STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of VGT-309, a Tumor-Targeted, Activatable Fluorescent Imaging Agent, to Identify Cancer in Subjects Undergoing Lung Cancer Surgery
Name of Test Drug:	VGT-309
Study Number:	VGT-309-2-2021USA
Protocol Version:	Amendment 4
Protocol Date:	20 May 2022
Analysis Type:	Final
Analysis Plan Version:	1.0
Analysis Plan Date:	27 October 2023
Analysis Plan Author:	[redacted]

AUTHOR(S):

[redacted]	**Signature**	**Date**

SPONSOR APPROVAL:

[redacted]	**Signature**	**Date**

[redacted]	**Signature**	**Date**

CONFIDENTIAL AND PROPRIETARY INFORMATION

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AUC	Area under the curve
BMI	Body mass index
BPM	Beats per minute
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRO	Contract research organization
CSE	Clinically Significant Event
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data monitoring committee
ECG	Electrocardiogram
FN	False Negative
FP	False Positive
FR	Federal Register
GEE	Generalized Estimating Equation
HLT	High level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent to treat
IVRS/IWRS	Interactive voice/web response system
LLT	Lower level term
MedDRA	Medical dictionary for regulatory activities
NIR	Near-Infrared
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PT	Preferred term
ROC	Receiver Operating Characteristic
SAP	Statistical analysis plan
SOC	System organ class
TFLs	Tables, figures, and listings
TN	True Negative
TP	True Positive
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) to be implemented during the analyses of data collected within the scope of Protocol VGT-309-2-2021USA [A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of VGT-309, a Tumor-Targeted, Activatable Fluorescent Imaging Agent, to Identify Cancer in Subjects Undergoing Lung Cancer Surgery] sponsored by Vergent Bioscience, Inc. This SAP will be finalized before database lock. Any deviations from this plan after SAP finalization will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary efficacy objective of this study is the identification of the proportion of subjects with at least one Clinically Significant Event (CSE) as defined by:

- [redacted]
- [redacted]
- [redacted]

2.2. Secondary Objectives

The secondary objective of this study is to evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of VGT-309 to detect cancer utilizing NIR fluorescence and histopathology results.

2.3. Safety Objective

The safety objective of this study is to determine the safety and tolerability of VGT-309 when used as a fluorescent imaging agent in subjects with suspected or proven lung cancer.

3. STUDY DESIGN

This is a Phase 2, open-label study to evaluate the safety and efficacy of VGT-309, a tumor-targeted, activatable fluorescent imaging agent, to identify cancer in subjects undergoing lung cancer surgery. A total of 40 subjects will be enrolled to ensure at least 38 evaluable subjects with the option to expand enrollment by protocol amendment if deemed necessary to meet primary and/or secondary objectives. Following agreement with and signing of the informed consent, subjects will undergo screening measurements for the study.

Assessments include the following, unless they have been done within 4 weeks prior to the anticipated dosing:

1. Medical, surgical and medication history.
2. Complete physical exam, including vital signs and weight.
3. Standard pre-operative chemistry, hematology, coagulation, and urinalysis clinical laboratory studies.
4. 12-lead ECG.
5. Serum pregnancy test for females of child-bearing potential.

Following clearance of all enrollment criteria, each subject will receive an IV administration [redacted] VGT-309 at 12-36 hours prior to surgery (refer to section VGT-309 Dosing, below). Upon dosing, subjects will be observed for up to 2 hours and asked about possible treatment emergent adverse events. Subjects will undergo surgical resection as planned and within the time specified following VGT-309 dosing. Measurements of efficacy will be taken during surgery and during the pathological examination of all surgical specimens. (Refer to Efficacy Endpoints and Efficacy Assessments sections).

Following surgery, subjects will be monitored for safety during their hospitalization. After discharge from the hospital, and approximately 14 days post-surgery, the subjects will be contacted by telephone to assess their well-being. Between 19 to 39 days post-surgery, subjects will either return to the clinic or participate in a telehealth visit for final safety assessments. If there are no adverse events requiring further follow up, subjects will then be released from the study. If a subject chooses to withdraw from the study prior to the final visit, they will be asked to undergo a final safety assessment before their departure.

