# STATISTICAL ANALYSIS PLAN

## 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

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| SAP | Statistical Analysis Plan |
| Ad-RTS-hIL-12 | [redacted] |
| AE | Adverse Event |
| aPTT | Activated Partial Thromboplastin Time |
| ATC | Anatomical Therapeutic Chemical |
| BEP | Biomarker Evaluation Population |
| BMI | Body Mass Index |
| BPM | Respiratory Rate |
| BSA | Body Surface Area |
| CD | Cluster of Differentiation |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CSF | Cerebrospinal Fluid |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of Variation |
| DD | Drug Dictionary |
| DIPG | Diffuse Intrinsic Pontine Glioma |
| DLT | Dose-Limiting Toxicity |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EP | Enrolled Population |
| ESP | Evaluable Safety Population |
| hIL-12 | Human Interleukin-12 |
| ICF | Informed Consent Form |
| ID | Identity |
| IFN-γ | Interferon-Gamma |
| IP-10 | IFN-Γ-Induced Protein 10 |
| iRANO | Immunotherapy Response Assessment for Neuro-Oncology |
| KM | Kaplan-Meier |
| LDH | Lactate Dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGMT | Methylguanine-DNA Methyltransferase |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| OSP | Overall Safety Population |
| PD | Pharmacodynamics |

| Abbreviation | Definition |
|---|---|
| PFS | Progression -Free Survival |
| PK | Pharmacokinetic(s) |
| PKP | Pharmacokinetics Population |
| PO | Oral(Ly) |
| PT | Preferred Term |
| QD | Once Daily |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SRC | Safety Review Committee |
| TEAE | Treatment-Emergent Adverse Event |
| Vp | Viral Particles |
| WHODrug | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the proposed statistical analyses in concert with Ziopharm Protocol ATI001-103 Amendment 2 entitled: 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

This (SAP) will describe the statistical methods used for all analyses and data presentation for reporting safety, efficacy, pharmacodynamics (PD) and immunology of Ad-RTS-hIL-12, administered by intratumoral injection plus veledimex administered PO for Ziopharm study protocol ATI001-103 Amendment 2. The Pharmacokinetics (PK) and exploratory analysis for PD endpoints will be summarized in a separate analysis plan.

Importantly, and where applicable, this SAP contains a more detailed explanation of the statistical analyses described in the protocol. It includes additional and sometimes technical discussion for implementing statistical procedures along with the assumptions and data handling rules of how an analysis is performed. Details describing the data listings, summary tables and figures will be presented in a corresponding Tables, Listings and Figures excel spreadsheet.

**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 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 (Warren 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.

Systemic recombinant IL-12 in clinical trials has been effective in the treatment of cancer but has limited utility due to systemic toxicity (Atkins, Robertson et al. 1997, Leonard, Sherman et al. 1997, Rodolfo and Colombo 1999). To circumvent these challenges and improve the therapeutic index, Ziopharm developed a gene therapy that permits well controlled local expression of IL-12 within the tumor microenvironment. Ziopharm is developing Ad-RTS-hIL-12 + veledimex for

treatment of patients with solid tumors. The investigational product, Ad-RTS-hIL-12 + veledimex, is comprised of 2 components: Ad-RTS-hIL-12 (Component 1) and veledimex (Component 2). Both components are necessary for the production of the active moiety, human interleukin-12 (hIL-12).

# 2. STUDY DESIGN OVERVIEW

## 2.1. Overall Study Design before Amendment 2

As originally designed, this was a multicenter Phase I/II open-label study, of Ad-RTS-hIL-12 administered by intratumoral and varying oral (PO) veledimex doses in pediatric brain tumor subjects. This study will investigate one fixed intratumoral Ad-RTS-hIL-12 dose [redacted] and escalating veledimex doses (10 mg and 20 mg) to determine the safe and tolerable Phase II pediatric dose based on the safety profiles observed in the presence of variable corticosteroid exposure.

Eligible subjects were to be stratified into one of two arms, according to diagnosis.

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

Arm 1 was 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).

- Subjects in Arm 1 will receive one veledimex dose before the resection procedure.
- Samples (tumor, blood, and CSF, if available) will be collected during the resection procedure to determine the veledimex concentration ratio between the tumor, blood, and CSF if available.
- Subjects will receive Ad-RTS-hIL-12 [redacted] by freehand injection. After Ad-RTS-hIL-12 injection, subjects will continue PO veledimex for 14 days for a total of 15 doses of veledimex. The study schema for Arm 1 is outlined in Figure 1.

[redacted]

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

Subjects in Arm 2 will receive a single Ad-RTS-hIL-12 [redacted] dose by stereotactic injection into the intratumoral site and will receive PO veledimex for 14 days for a total of 14 doses of veledimex. The study schema for Arm 2 is outlined in Figure 2.

- Arm 2 was open only to subjects with DIPG who are post prior standard focal radiotherapy (≥ 2 weeks and ≤ 10 weeks).
- Arm 2 subjects will receive a single Ad-RTS-hIL-12 (2 x $10^{11}$ vp) dose by stereotactic injection and will receive veledimex PO daily for 14 days.

[redacted]

## Cohorts

Study arms and assigned doses will be divided into 4 cohorts (Table 1).

**Table 1: ATI001-103 Study Design**

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

[a] Doses are BSA-adjusted doses

Subject enrollment and veledimex dose escalation were to proceed according to a standard 3+3 design, modified to independently evaluate 2 groups (arms) of subjects that may exhibit different safety and tolerability profiles, with the first cohort of each arm receiving 10 mg veledimex, followed by the second cohort receiving 20 mg veledimex.

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, enrollment may be opened for Cohort 2 and Cohort 3. Once the last subjects in both Cohort 2 and Cohort 3 complete the DLT evaluation period, enrollment may be opened for Cohort 4.

