CLINICAL STUDY PROTOCOL

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

Sponsor: Vergent Bioscience, Inc
[redacted]

Protocol Number: VGT-309-2-2021USA

Medical Emergencies: [redacted]

Version: Amendment 4
20 May 2022

Replaces: Amendment 3, 12 May 2022
Amendment 2, 20 April 2022
Amendment 1, 14 February 2022

Confidentiality Statement

[redacted]

VERGENT BIOSCIENCE, INC. – PROTOCOL APPROVAL

Amendment 4 – 20 May 2022

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Protocol Version/Date:	Amendment 4 20 May 2022
Replaces:	Amendment 3, 12 May 2022 Amendment 2, 20 April 2022 Amendment 1, 14 February 2022
Sponsor Name:	Vergent Bioscience, Inc [redacted]

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator: [redacted]

Principal Investigator Signature: _____

Date: _____

Study Synopsis

Sponsor	Vergent Bioscience, Inc. [redacted]
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
Protocol Number	VGT-309-2-2021USA
Principal Investigator	[redacted]
Study Centers	[redacted]
Investigational Medicinal Product (IMP)	VGT-309 for Injection, 10 mg/vial
Primary Efficacy Objective	Identification of the proportion of subjects with at least one Clinically Significant Event (CSE) as defined by: [redacted]
Safety Objective	To determine the safety and tolerability of VGT-309 when used as a fluorescent imaging agent in subjects with suspected or proven lung cancer
Secondary Efficacy Objectives	To evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of VGT-309 to detect cancer utilizing near-infrared (NIR) fluorescence and histopathology results.
Introduction and Rationale	[redacted]

	[redacted]
Primary Endpoints - Efficacy	The proportion of subjects with at least one Clinically Significant Event (CSE) as defined by: [redacted]
Safety Endpoints	Assessment of clinical laboratory tests, physical exam results, ECGs and vital signs measurements at various time points during the study, and documentation of treatment-emergent adverse events
Secondary Endpoints - Efficacy	1. Sensitivity [redacted] 2. Specificity [redacted] 3. Positive predictive value (PPV) [redacted] 4. Negative predictive value (NPV) [redacted] * TP = true positive, FP = false positive, TN = true negative, FN =false negative
Study Population	A total of 40 subjects scheduled to undergo standard of care surgical resection for a lung nodule that is suspected or proven to be lung cancer will be enrolled to ensure at least 38 evaluable subjects.

	[redacted]
Inclusion Criteria	In order to be enrolled in the study the subject must: 1. Be willing and able to sign the informed consent and comply with study procedures. 2. Be between the ages of 18 and 85, inclusive. 3. Be male or female and meet the following conditions: a. Female participants must be of non-childbearing potential, or, b. If of childbearing potential be non-pregnant or non-lactating and agree to use highly effective contraception from screening through Day 30. c. Male participants, if not surgically sterilized, and if engaging in sexual intercourse with a female partner of childbearing potential, must be willing to use highly effective contraception from screening through 30 days post-dose and agree not to donate semen during this waiting period. d. Highly effective contraception involves the use of a condom for the male, plus one of the following for the female: • Oral, injectable, implantable, intravaginal, or transdermal hormonal contraceptives, or • Intrauterine device or intrauterine hormone-releasing system • NOTE: Participants who abstain from heterosexual intercourse as their usual and preferred lifestyle, will not be required to use contraception as described above. They are required to maintain abstinence from screening through Day 30. 4. Have a lung nodule or mass that might be considered primary lung cancer or lung metastases, whether or not it is biopsy-proven. 5. Be scheduled to undergo standard of care surgical resection for a lung nodule or mass with diagnostic and/or curative intent and meet all pre-operative surgical and anesthesia acceptance criteria. 6. Have acceptable kidney and liver functions at study entry as evidenced by: [redacted] 7. Have an ECOG score of 0-2. 8. Meet all standard surgical and general anesthesia requirements. 9. Have not participated in a clinical trial within the last 30 days.
Exclusion Criteria	The subject may not be enrolled in the study if: 1. They are not a candidate for standard of care surgery based on opinion of the surgeon, anesthesiologist, or other consulting physician.

