STATISTICAL ANALYSIS PLAN (SAP) VERSION 1.0

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

18AUG2021

BASED ON:

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

Date of Protocol:

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

Sponsor: Ziopharm Oncology, Inc.

[redacted]

STUDY DRUG:

AD-RTS-HIL-12 + VELEDIMEX IN COMBINATION WITH CEMIPLIMAB

PROTOCOL NUMBER:

ATIOO 1 -204 AMENDMENT 2

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

[redacted]

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

[redacted]

Project Statistician, Ziopharm Oncology, Inc. | Signature | Date

This document has been reviewed and accepted by:

[redacted]

Head of Biostatistics, or designee
Ziopharm Oncology, Inc. | Signature | Date

[redacted]

Medical Monitor, or designee
Ziopharm Oncology, Inc. | Signature | Date

[redacted]ons, or designee
Ziopharm Oncology, Inc. | Signature | Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD	Cluster of Differentiation
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRP	C-Reactive Protein
CTLA-4	Cytotoxic T Lymphocyte-Associated Antigen
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
GBM	Glioblastoma
HEENT	Head, Eyes, Ears, Nose, And Throat
hIL-12	Human Interleukin-12
ICF	Informed Consent Form
IFN-γ	Interferon Gamma
IL	Interleukin
INR	International Normalized Ratio
IP-10	Interferon Gamma-Induced Protein 10
iRANO	Immunotherapy Response Assessment for Neuro Oncology
IV	Intravenous(Ly)
LDH	Lactate Dehydrogenase
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PO	Oral(Ly)

PP	Per Protocol
PR	Partial Response
PSP	Pseudo-Progression
PT	Preferred Term
PT	Prothrombin Time
PTT	Partial Prothrombin Time
Q3W	Every 3 Weeks
QD	Each Day
RBC	Red Blood Cell
RTS	Rheoswitch Therapeutic System®
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
TCR	Tumor T Cell Receptor
TEAE	Treatment-Emergent Adverse Events
WBC	Including White Blood Cell
WFNOS	World Federation of Neuro-Oncology Societies

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the proposed statistical analyses in concert with Ziopharm Protocol ATI001-204 Amendment 2 entitled: A Phase II Study of Ad-RTS-hIL-12 + Veledimex in Combination with Cemiplimab(Libtayo®) in Subjects with Recurrent or Progressive Glioblastoma.

Importantly, and where applicable, all references pertaining to the protocol in this SAP are meant to imply "contains a more detailed explanation of the statistical analyses" in the Protocol ATI001-204 Amendment 2. 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.

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

Please refer to the finalized protocol and its amendments to follow the plan as originally envisioned.

Protocol Chronology

- Amendment 2: 08Jan2020
- Amendment 1: 09May2019
- Original: 07Feb2019

2. OBJECTIVES

Primary Objective

- To determine the safety and efficacy of intratumoral [redacted] (Ad-RTS-hIL-12) and oral (PO) veledimex (RTS activator ligand) in combination with cemiplimab(Libtayo®) when treating subjects with recurrent or progressive glioblastoma. This determination will be based on the drug safety profile in combination with the estimate of Overall Survival (OS), representing the potential clinical efficacy for which late-stage clinical trials may be planned based on the estimates obtained.

Secondary Objectives

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

3. INVESTIGATIONAL PLAN

3.1. Study Design and Plan

This is [redacted] multicenter Phase II uncontrolled study of an intratumoral injection of Ad-RTS-hIL-12 [redacted] and veledimex (20 mg) administered PO in combination with cemiplimab (350 mg) administered intravenously (IV) in subjects with recurrent or progressive glioblastoma.

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

A detailed account of the study procedures is illustrated in ATI001-204 Protocol Amendment-2 Section 12 Table 1 Schedule of Study Procedures.

3.2. Stopping Rules

The stopping rules of the study are portrayed in section 10.9 of the Protocol. Specifically from Day -7 to 30 days after completion of Ad-RTS-hIL12 + veledimex dosing, Subject stopping rules criteria were defined along the lines of the following:

- If any subject experienced a death (other than death related to progressive disease).
- If any subject, during the initial treatment period (Day -7 to Day 28) experiences a related SAE that has immediately life-threatening consequences requiring urgent intervention or:
  - Results in death;
  - Requires major operative intervention;
  - Or is a related grade 4 hematologic toxicity that persists for 5 days:

If any of the above occurred, then enrollment of new subjects will be paused, pending review of the event by the Safety Review Committee.

A formal Safety Review Committee (SRC) was to be comprised of the study Investigators and the Medical Monitor. The SRC was to evaluate whether to recommend if changes to the enrollment of additional subjects should be modified, after its review of an event(s) described above including, but not limited to,

- Potentially modifying the dose and schedule of veledimex.
- To amend the protocol prior to enrollment of additional subjects, or,
- To discontinue enrollment in the study.

Section 10.10 of the protocol enumerates dose modification and dose delay specifications according to the criteria shown in Table 2.

Concomitant therapy described in section 11 of the protocol, conveys permitted and prohibited medications/therapies.

3.3. Study Endpoints

3.3.1. Primary Endpoint

The primary endpoint for evaluation of efficacy is:

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

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

3.3.2. Secondary Endpoints

Secondary endpoints include:

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

3.4. Treatments

The current plan for the Phase II study in glioblastoma is to begin dosing with:

- Cemiplimab (Libtayo®) at 350 mg Intravenously (IV) on day -7 (±3 days), then again on day 15 and then on:
  - Day 36 (±3 days), Day 57 (±3 days),
  - then subsequently for every 3 weeks (Q3W ±7 days) until confirmed progression (iRANO), unacceptable toxicity or subject withdrawal.
- On Day 0 (day of Ad-RTS-hIL-12 administration) subjects will take one dose of veledimex 3±2 hours prior to injection of Ad-RTS-hIL-12 and Ad-RTS-hIL-12 [redacted] will be administered by freehand injection.
  - After tumor resection and Ad-RTS-hIL-12 injection, veledimex will be administered orally for 14 days. The first post-resection veledimex dose is to be

given on Day 1. Subsequent veledimex doses are to be taken once daily, in the morning and within approximately 30 minutes of a regular meal. The first veledimex dose following Ad-RTS-hIL-12 injection is expected to be administered when the subject is at the clinical site, under careful medical supervision by the clinic staff to ensure that the subject does not have difficulty swallowing the capsules.

- Thereafter, subjects may be allowed to self-administer the remaining once daily doses as described. Subjects are to be instructed to take the appropriate number of capsules in the same way for each of the remaining treatment period days and may be reminded to do so by phone on non-visit days.
- Subjects should NOT make up any missed doses.
- Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the once daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses, and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff on Day 15, so that staff can properly assess dose compliance.

3.5. Dose Adjustment/Modifications

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

Veledimex and cemiplimab dose delays and dose reductions for individual subjects will be allowed in the event of an adverse event, according to the criteria specified in protocol section 10.10.

3.6. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 9.1 and 9.2 of the protocol. All inclusion/exclusion information on safety patients will be included in a by-patient listing. For patients who did not satisfy these criteria, the criteria numbers will be listed with the deviation. The key change to the inclusion criteria depicted in amendment 2 was that multifocal disease was not prohibited; although, subjects must not have more than 5 enhancing lesions.

4. STATISTICAL METHODS

4.1. Sample Size

Sample Size and Power Calculations

Based on Amendment 2, the plan was updated to accrue up to 36 subjects instead of 30 subjects (originally planned) to obtain approximately 25 subjects evaluable for efficacy.

A sample size of up to 25, will allow us to estimate an overall safety rate with a maximum 95% exact confidence interval half-width of approximately 0.19.

In addition, a Toxicity boundary based on repeated significance testing provided for a guideline to seriously consider stopping the trial if the number of subjects experiencing unacceptable toxicity exceeded the proportions below. The method for determination of the Toxicity boundary used the Toxbdry function in the Clinfun R package implementation of repeated significance testing methodology (Ivanova, Qaqish, & Schell, 2005).

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

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

The boundaries above were created assuming a 30% Toxicity rate is acceptable and 60% would be unacceptable. According to boundary conditions stated herein, a review was to be performed if applicable, after 5, 10, 15, 20 and 25 subjects reach Day 30. Serious consideration for stopping the clinical trial should be given if the number of subjects meeting the Stopping Rules criteria is determined to be greater than 3/5, 5/10, 8/15, 9/20, or 11/25, the values which form the lower boundary condition. The operating characteristics of the boundary conditions are calculated and displayed below.

Operating Characteristics:

Prob toxicity	Prob Cross. lower	Prob Stop lower	Expected Sample Size lo	Prob Cross. Hi bound	Prob Stop hi	Expected Sample Size hi
0.30	0.101	0.090	23.8	0.074	0.050	24.2
0.36	0.239	0.205	22.3	0.193	0.122	23.2
0.42	0.441	0.377	20.2	0.388	0.248	21.6
0.48	0.661	0.578	17.5	0.617	0.426	19.3
0.54	0.839	0.763	14.6	0.812	0.625	16.5
0.60	0.943	0.894	11.9	0.932	0.800	13.6

This patient population will be heterogeneous and as such, it is difficult to define a clear safety threshold for evaluation in combination with determination of OS, ORR and PFS.