The first subject in each 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).

### 2.1.1. Safety Review Committee (SRC) Recommendations After Review of Arm 1 Cohort 1

When the Safety Review Committee (SRC) reviewed the safety profile of the subjects treated in Arm 1 Cohort 1, (n=3), the SRC indicated that it was appropriate to dose escalate moving forward with:

- Arm 1, Cohort 2 and
- Arm 2, Cohort 1.

However due to issues with enrollment of supratentorial subjects, it was determined not to proceed with enrollment of Arm 1, Cohort 2 as originally planned. Therefore, the Arm 1 portion of the study was deemed concluded.

Ziopharm performed database lock upon the completion of Arm 1 Cohort 1, under Protocol Amendment 1.0 dated 25-Sep-2017. Arm 1 used the Medidata RAVE database, which was locked on 08-Nov-2019.

## 2.2. Amendment 2 Study Design Modifications

### 2.2.1. Amendment II overview

Protocol Amendment 2.0 was finalized 30-Oct-2019, and Arm 2 enrollment was opened, using the nowEDC database for data collection.

Table 2 summarizes the overall study status reflecting:

- Completion of Arm 1 Cohort 1 as described above.
- Removal of Arm 1 Cohort 2.
- DIPG subject enrollment beginning with Arm 2, cohort 3, at 10mg veledimex and, Arm 2, cohort 4 at 20mg veledimex PO daily dosing for 14 days.

**Table 2: ATI001-103 Amendment 2 Breakdown of Arm 1 Completed Cohort and Arm 2 Cohorts 3 and 4 for Phase I Dose Escalation**

| Arm | Cohort | Procedure | Veledimex Dose[a] Assigned | Status |
|---|---|---|---|---|
| 1 | 1 | Craniotomy | 10 mg | Complete |
| 2 | 3[b] | Stereotactic | 10 mg | Enrolling |
| 2 | 4 | Stereotactic | 20 mg | Future |

[a] Doses are BSA-adjusted doses
[b] Arm 1 Cohort 2 was removed in Protocol Amendment 2.

### 2.2.2. Study Design

This was to be a multicenter, open-label study of Ad-RTS-hIL-12 administered by intratumoral injection and veledimex PO doses in pediatric brain tumor subjects. This study was planned to 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. After completion of the phase I dose escalation cohort(s) in DIPG subjects enrolled in Arm 2, the SRC may

recommend expanding treatment based on its review of the data to a new cohort for up to 30 to 35 DIPG subjects. Such an expansion was to be considered the Phase II component of the study.

- The schedule of study procedures is presented in Appendix 1 ,
- The veledimex PK sampling schedule is presented in Table 3 and Table 4.

**Table 3: 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 4: Arm 2 Schedule of Veledimex Pharmacokinetic Sampling Times**

| Sample Number | Day 0 | Day 1 | Day 2 | Day 14 | Day 15 |
|---|---|---|---|---|---|
| 1 | | Pre-dose[a] | Predose[a] | Predose[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

### 2.2.3. Projection of Study Duration

The study duration is projected to be approximately 48 months. This assumes that after the enrollment and evaluation of cohort 4 for safety, that the SRC recommends expansion of enrollment into the phase 2 single arm cohort of up to 30 to 35 eligible subjects to obtain at least 30 subjects deemed evaluable for OS. The breakdown of timing suggests:

- Arm 2 enrollment of phase I cohorts is approximately 12 months
- 30 to 35 evaluable DIPG subject enrollment begins one month after the SRC recommends expanding enrollment into a phase 2 component.
- Enrollment to accrue Phase II DIPG subjects is projected to be 12 months.
- Then at least 24 months of follow-up of the last subject enrolled and treated as part of the phase 2 projection.

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

- Screening period of up 28 days
- Study treatment period of up to 15 days
- Survival status through 24 months from the first dosing date.

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

### 2.2.4. Sample Size

Originally, the choice of the number of subjects was based on the standard 3 + 3 design, modified for independent evaluation of 2 subject arms that may exhibit different safety and tolerability profiles.

- Without the phase II component, it was projected that approximately 24 subjects may have been enrolled including 3 to 6 subjects per cohort.
- 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.

### 2.2.5. Randomization

This is an open-label study, and subjects will not be randomized.

# 3. STUDY OBJECTIVES

## 3.1. Amendment 2 Revision of Objectives.

Revisions to the objectives of ATI001-103 Amendment 2 are described in a “before, after” presentation depicting changes to the primary, secondary and exploratory objectives in the following three subsections. Most revisions are in underlined red font indicating additions to the original wording to capture the potential of expanding the current trial to a Phase II trial in DIPG eligible subjects.

### 3.1.1. Primary Objectives (before and revised) for Amendment 2:

**Primary Objective Before Amendment 2:**

- To determine the safety and tolerability of intratumoral Ad-RTS-hIL-12 and varying PO veledimex doses in pediatric brain tumor subjects.

**Primary Objective revised for Amendment 2:**

- 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)

### 3.1.2. Secondary Objectives (before and revised) for Amendment 2:

**The Secondary objectives Before Amendment 2 were:**

- To determine the recommended Phase II veledimex dose in pediatric brain tumor subjects when given with intratumoral Ad-RTS-hIL-12.
- To determine the pharmacokinetics (PK) of veledimex in subjects treated with Ad-RTS-hIL-12 + veledimex.
- 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]
- 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.
- To determine overall survival (OS) of subjects treated with Ad-RTS-hIL-12 + veledimex.