4. DETERMINATION OF SAMPLE SIZE

[redacted]

5. TYPE OF PLANNED ANALYSIS

This analysis plan outlines planned analysis procedures for the Final Analysis, as described below. Data outliers and other raw data issues are planned to be identified and logged on a rolling basis throughout the study, with appropriate resolution decided upon and documented prior to the planned analyses outlined below. The Final Analysis will take place after the study is completed and the database has been locked. All tables, figures, and listings described in this SAP are planned to be included in the final analysis.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES

6.1. Data Presentation and Summarization

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Conference on Harmonisation (ICH) numbering convention will be used for all TLFs. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Other summaries (e.g., quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. Summaries will generally be presented by treatment cohort and for all participants overall. P-values will be presented for hypothesis testing, with a value of 0.05 being the threshold of significance under which the null hypothesis can be rejected.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher. Tables, listings, and figures will be provided in PDF format.

6.2. Missing or incomplete dates

The most conservative approach will be systematically considered. [redacted]

[redacted]

Stop Dates

[redacted]

6.3. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table and listing.

Inclusion in the analysis set will be determined prior to database lock. A summary of the number and percent of participants in each analysis set will be provided. A by-participant listing of each analysis set will also be provided.

6.3.1. Enrolled Population

This population consists of all subjects who are enrolled in the study (signed informed consent).

6.3.2. Safety Population

This population consists of all subjects who have enrolled in the study and received any amount of VGT-309.

6.3.3. Efficacy Population

This population consists of all subjects who have received any amount of VGT-309 and have surgery with NIR imaging.

7. STUDY POPULATION

In general, subjects who signed informed consent and were enrolled for the study will be used for data summaries and listings for subject disposition. Safety population will be used for safety summaries and listings, while Efficacy Population will be used for all efficacy analyses, unless otherwise specified.

7.1. Subject Disposition

7.1.1. Subject Enrollment and Disposition

A summary of subject disposition will be provided and will present the number of subjects enrolled, and the number and percent of subjects:

- Included in the Safety analysis set;
- Included in the Efficacy analysis set;
- Completing the study (includes the study treatment period and any post-treatment follow-up period); and
- Not completing the study, (with summary of reasons for not completing the study).

[redacted]

[redacted]

7.1.2. Exposure to Study Drug

Extent of exposure to study drug will be summarized for the safety population. [redacted]

7.2. Protocol Deviations

All protocol violations and deviations will be summarized by classification category (major/minor) and listed.

7.3. Inclusion/Exclusion Criteria

Subjects who did not meet inclusion/exclusion criteria will be listed for all screened subjects, along with the criterion number and description not met.

7.4. Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, BMI) will be summarized using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. The summaries of demographic data and baseline characteristics will be provided for the safety analysis set.

7.5. Medical History

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (version 25.0). Participants will only be counted once at each level of summation. Summaries will be sorted by decreasing total incidence by SOC (overall) and then by PT (within each SOC); for SOCs or PTs (within SOC) with the same frequency, sorting will be performed alphabetically. By-participant listings of this information will also be provided along with onset and resolution dates and grades (collected in the CRF if the condition is ongoing).

7.6. Prior and Concomitant Medications

Concomitant medications are defined as medications that started on or after the treatment start date or were ongoing at the date of treatment start. Prior medications are defined as medications that started and stopped prior to the date of treatment start.
Medications will be coded using the World Health Organization (WHO) Drug Dictionary B3 Global (updated March 2022) and Anatomical Therapeutic Chemical (ATC) Level 4 drug classes and preferred drug names (PN) will be attached to the clinical database. The number and percentage of subjects with at least one instance of medication use will be summarized by ATC class and PN (within ATC class) ordered by decreasing total incidence of ATC and PN (within ATC); ties in frequency will be broken alphabetically. Patients will only be counted once at each level of summation. By-participant listings will also be provided.