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

Enrollment objectives:

- [redacted]. The total amount of virus delivered to each site will be recorded in the electronic Case Report Form (eCRF). If the total administered (injected) volume is less than planned, the reason will be provided. Care should be taken to avoid intraventricular or basal cisternal injection or other critical locations.
- [redacted]
  - [redacted]
- Subjects who withdraw from the study or do not receive each study drug may be replaced. All dosed subjects will be included in the overall safety assessment.
  - No subjects were replaced.

4.2. Randomization, Stratification, and Blinding

Not Applicable

4.3. Interim Analyses

There were no formal preplanned interim analyses for efficacy.

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

4.4. Data Management

Ziopharm Data Management directs and oversees the administration of the ATI001-204 eCRF database. The clinical trial data from all screened and enrolled subjects populate the ATI001-204 database which is also managed by a third-party contract research organization (CRO). In addition, the ATI001-204 protocol provided for study objectives for which the data obtained are not part of the eCRF. Instead, the data are acquired based on the data transfer agreements (DTA) from 7 external data sources denoted as "vendors" summarized in Table 1 below. Specifically:

- The ATI001-204 clinical database consists of N=40 FAS subjects for whom at least one of the following study treatments were received: Ad-RTS-hIL-12, veledimex, cemiplimab.
- The imaging data objective originally to be undertaken with Bioclinica was put on hold and not performed.

- For completeness it is noted that there are subjects who also have data in the database who are classified as screen failures for whom we are not counting for the purpose of this description. Subjects that were enrolled but did not receive treatment were withdrawn and will not be included in any analysis population.
- A summary of the number of screen failures signing an informed consent is provided in the subject disposition.
- Extraction of Raw SAS datasets from the EDC database will be converted into Study Data Tabulation Model (SDTM) SAS datasets based on CDISC.

4.4.1. Locking the Database

Preparation for locking the ATI001-204 clinical database will occur when all subjects (n=40) have been reviewed and it has been established that there are no outstanding queries to be resolved.

4.5. Populations for Analysis

4.5.1. Screened for eligibility and not treated: (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.

4.5.2. Full Analysis Set (FAS)

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

4.5.3. Per Protocol (PP)

The per protocol population will comprise subjects who have received Day -7 of cemiplimab, the injection of Ad-RTS-hIL-12 with at least one post IL-12 dose of veledimex, at least one post IL-12 dose of cemiplimab (e.g., Day 15), and 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. Estimates of the overall OS hazard rate, the OS at prespecified timepoints, PFS and the ORR will be based on the PP population.

4.5.4. Evaluable Safety Population (ESP)

The ESP is a subset of the FAS. Regardless of major protocol deviations, these subjects have received at least one of the following:

- Day -7 of cemiplimab,
- the injection of Ad-RTS-hIL-12 with at least one post IL-12 dose of veledimex,
- and at least one post IL-12 dose of cemiplimab (e.g., Day 15).

[redacted]

4.5.6. Completers

The completers population is defined as all eligible subjects who completed all phases of the trial without any major protocol deviations.

4.6. General Statistical Considerations

Continuous data, where applicable, will be described using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by subject identifier.

Subjects will be identified in the listings by the subject identification number concatenated with the investigator number.

When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to the first dose of treatment (any of the Ad-RTS-hIL-12, veledimex and cemiplimab) is taken. The study day will be calculated as assessment date - first dose date + 1.

All analyses will be conducted using SAS Version 9.4 or higher.

All data are summarized based on the visit name collected on the CRF page.

4.7. Data Presentation Conventions

The presentation of summary statistics and the conventions for preparing data listings for combining the data for all treated FAS subjects (n=40) are described along the lines of what follows:

- Unless otherwise specified, baseline is the last observation before the first study drug administration. (See section on data handling conventions for more details.) The baseline lesion assessment is considered within 72 hours following Ad-RTS-hIL-12 injection.
- Unless otherwise specified, percentages will be calculated based on the number of patients based on non-missing data as the denominator.
    - A missing values category will also be defined to ensure all subjects are accounted for in prespecified populations for analyses.
- In analyses presented over time by visit, no imputations will be performed on missing data. All analyses will be based on the observed data.
    - The effective sample sizes at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.
    - When applicable, additional derived variables will be created based on specifications with or without protocol deviations and violations to assess the comparability and the influence of such deviations. Summary statistics will be provided for continuous variables (e.g., age).
        - Unless otherwise stated, this will consist of the number of subjects with a non-missing value of the variable (n), mean, standard deviation, median, minimum and maximum.
    - The same number of decimal places as in the raw data will be presented when reporting the minimum and the maximum summary statistics,
        - One more decimal place than in the raw data will be presented when reporting the mean, and the median.

  - Two more decimal places than in the raw data will be presented when reporting the standard deviation.
- Frequency counts will be provided for categorical variables (e.g., gender).
  - Unless otherwise stated, this will consist of the number of subjects with a response in a particular category and the percentage of the total number of subjects in that column.
  - Unless otherwise stated, categories for missing responses will be included in both the display and in the calculation of percentages (i.e., they will be included in the denominator).
  - Percentages will be rounded to one decimal place.
  - Percents equal to 100 will be presented as 100% and percents will not be presented for zero frequencies.

4.7.1. Overview of Statistical Summaries by Defined Populations

Subject populations will be evaluated and used for presentation and analysis of the following:

- The FAS will be used for summaries of subject disposition, baseline characteristics and for safety. In addition, the FAS will be used in secondary analyses of OS, ORR, and PFS.
- The PP population is to be used for the primary analysis of OS, ORR, PFS and OS.
- When applicable the ESP will be used for analysis of dose limiting toxicities.
- [redacted].

4.7.2. 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. In general, no subject was planned to be removed from any analysis population because of a protocol deviation.

In accordance with ICH E3, patient eligibility violations and important post- treatment protocol deviations will be identified and listed by patient 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 was not withdrawn.
- Prohibited concomitant medications.
- Treatment deviation.
- Other protocol deviation.

All protocol deviations will be categorized as either major or minor. The list of protocol deviations along with whether the deviation is classified denoting a major or minor categorization will be finalized prior to database lock.

Major protocol deviations will be presented in a summary table by protocol deviation category for the FAS. Protocol deviations will be presented in a listing.

4.7.3. Relevant Protocol Deviations (RPD)

Originally, relevant deviations from the study protocol were to be documented and accounted for in presenting the data listings and descriptive statistical analyses. Any changes from planned protocol-specified analyses were to be defined in the SAP and reported in the CSR. Instead, protocol deviations will not be produced by Biostatistics. Instead, protocol deviations will be described with an in-text table as applicable in the final CSR. The relevant protocol deviations are described in the Table 2 below.

Table 2: List of Relevant Protocol Deviations

Number	RPD Criteria
1	Poor treatment compliance for either cemiplimab or veledimex (less than 80% of expected total dose of either treatment)
2	Taking prohibited concomitant medication including CYP3A4 inhibitor
3	Others