**Secondary Objectives Revised for Amendment 2:**

- 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]

# 4. STUDY ENDPOINTS AND EVALUATIONS FOR PHASE I COHORTS

## 4.1. Study Endpoints

### 4.1.1. Primary Endpoint

- Assessment of safety and tolerability of Ad-RTS-hIL-12, administered by intratumoral injection plus veledimex administered PO, as determined by the AE rate and the occurrence of DLTs analyzed specifically for each cohort.

### 4.1.2. Secondary Endpoints

- Determination of the recommended pediatric Phase II 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 (Arm 1 only)

[redacted]

- Investigator assessment of response, including objective response rate (ORR) and progression-free survival (PFS)
- Overall Survival (OS)

[redacted]

## 4.2. Baseline and Demographic Characteristic Evaluations

- Demographics
- Baseline characteristics
- Medical history
- Prior therapies/surgeries
  - Surgical history
  - Brain tumor diagnosis
  - Prior cancer treatment
- Concomitant medications/procedures

## 4.3. Dose Limiting Toxicity (DLT)

Dose Limiting Toxicities are defined as events that occur during the first 28 days (Day 0 - Day 28) that meets one of the following criteria:

- 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 $\geq$ 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 $\geq$ 5 days

Note: Diagnostic brain tumor biopsy is not considered a DLT.

- Seizures, headache, and cerebral or pontine edema are commonly observed in this population.

  - The grade of toxicity will be recorded.
  - However, unless a relationship to study drug is documented to be the main contributory factor, the AE will not be considered a DLT.
- Transient neurological changes are expected in Arm 2 and will not be considered a DLT unless they last > 10 days.

## 4.4. Recommended Pediatric Phase II Veledimex Dose

The recommended pediatric Phase II veledimex dose will be determined using the Evaluable Safety Population (ESP) which is defined in Section 5 .

- 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.

The recommended pediatric Phase II dose will also be determined in the context of variable corticosteroid exposure and will be reported as such.

## 4.5. Safety Evaluations

The safety evaluations include:

- Adverse Events (AEs)
- Extent of study drugs exposure
- Treatment compliance and modification
- Clinical laboratory assessments including hematology, coagulation, serum chemistry and urinalysis
- Vital signs including weight
- Physical exams including targeted neurological exam
- Electrocardiogram (ECG)
- Lansky, Karnofsky, and ECOG performance Status
- Pregnancy test

## 4.6. Efficacy Evaluations

The secondary efficacy endpoints include Investigator assessment of ORR, PFS and OS. The Investigator assessment of ORR and PFS will be determined for each cohort according to the baseline (Day 2) iRANO assessment, with tumor response characterized by iRANO criteria for adults, pending issuance of pediatric criteria.

The following variables will be used for the determination of tumor response variables and OS by subject ID:

- Tumor response by iRANO for
  - Target, non-target and non-enhancing lesions.

  - Overall response
- ORR defined as sum of partial responses and complete responses.
- PFS defined as duration of time from first dose of the study drug to the date of disease progression, or death of any causes, whichever occurs earlier, plus 1 day.
- OS defined as the duration of time from first dose of the study drug to the date of death. Subjects who are still alive 2 years after first does of study drug will be censored at the last follow up contact date.

## 4.7. Pharmacokinetic Assessment

Veledimex PK parameters will be determined based on blood (plasma) levels of veledimex using WinNonLin Phoenix 64 and will include, but are not limited to, the maximum plasma concentration, time to maximum plasma concentration, and area under the curve. The PK analysis will be described in a separate analysis plan.

Only PK concentrations will be summarized in this SAP.

[redacted]

# 5. ANALYSIS POPULATIONS AND APPLICATIONS

## 5.1. Enrolled Population (EP) including Screen Failures

- The EP includes all subjects who signed an informed consent who were subsequently evaluated for eligibility.
- Subjects screened for eligibility and not treated are denoted as Screen Failures.
- Screen Failures are subjects who signed an informed consent and subsequently:
  - Did not meet the eligibility criteria of the protocol, or,
  - Withdrew consent to be treated before receiving any experimental treatment.

The number of subjects who were screened and not treated will be described in the subject disposition where applicable.

## 5.2. Full Analysis Set (FAS) or the Overall Safety Population (OSP)

The Full Analysis Set (FAS) or the OSP includes every subject who received at least one dose of any study drug recorded in the Data Management (DM) database excluding screen failures.

- The data analysis for Adverse Events or other Safety variables will be performed on the OSP.
- In the event, the phase II component of the study is implemented and a prespecified null hypothesis comparing study treatment in DIPG subjects with either historical control assumptions or an external control is likely, the primary analysis of OS will be based on the OSP population.

## 5.3. Per Protocol (PP) Population or the Evaluable Safety Population (ESP)

The PP population is defined as the ESP. The ESP is a subset of the FAS.

- The ESP includes subjects who received Ad-RTS-hIL-12 + at least one dose of their cohort-specific dose of veledimex.
- The ESP are also subjects who have not had a major protocol deviation for which the key efficacy endpoints could be regarded as confounded or uninterpretable.
- Subjects who have had minor protocol deviation(s) that are thought not to impact efficacy will be included in this analysis population.

The ESP will be used for

- Making decisions regarding escalation to higher veledimex doses for Arms 2 cohorts, based on a standard 3 + 3 design.
- Any tables, figures, or listings for dose recommendation and DLT evaluation by the SRC
- In the event, the phase II component of the study is implemented, the secondary analysis of the overall OS hazard rate, the OS at prespecified timepoints, PFS and the ORR will be based on the ESP population.

## 5.4. Pharmacokinetics Population (PKP)

The PKP includes all subjects who receive veledimex with sufficient PK time points. All Pharmacokinetics analyses will be based on the PKP.

