Table 4a and re-named ATI1-001 103 Cohorts. The following footnote was added: Doses are BSA-adjusted doses. Table 7 was updated and moved to become Table 4b (Veledimex Dosing Table). Moved from Section 10.2.1, BSA-Adjusted Dosing ~~Table 4: ATI1-001 Study Design~~ The starting dose in Cohort 1 will be 10 mg, which is approximately 5.3 mg/m2. The actual administered dose will depend on the subject's BSA and available capsule sizes (Table 4b). Because veledimex is an PO agent and is supplied in a fixed capsule size (5 mg and 20 mg), the actual administered dose is based on a subject's BSA and is bound by the rounding constraints set by 5 mg. The Sponsor developed a BSA-adjusted dosing algorithm designed to enable dosing within 25% of the target mg/m2 dose. If a subject's BSA would expose the subject to < 75% or > 125% of the target assigned dose, the actual administered dose will be modified to ensure that the target mg/m^2 dose is achieved. Minimum BSA restrictions for enrollment must be met in order for a subject to be appropriately dosed. Potential subjects whose BSAs do not have a	[redacted]

Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
	correlated administered dose may be enrolled at the discretion of the Investigator and the Medical Monitor, but will not be considered in the assessment of the recommended pediatric Phase 2 dose. Dosing of these subjects can only commence once the cohort has been reviewed by the SRC and determined that the dosing at the specified level (10 mg or 20 mg) is appropriate for escalation or as the recommended Phase 2 pediatric dose. These subjects will be analyzed separately. The dosing table (Table 4b) illustrates this algorithm and captures the BSA-adjusted actual administered dose that subjects would receive at assigned dose levels based on a minimum capsule size of 5 mg.	
7.3 Dose Escalation and De-Escalation Decision Rules	~~If in the de-escalation cohort there are fewer than 2 DLTs, the SRC may determine that the recommended pediatric Phase II dose has been reached or may consider escalating by 5 mg (eg, 10 mg up from 5 mg).~~	[redacted]
7.4 Dose-Limiting Toxicity	~~If judged appropriate by the SRC, certain DLTs that would otherwise preclude dose escalation (eg, observed in the presence of a prohibited cytochrome p450 (CYP450) 3A4 medication) may not limit the ability to escalate to the next dose.~~	[redacted]
14.8. Sponsor and Investigator Responsibility for 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 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.	[redacted]
17.6. Institutional Review Board / Independent Ethics Committee	As part of the review of the study, the IRB/IEC will be provided the protocol, the Investigator Brochure, and informed consent documents, including age appropriate assent forms per each institution's standards in order to determine that the study meets the requirements of 21 CFR 312.50, Subpart D.	[redacted]

Updates due to new SAE reporting process:

Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
14. 7. Reporting Dose-Limiting Toxicities and Serious Adverse Events	[redacted]	[redacted]

Updates for internal consistency:

Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
Synopsis (Study Design)	Each cohort will consist of subjects ≤ 21 years-of-age who meet eligibility criteria. Once the last subject in Cohort 1 completes the dose-limiting toxicity (DLT) evaluation period and the SRC has approved, enrollment may be opened for Cohort 2 and Cohort 3. Once the last subjects in ~~Cohorts 2 and~~ Cohort 3 completes the DLT evaluation period and the SRC has approved, enrollment may be opened for Cohort 4.	Updated for internal consistency with section 7.2.
Tables 2 and 3	[b] PK Collections: post-dose PK collections will have a ± 30-minute draw window	Added for clarity
Table 5	Moved from the body of the table to after the table: After completion of a cohort, if it has been determined that the recommended pediatric Phase 2 dose has not been reached, escalation to the next cohort will proceed once recommended and authorized by the SRC. Subject Count column added	Administrative change for clarity
7.4 Dose-Limiting Toxicity	• Nausea and vomiting will not be considered a DLT unless at least Grade 3 or 4 and refractory to antiemetics (i.e, defined as symptoms	Updated for clarity

	unrelieved by maximal medical support as directed by the PI (per institutional guidelines) in consultation with the medical monitor). • Any Grade 4 or higher hematologic toxicity (except thrombocytopenia) that is at least possibly related to study drug and lasts ≥ 5 days	