	2. They have a known allergy or reaction to ICG, other radiographic contrast agent, or any component of VGT-309. [redacted] 4. They are prisoners, institutionalized individuals, or are unable to consent for themselves. 5. Have any other co-morbidity or habit that the Investigator believes will interfere with their ability to comply with and complete the study.
Study Methodology and 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. [redacted] [redacted] 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.
VGT-309 Description	[redacted]

	[redacted]
VGT-309 Dosing	The dose for this study is 0.32mg/kg of VGT-309 and [redacted] The Data Safety Committee (DSC) may recommend that the dose be modified downward (see below). [redacted]
Data Safety Committee (DSC)	A Data Safety Committee will be appointed by Vergent Bioscience and will include at a minimum: [redacted]
Enrollment Period	It is expected that the time required to enroll 40 subjects in this study will be approximately 8 months.
Study Duration	Each subject may expect to be on study for up to 96 days: [redacted]

Primary Efficacy Assessments	[redacted]
Secondary Efficacy Assessments	[redacted]

Safety Assessments	• Treatment-emergent adverse events.
	• Clinical laboratory assessments of blood and urine:
	  ○ Hematology – Standard panel
	  ○ Coagulation – INR and APTT
	  ○ Chemistry – Standard panel including liver function tests (LFTs) and amylase
	• Pre- and post-dose ECGs.
	• Vital signs (BP, HR, temp, resp).
	• Additional studies if identified during the trial as being necessary to adequately assess safety.

Statistical Methods and Considerations	**Sample Size:** [redacted] **Efficacy:** A descriptive analysis of the baseline subject and tumor characteristics will be performed. Quantitative data will be presented as a standard set of summary statistics (n/mean (standard deviation)/median/minimum/maximum). Categorical data will be expressed as frequency (%). For the primary endpoint analysis, the proportion of subjects undergoing NIR imaging with at least 1 CSE will be identified and [redacted]

	[redacted] All data analyses will be performed for all subjects as a group. **Safety:** Adverse event (AE) data will be listed by subject. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to study drug discontinuation will be summarized by treatment group, system organ class, and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Listings of individual subject laboratory results will be provided. Laboratory results and change from baseline for selected lab tests will be summarized by treatment at scheduled visits. Twelve-lead ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate. Individual data for physical examination findings, prior and concomitant medications and medical history will be provided.

List of Abbreviations:

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CT	Computed Tomography
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSC	Data Safety Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hgb	Hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
kg	kilogram
L	Liter
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	Milliliter
NIR	Near-infrared (imaging)
NOAEL	No-Observed-Adverse-Effect-Level
PI	Principal Investigator
PK	Pharmacokinetic
RBC	Red Blood Cell
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SD	Sprague-Dawley (rats)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Total cholesterol
TG	Triglyceride

1. INTRODUCTION

A comprehensive review of VGT-309 is contained in the Investigator's Brochure supplied by the Sponsor, Vergent Bioscience, Inc. The Investigator's Brochure should be reviewed prior to initiating the study.

1.1 Background and Rationale

[redacted]

Non-small cell lung cancer is a particularly lethal cancer, for which the best opportunity for cure comes from early detection and complete resection at surgery. Great advances in minimally invasive surgery (robotics; video-assisted thoracic surgery) have provided the opportunity to reduce the impact of major lung resection on the subject with lung cancer.

This has come at the cost of increasing difficulty in localizing small cancers deep in the lung parenchyma due to the elimination of the ability to palpate the lung through a large thoracotomy incision. Currently this is overcome by one of three methods: - a) remove a larger amount of tissue than required for biopsy of a suspicious lesion; b) wait until a suspicious lesion has grown sufficiently to allow easier detection at surgery; or c) perform a thoracotomy.

None of these options is optimal. The first, because a large amount of lung may be unnecessarily removed if the lesion is not cancer; the second, because the opportunity for early curative surgery may be missed if the cancer spreads in the months waiting for it to grow further; and the third negates the proven benefit of minimally invasive surgery.

The use of a tumor-targeted, activatable fluorescent imaging agent that can be taken up and bound by cancer tissues and visualized by tumor-specific fluorescence under NIR light during the surgical procedure would solve this problem if the drug readily identified the lesion for the surgeon. This could allow early and well-targeted surgical biopsy and subsequent appropriate cancer surgery for the correctly identified population.

1.2 Nonclinical *In Vitro* and *In Vivo* Experience

[redacted]

1.2.1 Genotoxicity

[redacted]

1.2.2 Safety Pharmacology

Single dose safety pharmacology studies showed no specific CNS, respiratory, or [redacted]

1.2.3 Local Tolerance

[redacted]

1.2.4 Single Dose Toxicity in Sprague-Dawley Rats and Beagle Dogs

[redacted]

1.2.5 VGT-309 NIR imaging of Lung Tumors in Dogs

[redacted]

[redacted]

Refer to the Investigator's Brochure for further details.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1 Objectives:

2.1.1 Primary Efficacy Objective:

Identification of the proportion of subjects with <u>at least one</u> Clinically Significant Event (CSE) as defined by:

[redacted]

[redacted]

2.1.2 Secondary Efficacy Objective:

- To evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of VGT-309 to detect cancer utilizing near-infrared (NIR) fluorescence and histopathology results.