[redacted]

# 6. PLANNED ANALYSES

## 6.1. Changes from Planned Analysis

The major change to the original planned analyses is that for all practical purposes, statistical summaries of very small sample sizes will be avoided. Instead, relevant data listings by subject for the OSP and ESP will be presented along with descriptions of subject characteristics as applicable.

When Amendment 2 was implemented,

- Arm 2 enrollment was opened, using the nowEDC database.
- The data for Arm 1, Cohort 1, consisting of 3 subjects for whom the data were captured in Rave eCRF will be summarized separately from the data captured based on DIPG eligibility, beginning with Arm 2, cohort 3.
- After completion of enrollment of DIPG subjects in cohort 3 and cohort 4, the data from the Arm 1, cohort 1, may be combined for reporting purposes in which case remapping the data on the three subjects for whom the data are complete will be applied to creating derived variables like those to be chosen when data extractions from the nowEDC are implemented
- Therefore, this current version of the SAP for ATI001-103 based on amendment 2 will not include tables shell entries for Arm 1, Cohort 1.

**Interim Analyses**

There is no formal interim analysis planned for this study.

- There will be SRC meetings to evaluate the subjects' safety data.
- The SRC will determine whether the dosing at the specified level (10 mg or 20 mg) is appropriate for escalation or as the recommended Phase 2 pediatric dose.
- After the completion of phase I dose escalation of Arm 2, the SRC may recommend expanding the current study for one of the doses evaluated in either cohort 3 or 4 in which case a cohort expansion of up to 30 to 35 evaluable DIPG subjects will be enrolled.
- This new cohort of subjects will be defined and referenced as the Phase II component of the study.

**Final Analyses and Reporting**

All final planned analyses per protocol and this SAP will be performed only after database lock.

# 7. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

All analyses described in this plan are considered priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database, will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

For this study,

- Multiplicity adjustment will NOT be performed for analysis.
- Possible covariate effects will NOT be adjusted for analysis.
- No imputations for missing or partial data will be made.
- Data across multiple study sites will be pooled for an integrated summary.
- SAS version 9.4 or higher will be utilized for all listings and tables.

## 7.1. General Statistical Procedure

The descriptive statistics for continuous variables (e.g., age) will be the number of subjects with a non-missing value of the variable (n), mean, standard deviation (SD), median, quartiles (Q1, Q3), minimum and maximum. Mean, median, Q1, and Q3 will be reported to 1 more decimal place than the raw data. The SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

In addition to the above descriptive statistics, coefficient of variation (CV%), geometric mean and geometric CV% will also be used to summarize the drug veledimex concentration where applicable.

Coefficient of variation CV% is calculated as 100×(SD/mean). Geometric CV% is calculated as follows: $\mathrm{CV\%} = 100\ \mathrm{X}\ \sqrt{\exp(\hat{\sigma}^2) - 1}$, where $\hat{\sigma}^2$denotes the estimated variance of the log-transformed values.

Categorical variables will be summarized by frequency table which includes the number of subjects with a response in the category and the percentage of the total number of subjects in that particular column. Unless otherwise stated, missing responses will NOT be included in the analysis. Percentages will be rounded to one decimal place.

Unless otherwise stated, data will be tabulated by arm and dose cohort, and overall according to the defined population. If dose escalation is stopped before reaching higher veledimex doses, those columns will be omitted from the summaries.

All listings will be ordered by arm and dose cohort, and subject ID for available data.

### 7.1.1. Baseline Definition

The day of Ad-RTS-hIL-12 administration is designated as Day 0. Baseline value for safety and demographic data is defined as the last non-missing value closest, but prior to, the first dose of study drug veledimex or Ad-RTS-hIL-12. For tumor assessment, a baseline MRI will be performed within 72 hours of Ad-RTS-hIL-12 administration (Day 2).

### 7.1.2. Analysis Visit Window

For safety parameters excluding clinical laboratory data, measurements collected from unscheduled visits will NOT be included in the by-visit summary tables but will be included in the listings. Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit but will be used as the last assessment during the treatment period.

## 7.2. Data Handing

### 7.2.1. Age

For partial dates of birth with both the month and day missing, the month and day will be set to June 30. Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing. In listings of demographic data, the partial dates of birth as entered will be displayed.

### 7.2.2. Safety Data Handing

For all safety data, only observed data will be used for analyses, and missing data will not be imputed.

### 7.2.3. Handling of Repeated Clinical Laboratory Tests

For laboratories results at unscheduled visits, it will be treated as repeated laboratory results for the closest previous visit. The last repeat of laboratory results will be used in the summary tables for that visit. All the laboratory test results (original test results and repeated results) will be included in the data listings.

### 7.2.4. Handling of Partial Dates for AEs

When determining the AE, partial start dates of AEs will be assumed to be the closest possible date to date of first dose and are consistent with the partial date. Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

- A completely missing onset date will be coded as the date of first dose. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- If year is present, but both month and day are missing, or month is present, and day is missing,
  - if year < year of first dose date, then set missing month to December and missing day to last day of the month.
  - if year > year of first dose date, then set missing month to January and missing day to 1st day of the month.
  - if year = year of first dose date, then set missing month to the month of first dose and missing day to the day of first dose.
- If year and month are present, but day is missing,
  - if date of year and month < date of year and month of first dose, then set missing day to last day of the month.
  - if date of year and month > date of year and month of first dose, then set missing day to 1st day of the month.

  - if date of year and month = date of year and month of first dose, then set missing day to the day of first dosing.

- For all other cases, set the date to date for first dose.

### 7.2.5. Handling of Partial Dates for Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date.

- For Start Date,
  - If the start date is completely missing, then the start date will not be imputed. Medication will be assumed to be prior medication.
  - If the year is present and month or day are missing, then set missing month to January and missing day to 1st of the month.
- For End Date,
  - If the end date is completely missing, then the end date will not be imputed. Medication will be assumed to be ongoing.
  - If the year is present and the month or day are missing, then set missing month to December and missing day to last day of the month.

