STATISTICAL ANALYSIS PLAN

Protocol Title:	A Single-arm, Open-label Study of Ad-RTS-hIL-12 + Veledimex Following First-, Second-, or Third-Line Standard Treatment in Subjects with Locally Advanced or Metastatic Breast Cancer
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SIGNATURE PAGE

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1. LIST OF ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
Bpm	Beats per minute
°C	Degrees Celsius
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CV	Coefficient of variation
CTC, CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ºF	Degrees Fahrenheit
HER2	Human epidermal growth factor receptor 2
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
irDCR	Immune-related Disease Control Rate
irORR	Immune-related Overall Response Rate
irPD	Increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
irPR	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
irRC	Immune-Related Response Criteria
irSD	Not meeting criteria for irCR or irPR, in absence of irPD
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter(s) of mercury
N	Number of observations
n	Number of subjects
NCI	National Cancer Institute
ORR	Objective response rate

Abbreviation	Meaning
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
Std dev	Standard Deviation
SPD	Sum of perpendicular diameters
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
Vp	Viral particles
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

3. PRIMARY OBJECTIVES

- To evaluate the safety and tolerability of one cycle of Ad-RTS-hIL-12 immunotherapy a) following a first-, second-, or third-line standard treatment in HER2-negative (HER2-) subjects, or b) together with a first-, second-, or third-line anti-HER2 antibody therapy in HER2-positive (HER2+) subjects as defined by Section 12.4.2 in the protocol.

4. SECONDARY OBJECTIVES

- To estimate the progression rate at 12 weeks after the start of one cycle of Ad-RTS-hIL-12 immunotherapy
- To evaluate the overall response rate (ORR), defined as the rate of complete response (CR) plus the rate of partial response (PR) at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy
- To evaluate the disease control rate (DCR), defined as the proportion of subjects who have a CR, PR, or stable disease at 12 weeks following the start of one cycle of Ad-RTS-hIL-12 immunotherapy
- To evaluate the number of subjects whose baseline tumor status (stable disease or PR) improves to PR or better at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy
- To compare radiographic responses by irRC with conventional reporting by RECIST
- To explore the impact of treatment on tumor and blood immune biomarkers

5. STUDY DESIGN

5.1. Endpoints:

5.1.1. Primary Endpoint

The primary endpoint is the safety assessment of Ad-RTS-hIL-12 immunotherapy a) following a first-, second-, or third-line standard treatment in HER2- subjects, or b) together with a first-, second-, or third-line anti-HER2 antibody therapy in HER2+ subjects as defined by Section 12.4.2.

5.1.2. Secondary Endpoints

Secondary endpoints are as follows:

- The proportion failed by 12 weeks is denoted as the progression rate survival and is derived based on the sum of progression events, death events, and subjects who discontinue the trial due to an Adverse event (AE).
- The ORR, defined as the rate of CR plus the rate of PR at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy
- The DCR, defined as the proportion of subjects who have a CR, PR, or stable disease at 12 weeks following the start of one cycle of Ad-RTS-hIL-12 immunotherapy
- The number of subjects whose baseline tumor status (stable disease or PR) improves to PR or better at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy
- The radiographic responses by irRC with conventional reporting by RECIST
- Tumor and serum immune biomarkers

5.2. Overall Study Design

This is a single-arm, single-center Phase Ib/II study to examine the safety, tolerability, and preliminary efficacy of providing one cycle of Ad-RTS-hIL-12 immunotherapy following achievement of stable disease or PR on standard first-, second-, or third-line chemotherapy in breast cancer subjects. The subject population includes subjects with locally advanced or metastatic breast cancer of all subtypes. The safety of this therapy and the preliminary evidence of efficacy will guide further studies. Subjects are required to be in stable disease or PR after completion of a minimum of 12 weeks on standard chemotherapy. Subjects who have progressive disease (PD) or a CR after standard chemotherapy are not eligible for the study. Following entry into the trial, subjects will go on a treatment holiday from the standard chemotherapy and enter an immunotherapy phase of treatment.

Scans will be conducted 6 and 12 weeks after the start of Ad-RTS-hIL-12 immunotherapy for determination of tumor response. Radiographic PD at Week 6 must be confirmed at least 4 weeks later, either at Week 12 or earlier if clinically necessitated. In cases of slow tumor growth, the investigator may wait until confirmation of PD at 12 weeks to resume chemotherapy. In cases of unequivocal progression, the investigator may resume chemotherapy prior to 12 weeks and the subject will be considered as treatment failure at 12 weeks.

