ON TARGET LABORATORIES

CLINICAL STUDY PROTOCOL: OTL-2019-OTL38-007

Title:	A Phase 3, Randomized, Single dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules
Test Drug:	OTL38 Injection: folate analog ligand conjugated with an indole cyanine green-like dye as a solution in vials containing 1.6 mL at 2 mg/mL
Protocol Identification:	OTL-2019-OTL38-007
Sponsor Name and Address:	On Target Laboratories, Inc. [redacted]
Compliance Statement:	The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable national and local regulations.
Date of Protocol Amendment:	Version 1.0, 11 November 2019
[redacted]	[redacted] Signature

CONFIDENTIALITY STATEMENT

Medical Monitor Contact:

Name:	[redacted]
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]
E-mail:	[redacted]

Sponsor Contact:

Name:	[redacted]
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]
E-mail:	[redacted]

Sponsor Regulatory Contact:

Name:	[redacted]
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]
E-mail:	[redacted]

[redacted] will notify the On Target US Regulatory representative about any SAE/SUSAR/unanticipated ADE report that it receives. In addition, [redacted] will provide to On Target Regulatory the initial documents regarding a SAE/SUSAR/unanticipated ADE and follow-up documents regarding each event on proper FDA forms. This information will be supplied to On Target expeditiously in order for On Target to submit the safety information to the FDA within the safety reporting time regulations.

[redacted] will notify all sites of any SAE/SUSAR/unanticipated ADE report it receives. It is each Investigator's responsibility to forward to the site's IRB/EC all SAE/SUSAR/unanticipated ADE reports from other sites that are transmitted on behalf of the Sponsor by [redacted].

SERIOUS ADVERSE EVENT, SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS, AND UNANTICIPATED ADVERSE DEVICE EFFECT REPORTING

CONTACT [redacted] WITHIN 24 HOURS OF LEARNING OF ANY SERIOUS ADVERSE EVENT, SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS AND UNANTICIPATED ADVERSE DEVICE EFFECT.

IF THE SERIOUS ADVERSE EVENT IS FATAL OR LIFE THREATENING, THE SPONSOR AND [redacted] MUST BE INFORMED IMMEDIATELY.

Complete and fax a Serious Adverse Event report form and provide any supporting documentation to [redacted] as described below:

CRO SAFETY GROUP:	**MEDICAL MONITOR**
[redacted]	[redacted]

To discuss SAE with the Medical Monitor, contact [redacted] at the numbers provided above.

Follow-up information to serious AEs must be provided to [redacted] within 24 hours of investigator awareness in the same manner detailed above.

1 PROTOCOL SYNOPSIS

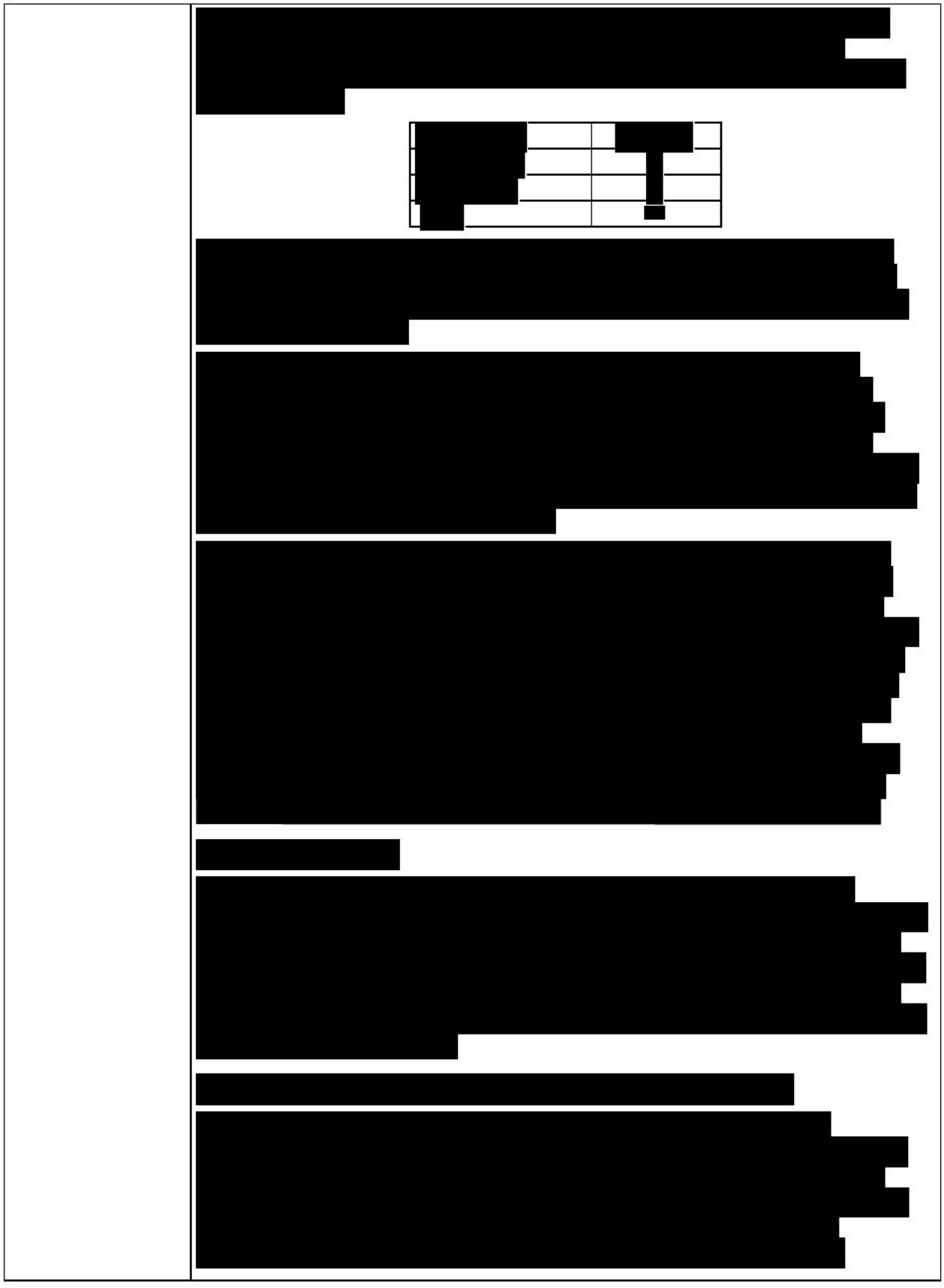
Study Title	A Phase 3, Randomized, Single dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules
Protocol Number	OTL-2019-OTL38-007
Sponsor	On Target Labs, Inc. [redacted]
Investigational Product	OTL38 Injection: folate analog ligand conjugated with an indole cyanine green-like dye as a solution in vials containing 1.6 mL at 2 mg/mL
Primary Objectives	1. To confirm the efficacy of OTL38 used with Near Infrared (NIR) fluorescent imaging to detect at least one of the following outcomes in adult subjects scheduled to undergo surgical resection for known or suspected cancer in the lung: [redacted]
Secondary Objectives	The secondary objectives are: 1. To estimate the Sensitivity and False Positive Rate [redacted] 2. To estimate the Sensitivity and False Positive Rate [redacted] 3. To estimate the Sensitivity and False Positive Rate [redacted] 4. To estimate the Sensitivity and False Positive Rate [redacted] 5. To evaluate the efficacy of OTL38 used with Near Infrared (NIR) fluorescent imaging to detect a Clinically Significant Event (CSE) in subjects with confirmed cancer in the lung. 6. To estimate the Sensitivity and False Positive Rate [redacted]

Exploratory Objectives	[redacted]
Safety Objectives	1. To assess the safety and tolerability of single intravenous doses of OTL38. 2. To assess the safety of the Fluorescence Imaging Systems for intraoperative imaging when used with OTL38.
Study Population	Adult subjects with a suspected primary diagnosis, or at high clinical suspicion of cancer in the lung warranting surgery based on CT and/or PET or other imaging.
Study Design	This is a phase 3, multi-center, randomized, single dose, open-label study in adult subjects with suspected cancer in the lung scheduled to undergo endoscopic or thoracic surgery per CT/PET or other imaging based on standard of care. [redacted]

	[redacted]
Treatment	• OTL38 is a folate analog ligand conjugated with an indole cyanine green-like dye. • Each subject will be administered a single intravenous dose of 0.025 mg/kg OTL38. • The imaging systems used in this study do not have market clearance for use with OTL38 and are therefore considered investigational for the purposes of this study. Full specifications for the [redacted] of this protocol. The imaging system used for each subject undergoing fluorescence imaging by the investigational site will be recorded in the eCRF. • Subjects will be evaluated in situ by only one camera. • Subjects will complete a single intravenous dose of OTL38 [redacted]
Study Duration	• Recruitment period is estimated at 18 months • The maximum duration a subject is in the study is 2 months (up to 1month screening; 1month study duration)