5. SUBJECT DISPOSITION

5.1. Disposition: Subjects Screened and not treated with any experimental study treatment

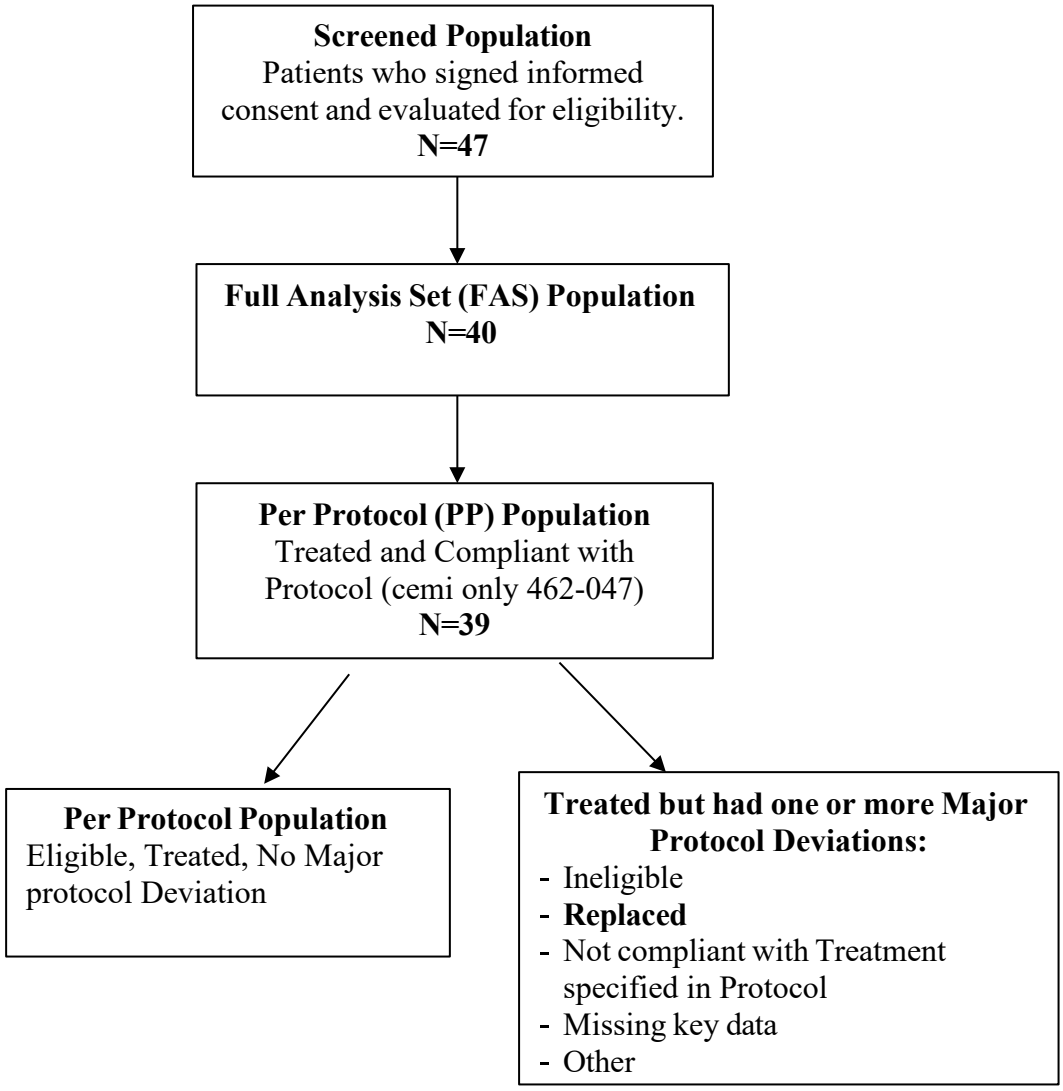
Subjects screened for study eligibility for whom experimental study treatment was not received regardless of the reason will be denoted as Screen Failures. The number of subjects screened and not treated is reported as part of the subject disposition and nowhere else. These subjects are not included in any study listings or analyses and are not part of the study population for whom the results of the study are reported.

5.2. Disposition: The FAS Population

After displaying the number of subjects screened and not treated, the subject disposition presents the number of subjects in the FAS population as the starting point. All percentages will be based on the number of FAS subjects. Subsequently the table illustrates:

- The number and percent of subjects who:
  - Complete the study,
  - Discontinue from the study by reason for treatment discontinuation and study discontinuation.
- Subjects who discontinued from veledimex.
- Subjects who discontinued from cemiplimab.
- The number and percentage of subjects in each analysis population:
  - PP population and
  - [redacted].
  - If applicable, important protocol deviations will be summarized and listed.
- A summary of the subjects excluded from the PP population and the reasons for exclusion.
  - Patients could be excluded from the PP population for more than one reason.

Figure 1: Patient Disposition for Protocol Defined Populations



6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (years), sex, race, and ethnicity. The baseline characteristics consist of baseline height (cm) and baseline body mass index (BMI) (kg/m^2). Body mass index is calculated as (body weight in kilograms)/(height in meters)^2.

Age (years), baseline height (unit), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of sex (Male, Female), race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino and Unknown), will also be reported. Percentages will be based on the total number of subjects in the FAS.

Age is taken to be the subject's age on the date of the Screening visit. Conversions for height and weight are as follows:

- Height (cm) = Height (inches) x 2.54
- Weight (kg) = Weight (lb) x 0.454

Demographics will be listed and tabulated using descriptive statistics.

Subject demographic and baseline characteristics will be presented in a listing.

6.2. Baseline Disease Characteristics

Subject’s baseline disease characteristics will be summarized according to the conventions described previously for descriptive statistics of continuous and categorical variables. In addition, baseline characteristics will be transformed into subject characteristic grouping variables for further exploration of the FAS illustrated below.

- Age category

<65 vs ≥65

- Gender

Female vs Male

- MGMT

unmethylated vs methylated

- Hispanic or Latino

yes =1 vs no=0

- Race

White vs not White

- IDH

wild-type vs mutated

- Prior Steroid use > four weeks before day -7

yes=1 vs no=0

- Enhanced Lesion

unifocal vs Multifocal

- Number of Lesions at Entry

1 vs > 1

- KPS Screening, N(%)

≥70 to 90 vs ≥90

6.3. Alcohol, Tobacco and Caffeine Usage

Not Applicable

6.4. Medical History

6.4.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of subjects in the FAS.

Subject medical history data including specific details will be presented in a listing.

6.4.2. Disease-Specific History

Disease specific history will consist of initial disease status, grade at initial diagnosis, initial MGMT gene promoter status and initial IDH status. Disease specific history will be summarized by frequency count and percentage based on FAS population.

Subject disease-specific history data including specific details will be presented in a listing.

7. TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization Drug Dictionary (WHO-DD V5).

- Prior medications are defined as medications with a stop date occurring before the first dose of treatment (any of the Ad-RTS-hIL-12, veledimex and cemiplimab) is taken.
- Concomitant medications are those medications taken after the initial dose of study drug. Concomitant medications are defined as medications that are ongoing on the first dose date, or with a start date missing or occurring on or after the first dose date.
- Concomitant medications, including blood products, vitamins, and other supplements received during the screening period (28 days) prior to initiating study treatment will be recorded. Concomitant medications will continue to be collected through 90 days after the subject's last dose of any study drug.

For inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.

Missing stop dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month.
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the

end date is within 28 days prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as prior and concomitant.

7.1.1. Prior Medications

The total number of prior medications and the number and percentages of subjects with at least one prior medication will be summarized. The number and percentages of all prior medications will be summarized and listed by drug class and preferred term. All summaries will be performed using the FAS.

7.1.2. Concomitant Medications

The total number of concomitant medications and the number and percentages of subjects with at least one concomitant medication will be summarized. The number and percentages of all concomitant medications will be summarized and listed by drug class and preferred term. All summaries will be performed using the FAS.

7.2. Study Treatments

For Ad-RTS-hIL-12, cemiplimab and veledimex, separate summaries will be provided for details in administration using descriptive statistics based on FAS. All administration details will be presented in a listing.

7.2.1. Extent of Exposure

Details of study drug administration and dose modifications will be listed as follows.

7.2.1.1. Ad-RTS-hIL-12

Total volume received, number of sites and whether the dose was modified will be tabulated.

7.2.1.2. Veledimex

The total dose received (mg) for each study treatment will be calculated based on the Drug Accountability CRFs including the oral dosing diaries. Dosing details are summarized per subjects for each dosing cohort. Dose and dose modifications per subject treated will be listed. The number of doses received will be tabulated.

Subject veledimex dosing compliance will be determined for each subject as the total number of tablets dispensed minus the total number of tablets reported as not taken, divided by the total number of tablets dispensed, multiplied by 100.

- Subgroups for dosing compliance may be explored (e.g. compare subgroup of subjects who are 100% (80%) dosing compliant with subgroup of subjects <100% (<80%) dosing compliant).
- Extent of exposure will not be calculated for Ad-RTS-hIL-12 as it will be administered only on Day 0.

7.2.1.3. Cemiplimab and Veledimex, Duration of Exposure

For cemiplimab and veledimex, duration of exposure is defined as the total number of days a subject is exposed to any study drug and will be presented as the total number of days from the first dose date (Day -7 for cemiplimab and Day 0 for veledimex) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the End of Treatment page on the CRF. If the last dose date on the End of Treatment page is missing, or if a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used.

- The duration of exposure to study drug will be summarized for cemiplimab and veledimex for all subjects in the FAS.
- The total dose for each study drug will be summarized for cemiplimab and veledimex for all subjects in the FAS.
- A summary of each subject's exposure will be presented in a listing.

7.2.2. Treatment Compliance and Modifications

For Ad-RTS-hIL-12 and cemiplimab, the number and proportion of subjects receiving treatment will be summarized at each scheduled dosing visit.

For veledimex, compliance will be calculated for each subject by making the determination whether a subject takes all doses of study drug as instructed. The number of capsules taken will be calculated by subtracting the number of capsules returned from the number of capsules dispensed. The overall study drug compliance (%) will be calculated by dividing the total number of capsules taken during subject's study period by the total number of capsules expected to be received based on the schedule of events and then multiplying by 100.

Compliance (%) = [(total no. of capsules dispensed – total no. of capsules returned) / (No. of days in interval *No. of capsules prescribed per day)] * 100.

Summary statistics on percentage of veledimex compliance as well as the number and percentage of subjects in each compliance category (<80%, 80-100% compliant) will be presented overall.

A subject is considered compliant to veledimex if overall study drug compliance is greater than or equal to 80%. A categorical summary of whether subjects were compliant (yes/no) will be presented.

Percentages will be calculated out of the number of subjects who were dosed in the FAS.