# 8. PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

- Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.
- Where applicable, important protocol deviations will be categorized as major protocol deviations.
  - Protocol deviations that are not deemed important protocol deviations are classified as minor protocol deviations
- The list of protocol deviations along with whether the deviation is classified as major or minor will be finalized prior to database lock.

No subject will be removed from any analysis population because of a protocol deviation.

In accordance with ICH E3, subject eligibility violations and important post- treatment protocol deviations will be identified and listed by subject ID and study center. Major deviations that are considered to potentially impact the efficacy or safety analyses will be tabulated. Important protocol deviations will be identified prior to database lock. Protocol deviations will be listed and summarized by type.

- Deviation from inclusion/exclusion criteria
- Withdrawal criteria met during the study but subject ID was not withdrawn
- Prohibited concomitant medications
- Treatment deviation
- Other protocol deviation

# 9. SUBJECT DISPOSITION

**Subject Disposition**

The completion status of subjects treated by any experimental treatments will be summarized overall and by treatment arm and dose cohort based on the OSP. The primary reasons for treatment and study discontinuation will be summarized by treatment arm and dose cohort based on the OSP.

Subjects who are screen failures are not subjects that are treated on any study treatment and are only counted as the part of the subject disposition denoted as screened and not treated.

# 10. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

## 10.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed and described by subject ID (instead of being tabulated using descriptive statistics by treatment arm and dose cohort) for the OSP.

- Demographic variables include:
  - Age (years)
  - Sex
  - Race
  - Ethnicity
- Baseline characteristics include:
  - Height (cm)
  - Weight (kg)
  - BMI (body mass index, $kg/m^2$, calculated as Weight (kg) / Height $(m)^2$)
  - ECOG performance status, KPS, lansky

Conversions for Height and Weight are as follows:

Height (cm) = Height (inches) x 2.54

Weight (kg) = Weight (lb) x 0.4536

## 10.2. Medical History

The medical history will be coded using the current version of the Medical Dictionary for Regulatory Activates (MedDRA). Originally, the frequency count and percentage of subjects who experience any medical conditions were to be tabulated by system organ class (SOC) and preferred term (PT) of MedDRA for all subjects and by treatment arm and dose cohort for the OSP. Instead, medical history, will be listed and described by subject ID.

If the same PT or SOC is reported more than once for a subject ID, the subject ID will only count once in the corresponding incidence of PT or SOC.

Listings will be presented by treatment arm, dose cohort, and subject ID for the EP.

## 10.3. Prior Therapies/Surgeries

Listings will be presented by treatment arm and dose cohort, by subject ID for the EP. Listings will summarize prior therapies, surgeries, and/or concomitant disease by treatment arm and dose cohort for the OSP

- (instead of Frequency counts and percentages for the summary of prior therapies, surgeries or concomitant disease by treatment arm and dose cohort for OSP).
- The therapies/surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

Where applicable, the following variables may be included as part of the subject listing:

- Relevant Disease under study
  - Any relevant past or concomitant disease
  - Most severity/CTCAE grade
- Surgery History
  - Any relevant past surgeries
  - Most severity/CTCAE grade
- Brain tumor diagnosis
  - Initial grade
  - Initial MGMT gene promoter status
  - Initial IDH status
  - Current disease status
  - Current grade
  - Current MGMT gene promoter status
  - Current IDH status
- Prior cancer treatment
  - Any cancer related therapy

- Treatment type
- Best response
- Disease under study

If the subject experienced multiple surgeries, the most severe grade will be used for the summary.

## 10.4. Prior and Concomitant Medications/Procedures

All medications as documented by Investigator will be coded using the World Health Organization Drug Dictionary (WHODrug, Sept 2016).

Prior medications are defined as medications that were started before the start of the study treatment and either ended before the start of the study treatment or continued after study treatment.

Concomitant medications are defined as non-study medications that were either initiated before study treatment and continued during the study treatment or initiated on/after study treatment but within the initial follow-up period (through Day 56).

In general, listings by treatment arm and dose cohort, and subject ID for concomitant medications and concurrent Medical Procedures will be provided for the OSP (instead of using frequency tables).

The prior and concomitant medications will be tabulated by subject ID, along with the treatment arm and dose cohort, ATC term 2 and the Preferred term for OSP.

- If the start and stop dates of the concomitant medications do not clearly define the period(s) during which a medication was taken, it will be assumed to have been a concomitant medication.
- For summary listings, if a subject has taken a medication more than once, the subject will be only counted once for the medication.
- Medications initiated prior to the start of first dose of study drug and are continued after the first dose of study drug will be counted as both prior and concomitant medications.

# 11. DOSE LIMITING TOXICITIES (DLT)

In general, listings by subject ID for DLT data by treatment arm and dose cohort, will be provided for the ESP.

The number of DLTs and the proportion of subjects with any DLT and each type of DLT will be summarized by treatment arm and dose cohort for the ESP if applicable.

# 12. RECOMMENDED PEDIATRIC PHASE II VELEDIMEX DOSE

The recommended pediatric Phase II dose in the study will be determined in the context of variable corticosteroid exposure and other factors.

Where applicable, listings along with descriptive statistics will be used to tabulate the total corticosteroid daily dose (mg) by arm and dose cohort, and visit for the ESP.

As originally planned, listings including demographics could be provided for the total corticosteroid daily dose by arm and dose cohort, visit and subject ID for the OSP.

# 13. SAFETY ANALYSIS

## 13.1. Adverse Events (AEs)

AEs will be coded using MedDRA and will be classified by SOC and PT of MedDRA. All AEs will be captured up through day 56.