Eligibility Criteria	**Inclusion:** 1. Male and Female subjects 18 years of age and older 2. Have a primary diagnosis, or a high clinical suspicion, of cancer in the lung warranting surgery based on CT/PET or other imaging 3. Are scheduled to undergo surgical thoracoscopy for diagnostic wedge resection followed by anatomic lung resection 4. Female subjects of childbearing potential or less than 2 years postmenopausal agree to use an acceptable form of contraception from the time of signing informed consent until 30 days after study completion 5. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and to return for the required assessments **Exclusion:** 1. Previous exposure to OTL38 2. Any medical condition that in the opinion of the investigators could potentially jeopardize the safety of the subject 3. History of anaphylactic reactions to folate, including synthetic folic acid (pteroylmonoglutamic acid) and contrast agents containing indocyanine green for near infrared imaging. Subjects with a medical history of 'idiopathic anaphylaxis' will require evaluation. 4. History of allergy to any of the components of OTL38, including folic acid 5. A positive serum pregnancy test at Screening or a positive urine pregnancy test on the day of surgery or day of admission for female subjects of childbearing potential 6. Clinically significant abnormalities on electrocardiogram (ECG) at screening. 7. Presence of any psychological, familial, sociological condition or geographical challenges potentially hampering compliance with the study protocol and follow-up schedule 8. Impaired renal function defined as eGFR< 50 mL/min/1.73m2 9. Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >2x ULN for total bilirubin except in subjects with Gilbert's syndrome. 10. Received an investigational agent in another investigational drug or vaccine trial within 30 days prior to the administration of study drug 11. Known sensitivity to fluorescent light
Number of Subjects	Up to approximately 130 subjects
Number of Investigator Sites	Up to approximately 15 investigational sites

Assessments	Refer to the Schedule of Assessments
Study description	The study will include a screening period of up to 28 days prior to planned surgery. Eligible subjects will undergo assessments (per Schedule of Assessments) on the day of the infusion, including a 12- lead ECG to be done at least 15 minutes prior to infusion. **Infusion of OTL38** A single dose of OTL38 will be infused IV over approximately 60 minutes. [redacted]



	[redacted]
Study Endpoints	**Primary** The proportion of FAS subjects who have a Clinically Significant Event (CSE). [redacted] **Secondary** The secondary efficacy endpoints are: 1. Sensitivity and False Positive Rate [redacted] a) [redacted]

b) [redacted]

[redacted]

2. [redacted]

a) [redacted]

[redacted]

b) [redacted]

[redacted]

3. [redacted].

a) [redacted]

[redacted]

b) [redacted]

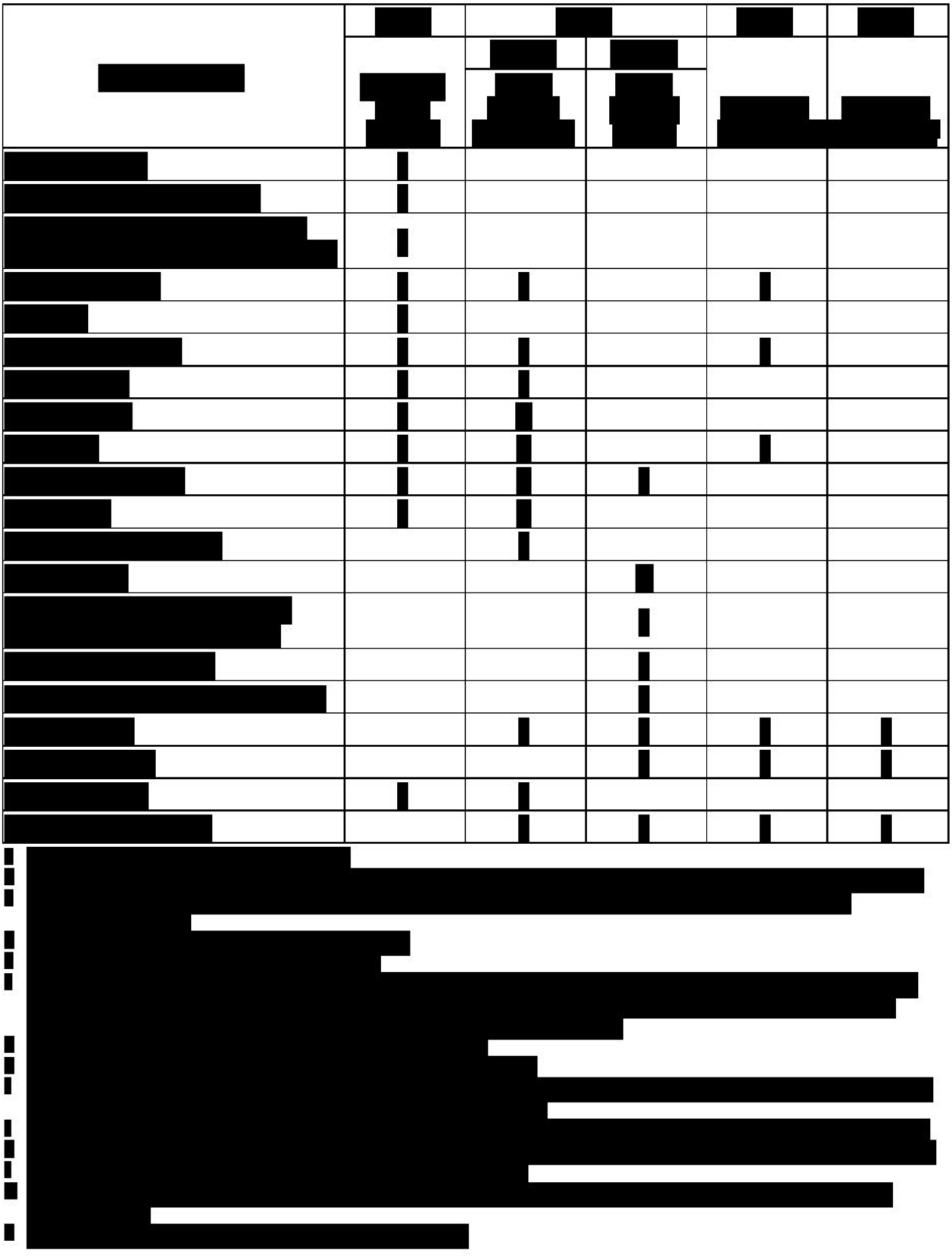
[redacted]

4. [redacted]

	a) [redacted] b) [redacted] 5. [redacted] 6. [redacted] a) [redacted] b) [redacted] **Safety** 1. Incidence rates of all treatment-emergent AEs (TEAEs), adverse device effects (ADEs), and SAEs, from the time of OTL38 administration through follow-up Visit 4. 2. Evaluation of laboratory parameters (chemistry and hematology) and vital signs 3. Evaluation of electrocardiograms (ECG) before and after study drug administration.
Sample Size Estimation	**Sample Size Estimation** [redacted]

	[redacted]
Statistical Methods	The primary analysis of the CSE primary efficacy endpoint will be a one-sample test for a proportion via an exact binomial test conducted at the two-tailed alpha level of 0.05. [redacted] **Analysis of Secondary Efficacy Endpoints** The sensitivity endpoints described above will be analyzed [redacted]
Safety	Safety will be described via subject incidence of treatment emergent adverse events (TEAEs) including serious TEAEs as well as adverse device effects (ADEs). Additionally, summary statistics and/or shift tables will be provided for vital signs, physical exams, ECGs, and laboratory parameters at baseline and post-baseline measurements. All subjects exposed to OTL38 and/or the imaging system will be evaluated for safety and be included in the Safety Analysis Set.

2 SCHEDULE OF ASSESSMENTS



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List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
API	Active Pharmaceutical Ingredient
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CRO	Contract Research Organization
CSE	Clinically Significant Event
CT	Computed/Computerized Tomography
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Sets
FDA	United States Food and Drug Administration
FITC	Fluorescein isothiocyanate
FN	False Negative
FP	False Positive
FR	Folate Receptor
FPR	False Positive Rate
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICG	Indole Cyanine Green
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
KD	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging

Abbreviation	Definition
NIR	Near Infrared
OTL	On Target Laboratories
PPAS	Per Protocol Analysis Sets
PET	Positron-emission tomography
PHI	Protected Health Information
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SfAS	Safety Analysis Set
SUSAR	Suspected unexpected serious adverse reaction
TAM	Tumor Associated Macrophages
TBR	Tumor to Background Ratio
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
TPR	True Positive Rate
ULN	Upper limit of the normal range
VATS	Video-assisted Thoracoscopy
WHO	World Health Organization

3 BACKGROUND INFORMATION

3.1 Background

Lung Cancer is the leading cause of cancer related deaths in the United States, with an estimated projection of 142,670 lung cancer related deaths for 2019. Of new cases of cancer, lung cancer is the second most frequent diagnosis, with an estimated projection of 228,150 newly diagnosed cases for 2019 (SEER 2019). Surgery remains the best option for subjects presenting with operable Stage I or II cancers, however the five-year survival rate for these candidates remains concerningly low at 57.4% for localized disease and 30.8% for regional disease (SEER 2019).

The rates of local recurrence suggest that surgeons are unable to completely detect and remove primary tumor nodules. In addition to the primary nodules, local recurrence can also be attributed to synchronous lesions that are not identified on pre-operative imaging and not found during the initial surgery (Chang 2007, Fabian 2011). Positive surgical resection margins (the distance from the primary tumor to the closest resection margin) also contribute to the recurrence rate (Sienel 2007). During video-assisted thoracoscopic surgery (VATS), smaller and deeper nodules are not always identified (Cerfolio 2008, Nakashima 2010). To help identify these smaller or deeper nodules, methods such as CT-guided hookwire, may be useful in identifying the nodule during VATS surgery, but the procedure of inserting the hookwire, can cause severe complications including embolism (Suzuki 2014).

Incomplete resection of non-small-cell lung cancer negatively impacts survival rates (Osarogiagbon 2016). Local recurrences are more frequent in patients with segmentectomy than lobectomy (Sienel 2007). The risk of recurrence increases if malignant synchronous lesions are not identified pre-operatively or during surgery and are not removed (Fabian 2011, Yoon 2006). Improved survival after complete resection of synchronous lesions has been shown to be similar to that of complete resection of solitary nodules in node-negative patients. Furthermore, this holds true even when synchronous lesions occur in the ipsilateral lung, or a different lobe, or bilaterally (Chang 2007, Voltolini 2010).