8. EFFICACY ANALYSIS

No formal hypothesis testing will be performed for primary and secondary endpoints. Estimates of the single arm will be determined and will be compared numerically with historical control estimates, wherever applicable.

Observed data will be presented over all study centers. No imputation of values for missing data will be performed.

In general, all estimates will be calculated considering two-sided 5% level of significance. No adjustments for covariates will be made.

- See Section 10 of this document for all changes to originally preplanned efficacy analyses.

8.1. Primary Efficacy Endpoint

The primary endpoint for evaluation of efficacy is the OS hazard rate which is performed by estimating the hazard rate based on the accrual and follow-up of all treated subjects. Subjects will be followed from the first date of treatment up to 2 years for overall survival.

OS is defined as the duration of time from the first dose of study drug (i.e., cemiplimab at Day -7) to the date of death from any cause. Censoring will be considered as below:

- Subjects who discontinue study will be censored at date of discontinuation.
- Subjects who are lost to follow-up will be censored at last follow-up contact date.
- If the subject has not died, the subject is censored if still alive up to 2 years from the first dose of study drug received.

All summaries and analyses for the primary efficacy endpoint will be based on per-protocol population.

8.2. Primary Analysis for OS

The primary analysis for estimating the hazard rate for the time to OS denoted as the function S(t) will be performed on the PP population using the Kaplan Meier (KM) Product-Limit estimation method. A secondary analysis will also be implemented for the FAS. Using the KM method:

- The median survival time along with the 95% Confidence Interval (CI) will be constructed.
- The 25^{Th} and 75^{th} quartile of survival time will also be provided supplemented by the Kaplan-Meier plot of OS.

8.2.1. Assumption Testing

No assumption check is planned for the Kaplan-Meier method.

[redacted]

Patient Characteristic Subgroup Factors

Among the patient factors to be explored are the following patient derived variables.

Age category

- <65 vs ≥65

Gender

- Female vs Male

MGMT

- unmethylated vs methylated

Hispanic or Latino

- yes =1 vs no=0

Race

- White vs not White

IDH

- wild-type vs mutated

Prior Steroid

- yes=1 vs no=0

Enhanced Lesion

- unifocal vs Multifocal

Number of Lesions at Entry

- 1 vs > 1

KPS Screening, N (%)

- ≥70 to 90 vs ≥90

veledimex Dosing Compliance

- <100% (<80%) vs 100% (≥80%)

8.2.3. Estimation of OS using Parametric Survival Assumptions for S(t)

In addition to estimating S(t) based on the KM method, S(t) will be estimated under the assumption that S(t) is Weibull distributed for shape and scale parameters to be explored.

8.3. Secondary Efficacy Endpoints

All secondary endpoint determination related to tumor assessment is based on the investigator assessment. If applicable an independent review committee (IRC) will also perform tumor response and tumor progression assessments based on the methods of tumor assessment defined in the IRC charter. Secondary endpoints for estimation include:

8.3.1. The OS rate at fixed timepoints 6, 12, 18 and 24 months

- OS rates will be derived from the KM estimate along with the corresponding two-sided 95% CI estimated using Greenwood's formula for the variance and the log-log transformation applied to the survivor function S(t)

8.3.2. Overall PFS and PFS rate at fixed timepoints 6, 12, 18 and 24 months

- Overall PFS and the PFS rate of pseudo-progression (PSP) will also be estimated. at month 6, 12, 18 and 24 with corresponding 95% confidence interval (CI).

PFS is defined as the duration of time from the first dose of study drug (i.e., cemiplimab at Day -7) to the confirmed progression (as determined by immunotherapy Response Assessment for Neuro Oncology (iRANO) criteria) or death from any cause, whichever occurs first. Censoring will be considered as below:

- Subjects who discontinue study without any event will be censored at date of discontinuation.
- Subjects who are lost to follow-up without any event will be censored at last follow-up contact date.
- If the subject has no progression or not died, the subject is censored if still alive up to 2 years from the first dose of study drug received.

The time to PFS will be estimated on the PP population using the Kaplan Meier (KM) Product-Limit estimation method. The median PFS will be summarized along with corresponding 95% CI. A Kaplan-Meier plot of PFS will also be provided.

Pseudo-progression (PSP) is a term used to describe the appearance of radiographic disease progression due to increase contrast enhancement on MRI without true tumor progression. The increase in contrast enhancement can be influenced by several parameters including differences in radiologic technique, the amount of contrast agent used, the timing of the contrast agent administration relative to the imaging, postsurgical changes, infarction, treatment related inflammation, seizure activity, sub-acute radiation effects, radiation necrosis, and corticosteroid use. Consideration of these factors by experts and clinical experience is likely to identify these subjects.

Number and proportion of subjects with PSP will be summarized with corresponding two-sided 95% confidence interval (CI).

8.3.3. Objective Response Rate (ORR) at 6, 12, 18 and 24 months

The ORR, determined according to Recist 1.1 confirmed response criteria instead of iRANO criteria will be summarized at month 6, 12, 18 and 24 with corresponding two-sided 95% confidence interval (CI).

8.3.4. Tumor Response Rate

- Determination of tumor response will be performed on each subject in the PP population.
- The Tumor response rate of Ad-RTS-hIL-12 + veledimex when administered in combination with cemiplimab will be estimated at 6, 12, 18 and 24 months.
- Tumor response will be defined by radiographic and clinical criteria. Complete response (CR) or partial response (PR) will be first assessed by radiographic changes that indicate a reduction of bi-dimensional tumor size as per Recist 1.1 criteria. In addition, changes in neurologic function and steroid use will be considered to determine stable disease (SD).

8.3.5. Best Overall Response (BOR)

The BOR was not originally included in the protocol and has been added as a new secondary endpoint. The BOR will be determined for each subject based on the applicable tumor assessment results for both the investigator and the IRC.

The best overall response (BOR) is a derived variable that summarizes for each treated subject the best tumor response recorded on the eCRF based on the investigator assessment.

- Tumor response data collected before evidence that the subject received a new anticancer treatment.

The BOR categories are defined as:

- Complete Response
- Partial Response
- Stable Disease
- Progressive Disease

- Not Evaluable (if subject has BOR assessment but is denoted Not Evaluable)
- No Response (if subject has no BOR assessment).

[redacted]

8.4. **Other Efficacy Endpoints:** Karnofsky Performance Status (KPS)

The KPS measures the ability of cancer subjects to perform ordinary tasks. Scores range from 0 to 100 with a higher score meaning that the patient is better able to carry out daily activities. The KPS is used to determine a patient's prognosis and to measure changes in a patient's ability to function, Subjects must have a KPS score of ≥ 70 at the Screening Visit to be eligible to participate in the study.

KPS measures were planned to be taken at screening, Day -7, Day 0, Day 14, Day 36 and every 3 weeks thereafter. KPS observed values will be provided in listings. Originally planned, changes from baseline at each scheduled visit were to be performed to summarize descriptive statistics. See other efficacy variables under Section 10 describing the changes to the planned analysis.

9. SAFETY ANALYSIS

All analyses of safety will be conducted using the FAS. Abnormal laboratory test results, will be captured as Adverse Events (AE)s. Safety evaluations will use calculations to determine estimates of the incidence, intensity, and the type of AE and SAE's based on preferred term coding.

All clinical findings will be further inspected through a clinical review of relevant parameters including AEs, serious adverse events (SAEs), laboratory values (hematology, serum chemistry, and urinalysis), body weight, vital signs, physical examinations, and ECOG performance status. Where applicable the Safety will also be summarized using the ESP. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

9.1. Adverse Events

9.1.1. Treatment-Emergent Adverse Effects (TEAE)s

The primary presentation of AE's will be prepared without regard to causality or relationship to study treatment. In addition, summaries of all TEAEs, treatment-related TEAEs and of all SAEs will be tabulated by System Organ Class (SOC), Preferred Term (PT), and Common Terminology Criteria for Adverse Events (CTCAE) grade of TEAE.

A TEAE is defined as an AE that meets any of the following conditions:

- Begins on or after the first dose of study drug and before the stop of study drug + 90 days.
- Begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the stop of study drug + 90 days.
- Is completely missing an onset date and an end date.
- Is completely missing an onset date and the end date is on or after the first dose of study drug.

Verbatim terms captured on the eCRF will be mapped to PTs and SOC using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0 or higher for purposes of TEAE summarization.

9.1.2. Incomplete Onset or end date Imputation Conventions

If the onset date or the end date of an AE is incomplete, the following conventions for date imputation of the AE onset and end dates will be applied.

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug

month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month.
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

9.1.3. Incidence of Adverse Events

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to study termination, and AE leading to death will be presented.

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided. The number and percentage of subjects and the number of events will also be presented by SOC and PT. At each level of summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the FAS. The number of events at each level of SOC and PT will also be summarized.

A summary of TEAEs will also be presented in descending order from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

All AEs will be provided in subject listings.