Severity: The severity of AEs will be assessed according to the NCI CTCAE v. 4.03 ranging from Grade 1 to Grade 5.

TEAE: A treatment emergent AE (TEAE) is defined as any AE that begins, or any preexisting condition that worsen in severity during the treatment period. For determination of TEAEs during the treatment period, AEs with the greatest severity before baseline will be used as a benchmark for comparison of AEs occurring captured up through day 56.

Relationship (Causality): AEs that have possibly, probably or related relationship to the study drug are defined to be Related to the study drug. Otherwise, the AE will be defined as Not Related. AEs for which the relationship to the study drug is missing will be considered as related to the study drug. AEs with the closest relationship to the study drug will be used for the summary.

TEAEs will be tabulated by subject ID in listings by treatment arm and dose cohort, SOC and PT according to the relationship to study drug(s), the severity and seriousness for the OSP. The following types of TEAEs will be provided:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade ≥ 3
- TEAEs by PT in decreasing frequency
- Drug-related TEAEs by SOC and PT
- Drug-related TEAEs by PT in decreasing frequency
- Serious TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT

- TEAEs leading to dose interruption by SOC and PT
- TEAEs leading to dose reduction by SOC and PT

If the same PT or SOC is reported more than once for a subject, the subject will only be counted once in the corresponding incidence of PT or the SOC.

To avoid overcounting events for a given PT or SOC, only the most severe and the most closely related PT and/or SOC term will be included for each subject ID in tabulations by severity (i.e., CTCAE toxicity grade) and relationship,

For all subjects in the OSP, AEs, serious AEs and AEs leading to treatment discontinuation will be listed by the subject ID, by the treatment arm and the dose cohort.

In tabulation by severity (i.e., CTCAE toxicity grade) and relationship, for a given PT or SOC, only the most severe and most closely related PT and SOC will be included for each subject.

## 13.2. Extent of Study Drugs Exposure

Listings of exposure of study drugs (veledimex and Ad-RTS-hIL-12) will be provided by treatment arm, dose cohort and subject ID for the OSP.

### 13.2.1. Ad-RTS-hIL-12 Injections

The total volume received, the number of sites and whether the dose was modified will be tabulated by subject ID.

### 13.2.2. Veledimex Exposure

The number and percentage of subjects exposed to the veledimex study drug will be provided by treatment arm and the dose cohort, for the OSP.

Listings of treatment compliance and modification of study drug veledimex will be provided by the treatment arm, dose cohort, and subject ID for the OSP.

Veledimex study drug exposure will be summarized by subject ID for:

- Duration of exposure
  - In days, defined as last dose date – first dose date + 1
- Cumulative dose
  - Actual cumulative dose (mg), defined as the sum of all doses taken during the treatment period.
  - Expected cumulative dose (mg), defined as sum of all doses assigned during the treatment period.
- Dose intensity
  - Actual dose intensity (mg/day), defined as the actual cumulative dose (mg) divided by the duration of exposure (days).
  - Expected dose intensity (mg/day), defined as the expected cumulative dose (mg) divided by the duration of exposure (days).

- BSA-adjusted dosing
  - defined as the actual administered dose divided by body surface area (BSA).
  - BSA-adjusted dosing <75%, 75%-125%, and >125% will be categorized for summary.

## 13.3. Treatment Compliance and Modification

Veledimex study drug treatment compliance and any modifications to the dose and schedule of treatment will be summarized by subject ID for the following variables:

- Relative dose intensity (%)
  - defined as the actual dose intensity (mg/day) divided by the expected dose intensity (mg/day), expressed as a percentage.
- Dose interruptions by subject ID
  - The number of subjects with any dose interruptions
  - Time in days from first dose date to date of first dose interruptions for any reason:
  - Time in days from first dose date to date of first dose interruption due to AEs
  - Total days of dose interruptions due to AEs
- Dose reduction
  - Number of subjects who were classified as receiving a dose reduction
  - Time in days from first dose date to the date of first dose reduction due to AEs
  - Total days of dose reduction due to AEs for subjects experiencing a dose reduction

## 13.4. Clinical Laboratory Assessments

Clinical laboratory assessments include hematology, coagulation, serum chemistry and urinalysis. Laboratory tests will be performed in a central laboratory. Laboratory values will be converted to standardized units. Only numerical values will be used for summary of continuous parameters.

For hematology, coagulation and serum chemistry laboratory parameters, subject listings will be provided for values at baseline and changes from baseline instead of descriptive summary tables by treatment arm, dose cohort and visit for the OSP.

In addition, laboratory test results will be categorized by CTCAE toxicity grades according to the normal ranges of the central laboratory. Subject listings will provide the shift from baseline to worst post-baseline extreme values denoting the visit for which the worst post-baseline shift occurred. Laboratory results with toxicity grades missing at either baseline or at post-baseline will not be used for summarizing the worst post-baseline shift by subject ID. The number of subjects who have both baseline and post-baseline laboratory values will be summarized where applicable.

Urinalysis laboratory parameters are summarized by subject ID (instead of Frequency tables used to summarize the urinalysis laboratory parameters by treatment arm and dose cohort, and visit.).

Separate listings by subject ID for each subject ID visit will be summarized for all laboratory tests where applicable for the OSP. Both laboratory parameters' values in the original unit collected and standardized units will be listed.

## 13.5. Vital Signs including Weight

The vital signs' parameters include systolic and diastolic blood pressure (mmHg), heart rate (bmp), respiratory rate (breaths/minute), temperature ($^0$C) and weight.

Observed vital signs will be summarized in listings by subject ID for the OSP (instead of using descriptive statistics by treatment arm, dose cohort and visit for the OSP).