Positive resection margins are often found in many cancer surgeries including lung cancer (Orosco 2018). An increased margin distance has been shown to be associated with a lower risk of local recurrence, with a 10-mm margin distance having a 45% lower recurrence risk than a 5-mm distance (Mohiuddin 2014). In wedge resection for small non–small cell lung cancer, increasing the margin distance less than or equal to 15 mm significantly decreased the local recurrence risk, with no evidence of additional benefit beyond 15mm (Mohiuddin 2014). Therefore, ensuring a negative margin through imaging is important to ensure lower rates of recurrence-free disease and thus, overall survival.

Lung-sparing procedures such as wedge resection or segmentectomy are also important, particularly for patients with poor pulmonary reserve. Furthermore, lobectomy to remove synchronous lesions has not been shown to improve immediate or long-term survival above lung sparing sub-lobar resections (Toufektzian 2014). Intraoperative imaging techniques that increase the accurate identification of cancerous synchronous lung lesions may mitigate the need for unnecessary lobectomy or pneumonectomy.

Intra-operative identification of cancer using real-time imaging modalities that provide tumor identification and demarcation have the potential utility in:

- Increasing the possibility of complete removal of cancer without compromising healthy tissue
- Reducing the occurrence of positive resection margins
- Potentially improving overall survival rates
- Improved staging of the tumor.
- Localization of the primary nodule seen on CT/PET
- Removal of additional lesions not previously noted on CT/PET
- Identification of cancerous positive margins of excised tumors

The combination of real-time imaging with tumor-specific fluorescent imaging agents may facilitate optimal resection of lung cancer.

3.2 Rationale

Approximately 85% of lung and pleural malignancies express folate receptor positive nodules (FR+), thus making folate receptors (FR) ideal targets for imaging agents such as OTL-38 (Shen 2015). OTL38 has been observed in preliminary Investigator Initiated studies as being effective in identifying non-malignant lung nodules. These nodules (such as granulomas) do not necessarily pose a threat to the patient's life, but are still targeted for removal by a surgeon to confirm the absence of cancer. Both malignant adenocarcinoma and benign lung nodules that fluoresce in situ are noted to have infiltrates of tumor associated macrophages (TAMs) expressing FR on immunohistochemistry (De Jesus 2015, Shen 2015). Therefore, this intraoperative imaging of lung cancers and nodules would be well-suited in the reduction of positive margins, identification of synchronous lesions, localization of sub-centimeter nodule and tumor tissue, and potentially improving clinical outcomes in these patients. Chemotherapy does not appear to affect FR expression in cancer specimens as examined by immunohistochemistry thus prior treatment is unlikely to affect utility of FR ligands as imaging agents (Crane 2012, Okusanya 2014). Since FRα is normally expressed only in the proximal tubules of the kidneys and in the choroidal plexus, uptake of OTL0038 in the kidneys is possible (Ross 1994). However, the imaging described in this protocol will not involve tissue proximal to the kidneys.

While folate will initially distribute to all cells, redistribution, metabolism, and excretion will eliminate most of this agent from healthy tissues within 2-3 hours. Tumor cells that over expresses FR will retain folate and any fluorescent labeled folate conjugate (Leamon 1993). On Target Laboratories, Inc. has developed OTL0038, a folate analog ligand conjugated with an indole cyanine green-like dye developed by On Target Laboratories, Inc. as a tumor-imaging agent for patients with tumors that overexpress FR. [redacted]

3.3 Investigational Product

The resulting imaging agent, OTL0038, is the active pharmaceutical ingredient (API) of the drug product, OTL38 Injection (also known as OTL38). All nonclinical studies were conducted with API (drug substance) while clinical studies used OTL38 Injection.

[redacted]

The safety profile of OTL0038 has been characterized in a comprehensive series of non-human pharmacokinetic and toxicology studies. The results of the OTL0038 Phase 1-enabling nonclinical safety program in rats and dogs demonstrated the safe use of OTL0038 as an intraoperative imaging agent. [redacted]

3.3.1 Prior Clinical Experience

OTL has completed the following clinical studies:

- Phase 1a Clinical Study of OTL38 in healthy volunteers, dosed in 23 subjects with a dose range [redacted]
- Phase 1b Clinical Study of OTL38 for the intra-operative imaging of folate receptor alpha positive ovarian cancer, dosed in 12 subjects with a dose range [redacted]
- Phase 2 Ovarian Clinical Study of OTL38 for the intra-operative imaging of folate receptor alpha positive ovarian cancer, [redacted]
- Phase 2 Lung Clinical Study of OTL38 for the intra-operative imaging of folate receptor alpha positive lung cancer, [redacted]
- On Target has also initiated an Ovarian Phase 3 Clinical Study of OTL38 for the intra-operative imaging of folate receptor alpha positive ovarian cancer that is currently on-going. [redacted]
- [redacted]
  - [redacted]
  - [redacted]

3.3.2 Phase 1a Study of OTL38 Injection in Healthy Volunteers [redacted]

This was an ascending dose, randomized, placebo-controlled study in which subjects received a single intravenous (iv) dose of OTL38 [redacted]

[redacted]

3.3.3 Phase 1b Ovarian Cancer Study [redacted]

Ten subjects reported a total of 35 adverse events. The most common adverse events were post-surgical wound pain/discomfort, fatigue, abdominal pain/discomfort, nausea and vomiting. All events were graded as mild and all resolved within 1 day of the administration of OTL38. The majority of events were assessed as unrelated by the investigator. The events of nausea and vomiting in the same subject required the administration of an anti-emetic medication (ondansetron).

One subject who received a dose of [redacted] OTL38 developed two serious adverse events consisting of post-operative hospital-acquired pneumonia requiring antibiotics and coughing-induced wound dehiscence requiring surgical repair. These events were considered unrelated to OTL38 administration. No deaths occurred during the study.

3.3.4 Phase 2 Ovarian Cancer Study [redacted]

[redacted]

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

[redacted]

3.3.5 Phase 2 Lung Cancer Study [redacted]

OTL38 injection was evaluated in 100 subjects dosed with 0.025mg/kg with known or suspected lung cancer. [redacted]

[redacted]

A summary of safety findings from this study is as follows:

- Most subjects in the Safety population (94/100) had at least one TEAE during the study.
- Study drug infusion was interrupted in 20/100 subjects due to study drug-related AEs (mild-moderate infusion reaction, nausea, vomiting). Infusion was not restarted for 6 subjects with infusion related AEs that were considered related to study drug. These subjects were discontinued from the study. Most AEs resolved the same day.
- The most common TEAEs occurring in subjects were procedural pain (50/100; 50.0%), nausea (33/100; 33%), cough (29/100; 29%), incisional site pain (20%), vomiting (17/100; 17%) pneumothorax (17/100; 17%).
- Most subjects reported TEAEs of grade 2 (moderate) severity (41/100; 41%). Grade 1, grade 3, grade 4 TEAEs were reported by 24%, 25% and 4% of subjects, respectively.
- Most of severe or life-threatening TEAEs were due to post-surgical pain (4/29; 13.8%); hypertension (4/29; 13.8) and pneumonia (3/29 10.3%).
- There were 20 (20%) subjects with a study drug-related TEAE. [redacted]

[redacted]

- With the exception of the 20 infusion reactions, all TEAEs were typical of those anticipated in the subject population undergoing this type of surgical procedure.
- There were no TEAEs that were considered related to the imaging system.
- There were 14 (14%) subjects with SAEs, none of which were related to study drug. The type and frequency of SAEs was considered consistent with the underlying disease status and medical history of the subjects.
- No subject died during the study.

3.3.6 Other Clinical Experience in Lung and Pituitary Cancer:

[redacted]

Please refer to the Investigator's Brochure for more detailed information on OTL0038 and OTL38 Injection.

3.4 Risks and Benefits of OTL38

3.4.1 Risks

The issues of possible concerns with the use of the OTL38 imaging systems are:

- Presence of an imaging system in the operating room
- Phototoxicity or thermal damage from the light source
- Nonspecific localization of OTL38
- Failure of OTL38 to bind to receptors
- Fading of the chromophore (photobleaching)
- Inability to excite the dye in OTL38 or to record emission
- Adverse events suggestive of hypersensitivity

[redacted]

3.4.2 Benefits

The potential benefits of OTL38 for lung nodule and lesion imaging are:

- Localization of the primary nodule seen on CT/PET
- Increasing the possibility of complete removal of primary nodules and/or cancer without compromising healthy tissue
- Removal of additional lesions not previously noted on CT/PET
- Identification of cancer positive margins of excised tumors
- Reducing the occurrence of positive resection margins
- Improved staging of the tumor.
- Potentially improving overall survival rates

All three CSE components are individually sufficient to identify a clinical benefit as the surgeon would not have been able to identify the CSE by white light and/or palpation alone. Although the use of OTL38 is not intended to change the surgeon's opinion to remove additional tissue based on experience, visualization, or tactile senses, the identification of cancerous lesions identified with NIR alone can lead to improved resection of the cancer and better surgical outcomes.

4 STUDY OBJECTIVES

4.1 Primary

1. To confirm the efficacy of OTL38 used with Near Infrared (NIR) fluorescent imaging to detect at least one of the following outcomes in adult subjects scheduled to undergo surgical resection for known or suspected cancer in the lung:

[redacted]

4.2 Secondary

The secondary objectives are:

1. To estimate the Sensitivity and False Positive Rate [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

4.3 Exploratory

[redacted]

4.4 Safety Objectives

1. To assess the safety and tolerability of single intravenous doses of OTL38.
2. To assess the safety of the Fluorescence Imaging Systems for intraoperative imaging when used with OTL38.