9.1.4. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship (i.e., “Related” and “Not Related”) to Ad-RTS-hIL-12 + veledimex and cemiplimab will be presented separately in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Not Related”, “Unlikely”, “Possible”, “Probable”, and “Definite”. In the TEAE relationship table, if a subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. TEAEs that are missing a relationship or with a relationship other than “Not Related” or “Unlikely” will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship or the actual relationship respectively. Percentages will be calculated out of the number of subjects in the FAS.

As described in Section 9.1.1 , the TEAE data will be categorized and presented by SOC, PT, and relationship.

9.1.5. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the case report form (CRF) page. The possible severities are "Mild," "Moderate", "Severe", "Life-threatening" and "Death". In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe level will be presented. TEAEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the FAS.

The TEAE data will be categorized and presented by SOC, PT, and severity, similar to that described in Section 9.1.1 .

9.1.6. Serious Adverse Events

The seriousness of an AE should be assessed by the investigator independently from the severity of the AE. An AE is considered a serious adverse event (SAE) if at least one of the following conditions applies:

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

may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs will be presented in a table. Treatment-emergent SAEs by relationship to study drug will be presented in a table. A treatment-related treatment-emergent SAE is a treatment-emergent SAE with any relation to study drug other than "Not Related" or "Unlikely". Treatment-emergent SAEs that are missing a relationship will be presented in the table as "Related" but will be presented in the data listing with a missing relationship. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the FAS.

The treatment-emergent SAE data will be categorized and presented by SOC and PT, similar to that described in Section 9.1.1.

9.1.7. Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs with a study drug action taken of "Drug Withdrawn" will be presented in a table separately for Ad-RTS-hIL-12, veledimex and cemiplimab. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the FAS within the subgroup category.

The summary of TEAEs with a study drug action taken of "Drug Withdrawn" will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. Within each SOC, the PTs will be presented in alphabetical order.

9.1.8. Death

A summary of AEs where the answer to "Outcome" is "Fatal" will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated based on the FAS.

The summary of AEs where the answer to "Outcome" is "Fatal" will also be presented in descending order of frequency from the SOC with the highest incidence to the SOC with the lowest incidence. Within each SOC, the PTs will be presented in alphabetical order.

All subjects who have an AE with an outcome of "Fatal" will be presented in a listing. The listing will include the primary cause of death and the number of days elapsed between (day -7) and death.

9.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory, no conversion will be done.

Summary tables will be presented for clinical laboratory tests with numeric values for subjects in the FAS. Observed results at each visit will be presented.

All relevant clinical laboratory tests will be classified as Low, Normal, and High, or Normal/Abnormal according to the normal ranges. This categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit. Extreme post-baseline results will also be summarized.

When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a subject has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

9.2.1. Hematology

The following laboratory tests will be included: complete blood count (CBC), including white blood cell (WBC) count with differential, red blood cell (RBC) count, hematocrit, hemoglobin, red blood cell indices, mean corpuscular volume (MCV), and platelet count. All hematology data by will be presented in a listing.

9.2.2. Serum Chemistry

The following laboratory tests will be included: Aspartate transaminase (AST), Alanine transaminase (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, and bicarbonate. All chemistry data by subject will be presented in a listing.

9.2.3. Urinalysis

The following laboratory tests will be included: appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals and cells may be done if indicated. All urinalysis data by subject will be presented in a listing.

9.2.4. Coagulation

The following laboratory tests will be included: activated partial thromboplastin time (aPTT) or partial prothrombin time (PTT) and prothrombin time (PT) or International normalized ratio (INR). The acute phase reactants include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). All coagulation data by patient will be summarized and will be presented in a listing.

[redacted]

9.3. Vital Sign Measurements

Originally, all vital sign data by patient were planned for data summarization. Vital sign measurements are obtained for: height (cm), weight (kg), systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths/minute) and temperature (°C).

The conversion for temperature is as follows:

- Temperature (°C) = (Temperature (°F) - 32) x (5/9).

Summary Listings for vital sign data include:

- the observed results for each scheduled visit.
- the change from baseline for each scheduled post-baseline visit. for:
  - systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), pulse (bpm), respiration (breaths/minute) and weight for subjects in the FAS.

See variables under Section 10.6 under Section 10 describing the changes to the planned analysis.

9.4. Physical and Neurological Examination

Originally, all physical and neurological examination data by patient were planned for data summarization along the lines of the following. In general,

- Physical examination data were to be provided in patient listings.
- Results of the targeted neurological exam were also to be listed and summarized.
- Clinically significant abnormalities that are identified during physical examinations were to be reported as adverse events.
- The disposition of each physical examination (whether performed or not) and the date the physical examination was performed was to be provided in individual patient listings**.**

A table was being planned to produce a summary of the physical examination results for the FAS. Each visit captures the status of a body system and any finding associated with the body system as normal, abnormal, or not done. The summary was planned to include the number and percentage of subjects with each physical examination outcome for the following body systems: skin, head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurological, blood/lymphatic, musculoskeletal and other. Physical examination results for all subjects were also planned for presentation in listings.

See variables under Section 10.6 , a subsection under Section 10 describing the changes to the planned analysis.

9.5. Electrocardiogram

Originally, electrocardiogram data by patient were planned for data summarization along the lines of the following. All subjects were to have a standard 12-lead electrocardiogram (ECG) performed during the study as clinically indicated. QT intervals were to be corrected according to the Bazett and Fridericia's formula. For summarization, results were to be converted into Bazett's correction. Electrocardiogram data for all subjects were to be presented in a listing.

The ECG interpretations was to be summarized in shift tables comparing the ECG values of each post-baseline visit with the value at the baseline visit for the FAS. In addition, the worst post-baseline ECG value was to be compared with the value at the baseline visit (with worst of all being Abnormal Clinically Significant and best being Normal).

Summary tables presenting observed values and changes from baseline were to be presented for heart rate (bpm), PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT Interval (msec), QTcB Interval (msec) for subjects in the FAS. Changes from baseline to each scheduled post-baseline visit will be presented.

See variables under Section 10.6 a subsection under Section 10 describing the changes to the planned analysis.

10. CHANGES TO THE PLANNED ANALYSIS

10.1. Transition to Describe Statistical Considerations implemented in Support of Producing an Abbreviated Study Report.

Originally, this SAP was being planned to support the creation of a full clinical trial study report (CSR). The decision to modify the final CSR based on a full CSR assumption to what is now being planned as an abbreviated CSR has led to the changes of this SAP which are summarized below.

As originally envisioned in the study Amendment 2 (08Jan2020) of the protocol, the following analyses described previously in Section 8 will not be included as part of the final statistical analysis.

10.2. Secondary Efficacy Endpoints

10.2.1. Estimation of OS using Parametric Survival Assumptions for S(t)

10.2.2. The OS rate at fixed timepoints 6, 12, 18 and 24 months

10.2.3. Overall PFS and PFS rate at fixed timepoints 6, 12, 18 and 24 months

10.2.4. Objective Response Rate (ORR) at 6, 12, 18 and 24 months

10.2.5. Tumor Response Rate Based on Subject Tumor Response Data

10.2.6. Best Overall Response (BOR)

[redacted]

10.4. Other Efficacy Endpoints

See original preplanning for KPS under Section 8.4 of other efficacy endpoints. Originally planned, changes from baseline at each scheduled visit may not be performed to summarize descriptive statistics.

[redacted]

10.6. Other Endpoints Captured on the eCRF

The abbreviated CSR will not include the production of descriptive statistics and listings for the following preplanned assessments.

10.6.1. Vital Sign Measurements

See original preplanning under Vital Sign Measurements in Section 9.3 .

10.6.2. Physical and Neurological Examination

See original preplanning under Physical and Neurological Examination in Section 9.4 .

10.6.3. Electrocardiogram

See original preplanning under Electrocardiogram in Section 9.5 .

11. GENERAL METHODS FOR PERFORMING STATISTICAL ANALYSES AND DATA HANDLING CONVENTIONS

The data conventions for preparing applicable tables and data listings for combining the data for all treated FAS subjects (n=40) are as follows:

11.1. Missing Data

- No imputations for missing or partial data will be made
- In analyses presented over time by visit, no imputations will be performed on missing data.
- All analyses will be based on observed data only without protocol deviations and violations.
- The effective sample sizes at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.

Unless otherwise specified,

- percentages will be calculated based on the number of patients with non-missing data as the denominator.
- A missing values category will also be defined to ensure all subjects are accounted for in prespecified populations for analyses
- In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

The algorithms for imputation of partial dates vary depending on the parameter. These will be provided in the programming specifications that will be prepared for this study.

When applicable, unless otherwise specified, the following general imputation rules will be used for a missing date in the assessment of an event:

- If all parts of the date are missing, the date will not be imputed.
- In the case where only the start day of an event is missing, it will be replaced by the start day of study treatment if the event occurs in the same month and year. Otherwise, it will be replaced by the first of the month.
- If the stop day is missing, the stop day of the event will be replaced by the stop day of study treatment. Otherwise, the last day of the month will be used to replace the missing stop day.
- If both the start day and month of an event are missing, the start day and month will be replaced by the start day and month of study treatment if the event and the start of the treatment occur in the same year; otherwise, it will be replaced by 1st of January.
- All imputed dates must be prior to the dates of withdrawal of consent, lost to follow-up, and death.