14.3.1. Serious Adverse Event	• 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. Important medical events also include:
	Updated formatting for the following (now sub-bullets) to the above:
	  • New cancer: Occurrence or diagnosis of a new cancer during the trial is considered an SAE. (This does not pertain to metastasis of current disease);
	  • Any AE associated with an overdose of the study drug: An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the Investigator per protocol.
		Administrative change for accuracy

Document	Minor wording updates and typographical/clerical updates were made throughout	Updated for clarity

PROTOCOL AMENDMENT

Summary of Changes

Protocol Title:	A Phase I/II Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects
Protocol Number:	ATI001-103
Study Drug:	Adenovirus-RheoSwitch Therapeutic System®-human interleukin-12 (Ad-RTS-hIL-12) and veledimex (RTS activator ligand)
Date of Protocol:	Amendment 2: 30Oct2019 Amendment 1: 25Sep2017 Original: 04Apr2017

NOTE TO INVESTIGATORS

Amendment 2 dated 30 October 2019 will be used to conduct the study in place of any preceding version of this protocol. Ziopharm Oncology, Inc. will implement this version as of 30 October 2019. This protocol should be submitted to your IRB promptly.

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ATI001-103 Amendment 2

1. Summary and Rationale for Changes

Ziopharm is amending the clinical protocol for the ATI001-103 study, "A Phase I/II Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects" based on meetings with the Safety Review Committee (SRC) to further explore Arm 2, which is in line with Ziopharm's long-term goal of impacting DIPG patients.

2. Tabular Summary of Revisions Implemented in the Amended Protocol

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
Title of Study	Section 1. Title Page Section 18. Protocol Approval	A Phase I**/II** Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects	Addition of Phase II expansion cohort in Arm 2 to provide a better estimate of overall survival.
Primary, Secondary, and Exploratory Objectives	Section 6. Study Objectives	**Primary Objective:** • **Phase I/II:** To determine the safety and tolerability of intratumoral Ad-RTS-hIL-12 and varying ~~**PO**~~ veledimex doses **administered PO** in pediatric brain tumor subjects **(supratentorial and/or DIPG)** **Secondary Objectives:** • **Phase I:** To determine the recommended Phase II veledimex dose in pediatric brain tumor subjects when given with intratumoral Ad-RTS-hIL-12 **(supratentorial and/or DIPG)** • **Phase I/II:** To determine the pharmacokinetics (PK) of veledimex in subjects treated with	To align with addition of Phase II expansion cohort in Arm 2.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		Ad-RTS-hIL-12 + veledimex **(supratentorial and/or DIPG)** • **Phase I:** To determine the veledimex concentration ratio between the brain tumor and blood in subjects treated with Ad-RTS-hIL-12 + veledimex (Arm 1 only) • **Phase I/II:** To evaluate cellular and humoral immune responses elicited by Ad-RTS-hIL-12 + veledimex in pediatric brain tumor subjects **(supratentorial and/or DIPG)** • **Phase I/II:** To determine investigator assessment of response, including tumor objective response rate (ORR) and progression-free survival (PFS) of subjects treated with Ad-RTS-hIL-12 + veledimex **(supratentorial and/or DIPG)** • **Phase I/II:** To determine overall survival (OS) of subjects treated with Ad-RTS-hIL-12 + veledimex **(supratentorial and/or DIPG)** [redacted]	
N/A	Section 1. Title Page	[redacted]	[redacted]

<table>
<tr><th>Section in Clinical Protocol Summary (Section 4)</th><th>Section in Amended Protocol</th><th>Revised or Deleted Text/Section</th><th>Rationale for Change</th></tr>
<tr><td>Cohorts</td><td>Section 7.1 Overall Study Design</td><td>
Arm 1: This study has been modified to explore one veledimex dose in Arm 1: 10 mg.
Arm 2: This study is designed to explore <s>2</s>two veledimex doses in Arm 2: 10 mg and 20 mg. Subject enrollment and veledimex dose escalation will proceed according to a standard 3+3 design<s>, modified to independently evaluate 2 groups (ie, arms) of subjects that may exhibit different safety and tolerability profiles, with the</s> . The first cohort <s>of each arm receiving</s>will receive 10 mg veledimex followed by the second cohort <s>of each arm</s> receiving 20 mg veledimex.

Arm 1 and Arm 2 subjects may exhibit different safety and tolerability profiles. The 3+3 standard study design has been modified to independently evaluate the two arms separately.