2.1.3 Safety Objective:

- To determine the safety and tolerability of VGT-309 when used as a fluorescent imaging agent in subjects with suspected or proven lung cancer.

2.2 Endpoints:

2.2.1 Primary Efficacy Endpoints:

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

[redacted]

2.2.2 Secondary Efficacy Endpoints:

1. Sensitivity [redacted]
2. Specificity [redacted]
3. Positive predictive value (PPV) [redacted]
4. Negative predictive value (NPV) [redacted]

* TP = true positive, FP = false positive, TN = true negative, FN =false negative.

[redacted]

2.2.4 Safety Endpoints:

- Clinical laboratory tests.
- Physical exam results.
- 12-lead ECGs.
- Vital signs measurements.
- Documentation of treatment-emergent adverse events

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. [redacted]

Following agreement with and signing of the informed consent, subjects will undergo screening and baseline 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, height and weight.
3. Standard pre-operative chemistry, hematology, coagulation and urinalysis clinical laboratory studies.
4. 12-lead ECGs.
5. Serum pregnancy test for females of child-bearing potential.

Following clearance of all enrollment criteria, each subject will receive an IV administration of [redacted] VGT-309 at 12-36 hours prior to surgery (See Section 4 – Study Drug – VGT-309). 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.

Following surgery, subjects will be monitored for safety during their hospital stay. 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 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. STUDY DRUG – VGT-309

VGT-309 will be administered as an IV infusion over 15 to 20 minutes. Following are details related to VGT-309 preparation, packaging and labeling and storage. Additional details will be supplied in the Pharmacy Manual.

4.1 VGT-309 Description

VGT-309 will be supplied in a lyophilized form in 5ml vials containing 11mg of VGT-309. [redacted]

4.2 VGT-309 Proposed Dose

The dose for this study is 0.32mg/kg of VGT-309 [redacted]

4.3 VGT-309 Preparation

VGT-309 is stored frozen and must be thawed at room temperature for at least 30 minutes but not more than 2 hours before it is prepared for dosing.

[redacted]

4.4 VGT-309 Dose Administration

VGT-309 will be given as an IV infusion, utilizing a syringe pump, over 15 to 20 minutes between 12-36 hours prior to start of the planned surgery.

4.5 VGT-309 Storage and Accountability

VGT-309 will be stored frozen (-25 to -15°C) in a secure, locked area under the responsibility of the clinical research unit pharmacy or its designee.

The Investigator or Investigational Pharmacy must maintain accurate records of the receipt of all study drug, including date received, lot number, amount received, condition of the package and the disposition. Dispensing records will be maintained including the date and amount of study drug dispensed and the identity of the subject receiving the study drug.

Following dosing, all empty vials will be retained until reconciliation with the dispensing and shipping records is complete. Empty vials may then be destroyed using investigative pharmacy policy.

Following final reconciliation, unused study drug may either destroyed according to site guidelines or returned to Vergent Bioscience, Inc., or designee.

4.6 VGT-309 Packaging and Labeling

Labels will be in compliance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients according to Annex 13 of GMP. Specifically, labels will contain:

- "Limited by Federal Law to Investigational Use" statement.
- Study Drug name, route of administration and amount of VGT-309 in the vial.
- Lot number.

- Storage conditions.
- Sponsor name (Vergent Bioscience, Inc).
- Manufacturer.

5. SUBJECT POPULATION

5.1 Enrollment

This study plans to enroll a total of 40 subjects scheduled to undergo standard of care surgical resection for a lung nodule that is suspected or proven to be of concern to ensure at least 38 evaluable subjects. [redacted]

5.2 Inclusion Criteria

In order to be enrolled in the study, the subject must:

1. Be willing and able to sign the informed consent and comply with study procedures.
2. Be at least 18 years of age.
3. Be male or female and meet the following conditions:
   a. Female participants must be of non-childbearing potential, or,
   b. If of childbearing potential be non-pregnant or lactating and agree to use highly effective contraception from screening through Day 30.
   c. Male participants, if not surgically sterilized, and if engaging in sexual intercourse with a female partner of childbearing potential, must be willing to use highly effective contraception from screening through 30 days post-dose and agree not to donate semen during this waiting period.
   d. Highly effective contraception involves the use of a condom for the male, plus one of the following for the female:
      - Oral, injectable, implantable, intravaginal, or transdermal hormonal contraceptives, or
      - Intrauterine device or intrauterine hormone-releasing system.