5 STUDY DESIGN

5.1 Overall Investigation Plan

This is a phase 3, multicenter, randomized, single dose, open-label, pivotal study in patients known or suspected cancer in the lung scheduled to undergo endoscopic or thoracic surgery per CT/PET imaging based on standard of care. This includes wedge resection, lobectomy and thoracotomy and/or completion pneumonectomy.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet all the inclusion criteria listed below:

1. Male and Female patients 18 years of age and older
2. Have a primary diagnosis, or a high clinical suspicion, of cancer in the lung warranting surgery based on CT/PET or other imaging
3. Are scheduled to undergo surgical thoracoscopy for diagnostic wedge resection followed by anatomic lung resection
4. Female patients of childbearing potential or less than 2 years postmenopausal agree to use an acceptable form of contraception from the time of signing informed consent until 30 days after study completion
5. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and to return for the required assessments

5.2.2 Exclusion Criteria

Patients will be excluded if they meet any of the exclusion criteria listed below:

1. Previous exposure to OTL38
2. Any medical condition that in the opinion of the investigators could potentially jeopardize the safety of the patient
3. History of anaphylactic reactions to folate, including synthetic folic acid (pteroylmonoglutamic acid) and contrast agents containing indocyanine green for near

infrared imaging. Patients with a medical history of 'idiopathic anaphylaxis' will require evaluation.

4. History of allergy to any of the components of OTL38, including folic acid
5. A positive serum pregnancy test at Screening or a positive urine pregnancy test on the day of surgery or day of admission for female subjects of childbearing potential
6. Clinically significant abnormalities on electrocardiogram (ECG) at screening.
7. Presence of any psychological, familial, sociological condition or geographical challenges potentially hampering compliance with the study protocol and follow-up schedule
8. Impaired renal function defined as eGFR< 50 mL/min/1.73m2
9. Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >2x ULN for total bilirubin excluding those patients with Gilbert's syndrome.
10. Received an investigational agent in another investigational drug or vaccine trial within 30 days prior to the administration of study drug
11. Known sensitivity to fluorescent light

5.3 Study Assessments

The assessments for this study are listed in Section 5.8.

5.4 Patient Discontinuation Criteria

Although a single dose of study drug is infused on Day 1, a patient may be withdrawn from the study for any of the following reasons:

- Request of the patient or patient's representative
- AEs or adverse device effects (ADEs) based on the judgment of the Investigator
- The Investigator decides that it is in the patient's best interest
- The patient is noncompliant with the protocol
- Lost to follow-up
- Death

If a subject is withdrawn at any time, the reason(s) will be recorded on the relevant page of the electronic case report form (eCRF).

Patients discontinued due to AEs or ADEs will be monitored until resolution or stability of the event based on the judgment of the investigator.

5.5 Replacement of Dropouts

Subjects withdrawing or dropping out prior to completion of Visit 2b (surgery) will be replaced.

5.6 Study Drug Information and Dosage

5.6.1 Identification and Description of Test Article

OTL38 will be supplied in vials containing 1.6 mL of solution of 2 mg/mL OTL38 for a total of 3.2 mg of drug per vial. The contents of the vial are a frozen blue-green solution.

5.6.2 Packaging and Labeling

The study medication will be packaged in vials and labelled by the Sponsor's clinical supplies designee.

The labels will include:

Name and contact information for the Sponsor:
On Target Laboratories, Inc.
[redacted]

Route of administration: injection

Quantity supplied: 3.2 mg OTL38 per vial

Pharmaceutical dosage form: [redacted]

Storage conditions: keep frozen [redacted]

CAUTION: New Drug – Limited by Federal Law To Investigational Use

Lot number

Manufacturing date in day/month/year format.

Retest or Expiration date in day/month/year format

5.6.3 Storage and Handling of Test Article

The study medication will be packaged in vials and labelled by the Sponsor's clinical supplies designee.

Study medication should be stored [redacted] and with protection from light (see Site Study Reference Manual).

A Research Pharmacist or other trained and qualified healthcare professional will prepare the IV solutions according to instructions provided by On Target Laboratories at the assigned dose. All prepared solutions should be protected from light and refrigerated (between 2-8°C) until use (see Site Study Reference Manual).

5.6.4 Study Drug Administration

OTL38 will be prepared following the Dose Preparation for OTL38 Injection Pharmacy Manual OTL38 will be administered intravenously over approximately 60 minutes. [redacted]

5.6.5 Camera/Imaging System

The imaging systems used in this study are not approved for use with OTL38, and are therefore considered investigational for the purposes of this study. Technical data for the [redacted] The imaging system used for each subject will be recorded in the eCRF.

5.6.6 Training Requirements

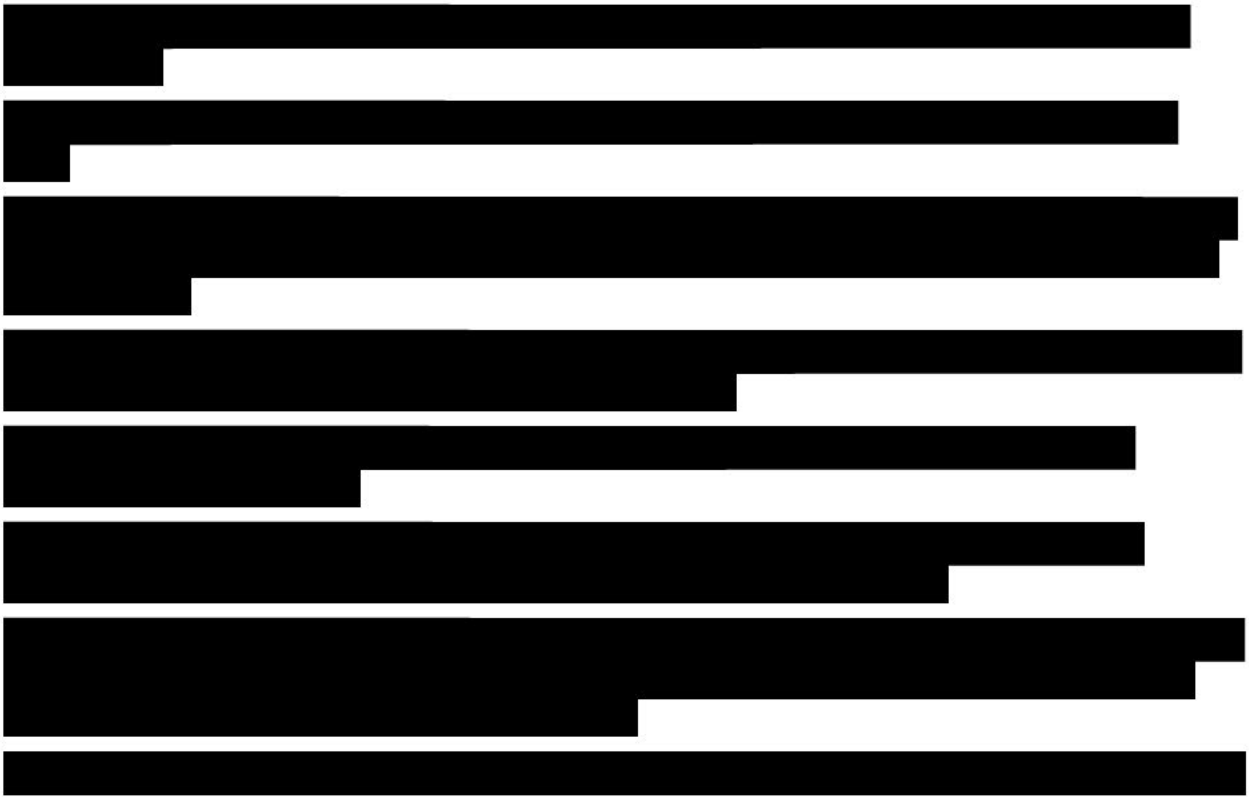
At each site, investigators will image their first eligible patient meeting inclusion and exclusion criteria under the guidance of personnel trained in the use of the imaging agent and NIR camera system. The purpose of this training is to ensure correct use and operation of the camera system.

5.6.7 Tumor to Background Ratio

For cameras that are capable of doing so, tumor-to-background ratio will be calculated for each patient for comparison [redacted]

5.6.7.1 Summary of the Camera/Imaging System Requirements

[redacted]



5.6.7.2 Quality System Requirements

On Target Laboratories outsources design and contract manufacturing for the final device and its labeling, and packaging. As part of the On Target Laboratories Supplier Approval Process, the contract manufacturer's quality system and compliance with the following federal and international regulations are assessed:

- USA 21 CFR Part 820: Code of Federal Regulations, Quality System Regulations; current edition
- ISO 13485:2003 Medical Devices – Quality management systems – Requirements for regulatory purposes
- Medical Device Directive: Council Directive 93/42/EEC concerning medical devices

5.7 Prior and Concomitant Medications

5.7.1 Prior Medications

Prior medications will include all recorded medications and supplements a patient was taking during the screening period that were stopped prior to administration of the study drug. These should be recorded in the eCRF.

5.7.2 Allowed Medications

Necessary supportive measures for optimal medical care will be given throughout the study. Additional care may be administered as indicated at the discretion of the treating physician, and where appropriate after discussion with the medical monitor.

5.7.3 Concomitant medications

Concomitant medications will include all medications that started, or were continuing, during or after administration of the study drug. All concomitant medications and supportive therapy administered starting Day 1 prior to the infusion of OTL38 until the final study visit must be recorded on the appropriate case report form (eCRF).