The study arms and assigned doses will be divided into <s>4</s>three cohorts as shown below:
<table>
<tr><th><s>Cohort</s> Arm</th><th>Cohort <s>Arm</s></th><th>Procedure</th><th><s>Assigned</s> Veledimex Dose[a] Assigned</th></tr>
<tr><td>1</td><td>1</td><td>Craniotomy</td><td>10 mg</td></tr>
<tr><td><s>3</s>2</td><td><s>2</s>3[b]</td><td>Stereotactic</td><td>10 mg</td></tr>
<tr><td><s>4</s>2</td><td><s>2</s>4</td><td>Stereotactic</td><td>20 mg</td></tr>
</table>
[a] Doses are BSA-adjusted doses
[b] Arm 1 Cohort 2 was removed in Protocol Amendment 2. The SRC reviewed the safety profile of Arm 1 Cohort 1 and determined it was appropriate to move forward with Arm 1, Cohort 2 and Arm 2, Cohort 1, however due to issues with enrollment of supratentorial patients, it was determined not to proceed with Cohort 2.
</td><td>Removed Arm 1 Cohort 2. The SRC reviewed the safety profile of Arm 1 Cohort 1 and determined it was appropriate to move forward with Arm 1, Cohort 2 and Arm 2, Cohort 1, however due to issues with enrollment of supratentorial patients, it was determined not to proceed with Cohort 2.

Clarification that enrollment of an expansion cohort is considered the Phase II portion of the study.</td></tr>
</table>

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		Note: After the completion of a phase I dose escalation cohort in Arm 2, the SRC may elect to expand that cohort by up to 30 DIPG patients, which will be considered the Phase II component of the study.	
Safety Oversight for Safety Evaluation	Section 7.2 Study Oversight for Safety Evaluation Table 1: Schedule of Study Procedures Section 12.3.3 Treatment Period – Days 0-14	The first level of safety oversight will occur through the site Investigator ~~**and Medical Monitor.**~~ **in conjunction with the Medical Monitor. The site Investigator will communicate with the Medical Monitor during the active dosing period for all subjects on a daily basis regarding clinical status and laboratory values, <u>prior</u> to the patient receiving the daily dose of veledimex, and additionally as clinically indicated.**	Based on SRC discussions regarding DIPG population, ongoing communication with the patient and the Sponsor is useful to the Medical Monitor in providing ongoing guidance.
Dose Escalation/Cohort Expansion Dose De-Escalation	Section 7.3 Dose Escalation, Cohort Expansion, and De-Escalation Decision Rules	Dose Escalation/**Cohort Expansion:** **Each subject in each dose escalation cohort (3+3 standard design) will be monitored for 28 days before subsequent subjects are enrolled. The SRC will convene after the final subject in Cohort 1 completes the 28-day DLT evaluation period. The SRC will make a recommendation regarding:** **• Opening enrollment of Cohort 3** **• Discontinuing the investigation** **The SRC will convene once the third and/or final subject in Cohort 3 completes the 28-day DLT evaluation period. The SRC will make a recommendation regarding:** **• Expansion of Cohort 3 (Phase II portion)** **• Opening enrollment of Cohort 4** **• Discontinuing the investigation** **The SRC will convene once the third and/or final subject in Cohort 4 completes the 28-day DLT evaluation period. Cohorts 1 and 3 will be reviewed independently by the SRC.**	Removal of Arm 1 Cohort 2, as above, and addition of Phase II expansion cohort by up to 30 patients in Arm 2 to provide a better estimate of overall survival.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		The SRC will make a recommendation regarding: **• Expansion of Cohort 4 (Phase II portion)** **• Discontinuing the investigation** **In addition to recommending dose escalation, cohort expansion, or discontinuation of treatment, as noted above, the SRC may recommend dose de-escalation at any point based on safety review.** Dose De-Escalation: **Based on their review, the SRC will recommend either that the cohort continue at the existing veledimex dose, begin dosing at a lower dose level, or that other measures be undertaken, including discontinuation of treatment. If it is determined that escalationIf it is determined that dose escalation or cohort expansion** should not proceed, dose de-escalation may be undertaken and the SRC will consider de-escalating the veledimex dose as follows: • De-escalation by increments of 5 mg from the cohort in which **~~2~~two** or more DLTs were observed **(eg,*e.g.*,** 15 mg, de-escalated from 20 mg) • If there are **~~2~~two** or more DLTs in the dose de-escalation cohort, the SRC will consider de-escalating the veledimex dose by an additional increment of 5 mg (**~~eg,~~*e.g.*,** 5 mg down from 10 mg) or declaring a previously studied dose level the recommended **Phase II** pediatric **~~Phase II~~** dose.	
Number of Subjects (planned)	Section 8.3 Subject Enrollment	**~~Approximately 24~~Up to 45** subjects may be enrolled into this study, including 3 to 6 subjects per cohort**, and the expansion cohort, if recommended by the SRC.**	Removal of Arm 1 Cohort 2, as above, and addition of Phase II expansion cohort by up to 30 patients in Arm 2 to provide a better estimate