Upon completion of Week 12, subjects who are considered to have stable disease or better will enter long-term follow-up for up to an additional 36 weeks. In the long-term follow-up period, scans will be performed at 18, 24, 36, and 48 weeks until a radiographic response of PD is confirmed.

The assessment of response will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 using tumor measurements from contrast-enhanced computed tomography (CT). Tumor response will also be assessed by Immune-Related Response Criteria (irRC) (Wolchok et al, 2009). Eligible subjects will also be asked to consent to allow ZIOPHARM to obtain scans and tumor measurements taken both a) prior to initiating the prestudy standard chemotherapy and b) after a minimum of 12 weeks of prestudy standard chemotherapy, and not more than 4 weeks prior to study enrollment, in order to confirm their stable disease or PR study entry status.

For subjects with HER2- disease, the Ad-RTS-hIL-12 immunotherapy is intended to be given as a chemotherapy holiday, for example, to avoid intolerable or undesirable toxicity of the standard therapy. Ad-RTS-hIL-12 immunotherapy must be started within 4 weeks of stopping the prestudy standard chemotherapy.

Subjects with HER2+ disease will receive Ad-RTS-hIL-12 immunotherapy in conjunction with first-, second-, or third-line anti-HER2 antibody therapy, i.e., subjects may continue anti-HER2-directed antibody therapy during the study period. Anti-HER2 antibody therapy will be administered according to the manufacturer's recommendations. Subjects with HER2+ breast cancer who continue the anti-HER2 antibody therapy need to recover from any anti-HER2-related AE/serious adverse event (SAE), i.e., the event must have resolved to Grade 1 or baseline, before starting Ad-RTS-hIL-12 immunotherapy.

The Ad-RTS-hIL-12 immunotherapy cycle is a 21-day cycle comprised of investigational product administration on Days 1 through 7 followed by rest on Days 8 through 21. On Day 1, enrolled subjects will receive the first dose of veledimex followed 3 hours ± 3 hours later by an intratumoral injection of Ad-RTS-hIL-12. The veledimex will continue to be given once daily on Days 2 through 7. The safety evaluation will be based on the occurrence of related, treatment refractory Grade 3 and 4 AEs within 21 days following the start of Ad-RTS-hIL-12 immunotherapy. A post-treatment safety assessment visit will be conducted on Day 21.

Immunologic biomarkers of response in blood and tumor will also be explored.
Full details of the study design can be found in the protocol.

5.3. Safety monitoring

A safety review committee (SRC) will convene after every 5th subject with HER2- disease has completed the Ad-RTS-hIL-12 immunotherapy cycle (i.e., after each subject has completed 21 days on study). The SRC will also convene after the first 5 subjects with HER2+ disease have completed the Ad-RTS-hIL-12 immunotherapy cycle. The SRC will consist of the investigator, medical monitor, and other appropriate Sponsor representatives. The SRC will review all available safety information (AEs/SAEs, laboratory parameter data, ECG, etc.). Tolerability will be evaluated separately for subjects with HER2- and HER2+ disease.

5.4. Sample size

A maximum of 40 subjects will be treated. Because this patient population is heterogeneous, it is difficult to define a threshold for a clear null and alternative hypothesis. This sample size will allow us to estimate an overall progression rate at 12 weeks with a maximum 95% exact confidence interval half-width of 0.16. This is based on an exact binomial calculation and is an estimate. However, analysis of progression-free survival will be conducted using Kaplan-Meier methods.

6. STATISTICAL METHODS

This study is designed to evaluate the safety and tolerability of one cycle of Ad-RTS-hIL-12 immunotherapy a) following a first-, second-, or third-line standard treatment in HER2- subjects, or b) together with a first-, second-, or third-line anti-HER2 antibody therapy in HER2+ subjects, thus the safety and efficacy analyses will be performed by HER2 status and overall.

6.1. 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.

No subject will be removed from any analysis population because of a protocol deviation.
Important protocol deviations include (but are not limited to):

- Deviation from inclusion/exclusion criteria
- Withdrawal criteria met during the study but subject was not withdrawn
- Prohibited concomitant medications.

Important protocol deviations will be identified prior to database lock. Protocol deviations will be listed and summarized by type.

6.2. Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data:

- The safety population will comprise all subjects who have received either the injection of Ad-RTS-hIL-12 or any doses of veledimex
- The veledimex-treated population will comprise subjects who have received the injection of Ad-RTS-hIL-12 and at least one dose of veledimex
- The veledimex-evaluable population will comprise subjects who have received the injection of Ad-RTS-hIL-12 and all 7 doses of veledimex

6.3. Data Handling Conventions

SAS version 9.1.3 or higher will be utilized for all listings and tables.