5.7.4 Prohibited Medications

No other investigational products will be allowed 30 day prior to study drug administration. If the patient is on any folate supplement (including multi-vitamin supplements or pre-natal vitamins), the patient will need to stop taking the supplement 48 hours before scheduled drug infusion.

[redacted]

5.8 Schedule of Events

5.8.1 Measurement and Evaluations

Please see Schedule of Assessments for a detailed study schedule, including all measurements and evaluations for the entire study period (Screening to Follow-up) presented in tabular form.

5.8.1.1 Visit 1 (Screening, up to Day -28)

Prior to the initiation of study-specific screening assessments the Investigator or designee must provide the patient(s) a complete explanation of the purpose and evaluations (procedures and assessments) of the study. Subsequently, the patient must sign and receive a copy of an Informed Consent Form and authorization of use and disclosure of protected health information (PHI) that was approved by the institutional review board (IRB). Once informed consent has been obtained, the eligibility of the patient will be determined, and Screening Period assessments will be performed.

- Signed informed consent
- Complete medical history including diagnosis or suspicion of lung nodules by CT/PET/MRI.
- Physical examination
- Height and weight

- Prior medication assessment
- Vital signs (temperature, blood pressure, and pulse rate)
- Serum Pregnancy test (for women of childbearing potential)
- 12-lead ECG
- Clinical laboratory assessments including hematology, chemistries, and urine analysis

5.8.1.2 Visit 2- (Day 0 and/or 1)

Study dug infusion can optionally occur the day before surgery

Day 0 or 1 – Infusion (Visit 2a)

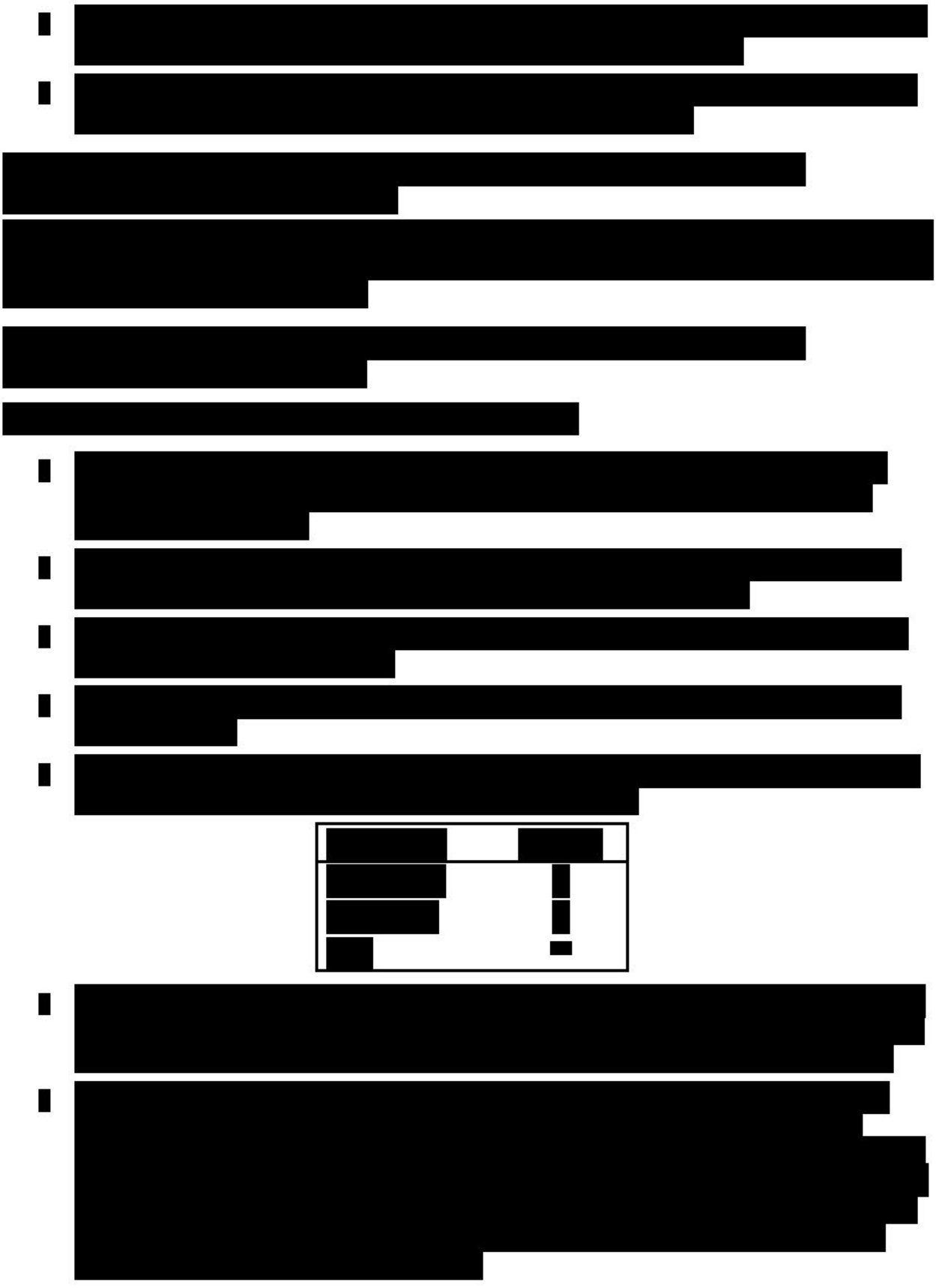
- Updated medical history
- Physical exam
- Prior and concomitant medications assessment
- Clinical laboratory and vital sign assessments will be performed prior to infusion.
- Urine pregnancy test (for women of childbearing potential) prior to infusion.
- 12-lead ECG will be collected at least 15 minutes prior to infusion, and at least 15 minutes prior to surgery after infusion of OTL38 is completed
- A single dose of OTL38 will be infused IV over 60 minutes and will be completed [redacted] to initiation of intraoperative imaging and the time will be recorded
- AEs will be recorded during infusion of OTL38
- [redacted]

Day 1 – Surgery (Visit 2b)

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]



[redacted]

5.8.1.3 Visit 3-Follow-up (Day 7 [± 4])

- Follow-up will be scheduled for Day 7 (± 4) on site
- AEs, ADEs, and concomitant medication information will be recorded.
- Clinical laboratory and vital sign assessments will be performed.

5.8.1.4 Visits 4-Follow-up (Day 28 [±4])

- Follow-up will be scheduled for Day 28 (±4) either via patient telephone interview or clinic visit
- AEs, ADEs, and concomitant medication information will be collected.

5.8.2 Surgical Reporting Schematics

[redacted]

5.8.3 Investigator Post-Surgery Questionnaire (Visit 2b)

After each surgery, the Investigator will fill out the questionnaire located within the study reference manual at the conclusion of each case.

5.8.4 Pathology Samples

All excised lesions will be processed as outlined in "Post-Surgery Tissue Processing". Please refer to the Study Reference Manual for additional details.

5.8.5 Camera/Imaging System Exposure (NIR Fluorescent Imaging Group Only)

A camera/imaging system will be used to identify tumor lesions under fluorescence prior to surgical excision of lesions, and again after surgical excision of lesions to identify persistent lesions. The Investigator will record the start and stop time for each in situ exposure to fluorescence imaging (pre-resection, post-initial resection, other [give reason]) in the eCRF. The total time of fluorescence will be calculated automatically.

Back table imaging will not be included in the fluorescence exposure time.

Status	**Time On Fluorescent Light**	**Time Off Fluorescent Light**
Before surgical excision		
After initial surgical excision		
Other (explain reason)		

6 STUDY ENDPOINTS

6.1 Primary

The primary efficacy endpoint is the proportion of FAS subjects who have a Clinically Significant Event (CSE). A CSE is defined as at least one of the following outcomes:

6.2 Secondary

The secondary efficacy endpoints are:

1. Sensitivity and False Positive Rate

cancer in the lung defined as the proportion of fluorescent light positive FR+ primary

[redacted]

4. [redacted]

[redacted]

[redacted]

6.3 Exploratory

[redacted]

6.4 Safety

1. Incidence rates of all treatment-emergent AEs (TEAEs), adverse device effects (ADEs), and SAE's. Treatment-emergent adverse events (TEAEs) are defined as starting, during or after exposure to study drug.
2. Evaluation of laboratory parameters (chemistry and hematology) and vital signs
3. Evaluation of Electrocardiograms (ECG) before and after study drug administration

7 PROCEDURES FOR REPORTING ADVERSE EVENTS

7.1 Adverse Events Definitions

The Investigator will monitor the occurrence of AEs during the course of the study that will end with Visit 4.

The following definitions of terms are guided by the United States Code of Federal Regulations (21 CFR 312.32(a)) and are included here.

Adverse event is any untoward medical occurrence in a patient associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event (adverse drug experience) or (suspected) adverse reaction means any adverse event or (suspected) adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life- threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is any (suspected) adverse reaction (any adverse event for which there is a reasonable possibility that the drug caused the adverse event) that is both serious and unexpected.

7.2 Adverse Device Effects Definitions

7.2.1 Adverse Device Effect

An ADE is defined as any untoward and unintended response to a medical device, in this study, the camera/imaging system. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, as well as any event that is the result of a user error [ISO 14155-1:2003 (E) 3.1].

All ADEs noted during the study will be reported in the eCRF.

7.2.1.1 Suspected Adverse Device Effect

A suspected ADE is a subset of all ADEs for which there is a reasonable possibility (i.e., evidence to suggest a causal relationship between the device and the ADE) that the device caused the event. Suspected ADE implies a lesser degree of certainty about causality than adverse device effect.