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
			of overall survival.
Inclusion Criteria	Section 8.1 Inclusion Criteria	**Arm 2**: Clinical presentation of DIPG and compatible MRI with approximately 2/3 of the pons included **and without evidence of dissemination.** Subjects should be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (*i.e.*, dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m^2/day).	To provide clarification on inclusion requirement.
Inclusion Criteria	Section 8.1 Inclusion Criteria	Have age-appropriate functional performance: a. Lansky score ≥ ~~50~~**40** (Appendix 1) or b. Karnofsky score > 50 (Appendix 2) or c. Eastern Cooperative Oncology Group (ECOG) score ≤ 2 (Appendix 3)	To ensure that eligible subjects are consistent across the different performance metrics.
Exclusion Criteria	Section 8.2 Exclusion Criteria	Use of heparin or acetylsalicylic acid (ASA) without consultation with the Medical Monitor **a. The use of systemic heparinization, or any ASA containing medications, is prohibited during active dosing with veledimex. Prophylactic heparin SC, per institutional protocol, or heparin when used for maintaining patency of an access port of a PICC line is permitted.**	Administrative Memo #1
N/A	Figure 4: Study ATI001-103 Schema: Arm 1 (Cohort 1) Figure 5: Study ATI001-103 Schema: Arm 2 (Cohorts 3 and 4)	Figure updated to correctly reflect, • Study ATI001-103 Schema: Arm 1 (Cohort 1) • Study ATI001-103 Schema: Arm 2 (Cohorts 3 and 4)	Administrative Memo #1 Removal of Cohort 2 as above.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
N/A	Table 1: Schedule of Study Procedures Section 12.3.3 Treatment Period – Days 0-14	**The patient should be contacted every day during the treatment period to discuss clinical status and updates on current/new adverse events. If the patient is discharged prior to Day 14, follow-up may occur via telephone. Successful contact and contact attempts will be documented in EDC.**	Based on SRC discussions regarding DIPG population, ongoing communication with the patient and the Sponsor is useful to the Medical Monitor in providing ongoing guidance.
N/A	Section 12.3.3 Treatment Period – Days 0-14	**Subjects should be instructed to remain in close proximity to the clinical site from Day 0-14.**	Due to the vulnerability of this population, advising the patient to remain local to the site would be beneficial to provide additional care by the PI, as needed.
N/A	Table 1: Schedule of Study Procedures Section 12.3.6 Treatment Period Day 2	The MRI scan designated on Day 2 ~~**should be taken within 72**~~ **has an allowable window of ± 24** hours ~~**of Ad-RTS-hIL-12 administration**~~ and will be considered the baseline scan for tumor response assessments.	Based on SRC discussion and clinical effect that has been seen on Day 2 in previous patients.
Statistical Methods-Analysis Populations	Section 16.1 Populations for Analysis	**This is an amendment to an ongoing study that has been previously described. For all practical purposes the connotation of the safety population for the planned safety analysis are subjects being denoted in defining the overall safety population (OSP) defined below to distinguish this group from the subgroup of subjects denoted as the**	To provide additional clarification regarding the analysis populations.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		evaluable safety population (ESP) who must receive Ad-RTS-hIL-12 and at least one dose of veledimex after injection. **This distinction provides for inclusion of both drug components (Ad-RTS-hIL-12 + veledimex) in order to evaluate dose escalation via the rule-based criteria fundamental to the 3+3 method. This means that during dose escalation if at least one of three Ad-RTS-hIL-12 treated subjects does not receive at least one dose of veledimex after injection, additional eligible subjects will be enrolled as applicable in order to achieve the samples size of three evaluable subjects to assist the SRC's evaluation when making a dose escalation or a dose de-escalation decision. Specifically,** • The OSP includes all subjects who received at least ~~1~~**one** dose of veledimex ~~**(pre-tumor resection and/or post-stereotactic procedure) and/**~~or ~~**all subjects who received**~~ Ad-RTS-hIL-12 • The ESP includes all subjects who received Ad-RTS-hIL-12 and at least ~~1~~**one** dose of veledimex after Ad-RTS-hIL-12 administration**., and are BSA conformant** • The Pharmacokinetics Population (PKP) includes all subjects who received veledimex with sufficient ~~**time points.**~~**timepoints**	
Statistical Methods-Tumor Response and Overall Survival Analyses	N/A	~~**Tumor**~~**If an SRC committee decision results in enrolling subjects into an expansion cohort, the primary analysis for tumor response ~~analysis~~ variables and OS** will be performed on the ESP **population. Secondary analyses will include all treated subjects as defined by the safety population denoted the OSP.** The Investigator assessment of ORR and PFS will be determined for each cohort. The OS	To provide additional clarification regarding the analysis of tumor response and overall survival