All listings will be ordered by HER2 status and subject number. Listings will present all available data.

Tables will summarize data for each HER2 status group and overall.

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 (std dev), median, minimum, and maximum. The same number of decimal places as in the raw data will be presented when reporting the minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 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 particular 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 1 decimal place.

No imputations for missing or partial data will be made.

Unless otherwise specified, baseline is the last observation before the first administration of study drug.

7. SUBJECT DISPOSITION

Study eligibility, inclusion and exclusion criteria, HER2 status, and population assignment will be listed.

The number and percent of subjects who discontinue from the study will be summarized by reason for discontinuation, HER2 status group, and overall.

The number and percentage of subjects in each analysis population will be tabulated.

Important protocol deviations will be summarized and listed.

8. BASELINE DEMOGRAPHIC CHARACTERISTICS

8.1. Demography

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

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 0.4536

Demographics will be listed and tabulated using descriptive statistics.

8.2. Medical History

Details of prior cancer treatment (chemo-, and immuno-therapies, radiation therapy, surgeries), current primary cancer diagnosis, initial diagnosis of breast cancer, diagnosis of metastatic disease and current disease status will be listed. Time in months since initial diagnosis, grading and type at time of initial diagnosis, and at grading, pathology and HER genotype types at Screening will be tabulated.

Prior cancer treatment information will be tabulated. This will include whether the subject had any previous treatment, treatment type, and the best response from previous treatment.

8.3. Previous and Concomitant Medication

Concomitant medications recorded during the study will be coded using the WHO-Drug version March 2016. Details of concomitant medications will be listed.

Medications will be tabulated according to whether they were being taken prestudy and/or during the study. Medications received in the period preceding consent (~28 days) in addition to those ongoing at Screening will be captured in the Case Report Form (CRF). Concomitant medications are any that were being taken on or after the first dose of study medication until completion of veledimex dosing. If the start and stop dates of the concomitant medications do not clearly define the period(s) during which a medication was taken, it will be assumed to have been a concomitant medication.

Previous and concomitant medications will be tabulated by preferred term and ATC term 2.

Non-pharmacological concomitant measures (e.g., procedures) will be listed.

9. SAFETY

Safety evaluations will be based on the incidence, intensity, and type of AEs and SAEs. Clinically significant changes in the subject's physical examinations, vital signs, ECG evaluations, and abnormal laboratory values will be captured as AEs. AEs, laboratory test results, ECG findings, and vital signs will be tabulated and presented for all subjects in the study, as well as by HER2 status group and CYP450 3A4 drug interacting use. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

9.1. Study Drug Exposure

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

9.1.1. Ad-RTS-hIL-12

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

9.1.2. Veledimex

Full details of each dose and dose modifications will be listed.

The number of doses received will be tabulated. Data will reflect date and mg of veledimex taken, % compliance (dose held by PI/Sponsor), % compliance (missed dose).

9.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher for purposes of summarization. All AEs occurring during the study will be included in data listings, presented by subject.

Treatment-emergent adverse events (TEAEs) will be summarized. Adverse events will be regarded as TEAEs if they occur during or after administration of the first dose of study drug (either veledimex or Ad-RTS-hIL-12) through the evaluation period for safety (in 6 weeks after first dose), regardless of the relationship to study drug. In addition, any event present at baseline that worsens in intensity or is subsequently considered to be drug related by the investigator will be considered a TEAE.

Summaries of all TEAEs, treatment-related TEAEs, and all SAEs will be tabulated by System Organ Class, Preferred Term, severity, and HER2 status group. For summaries of events, percentages will be calculated from the total number of events per group/dose cohort. For summaries of subjects, percentages will be calculated from the total number of subjects per group/dose cohort. Where a subject has multiple adverse events in a System Organ Class / Preferred Term, only the most severe will be included in summaries.

In addition to the full listing of all AEs, separate listings for AEs, leading to death, and AEs leading to study discontinuation will be presented.

9.3. Laboratory Evaluations`

All laboratory parameters will be converted to conventional units, usually SI units, for the purposes of summary. Listings will present the data in the original unit collected, as well as the converted value in conventional units. A separate listing will present all units used for data collection, along with the corresponding units and conversion factors.