7.2.1.2 Unanticipated Adverse Device Effect

An unanticipated ADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [21 CFR 812.3 (s)].

7.3 Reporting of Adverse Events

7.3.1 Adverse Events

The safety of all patients enrolled in this study will be recorded from the time of study drug administration and throughout the course of the study that will end with Visit 4.

All AEs will be recorded in the appropriate section of the eCRF. Patients withdrawn from the study because of AEs will be followed by the investigator until the outcome is determined. When appropriate, additional written reports and documentation will be provided.

All AEs beginning during or after the exposure to study drug must be reported to the sponsor or its designee if the onset of the AE was before Visit 4. All AEs that are judged by the investigator to be not related to study drug need not be reported to the sponsor or its designee after Visit 4. All AEs that are judged by the Investigator to be related to study drug administration must be reported to the sponsor or its designee regardless of how much time has elapsed since the last exposure to study drug.

7.3.2 Laboratory Abnormalities

To the extent possible, all clinically significant laboratory abnormalities observed during the course of the study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an AE of “renal failure” or elevated ALT/AST in the setting of an AE of “hepatitis”). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

In the absence of a reported AE identifying a clinical syndrome that encompasses the observed clinically significant laboratory abnormality that “isolated” laboratory abnormality itself should be reported as an AE.

Patients experiencing AEs or laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels, or are consistent with the patient’s then-current physical condition, in the opinion of the investigator.

7.3.3 Serious Adverse Events

Instructions for reporting Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR) are found on Page 2. A written report of all SAEs that occur after the administration of study drug and during the study (ending with Visit 4) must be submitted to the IRB/ethics committee (EC) and the Sponsor. SAEs/SUSARs must be reported to the Sponsor within 24 hours for a determination of expedited reporting to FDA, as described in Section 7.7. In all SAE reports, the investigator will advise whether or not the SAE is judged to be related to study drug administration. SAEs that occur after Visit 4 and are not reasonably associated with study drug do not require reporting per the instructions given below. All SAEs that are judged by the investigator to be at least possibly related to study drug administration must be reported to the sponsor or its designee regardless of how much time has elapsed since the last exposure to study drug. All SAEs must be submitted to the IRB/EC in an annual report per local reporting guidelines.

7.3.4 Reporting of Pregnancies

If a patient becomes pregnant during the course of the study, the investigator or site personnel must notify the Medical monitor (see Page 2 for details) within 5 working days after the investigator or site personnel become aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE must be met.

7.3.5 Disease Progression

The progression of lung cancer (in patients diagnosed as such) per se will not constitute an AE. However, if the progression of the lung cancer meets the criteria for an SAE, then it should be reported as an SAE (see Page 2).

7.4 Overdoses

Overdoses should be reported as a protocol violation. If an overdose results in an AE, the CRF AE page should be completed, and source documents included. If the overdose results in an SAE, then SAE reporting should be followed using the specific CRF pages with overdose information entered in the narrative section. All available clinical information relevant to overdose, including signs and symptoms, laboratory findings, and therapeutic measures or treatments administered, should be summarized and discussed.

7.5 Classification of Adverse Events by Severity

The investigator must categorize the severity of each AE according to the following:

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- Moderate: Events introduce a low level of inconvenience or concern to the participant, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- Severe: Events generally require systemic drug therapy or other treatment; they are usually incapacitating
- Life-Threatening: Risk of imminent death requiring immediate intervention.

7.6 Classification of Adverse Events by Relationship to Study Drug Administration

The relationship of each AE to the study drug administration will be assessed by the investigator; after careful consideration, according to the following guidelines:

Related: An adverse event that has a timely relationship to the administration of the study drug and follows a known pattern of response for which no alternative cause is present or may be excluded.

Possibly Related: An adverse event that has a timely relationship to the administration of the study drug, follows no known pattern of response, but a potential alternative cause does not exist

Not related: An adverse event for which there is evidence that it is definitely related to a cause other than the study; in general, no timely relationship to the administration of the drug exists, or if so, the event does not follow a pattern of response and an alternative cause is present

7.7 Adverse Events Qualifying for Expedited Reporting

All SUSARs, SAEs and unanticipated adverse device effects must be reported to On Target Laboratories or designee by telephone and in writing as soon as practical, but at least within 24 hours of initial report.

The investigator must report fatal and life-threatening SUSARs to the IRB within 7 calendar days of the initial receipt of information. On Target Laboratories or designee will report fatal and life-threatening SUSARs to the regulatory authorities and all investigators within 7 calendar days of the initial report of information.

The investigator must report non-fatal and non-life-threatening SUSARs to the IRB within 15 calendar days of the initial receipt of information. On Target Laboratories or designee will report non-fatal and non-life-threatening SUSARs to the regulatory authorities and all investigators within 15 calendar days of the initial report of information.

The investigator must report all unanticipated adverse device effects to the IRB within 10 calendar days of the initial receipt of information. On Target Laboratories or designee will report all unanticipated adverse device effects to the regulatory authorities and all investigators within 10 working days of the initial report of information.

8 DATA RECORDING, CRF PROCESSING, AND STATISTICAL ANALYSIS

8.1 Data Recording and CRF Processing

In place of recording patient data on paper CRFs, which will not be used in this study, site personnel are responsible for entering such data into the Electronic Data Capture (EDC) system. This system has been validated and is compliant with Food and Drug Administration (FDA), ICH, and European Union (EU) regulations and guidelines and with Department of Health and Human Services 21 CFR Part 11 rules for electronic records and electronic signatures. Sites will be instructed to refer to the full eCRF completion guidelines which will be provided as part of site initiation.

8.2 Statistical Methods

Outlined below are the descriptions of the analytic approaches to be employed to address the trial objectives. Additional details will be described in a Statistical Analysis Plan (SAP) which will be finalized prior to database lock and the final analysis.

8.2.1 Sample Size Estimation

[redacted]

8.2.2 Analysis Sets

The following definitions will be used to derive the analysis sets for the study.

Full Analysis Set (FAS): [redacted]

Per Protocol Analysis Set (PPAS):

Safety Analysis Set (SfAS): The safety analysis set will include all patients exposed to OTL38 and/or the imaging system.

8.2.3 Description of Subgroups to be Analyzed

Using the FAS, descriptive summary statistics for the CSE endpoint will also be provided for the following subgroups:

- Age: < 65 Yrs. Vs. ≥ 65 Yrs.
- Race/Ethnicity
- Study Center

8.2.4 Subject Demographics, Baseline Disease Status, and Disposition

Descriptive statistics for subject demographics, baseline disease status, and subject disposition will be provided.

8.2.5 Statistical Analysis

8.2.5.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of FAS subjects who have a Clinically Significant Event (CSE).

8.2.5.2 Secondary Efficacy Endpoints

- Sensitivity and False Positive Rate (FPR)

8.2.5.3 Exploratory Efficacy Endpoints

In general, exploratory efficacy endpoints will be descriptive.

8.2.5.4 Safety Evaluations

Safety will be evaluated using the Safety Analysis Set and will include treatment emergent adverse events (TEAEs), adverse device effects (ADEs), serious adverse events (SAEs), vital signs, physical examinations, clinical laboratory measurements, electrocardiograms, and concomitant medications. Treatment emergent adverse events are adverse events occurring during or after study drug exposure. Adverse device effects occur during or after exposure to the imaging device and classified as device effects by the Investigator. In general, the analysis of safety will be descriptive. No data will be imputed except for partial dates if required to determine if a medical event is a TEAE or a medication concomitant with exposure to study drug.

In general, the baseline value will be considered the last non-missing value recorded for a particular safety parameter before exposure to study drug. Where relevant, changes from baseline summaries will also include the change from screening to pre-infusion.

8.2.5.4.1 Adverse Events and Adverse Device Effects

For subjects in the Safety Analysis Set, medical events occurring after the signing of informed consent but prior to exposure to OTL38 administration will be considered a study AE, but not a treatment emergent AE (TEAE). It is anticipated that study AEs will be sparse and presented in line listings. Treatment emergent adverse events (TEAEs) will be summarized via the MedDRA system organ class and preferred term using subject incidence rates. Data will be tabulated by severity, physician assessment of the relationship to study drug, serious TEAEs, and TEAEs leading to death or study withdrawal. Further description of TEAEs may be defined by temporal onset to study drug infusion. Additional summaries of TEAEs identified as ADEs will also be provided.

8.2.5.4.2 Clinical Laboratory Evaluations

The analysis of laboratory parameters will include descriptive statistics for the change from baseline to each post-baseline study visit as well as shifts from baseline to each post-baseline study visit for categorical lab parameters.

In addition, shift tables (i.e., low-normal-high at baseline versus low-normal-high at last visit will be provided where appropriate. Urinalysis and pregnancy results will not be summarized but will be provided in a data listing. For all relevant laboratory data, values above or below normal limits will be flagged along with the direction of abnormality in line listings.

8.2.5.4.3 Vital Signs

Vital signs will be summarized via descriptive statistics similar to that described above for clinical laboratory evaluations with regard to changes from baseline.

8.2.5.4.4 Physical Examination

Physical examination results will be provided in line listings only.

8.2.5.4.5 Electrocardiogram

Electrocardiogram results will be summarized and also provided in line listings.

8.2.5.4.6 Pathology and Immunohistochemistry

Pathology and immunohistochemistry results will be provided in line listings only.

8.2.5.5 Imaging System

Times on and off for in situ use of the imaging system for each subject will be provided in line listings by camera type. [redacted]

8.2.5.6 Prior and Concomitant Medications

The prior and concomitant medications will be coded to identify the drug class and preferred drug name. Concomitant medications will include all medications and supplements that started, or were continuing, during or after administration of the study drug. Prior medications will include all recorded medications and supplements a patient was taking during the screening period that were stopped prior to administration of the study drug.