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		is defined as the duration of time from the first dose of study drug to the date of death or, for subjects who are still alive **~~2~~two** years after first dose of study drug, subjects will be censored at the last follow-up contact date. A 2-sided confidence interval will be computed for the ORR. The PFS and OS will be analyzed using Kaplan-Meier methods**. If an expansion cohort to treat up to 30 subjects is not performed, instead of a statistical analysis of data from very small sample sizes, listings of the investigator assessment of ORR and PFS by subjects will constructed on the subjects treated during the dose escalation phase.**	
N/A	Section 16.2 Sample Size and Power Calculations	• The sample size chosen was based on clinical **~~consideration for a standard 3+3 study~~ considerations.** • **For Cohorts 1 and 3, treated at 10 mg, the 3+3 rule-based** dose escalation **~~design, modified for~~ criteria will be applied to provide an** independent **~~evaluation of 2 subject arms that may exhibit different~~algorithmic** safety **~~and tolerability profiles. Power calculation for comparison of AE rates are simply too inexact to be clinically meaningful because the AE rates are unknown and cannot even by approximately projected.~~assessment to either dose escalate from 10 to 20 mg or to consider de-escalation, as applicable. The SRC will incorporate the findings in combination with other clinical factors to make the final recommendation pertaining to dose escalation from 10 mg to 20 mg or de-escalation from 10 mg to 5 mg.** **~~Approximately 24 subjects may be enrolled into this study, including 3 to 6 subjects per cohort. Subjects who withdraw from the~~**	To provide statistical clarification regarding sample size and power calculations.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		~~**study during the DLT evaluation period (Day 0 to Day 28) for reasons other than toxicity or disease progression may be replaced.**~~ • **For Cohort 4, treated at 20 mg, the 3+3 rule-based dose escalation criteria will be applied to provide an independent algorithmic safety assessment to either confirm that 20 mg dosing is safe or to potentially de-escalate to a 15 mg dose for further evaluation based on the SRC recommendation.** **After the dose escalation de-escalation portion of the study phase 2 dose determination will be determined for both pediatric disease populations:** • **recurrent or refractory supratentorial brain tumor pediatric population** • **DIPG pediatric population** **At the discretion of the SRC, up to 30 evaluable DIPG subjects may be enrolled in the phase II expansion cohort, which will support time to OS estimation. The projection of this sample size is based on clinical considerations as well as numbers to obtain sufficient preliminary assessments of overall response. Additional details will be provided in the Statistical Analysis Plan.**	
N/A	Table 1: Schedule of Study Procedures Section 12.3.16 Unscheduled	• [redacted] • **A tumor sample should be collected once there is a concern for pseudo-progression as noted above. The biopsy at Day 56 is strongly recommended. Patients should remain on-study for continued**	Based on SRC discussions to enhance reliability of patient outcome.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
	Visit Collections	**follow-up until confirmed progression per iRANO or the patient meets other withdrawal criteria.** • **CSF may be collected at time of the time of MRI scans such as if sedation is clinically indicated or if an Ommaya reservoir is implanted. Collection is optional.**	
N/A	Table 1: Schedule of Study Procedures Section 12.3.2 Screening Section 12.3.6 Treatment Period Day 2 Section 12.3.11 Treatment Period Day 14 Section 12.3.13 Initial Follow-Up Period Day 28 (± 7 days) Section 12.3.14 Initial Follow-Up Period Day 56 (± 7 days) Section 12.3.15 Long-Term Follow-Up (every 8 weeks ± 1 week)	[redacted]	Based on SRC discussions to enhance reliability of patient outcome. [redacted]