   NOTE: Participants who abstain from heterosexual intercourse as their usual and preferred lifestyle, will not be required to use contraception as described above. They are required to maintain abstinence from screening through Day 30, AND

   Participants in a same sex relationship, must use a barrier form of contraception (e.g., condom, diaphragm) to protect against the transfer of the study drug in any bodily fluids.
4. Have a lung nodule or mass that might be considered primary lung cancer or lung metastases, whether or not it is biopsy-proven.
5. Be scheduled to undergo standard of care surgical resection for a lung nodule or mass with diagnostic and/or curative intent for lung cancer and meet all pre-operative surgical and anesthesia acceptance criteria.
6. [redacted]
7. Have and ECOG score of 0-2.
8. Meet all standard surgical and general anesthesia requirements.
9. Have not participated in a clinical trial within the last 30 days.

5.3 Exclusion Criteria

Subjects may not be enrolled in the study if they:

1. They are not a candidate for standard of care surgery based on opinion of the surgeon, anesthesiologist, or other consulting physician.
2. They have a known allergy or reaction to ICG, other radiographic contrast agent, or any component of VGT-309.
3. [redacted]
4. They are prisoners, institutionalized individuals, or are unable to consent for themselves.
5. Have any other co-morbidity or habit that the Investigator believes will interfere with their ability to comply with and complete the study.

5.4 Replacement of Subjects

Subjects who withdraw consent prior to receiving VGT-309 will be replaced. Subjects not meeting the evaluable criteria (having received VGT-309 and NIR imaging) *may* be replaced. Additional subjects may be added if determined necessary to adequately evaluate safety.

6. STUDY PROCEDURES

Refer to Attachment A: Schedule of Assessments

6.1 Study Visits

Up to 3 in-clinic/hospital visits and 1 follow up phone call are planned for this study. Additional visits may be added if follow up for an adverse event is needed or if screening cannot take place in a single visit. Investigators should schedule visits within the protocol-specified timelines unless they receive permission from Vergent, or unforeseeable events prevent the subject from complying.

For a complete schedule of study procedures, refer to the Schedule of Assessments presented in Attachment A. All study procedures must be recorded in source documentation (primary occurrence of a record) maintained by the clinical site.

6.1.1 Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the IRB-approved ICF must be obtained from the subject in accordance with local practice and regulations.

All subjects must be provided a written Informed Consent Form (ICF) describing the study with sufficient information for them to make an informed decision regarding their participation. Subjects will be given the opportunity to ask questions about the study prior to participation.

A copy of the ICF, signed and dated by the subject, must be given to the subject and documented in the subject's source documentation. The original signed consent form will be retained with the study records.

6.1.2 Screening (Days -60 to -1)

Once informed consent is obtained the following assessments will be done to establish a subject's eligibility for the study. Note: in cases where subjects have given consent for general pre-screening at the site, some of these assessments may be done by chart review.

When possible, the assessments should be done in the order listed here to avoid the demands of sample collection and ECG prior to the subject passing basic entry criteria requirements.

1. Review of eligibility requirements – inclusion and exclusion criteria.
2. Collection of demographic information and medical and surgical history, including review of prior and ongoing medications (taken in previous 30 days).
3. Physical Exam.
4. Height and weight measurements.
5. Vital signs measurement (blood pressure, pulse rate, respiratory rate and oral/tympanic temperature).
6. Standard 12-lead ECG (subject should be resting in a supine position for at least 5 minutes prior).
7. Blood sample collection for clinical chemistry, hematology and coagulation.
8. Urine sample collection for urinalysis.
9. In women of child-bearing potential, blood sample for serum pregnancy test.

Upon establishment of eligibility, subjects will be assigned to a dose and scheduled for admission to the hospital.

6.1.3 Day 1: VGT-309 Dosing

Subjects will check in to the hospital or infusion center as scheduled. After confirming their eligibility by reviewing their medical history and concomitant medications for any changes since screening, those subjects still considered eligible will undergo the following:

1. Targeted Physical Exam (Focus on heart, lungs and any area of change since screening).
2. Measurement of weight (ONLY if not done within 7 days prior to dosing).
3. Review of concomitant medications.
4. Vital signs measurement (blood pressure, pulse rate, respiratory rate and oral/tympanic temperature).
5. Standard 12-lead ECG (subject should be resting in a supine position for at least 5 minutes prior) (ONLY if not done within 4 weeks prior to dosing).
6. In women of child-bearing potential, blood sample for pregnancy test.
7. Blood sample for chemistry, hematology, coagulation. (ONLY if not done within 4 weeks prior to dosing).
8. Urine sample collection for urinalysis (ONLY if not done within 4 weeks prior to admission).
9. VGT-309 dosing to take place at 12-36 hours prior to induction of general anesthesia. (Refer to Section 4: Study Drug – VGT-309, for instruction on dose preparation and dosing procedures).
10. Upon dosing, VGT-309 subjects:
    - Will be observed and queried for possible adverse events.
    - Will have ECGs taken immediately after and 30 minutes after infusion ends.
    - Will have vital signs taken at 30 minutes and 2 hours after infusion ends.