The number and percent of subjects using concomitant medications will be tabulated by drug class and preferred drug name for all subjects in the safety analysis set. If a subject has more than one medication within a drug class, the subject will be counted only once in that drug class. If a subject has more than one medication that codes to the same preferred drug name, the subject will be counted only once for that preferred drug name. All percentages will use the number of subjects in the safety analysis set as the denominator. The tabular summary will be sorted by descending order of overall incidence for concomitant medications only. Prior medications will be presented in line listings only. Concomitant medications will also be provided in line listings.

8.2.5.7 Handling of Missing Data

In general, unless otherwise stated missing data will not be imputed.

[redacted]

[redacted]

[redacted]

8.2.5.8 Interim Analyses

There are no planned interim analyses. [redacted]

[redacted]

9 ETHICS

The study will be conducted in compliance with applicable ICH guidelines, the ICH E6 GCP guideline, and regulations, guidelines, and applicable laws of the locale and countries where the study is conducted. The study will be conducted with the approval of a duly constituted IRB/EC in accordance with the requirement of United States regulation Title 21 CFR Part 56 - Institutional Review Boards. The nature and risks of the study will be fully explained to each patient and written consent obtained in accordance with the requirements of 21 CFR 50 - Protection of Human Subjects. Patients will be informed of their rights, including the right to withdraw from the study at any time.

9.1 Patient Information and Consent

A properly executed, written informed consent in compliance with national and local regulations and GCP guidelines will be obtained from each patient prior to entering the study or performing any study-related procedures that are not part of the patient's standard care. The Investigator will submit a copy of the informed consent document to the IRB/EC for review and approval before patients are enrolled. The Investigator will provide a copy of the signed informed consent to the patient and the original will be maintained in the patient's medical record.

9.2 Institutional Review Board

The Investigator will provide the IRB/EC with all requisite material, including a copy of the protocol, IB, and the informed consent document. The study will not be initiated until the IRB/EC provides written approval of the protocol and the informed consent document and until approved documents have been obtained by the Investigator, and copies received by the Sponsor. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/EC and the Sponsor in accordance with the applicable government regulations and in agreement with the Sponsor.

10 STUDY ADMINISTRATION

10.1 Data

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

All data recorded during the study must be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Investigator will be responsible for the following:

- Monitoring study conduct to ensure that the rights of patients are protected;
- Monitoring study conduct to ensure trial compliance with GCP guidelines; and
- Monitoring accuracy, completion, and verification from source documents of study data.

10.2 Study Record Retention

US FDA regulations (21 CFR 312.62[c]) and the ICH Guideline for GCP (section 4.9 of that guideline) require that records and source documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Investigator for 2 years after the last marketing application approval in an ICH region or for at least 2 years since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

10.3 Patient Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs, and other documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the subject), must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

10.4 Publications

Following completion of the study, the results from the entire study, followed by the results from subsets of the study, may be reported at a scientific meeting and/or be published in a scientific journal. On Target Laboratories, Inc. will support these activities and will work with the Investigator(s) to determine how the meeting abstract, presentation and/or manuscript is written and edited, the number and order of authors, the meeting and/or journal to which it will be submitted, and other related activities. On Target Laboratories, Inc. acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has been completed.

11 INVESTIGATOR'S STATEMENT

I have read the protocol entitled "A Phase 3, Randomized, Single dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules" and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by On Target Laboratories, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by On Target Laboratories, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Signature of Investigator	Date (day/month/year)
Printed Name of Investigator	Site Number

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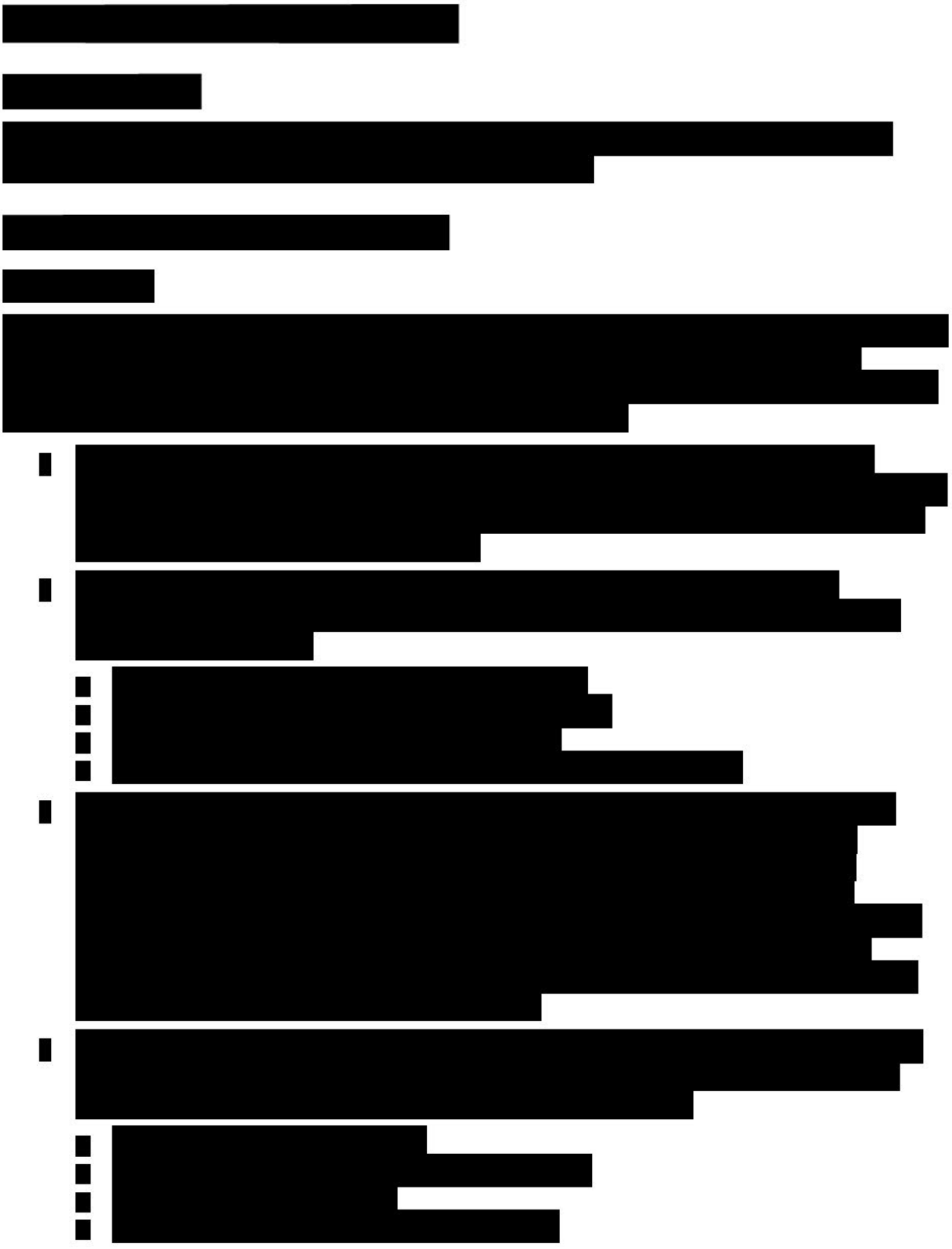
APPENDICES

Appendix 1. Detailed Description of the [redacted]

[redacted]



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[redacted]

[redacted]

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Appendix 2. Detailed Description of the [redacted]

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[redacted]

[redacted]

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[redacted]

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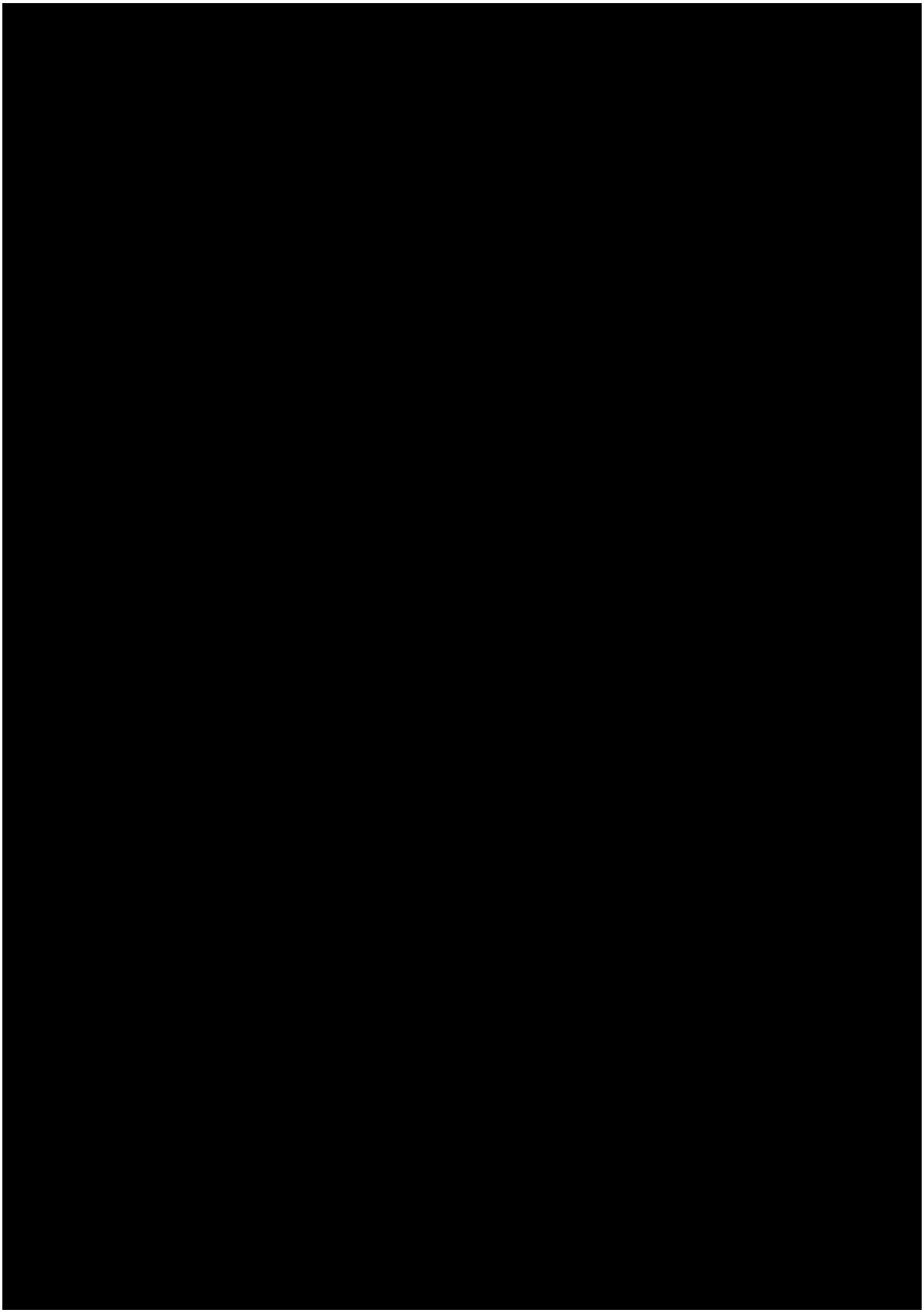