Conversion of temperature from Celsius to Fahrenheit is defined:

$$\text{Temperature } (^{o}C) = (\text{Temperature } (^{o}F) - 32) \times 5/9$$

Listings of vital signs, height and weight will be provided by subject ID for the OSP.

## 13.6. Physical Exams

Physical exams including general physical exam and targeted neurological exam will be tabulated by subject ID for the OSP.

## 13.7. Electrocardiogram (ECG)

Where applicable, a summary of actual values and changes from baseline will be provided by Subject ID for the OSP. This is in lieu of presenting the overall interpretation of ECG results be summarized using frequency tables by treatment arm, dose cohort, and visit for the OSP.

## 13.8. Lansky, Karnofsky and ECOG Performance Status

Where applicable, a summary of actual values and changes from baseline will be provided by Subject ID for the OSP.

Scores and changes from baseline for Lansky, Karnofsky and ECOG Performance Status will be tabulated by subject ID for the OSP.

Listings will be presented by subject ID based on EP for Lansky, Karnofsky and ECOG Performance Status.

## 13.9. Pregnancy Test

Pregnancy test results will be listed by arm and dose cohort, visits, and subject ID for the OSP.

# 14. EFFICACY ANALYSIS

Tumor response will be assessed using iRANO criteria at Day 14, 4 weeks (Day 28 ± 7 days), 8 weeks (Day 56 ± 7 days), and every 8 weeks (± 7 days) thereafter for all subjects. The analysis will be performed by arm and dose cohort for ESP.

Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

Listing will have presented for tumor response for OSP. Listing will be presented for all efficacy data by arm and dose cohort, and visit for ESP.

## 14.1. Tumor Response by iRANO

Frequency tables will be used to summarize response of tumor assessment for target, non-target and non-enhancing lesions, and overall response by arm and dose cohort, and visit using ESP.

## 14.2. Objective Response Rate (ORR)

ORR is the proportion of subjects meeting iRANO response criteria which is defined as sum of partial responses plus complete responses. ORR will be summarized using frequency tables by arm and dose cohort, and visit with 2-sided 95% exact binomial confidence interval (CI).

A figure similarly to a forest plot will be provided to display the response rates of each arm and dose cohort systematically along with a 2-sided 95% exact binomial confidence CI.

## 14.3. Progression Free Survival (PFS)

Progression-Free Survival (PFS) will be calculated as the time from baseline (Day 2) to date of disease progression or death, whichever occurs first. A subject who has neither progressed nor die will be censored on the date of last tumor response assessment. Subjects without valid baseline will not use for analysis. Subjects without post-baseline disease progression assessment will be censored at date of last non-progression disease response assessment or withdrawal.

The Kaplan-Meier (KM) method will be used to estimate the distribution of PFS for each arm and dose cohorts. Survival time will be summarized using descriptive statistics including 95% exact CI for median survival. Progression free survival rate at end of visit will also be included with 95% exact CI.

KM plots of PFS will be provided to graphically present the survival risk for each arm and dose cohort.

## 14.4. Overall Survival (OS)

OS is defined as the duration of time from first dose of the study drug to the date of death. Subjects who are still alive 2 years after first does of study drug will be censored at the last follow up contact date.

Details of death and survival time will be listed.

# 15. PHARMACOKINETIC ANALYSIS

Only PK concentration will be analyzed in this SAP. The PK concentration will be tabulated by arm and dose cohort, and visit for PKP.

Listings will be presented by arm and dose cohort, visit and subject ID for PKP.

## 15.1. Plasma PK Concentration Listings by Subject

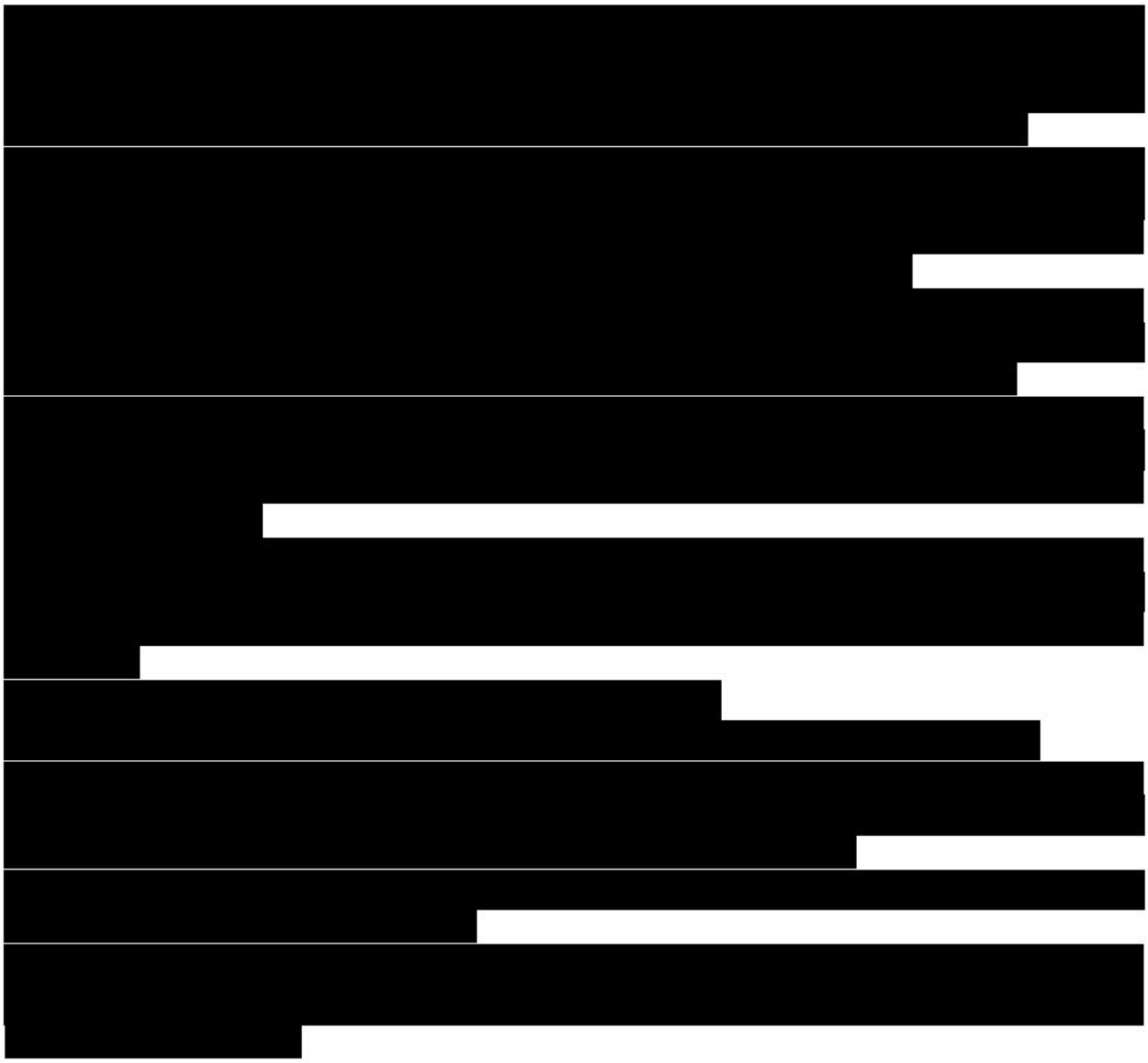
Plasma PK concentration of veledimex will be summarized by subject ID. These results will be tabulated by arm and dose, and visit.