6.1.4 Day 1 or 2: Surgery and Pathology

Following dosing with VGT-309, subjects will undergo planned standard of care surgical resection for their lung nodule or mass followed by pathological assessment of the resected tumor(s) and/or nodule(s) (Refer to Section 8: Efficacy Evaluations, for details).

6.1.5 Day 3: In-hospital follow up

The day after surgery (between 24 to 48 hours after surgery), subjects will undergo the following:

1. Targeted Physical Exam (Focus on heart, lungs and any area of change since screening).
2. Review of concomitant medications.
3. Vital signs measurement (blood pressure, pulse rate, respiratory rate and oral/tympanic temperature).
4. Blood sample for chemistry, hematology, coagulation.
5. Urine sample collection for urinalysis.
6. Observation for and solicitation of adverse events.

6.1.6 Day 14 +/- 2 days: Telephone follow up

Each subject will be contacted by telephone by a designated member of the study team, to inquire as to their general well-being, query for possible adverse events and any changes in their use of concomitant medications. If deemed necessary, a subject may be asked to return to the clinic for treatment or assessment of a possible adverse event.

6.1.7 Days 19 - 39: End of Study Follow up -OR- Early withdrawal

This visit may be conducted in clinic or by telehealth visit. During this visit or if the subject withdraws from the study early, the following assessments will be done:

1. Review of concomitant medications for changes since last visit.
2. Observation for and solicitation of adverse events.

Following completion of these assessments, subjects will be released from the study. Additional follow-up may be necessary if an SAE is reported and has not yet resolved (See Section 10.2.2 for details).

7. STOPPING THE STUDY OR EARLY WITHDRAWAL OF SUBJECT

This study may be stopped (terminated) by the Sponsor at any time and for any reason. Subjects on study at the time the study is stopped will be asked to complete all assessments in the Early Termination visit (see Attachment A).

NOTE: ***The study may also be stopped or delayed by the DSC as outlined in Section 9.1.2***.

7.1 Individual Subject Withdrawal

The participation of an individual subject in the study may be terminated in the following circumstances:

1. Withdrawal of informed consent by the subject.
2. Any occurrence that, in the Investigator's opinion, makes continued participation contrary to the subject's best interests.

If an Investigator removes a subject from the study, or if a subject declines further study participation, an Early Withdrawal Visit, consisting of the assessments required at the Day 30 visit, will be completed as soon as possible. It will be the responsibility of the Investigator to ensure that all withdrawn subjects receive appropriate follow-up and medical care if needed.

8. EFFICACY EVALUATIONS

Intra-operative and post-operative evaluations will be used to support the efficacy endpoints of the study.

8.1 Primary Efficacy Assessments:

[redacted]

8.2 Secondary Efficacy Assessments:

[redacted]

8.3 Intra-operative Evaluations

[redacted]

8.4 Post-operative Evaluations

Following completion of surgical procedures and imaging, the surgical specimen will be sent to the study pathologist who will conduct standard histological assessment of the surgical specimens. (See Pathology Manual)

9. SAFETY EVALUATIONS

9.1 Data Safety Committee (DSC)

9.1.1 Constitution of the DSC

A Data Safety Committee will be appointed by Vergent Bioscience and will include at a minimum:

- The Principal Investigator
- The Vergent Medical Monitor
- An Independent Physician Reviewer
- The Project Statistician

[redacted]

9.1.2 DSC General Rules

9.1.2.1 Safety Review

The study may be paused if any of the following occur:

[redacted]

9.1.2.2 Efficacy Review

[redacted]

9.2 Assessment of Safety

Safety will be assessed by the recording of adverse events, vital signs, changes in physical exam, 12-lead ECGs and the following clinical laboratory tests:

- **Hematology**

Hemoglobin (Hgb)	Hematocrit (Hct)
Platelet count	Red blood cell count
White blood cell count with differential	