8. EFFICACY ANALYSES

8.1. Definition of the Primary Efficacy Endpoint

The proportion of subjects with at least one Clinically Significant Event (CSE) as defined by:

A. [redacted]

[redacted]

C. [redacted]

8.2. Statistical Hypothesis for the Primary Efficacy Endpoint

[redacted]

8.3. Analysis of the Primary Efficacy Endpoint

Efficacy analyses will be performed on the efficacy population. [redacted]

[redacted]

8.4. Secondary Efficacy Endpoints

8.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Sensitivity: [redacted]
- Specificity: [redacted]

- Positive predictive value (PPV): [redacted]
- Negative predictive value (NPV): [redacted]

[redacted]

8.4.2. Analysis Methods for Secondary Efficacy Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

9. SAFETY ANALYSES

9.1. Adverse Events and Deaths

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Events will be summarized on the basis of the date of onset for the event. Only treatment-emergent adverse events (TEAEs), defined as any adverse event that begins on or after the date of administration of VGT-309, will be collected and analyzed in this study. For purposes of this document, AEs refers to TEAEs. An overall summary of TEAEs will be provided. The following summaries (number and percentage of subjects) of TEAEs (by System Organ Class and Preferred Term) will be provided:

- TEAEs
- Treatment-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- Treatment-related Serious TEAEs

All AEs collected during the study will be presented in a listing. Additionally, a listing will be provided for any AEs leading to death.

9.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0). System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

9.1.2. Adverse Event Severity

Each AE will be assigned a "Grade" based on the Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0 of the CTCAE will be used for this study. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings and will be considered the least severe for the purposes of sorting for data presentation.

9.1.3. Relationship of Adverse Events to Study Drug

The relationship of the Adverse Event to the study drug will be determined by the Principal Investigator, and assessed using the following definitions:

- **Related:** There is a distinct temporal relationship between the event onset and administration of the study drug. There is a known reaction to agent or chemical group or predicted by known pharmacology. The event cannot be explained by subject's clinical state or other factors.

- **Unrelated:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

Events for which the investigator did not record relationship to study drug will be considered related to study drug. Data listings will show relationship as missing.

9.1.4. Serious Adverse Events

An SAE is an AE from this study that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death).
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a subject who received study drug.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject *and* may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.1.5. Summaries of Adverse Events and Deaths

Summaries (number and percent of subjects) of adverse events (by SOC, and PT) will be provided using the safety analysis set as follows:

- All treatment-emergent adverse events,
- All treatment-emergent treatment-related adverse events,
- All treatment-emergent treatment-related serious adverse events,
- All treatment-emergent adverse events that caused permanent discontinuation from study drug,
- Deaths

A brief overall summary of TEAEs will show the number and percentage of subjects who had at least one of each of the above categories.

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC, each summary will also be presented by preferred term only, ordered by decreasing frequency.

In addition to the summaries, data listings will be provided for the following:

- All treatment-related adverse events
- Serious adverse events
- Deaths
- Adverse events leading to discontinuation of study drug

9.2. Clinical Laboratory Evaluation

Laboratory parameters (including clinical chemistry, hematology, urinalysis, coagulation) will be summarized using descriptive statistics at baseline and at each protocol-specified visit time points. Unscheduled visits will be listed. Changes from baseline will also be summarized.

All laboratory parameters and pregnancy test results will be provided in listings.

9.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) of

[redacted]

9.2.2. Shifts Relative to the Normal Range

The following summaries (number and percentage of subjects) relative to the respective laboratory test normal ranges will be provided by treatment group:

- Shift from baseline value (low, normal, or high) to post-baseline value (low, normal, or high) at each post-baseline analysis window.

9.3. Vital Signs

Vital signs will be summarized using descriptive statistics at baseline and at each protocol-specified visit time point. Unscheduled visits will be listed. Changes from baseline will also be summarized.

All vital signs data will be provided in listings.

9.4. Physical Examination

Physical Examination results will be listed.

9.5. Electrocardiogram

All ECG results will be listed. Overall interpretation and percent change for each parameter from baseline will be summarized by time point.

[redacted]

9.6. Other Safety Measures

The following safety measures collected will also be provided in listings:

- Pregnancy test results

10. REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guideline for Industry: E3 Structure and Content of Clinical Study Reports *Federal Register.* July 17, 1996 (61 FR 37320).

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: E9 Statistical Principles for Clinical Trials. *Federal Register*. September 16, 1998 (63 FR 49583).

U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Antiarrhythmic Drugs. *Federal Register*, October 19, 2005

Karjalainen J, Viitasalo M, Manttari M, Manninen V. 1994. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. *J Am Coll Cardiol* **23**:1547-1553.