11.2. Baseline Data

- Unless otherwise specified, baseline is the last observation before the first study drug administration.
- The baseline lesion assessment is considered to be the one within 72 hours following Ad-RTS-hIL-12 administration.
- If the schedule of events includes a baseline value (i.e. Day -7) lab just before study drug administration) that is not collected as planned for any reason, then the data collected for the variable known to be the last observation before the first dose of study drug will serve as the baseline value.
- In addition, the relevant section for each endpoint will describe the baseline values of subjects recorded as taken before study treatment according to schedule along with subjects for whom measurements should have been taken before study treatment but for whom those measurements were taken after study dosing was received.

11.3. Change from baseline

- Change from baseline is performed for Serum Chemistry, Hematology, Urinalysis, Vital Signs, ECG Results and the Karnofsky Performance Status (KPS) Score.

11.4. Measurements Collected Excluded from Predefined Analysis

- Populations or extra measurements that were repeated or obtained based on unscheduled visits may not be included in summary tables unless specified.
- Regardless of data inclusion for any analysis
  - Subject Listings will present all available data received in the electronic CRF (eCRF)
  - Where applicable subject listings will also present all final data received from data sources for which data external to the eCRF were captured for which data transfer agreement specifications were established.

11.5. Derived and Computed Variables

- Day 0 corresponds to the date of Ad-RTS-hIL-12 administration.
- Then more generally, Day n represents the elapsed number of days from Day 0, inclusive.
- Day n = Date of assessment – Date of Day 0.
- Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Day 0. Day −1 will be the day before Day 0, and in general, negative days will be measured backwards starting from Day −1.
- Day -7 corresponds to the first dosing date of subjects treated with Ad-RTS-hIL-12 and cemiplimab.

- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit for purposes of presentation.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded up to 1 significant digit for purposes of presentation.
- Age will be calculated in years relative to the date of informed consent based on the following SAS statement: Age = floor ((intck('month', date of birth, date of informed consent) – (day (informed consent) < day (date of birth))) / 12 (Check with LLX and Ziopharm Programming)
- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Pregnancy test data will be listed only.

11.6. Continuous Variables

- Summary statistics will be provided for continuous variables (e.g., age).
- Unless otherwise stated, summary statistics will report:
  - The number of subjects with a non-missing value of the variable (n), mean, standard deviation, median, minimum, and maximum.
  - The same number of decimal places as in the raw data will be presented when reporting minimum and maximum
  - One more decimal place than in the raw data will be presented when reporting mean and median
  - Two more decimal places than in the raw data will be presented when reporting standard deviation.

11.7. Categorical Variables

- Frequency counts will be provided for categorical variables (e.g., gender).
- Unless otherwise stated, frequency statistics will consist of the number of subjects with a response in a particular category and the percentage of the total number of subjects in that column.
- Unless otherwise stated, missing responses will be included in both the display and in the calculation of percentages (i.e., they will be included in the denominator).
- Percentages will be rounded to one decimal place.
- Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

11.8. Visit Windows Derived and Computed Variables Observed Cases and Last Observation Carried Forward, Missing Data and Outliers

- The statistical analysis planned for this study will be performed according to the actual visit dates and times and do not require the calculation of visit windows.
- However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan.
- As needed, visit windows will also be created for analysis, to include data collected at unscheduled visits.
- Visit windows will apply to all treatment arms.
  - When multiple visits occur within the same window, the visit closest to the target visit day will be selected.
  - When two visits are equidistant from the target day, the visit occurring latest in the window will be used for analysis.

11.9. Statistical Programming Conventions and Considerations

- SAS version 9.4 or higher will be utilized for all data analyses, summary tables, subject listings and figures.
- Derived datasets are also created using (SAS®) software unless specified otherwise.
- The definition of all derived variables and decodes for coded data must appear in the notes.
- Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.
- In general, summary tables and listings (e.g., post text tables and individual subject data listings) include a "footer" providing explanatory notes that indicate at a minimum:
  - Date of data extraction
  - Date of output generation
  - SAS complete program name, and path where it is stored including the path that generates the output
  - Any other output specific details that require further elaboration (e.g. CRF pages from which the data were obtained)
  - Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

- In general, the listings should be sorted and presented by treatment assignment, investigational site, and subject number. Treatment assignment and site can appear in the banner of the listing.
  - From left to right, the subject number, visit number, visit date, and relative day should appear.
  - When applicable, the data management tools and methods used in the processing of the data should be mentioned. The SOP dictating the data storage, data transfer, and data cleaning process should be stated.

11.10. Appendices to Distinguish Between Original and Revised ATI001-204 for TLF's

Statistical considerations were implemented in support of producing an abbreviated study report which led to a modification to the originally planned TLF specifications.

The modifications to the originally planned TLF specifications are described in the excel spreadsheet, "ATI001-204 Final TLF Shells".

- The Table of Contents (first tab of spreadsheet) describing the "Original ATI001-204 TLFs" has been extracted from the spreadsheet and is displayed in Appendix 1.
- The Table of Contents (second tab of spreadsheet) describing the "Revised ATI001-204 TLFs" has been extracted from the spreadsheet and is displayed in Appendix 2.

12. REFERENCES

Ahmed, R., Oborski, M. J., Hwang, M., Lieberman, F. S., & Mountz, J. M. (2014). Malignant gliomas: current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. *Cancer Management and Research, 6*, 149-170.

Fernandes, C., Costa, A., Osorio, L., Lago, P., Linhares, B., & Carvalho and Caeiro, C. (2017). Current Standards of Care in Glioblastoma Therapy. *Glioblastoma*, 197-241. doi:http://dx.doi.org/10.15586/codon.glioblastoma.2017.ch11

Ivanova, A., Qaqish, B., & Schell, M. (2005). Continuous Toxicity Monitoring in Phase II Trials in Oncology. *Biometrics, 61*, 540-545.

Iwamoto, F. M., Abrey, L. E., Beal, K., Gutin, P. H., Rosenblum, M. K., Reuter, V. E., . . . Lassman, A. B. (2009). Patterns of relapse and prognosis after bevacizumab failure in recurrent gliobastoma. *Neurology, 73*, 1200-1206.

Lieberman, F. (2017). Glioblastoma update: molecular biology, diagnosis, treatment, response assessment, and translational clinical trials (version 1; referees: 2 approved). *F1000Research, 1892*, 1-8.

Omuro, A., & DeAngelis, L. M. (2013). Glioblastoma and Other Malignant Gliomas: A Clinical Review. *Journal of the American Medical Association, 310*(17), 1842-1850.

Paolillo, M., Boselli, C., & Schinelli, S. (2018). Glioblastoma under Siege: An Overview of Current Therapeutic Strategies. *Brain Sciences, 8*(15). doi:10.3390/brainsci8010015

13. APPENDICES

APPENDIX 1: ORIGINAL ATI001-204 TLFS

APPENDIX 2: REVISED ATI001-204 TLFS

Table/Figure Number	Table Title	Population	Tab Name	
Table 14.1.1	Subject Disposition	All Subjects	Disp	
Table 14.1.2	Protocol Deviations	Full Analysis Population	Dev	
Table 14.1.3.1	Demography	Full Analysis Population	Demo	
Table 14.1.3.2	Baseline Characteristics	Full Analysis Population	BasChar	
Table 14.1.4	Medical History	Full Analysis Population	Mhx	
Table 14.1.5	High Grade Glioma Diagnosis	Full Analysis Population	Diagh	
Table 14.1.6	Prior Cancer Treatments	Full Analysis Population	Canhist	
Table 14.1.7	Previous Medications	Full Analysis Population	Meds	
Table 14.1.8	Concomitant Medications	Full Analysis Population	Meds	
Table 14.2	Best Overall Response	Per Protocol Population	BOR	
Table 14.2.1	Best Overall Response Concordance	Per Protocol Population	BORC	
Table 14.2.1.1	Objective Response Rate	Per Protocol Population	ORR	
Table 14.2.1.2	95% Confidence Intervals for Overall Response	Per Protocol Population	ORRci	
Table 14.2.2	Progression Free Survival	Per Protocol Population	PFS	Not required at this time
Table 14.2.3	Time to Overall Survival in Months	Per Protocol Population	OS	
[redacted]				
Table 14.3.1.1	Overall TEAEs Summary	Full Analysis Population	AEoverall	
Table 14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.3	Treatment-Related Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.4	Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.5	Adverse Events Leading to Discontinuation of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.6	Adverse Events Leading to Interruption of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.7	Adverse Events Leading to Dose Reduction of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.8	Adverse Events Leading to Death by System Organ Class and Preferred Term	Full Analysis Population	AEs	
Table 14.3.1.9	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Full Analysis Population	AEs	
Table 14.3.1.10	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity with CTCAE Toxicity Grade ≥ 3	Full Analysis Population	AESev	
Table 14.3.1.11	Serious Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AESev	
Table 14.3.1.12	Treatment Emergent Adverse Events by Preferred Term in Decreasing Frequency	Full Analysis Population	AEPT	
Table 14.3.1.13	Treatment-Related Treatment Emergent Adverse Events by Preferred Term in Decreasing Frequency	Full Analysis Population	AEPT	
Table 14.3.4.1	Listing of Abnormal Laboratory Values		Sig_lab	
Table 14.3.4.2	Listing of Clinically Significant Laboratory Values		Sig_lab	
Table 14.3.5.1	Ad-RTS-hIL-12 Injections	Full Analysis Population	Exp1	
Table 14.3.5.2	Veledimex Exposure	Full Analysis Population	Exp2	
Table 14.3.5.3	Cemipluma Exposure	Full Analysis Population	Exp3	
Table 14.3.6.1	Summary of Serum Chemistry Results	Full Analysis Population	Lab	
Table 14.3.6.2	Clinical Significance of Serum Chemistry Results	Full Analysis Population	Lab2	
Table 14.3.6.3	Summary of Hematology Results	Full Analysis Population	Lab	
Table 14.3.6.4	Clinical Significance of Hematology Results	Full Analysis Population	Lab2	
Table 14.3.6.5	Summary of Coagulation Results	Full Analysis Population	Lab	
Table 14.3.6.6	Clinical Significance of Coagulation Results	Full Analysis Population	Lab2	