- **Chemistry**

Urea	Creatinine
Total bilirubin	Alkaline Phosphatase
Aspartate transaminase (AST)	Alanine transaminase (ALT)
Gamma-glutamyl transferase (GGT)	Lactic dehydrogenase (LDH)
Glucose	Albumin
Total protein	Bicarbonate
Phosphate	Sodium
Potassium	Chloride
Calcium	Total cholesterol
Urate	Amylase

- **Coagulation:** INR, APTT
- **Urinalysis**

pH	Specific gravity
Protein	Glucose
Ketones	Bilirubin
Blood	Nitrites
Leukocytes	Urobilinogen
Microscopic urine analysis	

9.2.1 Adverse Events

NOTE: The content of this section is based on the FDA "Guidance for Industry and Investigators; Safety Reporting Requirements for IND and BA/BE Studies" issued in

December 2012. A copy of this guidance will be provided in the to the site and should be referred to if and when the following do not provide sufficient guidance for an investigator to make an assessment regarding the occurrence, severity, relationship and expectedness of an adverse event (AE).

Adverse event solicitation and recording will begin immediately following dosing with the study product (VGT-309) and will include only on-treatment (treatment-emergent) events. Any changes to a subject's health that occur between the signing of the informed consent and dosing will be recorded as updates to the subject's medical history.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Investigator (and/or designee) must document all AEs reported from the time of dosing through completion of the End-of-study Visit (Days 22-36). Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or 30 days after last dose and the Investigator will document available follow-up information on the subject's source documentation and CRF

9.2.1.1 Definition of an Adverse Event

The FDA Safety Guidance, referencing 21CFR312.32(a), defines an Adverse Event as follows:

> *Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*
>
> *An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.*

Adverse Events are **NOT**:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

9.2.1.2 Evaluating and Reporting of Adverse Events

All AEs (i.e., a new event or an exacerbation of a pre-existing condition) that occur after dosing with VGT-309 and up to 30 days post-dosing (if the subject is withdrawn due to an AE) or during the End-of-Study Visit (Days 22 – 36) must be recorded as an AE or SAE (if applicable), on the Adverse Event eCRF. The Investigator must follow all AEs until the AE resolves, or until the Investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the Investigator and Medical Monitor will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All subjects who have received any exposure to VGT-309 (even if dosing is not completed) will be evaluated for AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

All AEs must be promptly documented on the Adverse Event eCRF and assessed by the Investigator. Details of the event must include the dates of onset and resolution, severity, relationship to study drug, seriousness, and whether the event caused the subject to withdraw from the study, outcome and timing with regard to administration of the study drug.

Grade: 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. Refer to Section 9.1.2 for stopping rules based on the assigned Grade of AE.

Severity: Severity should be graded and recorded as follows:

- Mild: Awareness of event but easily tolerated.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Inability to carry out usual activity, incapacitating, requires medical intervention.

Relationship: 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).

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

9.2.2 Serious Adverse Events (SAEs)

All SAEs as defined below and that occur after the first dose of VGT-309 and up to 30 days post-dose must be reported to Vergent as soon as the site becomes aware of them. Any SAEs occurring more than 30 days after last study drug administration and considered at least possibly drug-related must also be reported.

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. (Refer to Section 9.2.4 for reporting of pregnancy)

NOTE: 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.

A life-threatening AE is defined as any adverse experience that places the subject in the view of the Investigator, at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

"Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute an SAE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, it is an SAE.

All deaths, regardless of cause, must be reported for subjects on study (within 28 days of last study drug dose). The SAE term should reflect the event that leads to the death with "death" recorded as the outcome

9.2.2.1 SAE Reporting Requirements to Vergent

The procedure for reporting SAEs, regardless of causal relationship, is as follows:

- Within 24 hours of the Investigator's knowledge of an SAE, the site must notify Vergent by phone call to their site monitor, medical monitor or other Vergent representative. They should also immediately complete the AE eCRF and select "Serious".
- This initial reporting of an SAE should contain as much information as is available to the Investigator. Submission of the SAE via the EDC should not be delayed in order to collect additional information to complete the form.
- Follow-up SAE reports may be generated in cases in which additional information becomes available. Hospital records, autopsy reports, and other documents may become available and scanned copies can be provided to Vergent when applicable. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.
- Vergent will distribute completed SAE forms, which may be used to notify the IRB/EC when applicable, via a secure internet-based document depository.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF. However, treatment medication should only be recorded in the narrative description section of the SAE form.

9.2.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs unless considered to be clinically significant by the site clinician. An abnormal laboratory result will be considered an AE if it induces clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g., discontinuation of the study drug, dose modification) or when the event is requiring treatment or other therapeutic intervention (e.g., iron supplements, blood transfusion, etc.).

The Investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significant abnormal laboratory results will be followed until they return to normal or become stabilized.

9.2.4 Pregnancy Reporting

Any pregnancy that occurs between dosing through Day 30, should be verified and recorded. Subjects will sign a separate consent form allowing the Study Site and Sponsor to follow up with them through 6 weeks post-delivery or termination of the pregnancy.

10. STATISTICAL METHODS

10.1 Sample Size Determination

[redacted] adjusted sample size of 40 is planned to achieve a minimum of 38 evaluable subjects.

10.2 Populations for Analysis

For purposes of analysis, the following populations are defined:

Table 01: Analysis Populations

Population	Description
Enrolled Population	All subjects who enrolled in the study.
Safety Population	All subjects who have enrolled in the study and received any amount of VGT-309.
Efficacy Population	All subjects who have received any amount of VGT-309 and have surgery with NIR imaging.

Additional analysis populations may be defined based on available data. Any additional analysis populations will be provided in the Statistical Analysis Plan (SAP).

10.3 Efficacy Analyses

Efficacy analyses will be performed on the efficacy population unless otherwise specified. All analyses will be performed for all subjects as a group. Quantitative data will be presented as a standard set of summary statistics (n, mean, standard deviation, median, minimum and maximum values). Categorical data will be expressed as frequency (%).

[redacted]

This study will be descriptive in nature, however, additional post-hoc statistical tests may be performed and will be further described in the SAP.

10.3.1 Primary Efficacy Objective

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

[redacted]

10.3.2 Primary Efficacy Endpoints

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

[redacted]

10.3.3 Secondary Efficacy Objectives

- To evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of VGT-309 to detect cancer utilizing near-infrared (NIR) fluorescence and histopathology results.

10.3.4 Secondary Efficacy Endpoints

1. Sensitivity [redacted]
2. Specificity [redacted]
3. Positive predictive value (PPV) [redacted]
4. Negative predictive value (NPV) [redacted]

* TP = true positive (fluorescent lesion that is cancer), FP = false positive (fluorescent lesion that is not cancer), TN = true negative (non-fluorescent lesion that is not cancer), FN =false negative (non-fluorescent lesion that is cancer).

[redacted]

[redacted]

10.4 Safety Analysis

Unless otherwise specified, safety analyses will be conducted in the safety population. Safety will be evaluated by assessment of clinical laboratory tests, PE, ECG and vital sign measurements at various time points during the study, and by the documentation of AEs.

10.4.1 Adverse Events

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. A treatment-emergent adverse event (TEAE) is defined as any adverse event that begins on or after the date of administration of VGT-309.

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.

No statistical testing will be performed. All AEs collected during the study will be presented in a listing. Additionally, a listing will be provided for any AEs leading to death.

10.4.2 Clinical Laboratory Data

Summaries of clinical laboratory results and change from baseline will be performed using descriptive statistics by scheduled visit. No statistical testing will be performed.

10.4.3 Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Twelve-lead ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate. No statistical testing will be performed.

11. RECORDING AND COLLECTION OF DATA

11.1 Case Report Form

The Investigator or designee will record all data collected by an Electronic Data Capture system (EDC) containing the electronic Case Report Form (eCRF) provided for that purpose. The site will be suitably trained on the use of the EDC and eCRF and appropriate site personnel will be provided electronic signatures.

All site entries will be made in a secured web site and the Principal Investigator will review the record for completeness. Upon completion of the review, the PI will sign electronically in the signature page of the eCRF.

The Investigator or designee will make necessary eCRF corrections. The investigator must authorize the corrections to the entered data on eCRF.

Specific instructions on use of the EDC system and guidelines for data entry and correction will be provided to the sites in the study manual.

11.2 Study Files and Subject Source Documents

Subject confidentiality is strictly held in trust by the participating investigators, research staff, Vergent and their designees. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Authorized representatives of Vergent may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a subject identification number to maintain confidentiality.

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original subject clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Subject clinical source documents may include, but are not limited to, subject hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, and consultant letters. The Investigator must assure that all original source documents are available to support monitoring activities.

11.3 Monitoring

During the study each site will be visited at regular intervals by a Vergent clinical research monitor. Monitoring visits will be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Investigator will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits and by prompt attention to any matters brought to his/her attention by the monitor.

11.4 Audit

ICH guidelines for GCP require independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The Investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by Vergent that will be suitable for inspection at any time by Vergent, its designees, and/or regulatory agencies. The Investigator understands and agrees to give access to the necessary documentation and files.