Absolute values and change from baseline in clinical laboratory parameters will be summarized by visit and HER2 status group. The incidence of normal and abnormal (subdivided into 'not clinically significant' and 'clinically significant') laboratory values will be tabulated by visit and HER2 status group.

Pregnancy test data will be listed only.

9.4. Vital signs

Details of vital signs will be listed.

Vital signs parameters include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (ºC).

The conversion for temperature is as follows:

$$\text{Temperature (ºC)} = (\text{Temperature (ºF)} - 32) \times 5/9$$

Absolute values and changes from baseline for vital sign parameters will be summarized by visit and HER2 status.

9.5. ECGs

Heart Rate (bpm), PR Interval (ms), QRS complex duration (ms), RR interval (ms), QT interval (ms) and QTc interval (ms) will be summarized for absolute values and changes from baseline (Screening visit) by visit and HER2 status group.

Overall electrocardiogram (ECG) finding categories will be summarized by visit and HER2 status group.

9.6. Body weight

Body weight (kg) will be summarized for absolute values and changes from baseline by visit, HER2 status group, and overall.

9.7. Physical exam

Results of the targeted neurological exam will be listed and summarized by HER2 status group. Physical examination data will be listed.

9.8. ECOG Performance Status

Results of the Eastern Cooperative Oncology Group (ECOG) Performance Status will be listed and will be summarized as a categorical variable by visit, HER2 status group, and overall.

10. EFFICACY

The tumor response will be assessed by RECIST v1.1 and irRC. Full details concerning the use of RECIST v.1.1 may be found in the Appendix 16.3 in the protocol and for irRC can be referred to the Section 9.2.2.7 in the protocol.

10.1. Progression rate

The proportion failed by 12 weeks is denoted as the progression rate, and is derived based on the sum of progression events, death events, and subjects who discontinue the trial due to an AE.
The progression rate will be summarized by HER2 status group and overall for the evaluable population.

An exact 2-sided 95% confidence interval for the proportion of subjects who failed treatment by 12 weeks will also be presented by visit and overall (based on the best response).

Objective Response Rate Tumor response following the start of Ad-RTS-hIL-12 immunotherapy will be assessed using RECIST v1.1. Overall response at Week 12 is based on the totality of the responses for target and non-target lesions, as shown in the table below:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The ORR is defined as the percentage of subjects who have CR or PR at 12 weeks. The ORR will be summarized by HER2 status group and overall. An exact 2-sided 95% confidence interval will also be presented by HER2 status and overall.

For this calculation, responders are defined as those experiencing a CR or a PR. Non-responders are those either with stable or progressive disease. Those subjects who cannot be assessed will be treated as non-responders for the purposes of deriving the percentage of responders and confidence intervals. In addition, the number of subjects whose baseline tumor status (stable disease or PR) improves to PR or better at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy with RECIST v1.1 will be listed and summarized by HER2 status and overall.

10.2. Disease Control Rate

The DCR is the proportion of subjects who have a CR, PR, or stable disease at 12 weeks following the start of Ad-RTS-hIL-12 immunotherapy using RECIST v1.1.

The DCR will be summarized by HER2 status group and overall. An exact 2-sided 95% confidence interval will also be presented.

For this calculation, responders are defined as those experiencing a CR, PR, or stable disease. Non-responders are defined as those with PD. Those subjects that cannot be assessed will be treated as non-responders for the purposes of deriving the percentage of responders and confidence intervals.

10.3. Tumor response rate by irRC

The tumor response by irRC is based on the sum of the 2 largest perpendicular diameters (SPD) of all index lesions at baseline to provide the total tumor burden. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden. The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- irCR: complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- irPR: decrease in tumor burden $\geq$ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD: not meeting criteria for irCR or irPR, in absence of irPD
- irPD: increase in tumor burden $\geq$ 25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

irORR and irDCR by irRC will be analyzed the same way as described above for tumor response using RECIST v1.1.

10.4. Progression-Free Survival (PFS) at Week 12

This is defined as the proportion of subjects who have 12-week progression-free survival after the start of Ad-RTS-hIL-12 immunotherapy. The PFS rate at Week 12 will be summarized by HER2 status group and overall.

An exact 2-sided 95% confidence interval will also be presented by HER2 status and overall.

10.5. Tumor and Serum Immune Biomarkers

Change and percent change from baseline in collected tumor and blood immune biomarkers will be summarized by visit, by HER2 status, and overall.

11. REFERENCES

Wolchok, J. D., Hoos, A., O'Day, S., Weber, J. S., Hamid, O., Lebbe, C., . . . Hodi, F. S. (2009). Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 23, 7412-7420.