Ying GS, Maguire MG, Glynn RJ, Rosner B. Calculating Sensitivity, Specificity, and Predictive Values for Correlated Eye Data. Invest Ophthalmol Vis Sci. 2020 Sep 1;61(11):29. doi: 10.1167/iovs.61.11.29. PMID: 32936302; PMCID: PMC7500131.

11. SOFTWARE

SAS Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

The following TFL numbering is completed according to ICH guidelines. The ICH heading number and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP. Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

List of Tables

ICH Heading	Table Number	Table Description	Analysis Population
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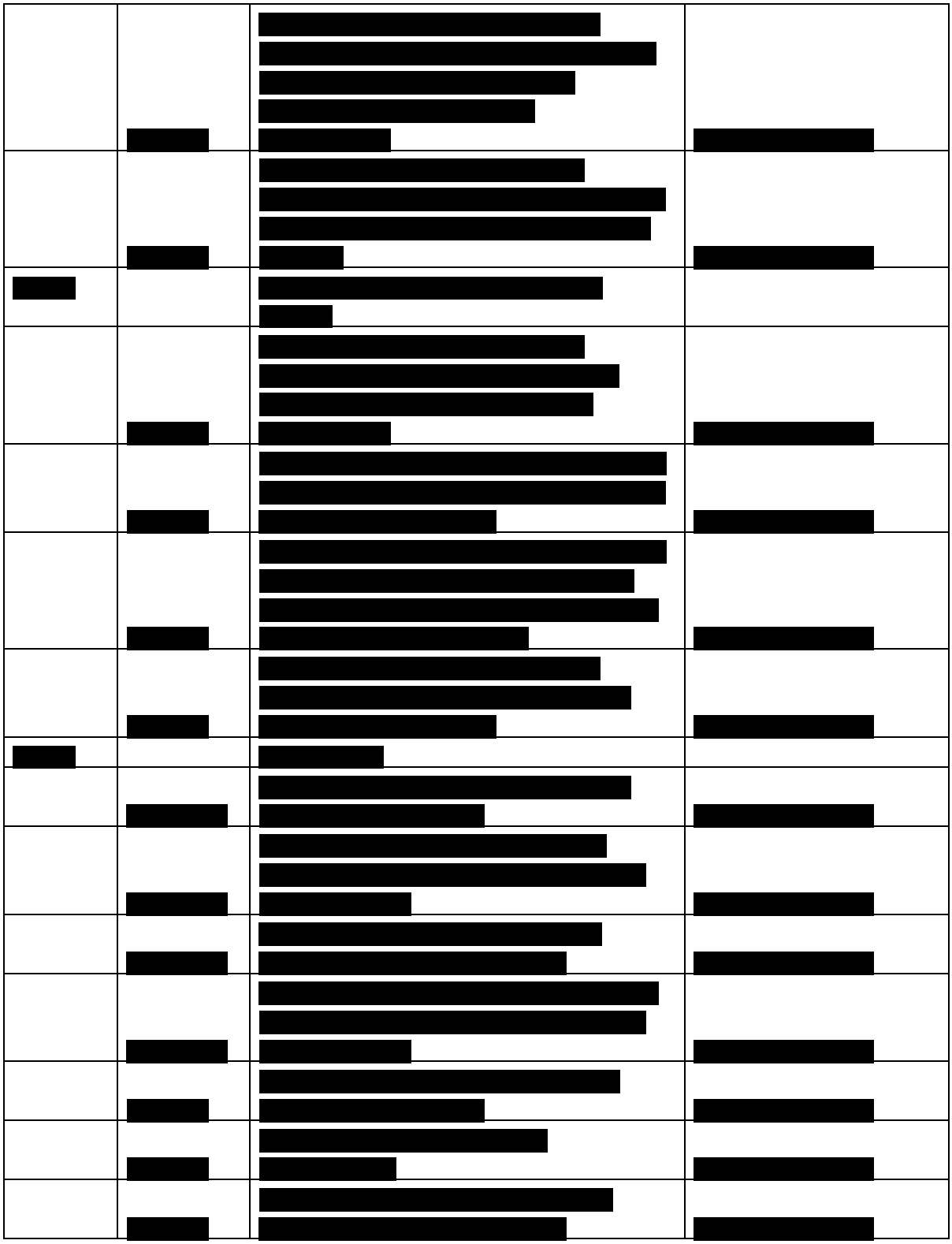

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