Table 14.3.6.7	Summary of Urinalysis Results	Full Analysis Population	Lab	
Table 14.3.6.8	Clinical Significance of Urinalysis Results	Full Analysis Population	Lab2	
Table 14.3.7	Summary of KPS	Full Analysis Population	KPS	
Table 14.3.8	Summary of Vital Signs	Full Analysis Population	Vitals	
Table 14.3.9	Summary of Weight	Full Analysis Population	Weight	
Table 14.3.10	Targeted Neurological Exam	Full Analysis Population	Neuro	
Table 14.3.11	ECG Findings	Full Analysis Population	ECG1	
Table 14.3.12	Summary of ECG Results	Full Analysis Population	ECG2	
Table 14.3.13	Dose Limiting Toxicities	Per Protocol Population	DLT	
Figure 14.2.3	Kaplan Meier plot of Progression Free Survival by Veledimex Dose			
Figure 14.2.4	Kaplan Meier plot of Overall Survival by Veledimex Dose			
Figure 14.2.5	Kaplan Meier plot of Progression Free Survival by Group			
Figure 14.2.6	Kaplan Meier plot of Overall Survival by Group			
Figure 14.2.7	Forest Plot	Per Protocol Population	FPLT	
Listing 16.2.1	Subject Disposition	Full Analysis Population	L_Disp	
Listing 16.2.3.1	Eligibility	Full Analysis Population	L_Elig	
Listing 16.2.3.2	Subject Population	Full Analysis Population	L_Pop	
Listing 16.2.2	Protocol Deviations	Full Analysis Population	L_Dev	
Listing 16.2.4.1	Demography and Baseline Characteristics	Full Analysis Population	L_Demo	
Listing 16.2.4.2	Medical and Surgical History	Full Analysis Population	L_Mhx	
Listing 16.2.4.3	High Grade Glioma Diagnosis	Full Analysis Population	L_Hgg	
Listing 16.2.4.4	Prior Cancer Treatment	Full Analysis Population	L_PriCnt	
Listing 16.2.4.5	Previous Medications	Full Analysis Population	L_Conm	
Listing 16.2.4.6	Concomitant Medications	Full Analysis Population	L_Conm	
Listing 16.2.4.7	Corticosteroid Dosage	Full Analysis Population	L_CDD	
Listing 16.2.4.8	Post Treatment Anti-Cancer Therapy	Full Analysis Population	L_PostCnt	
Listing 16.2.4.9	Concurrent Medical Procedures	Full Analysis Population	L_Npmed	
Listing 16.2.5.1	Ad-RTS-hIL-12 Injection	Full Analysis Population	L_DS1	
Listing 16.2.5.2	Veledimex Capsule Diary	Full Analysis Population	L_DS2	
Listing 16.2.5.3	Veledimex Dose Modification	Full Analysis Population	L_DS3	
Listing 16.2.6.1	Pre-Baseline Lesion Assessment	Full Analysis Population	L_Pbla	
Listing 16.2.6.2	Assessment of Target Lesions	Full Analysis Population	L_Tar	
Listing 16.2.6.3	Assessment of Non-Target Lesions	Full Analysis Population	L_NTar	
	~~Enhancing Non-Measurable Lesions~~	Full Analysis Population	L_Enh	
Listing 16.2.6.4	Non-Enhancing Lesions	Full Analysis Population	L_Nenh	
Listing 16.2.6.5	Evaluation of Overall Response	Full Analysis Population	L_Tovr	
Listing 16.2.7.7	Dose Limiting Toxicities	Full Analysis Population	L_Dlt	
Listing 16.2.7.1	Adverse Events	Full Analysis Population	L_Ae	
Listing 16.2.7.2	Treatment Emergent Adverse Events	Full Analysis Population	L_Ae	
Listing 16.2.7.3	Serious Adverse Events	Full Analysis Population	L_Ae	
Listing 16.2.7.4	**TEAEs** leading to Study Drug Dose Modification	Full Analysis Population		
Listing 16.2.7.5	TEAEs leading to **Study** Discontinuation	Full Analysis Population	L_Ae	
Listing 16.2.7.6	TEAEs with CTCAE Toxicity Grade ≥ 3	Full Analysis Population		
Listing 16.2.7.8	Deaths	Overall Safety Population	L_Deat	
Listing 16.2.6.6	Survival	Full Analysis Population	L_Surv	
Listing 16.2.6.7	Progression Free Survival Data	Full Analysis Population	L_Pfs	
Listing 16.2.6.8	Kaplan Meier Survival and Censoring Times	Full Analysis Population	L_Surv2	

Listing 16.2.8.5	SI Units and Conversion Factors	Full Analysis Population	L_Conv	
Listing 16.2.8.1	Serum Chemistry Data	Full Analysis Population	L_Labs	
Listing 16.2.8.2	Hematology ~~and Coagulation~~ Data	Full Analysis Population	L_Labs	
Listing 16.2.8.3	~~Hematology and~~ Coagulation Data	Full Analysis Population	L_Labs	
Listing 16.2.8.4	Urinalysis Data	Full Analysis Population	L_Labs	
Listing 16.2.9	Pregnancy Test	Full Analysis Population	L_Preg	
Listing 16.2.10	Vital Signs	Full Analysis Population	L_Vit	
Listing 16.2.11	ECG Data	Full Analysis Population	L_Ecg	
Listing 16.2.12	Physical Examination	Full Analysis Population	L_Phys	
Listing 16.2.13	Neurological Examination	Full Analysis Population	L_Neuro	
Listing 16.2.14	Karnofsky Performance Status	Full Analysis Population	L_Kps	
Listing 16.2.15	Visits	Full Analysis Population	L_Vis	
[redacted]				

Table/Figure Number	Table Title	Population	Tab Name		RAW	SDTM	ADaM	Table
Table 14.1.1	Subject Disposition	All Subjects	Disp			DS	ADSL	Disp table is done
Table 14.1.2	Protocol Deviations	Full Analysis Population	Dev			IE		
Table 14.1.3.1	Demography	Full Analysis Population	Demo		ENROLL/CDD/ HGGD/PBLES/ VS2	DM/DD/DS/ CM/ EX/QS	ADSL	Demo table is done
Table 14.1.3.2	Baseline Characteristics	Full Analysis Population	BasChar		ENROLL/CDD/ HGGD/PBLES/ VS2	DM/DD/DS/ CM/ EX/QS	ADSL	BasChar table is done
Table 14.1.4	Medical History	Full Analysis Population	Mhx			MH	ADMH	MHx table is done
Table 14.1.5	High Grade Glioma Diagnosis	Full Analysis Population	Diagh		ENROLL/CDD/ HGGD/PBLES/ VS2	DM/DD/DS/ CM/ EX/QS	ADSL	Diagh table is done
Table 14.1.6	Prior Cancer Treatments	Full Analysis Population	Canhist			CM/PR	ADCM	
Table 14.1.7	Previous Medications	Full Analysis Population	Meds			CM/PR	ADCM	
Table 14.1.8	Concomitant Medications	Full Analysis Population	Meds			CM/PR	ADCM	
Table 14.2	Best Overall Response	Per Protocol Population	BOR					
Table 14.2.1	Best Overall Response Concordance	Per Protocol Population	BORC					
Table 14.2.1.1	Objective Response Rate	Per Protocol Population	ORR					
Table 14.2.1.2	95% Confidence Intervals for Overall Response	Per Protocol Population	ORRci					
Table 14.2.2	Progression Free Survival	Per Protocol Population	PFS					
Table 14.2.3	Time to Overall Survival in Months	Per Protocol Population	OS			SS	ADTTE	
Table 14.2.3.1	OS for 20mg group 1 main study and 20 mg expansion for patients characteristics subgroups	Per Protocol Population	OSCAT					
Table 14.3.1.1	Overall TEAEs Summary	Full Analysis Population	AEoverall			AE	ADAE	AeOverall is done
Table 14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.3	Treatment-Related Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.4	Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.5	Adverse Events Leading to Discontinuation of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.6	Adverse Events Leading to Interruption of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.7	Adverse Events Leading to Dose Reduction of Study Medication by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done