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
N/A	Table 1: Schedule of Study Procedures Section 12.3.5 Treatment Period Day 1	Addition: **CT Scan, as clinically indicated**	Based on SRC discussions to enhance reliability of patient outcome.
N/A	Table 1: Schedule of Study Procedures Section 12.3.1 Study Tests, Exams, and Procedures	***All assessments should be performed prior to study drug administration, as applicable, unless otherwise stated.**	Clarification
N/A	Table 1: Schedule of Study Procedures	**[cc] Every 8 weeks from Day 56.**	Clarification
N/A	Table 1: Schedule of Study Procedures Section 12.3.8 Treatment Period Days 4-6 (to occur Day 4, Day 5, and Day 6)	**[gg] Assessments to be performed on Day 4, Day 5, and Day 6.**	Clarification
N/A	Table 1: Schedule of Study Procedures Section Section 12.3.1 Study Tests, Exams, and Procedures 14.2 Evaluation of	Adverse events will be **recorded from the time of consent and** followed through ~~**30 days after each subject's last dose of any study drug.**~~ **the initial follow-up period (Day 56).** AEs that are **ongoing at Day 56 and considered** drug related should be followed until resolved or no resolution is expected.	Clarification of safety reporting period. Inconsistent in Amendment 1. More conservative reporting period ICF through Day 56 vs. through 30 days last

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
	Adverse Events Section 14.6 Documenting Adverse Events Section 14.9 Follow-Up Information for Adverse Events		dose of any study drug (Day 44).
N/A	Section 14.5 Determination of Causality	**For any untoward medical occurrence that starts** before administration of study drug, 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 a**~~**s** an ~~**AE**~~**adverse event. If deemed unrelated** to a ~~**protocol required**~~**study-specific** procedure**, the event should be added to the Medical History eCRF.**	Clarification that before study drug administration determination of relatedness to protocol assessments is required to be determined an adverse event.
N/A	Section 11.2 Prohibited Medications	• ~~**NOTE: Care should be given when prescribing medications that are classified as**~~ CYP450 3A4 inducers, inhibitors, or substrates **(including vitamins and/or herbal supplements) are prohibited prior to the first dose of veledimex until after the last dose of veledimex. Consultation with the Medical Monitor is required.** • **Vitamins and/or herbal supplements are not recommended prior to the first dose of veledimex and until after the last dose of veledimex** due to	Clarification that CYP450 3A4 interacting drugs are prohibited during the treatment period and Medical Monitor consultation is required to ensure patient safety if administering.

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
		potential **drug-drug** interactions ~~**with the study drug. In the event that one is prescribed, consultation**~~**. Consultation** with the Medical Monitor is ~~**advised. All medications should be recorded in the CRF as indicated in the completion guidelines.**~~ **required.**	Due to the lack of research on certain vitamins/herbal supplements, as a precautionary measure these are not recommended without Medical Monitor consultation to ensure patient safety if administering.
Safety Evaluation	Section 7.7 Safety Monitoring and Adverse Effect Management Section 7.8 Severity Grading and Management of Local Reactions Section 14. Assessment of Safety Section 14.4 Determination of Severity	Safety will be evaluated in the Overall Safety Population (OSP) and the Evaluable Safety Population (ESP), as defined below, using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) **v**~~**4.03**~~ **5.0**	Administrative Memo #2

Section in Clinical Protocol Summary (Section 4)	Section in Amended Protocol	Revised or Deleted Text/Section	Rationale for Change
N/A	Section 16.4.2 Safety Analyses	The safety evaluation period extends from the date the subject signs the ICF or assent **form**, as applicable, ~~**until approximately 2 years after receiving study drug from**~~ **through the Initial Follow-up Period (**Day ~~**1 dosing,**~~**56),** unless the subject discontinues ~~**the trial**~~ **from active follow-up** due to ~~**1**~~**one** of the following reasons: • ~~**Documented progression**~~ • Symptomatic deterioration also denoted 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	Clarification on reasons for subject disconuation during the safety reporting period as these do not apply during this time period.