11.5 Retention of Data

All records connected with this clinical study will be retained for at least two years following the date of an approved marketing application [21 CFR 312.62(c)]; or at least three years from the formal discontinuation of VGT-309 development; or seven years from the end of the study, whichever is longer. All local laws regarding retention of records must also be followed. The

study site is required to retain all records until written notification allowing destruction is received from Vergent Bioscience, Inc.

12. PUBLICATION POLICY AND SHARING OF DATA

[redacted]

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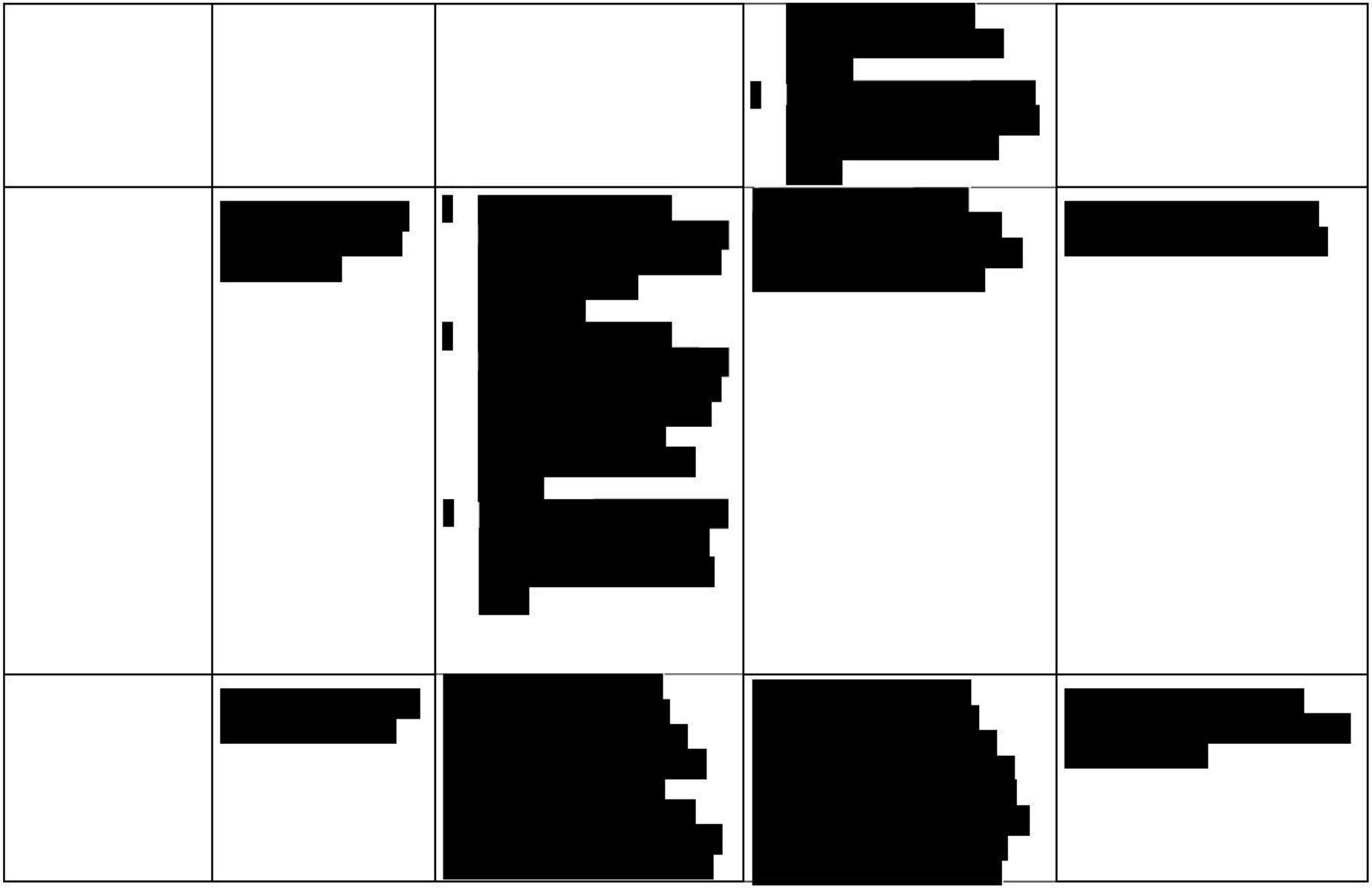
ATTACHMENT B: SUMMARY OF CHANGES:

Protocol Version	Location in Protocol	Original Text	Modified Text	Reason for Change
FINAL, [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Protocol Version	Location in Protocol	Original Text	Modified Text	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]



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