Table 14.3.1.8	Adverse Events Leading to Death by System Organ Class and Preferred Term	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.9	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Full Analysis Population	AEs			AE	ADAE	AEs tables are done
Table 14.3.1.10	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity with CTCAE Toxicity Grade ≥ 3	Full Analysis Population	AESev			AE	ADAE	AESev tables are done
Table 14.3.1.11	Serious Adverse Events by System Organ Class and Preferred Term	Full Analysis Population	AESev			AE	ADAE	AESev tables are done
Table 14.3.1.12	Treatment Emergent Adverse Events by Preferred Term in Decreasing Frequency	Full Analysis Population	AEPT			AE	ADAE	AEPT tables are done
Table 14.3.1.13	Treatment-Related Treatment Emergent Adverse Events by Preferred Term in Decreasing Frequency	Full Analysis Population	AEPT			AE	ADAE	AEPT tables are done
Table 14.3.4.1	Listing of Abnormal Laboratory Values		Sig_lab		LAB_NORMLAB/ LBCHEM1/ LBCOAG1/ LBHEMA1/ LBTHYR/ LBURIN1 / LBURIN2	LB	ADLB	
Table 14.3.4.2	Listing of Clinically Significant Laboratory Values		Sig_lab			LB	ADLB	
Table 14.3.5.1	Ad-RTS-hIL-12 Injections	Full Analysis Population	Exp1			EX/EC	ADEX	
Table 14.3.5.2	Veledimex Exposure	Full Analysis Population	Exp2			EX/EC	ADEX	
Table 14.3.5.3	Cemiplumab Exposure	Full Analysis Population	Exp3			EX/EC	ADEX	
Table 14.3.6.1	Summary of Serum Chemistry Results	Full Analysis Population	Lab			LB	ADLB	
Table 14.3.6.2	Clinical Significance of Serum Chemistry Results	Full Analysis Population	Lab2			LB	ADLB	
Table 14.3.6.3	Summary of Hematology Results	Full Analysis Population	Lab			LB	ADLB	
Table 14.3.6.4	Clinical Significance of Hematology Results	Full Analysis Population	Lab2			LB	ADLB	
Table 14.3.6.5	Summary of Coagulation Results	Full Analysis Population	Lab			LB	ADLB	
Table 14.3.6.6	Clinical Significance of Coagulation Results	Full Analysis Population	Lab2			LB	ADLB	
Table 14.3.6.7	Summary of Urinalysis Results	Full Analysis Population	Lab			LB	ADLB	
Table 14.3.6.8	Clinical Significance of Urinalysis Results	Full Analysis Population	Lab2			LB	ADLB	
Table 14.3.7	Summary of KPS	Full Analysis Population	KPS			QS	ADQS	
Table 14.3.8	Summary of Vital Signs	Full Analysis Population	Vitals					
Table 14.3.9	Summary of Weight	Full Analysis Population	Weight					
Table 14.3.10	Targeted Neurological Exam	Full Analysis Population	Neuro					
Table 14.3.11	ECG Findings	Full Analysis Population	ECG1			EG	ADEG	
Table 14.3.12	Summary of ECG Results	Full Analysis Population	ECG2			EG	ADEG	
Table 14.3.13	Dose Limiting Toxicities	Per Protocol Population	DLT					
Figure 14.2.3	Kaplan Meier plot of Progression Free Survival by Veledimex Dose							
Figure 14.2.4	Kaplan Meier plot of Overall Survival by Veledimex Dose							
Figure 14.2.5	Kaplan Meier plot of Progression Free Survival by Group							

Figure 14.2.6	Kaplan Meier plot of Overall Survival by Group							
Figure 14.2.7	Forest Plot	Per Protocol Population	FPLT					
Listing 16.2.1	Subject Disposition	Full Analysis Population	L_Disp					
Listing 16.2.3.1	Eligibility	Full Analysis Population	L_Elig					
Listing 16.2.3.2	Subject Population	Full Analysis Population	L_Pop					
Listing 16.2.2	Protocol Deviations	Full Analysis Population	L_Dev					
Listing 16.2.4.1	Demography and Baseline Characteristics	Full Analysis Population	L_Demo					
Listing 16.2.4.2	Medical and Surgical History	Full Analysis Population	L_Mhx					
Listing 16.2.4.3	High Grade Glioma Diagnosis	Full Analysis Population	L_Hgg					
Listing 16.2.4.4	Prior Cancer Treatment	Full Analysis Population	L_PriCnt					
Listing 16.2.4.5	Previous Medications	Full Analysis Population	L_Conm					
Listing 16.2.4.6	Concomitant Medications	Full Analysis Population	L_Conm					
Listing 16.2.4.7	Corticosteroid Dosage	Full Analysis Population	L_CDD					
Listing 16.2.4.8	Post Treatment Anti-Cancer Therapy	Full Analysis Population	L_PostCnt					
Listing 16.2.4.9	Concurrent Medical Procedures	Full Analysis Population	L_Npmed					
Listing 16.2.5.1	Ad-RTS-hIL-12 Injection	Full Analysis Population	L_DS1					
Listing 16.2.5.2	Veledimex Capsule Diary	Full Analysis Population	L_DS2					
Listing 16.2.5.3	Veledimex Dose Modification	Full Analysis Population	L_DS3					
Listing 16.2.6.1	Pre-Baseline Lesion Assessment	Full Analysis Population	L_Pbla					
Listing 16.2.6.2	Assessment of Target Lesions	Full Analysis Population	L_Tar					
Listing 16.2.6.3	Assessment of Non-Target Lesions	Full Analysis Population	L_NTar					
Listing 16.2.6.4	Non-Enhancing Lesions	Full Analysis Population	L_Nenh					
Listing 16.2.6.5	Evaluation of Overall Response	Full Analysis Population	L_Tovr					
Listing 16.2.7.7	Dose Limiting Toxicities	Full Analysis Population	L_Dlt					
Listing 16.2.7.1	Adverse Events	Full Analysis Population	L_Ae					
Listing 16.2.7.2	Treatment Emergent Adverse Events	Full Analysis Population	L_Ae					
Listing 16.2.7.3	Serious Adverse Events	Full Analysis Population	L_Ae					
Listing 16.2.7.4	TEAEs leading to Study Drug Dose Modification	Full Analysis Population						
Listing 16.2.7.5	TEAEs leading to Study Discontinuation	Full Analysis Population	L_Ae					
Listing 16.2.7.6	TEAEs with CTCAE Toxicity Grade ≥ 3	Full Analysis Population						
Listing 16.2.7.8	Deaths	Overall Safety Population	L_Deat					
Listing 16.2.6.6	Survival	Full Analysis Population	L_Surv					
Listing 16.2.6.7	Progression Free Survival Data	Full Analysis Population	L_Pfs					
Listing 16.2.6.8	Kaplan Meier Survival and Censoring Times	Full Analysis Population	L_Surv2					
Listing 16.2.8.5	SI Units and Conversion Factors	Full Analysis Population	L_Conv					
Listing 16.2.8.1	Serum Chemistry Data	Full Analysis Population	L_Labs					
Listing 16.2.8.2	Hematology Data	Full Analysis Population	L_Labs					
Listing 16.2.8.3	Coagulation Data	Full Analysis Population	L_Labs					
Listing 16.2.8.4	Urinalysis Data	Full Analysis Population	L_Labs					
Listing 16.2.9	Pregnancy Test	Full Analysis Population	L_Preg					
Listing 16.2.10	Vital Signs	Full Analysis Population	L_Vit					

Listing 16.2.11	ECG Data	Full Analysis Population	L_Ecg					
Listing 16.2.12	Physical Examination	Full Analysis Population	L_Phys					
Listing 16.2.13	Neurological Examination	Full Analysis Population	L_Neuro					
Listing 16.2.14	Karnofsky Performance Status	Full Analysis Population	L_Kps					
Listing 16.2.15	Visits	Full Analysis Population	L_Vis					
[redacted]								

DocuSign

Signer Events	Signature	Timestamp
[redacted]	[redacted]	[redacted]

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	31-Aug-2021 | 16:53
Certified Delivered	Security Checked	02-Sep-2021 | 10:28
Signing Complete	Security Checked	02-Sep-2021 | 10:29
Completed	Security Checked	02-Sep-2021 | 10:29

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Ziopharm Oncology (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Ziopharm Oncology:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
[redacted]

To advise Ziopharm Oncology of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at hyagnik@ziopharm.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Ziopharm Oncology

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to hyagnik@ziopharm.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Ziopharm Oncology

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

[redacted]..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Ziopharm Oncology as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Ziopharm Oncology during the course of your relationship with Ziopharm Oncology.