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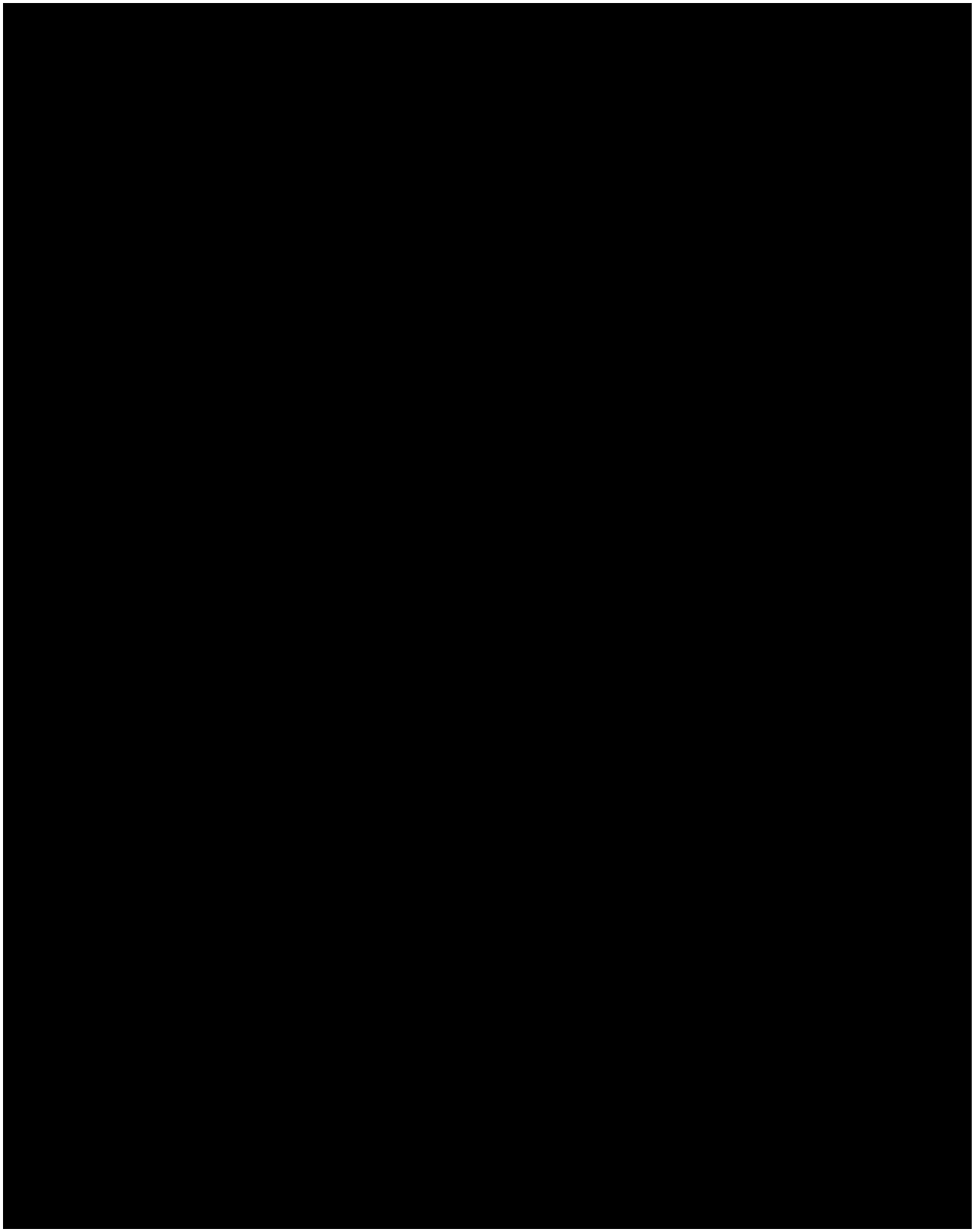
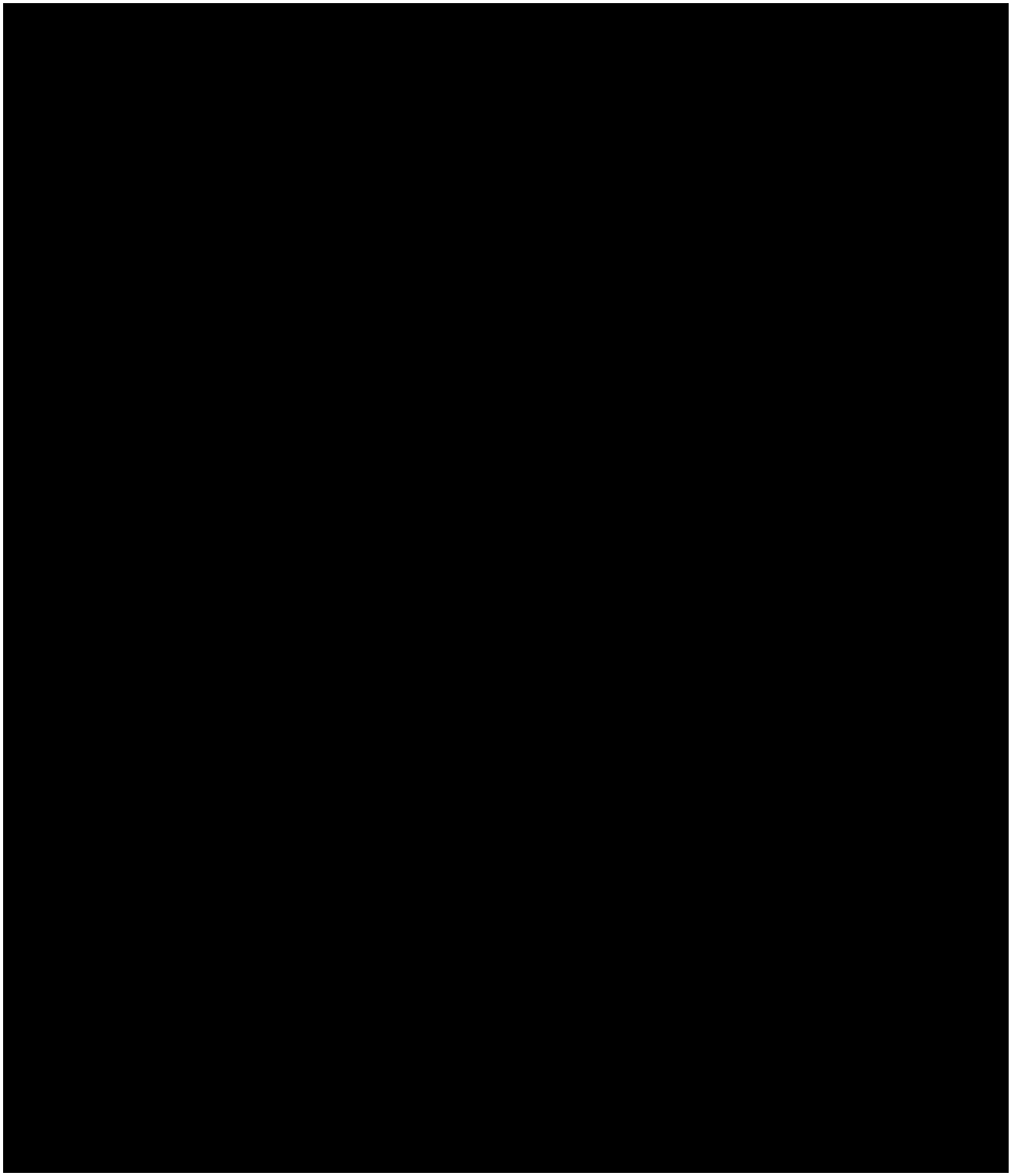
Appendix 3. Surgical Reporting Schematics (SAMPLE)





Appendix 4. Back Table Analysis (SAMPLE)