## 15.2. PK Concentrations in Brain Tumor (Arm 1 Only)

PK concentrations in Brain Tumor is only measured for subjects in study Arm 1. 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).

Descriptive statistics by subject ID will be listed to summarize the concentration of veledimex in brain tumor and in blood, and the ratio of the concentration in the brain tumor and in the blood by treatment arm and dose cohort where applicable.

# 17. REFERENCES



# APPENDIX 1. SCHEDULE OF EVENTS

## Schedule of Study Procedure

| | 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** | **Day 7** | **Day 8-13** | **Day 14** | **Day 15** | **Day 28± 7** | **Day 56± 7** | **Every 8 weeks (± 1 week)** |
| **Clinical Assessments** | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Medical/Cancer History[a,b] | X | | | | | | | | | | | | |
| Physical Exam[c], including targeted neurological exam | X | X | X | X | X | | X | | X | | X | | |
| Lansky PS[d], Karnofsky, or ECOG | 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 | | |
| 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[i] | X | X[i] | | X | | X | | |
| Coagulation Panel[j] | X | X | | | X | | X | | X | | | | |
| Serum Chemistry Panel[k] | X | X | X | X | X[k] | X | X[k] | | X | | X | | |
| Urinalysis Panel[l] | X | X | | | | | | | X | | | | |
| ECG[m] | X | X | | | X | | | | X | | | | |
| Eligibility Review | X | X | | | | | | | | | | | |
| Registration[n] | X | | | | | | | | | | | | |
| **Study Drug Administration** | | | | | | | | | | | | | |
| Ad-RTS-hIL-12 | | X[o,p] | | | | | | | | | | | |
| Veledimex Dose Arm 1 | | X | X[p,q] | X | X[i,k] | X | X | X | X[r] | | | | |
| Veledimex Dose Arm 2 | | | X[p,q] | X | X[i,k] | X | X | X | X[r] | | | | |
| Veledimex Dose Compliance/ Subject Diary[r] | | | X | X | X | X | X | X | X | | | | |
| [redacted] | | | | | | | | | | | | | |
| [redacted] | [redacted] | | [redacted] | | [redacted] | [redacted] | | | [redacted] | | [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[t] | X | | | | | X | X | | | |
| [redacted] | | [redacted] | | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | |
| [redacted] | | [redacted] | | | | | [redacted] | | [redacted] | | [redacted] | | |
| MRI Scans[w,x] | X[w,x] | | | X[w,x,y] | | | | | X[w] | | X[w,x] | X[w,x] | X[w,x] |
| Tumor Sample[u] (Arm 1) | | X | | | | | | | | | | | |
| Tumor Biopsy[u] (Arm 2) | | X | | | | | | | | | | | |
| CSF Sample[z] (Arm 1 only) | | X | | | | | | | | | | | |

[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 (ie, 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 2 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, and platelet count. On Day 3, hematology panel must be drawn, analyzed, and reviewed by Investigator and Medical Monitor prior to subject dosing with veledimex. Subjects should not be dosed with veledimex on Day 3 unless lymphocytes, platelets, and liver function tests have changed by ≤ 20% from baseline values and the Grade of any abnormality has not increased.

[j] Coagulation Panel: activated partial thromboplastin time (aPTT), 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. On Day 3, serum chemistry panel must be drawn, analyzed, and reviewed by Investigator and Medical Monitor prior to subject dosing with veledimex.

[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 (eg, 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. Subject should be instructed to call the clinical site if headache, hemiparesis, seizure, or other local reactions develop anytime and especially between study visits.

[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, 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 3 for Arm 1 and Table 4 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] PK and [redacted] blood samples should be obtained prior to Ad-RTS-hIL-12 injection (ie, predose).

[u] [redacted]

[w] Appropriate cancer staging procedures should be performed during screening. All imaging should 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 should be available for collection upon Sponsor request.

[y] The MRI scan designated on Day 2 should be taken within 72 hours of Ad-RTS-hIL-12 administration 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.