16. APPENDICES

16.1 STUDY INFORMATION

16.1.9 Documentation of Statistical Methods and Interim Analysis Plans

Statistical Analysis Plan, Version 4.0, 29 July 2021

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STATISTICAL ANALYSIS PLAN

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
Sponsor:	On Target Laboratories, Inc.
Protocol No.:	OTL-2019-OTL38-007
Protocol Version/Date	Version 1.0, 11 November 2019
Phase of Development:	3
Analysis Plan Version/Date:	Version 4.0, 29 July 2021
On Target Laboratories Approver:	[redacted]

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List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CI	Confidence Interval
CSE	Clinically Significant Event (CSE)
CSR	Clinical Study Report
CTDB	Clinical Trial Database
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
FPR	False Positive Rate
FR-	Folate Receptor Negative
FR+	Folate Receptor Positive
[redacted]	[redacted]
[redacted]	[redacted]
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NIR	Near Infrared
PPAS	Per Protocol Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SfAS	Safety Analysis Set
TBR	Tumor to Background Ratios
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
TPR	True Positive Rate

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1 INTRODUCTION

This statistical analysis plan (SAP) provides detailed information and guidance regarding the planned analyses to be conducted to address the trial objectives outlined in protocol OTL-2019-OTL38-007, Version 2.0, 02 January 2020, "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". Should an amendment to the finalized SAP become necessary prior to conducting the analysis, the Sponsor or its representatives will document any amendments including the date of the change and the rationale. Additional analyses beyond those planned in the SAP will be identified and described in the clinical study report (CSR). Draft tables, listings and figures will be provided in a separate document.

The statistical analysis, data integrity processes, and computer software validation will follow the SOPs provided by the Contract Research Organization conducting the operational aspects of the trial and should follow the statistical principles as outlined in ICH E9[1].

2 STUDY OBJECTIVES

2.1 Primary Objective

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]

2.2 Secondary Objectives

The secondary objectives are:

1. To estimate the Sensitivity and False Positive Rate [redacted]

[1] Guidance for Industry: E9 Statistical Principles for Clinical Trials. September 1998.

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[redacted]

2.3 Exploratory Objectives

[redacted]

2.4 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.

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3 OVERALL STUDY DESIGN

This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in subjects known or suspected of having cancer in the lung who are scheduled to undergo endoscopic or thoracic surgery per CT/PET imaging based on standard of care.

[redacted]

4 STUDY POPULATION

The study population will consist of adult subjects with a suspected primary diagnosis, or with high clinical suspicion of cancer in the lung, warranting surgery based on CT and/or PET or other imaging. See Section 5.2 of the protocol for a full list of eligibility criteria.

5 TREATMENT ASSIGNMENT

It is anticipated that all participating subjects will receive OTL38. [redacted] Randomized group assignment will be blinded until revealed for an individual subject. Once revealed, the randomized group assignment for an individual subject will no longer be blinded.

Subjects receiving OTL38 and randomized to [redacted] Further information regarding the randomization process will be detailed in a separate document.

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6 SAMPLE SIZE DETERMINATION

[redacted]

7 GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following general analysis and reporting convention will be applied for this study:

- For analysis purposes, baseline will be defined as the last recorded non-missing observation prior to exposure to study drug.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)". Percentages will be based on the relevant total category count excluding missing data if not otherwise mentioned. To ensure completeness, where relevant, summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a particular category. When the statistical methods use the term "proportion" to describe the calculation of a statistic it is understood that the proportion may be transformed into a percentage for the purposes of data presentation unless otherwise stated.

Continuous variables will be summarized using mean, SD, minimum, maximum, median, and number of subjects. The mean and median will be reported to one more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.

For tests of hypotheses, the associated p-value and confidence interval (CI) will be reported, where applicable. All p-values will be rounded to 3 decimal places; p-values that round to "0.000" will be presented as "<0.001".

Dates will be displayed as ddmmmyyyy (e.g., 24Jan2005).

Age (in years) will be calculated using the date of birth and the date of informed consent as (date of informed consent – date of birth) / 365.25.

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8 ANALYSIS SETS

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

8.1 Full Analysis Set (FAS)

The full analysis set [redacted]

- [redacted]

8.2 Per Protocol Analysis Set (PPAS)

The per protocol analysis set [redacted]

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

8.3 Safety Analysis Set (SfAS)

The safety analysis set will include all subjects exposed to OTL38 and/or the imaging system.

9 SUBJECT DISPOSITION AND PROTOCOL DEVIATIONS

9.1 Subject Disposition

Subject disposition will be summarized and include the following:

- The number of subjects signing informed consent
- The number of screen failures
- The number of subjects randomized
- The number and percent of subjects in each analysis set
- The number and percent of subjects who completed the study overall and by analysis set
- The number and percent of subjects who did not complete the study and the reason for early withdrawal overall and by analysis set

A data listing for all subjects in the SfAS with regard to disposition will also be provided.

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Subjects who sign the Informed consent form (ICF) but are not exposed to study drug or the imaging system will not be represented in any further analyses or line listings.

9.2 Protocol Deviations

All protocol deviations will be recorded in the [redacted] Clinical Trial Management System (CTMS) and will be reported in line listings. Major protocol deviations and deviations used for the definition of the PPAS (see Section 8.2) will be identified prior to database freeze for the final analysis of endpoints. Major protocol deviations will be analyzed by aggregate summary and line listings. For aggregate summaries, data will be presented overall and by randomized group assignment and for each analysis set. If the number of major protocol deviations is small, aggregate summaries will not be presented.

10 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Descriptive statistics for subject demographics and baseline characteristics will be provided. Demographic variables will include, but are not limited to age, sex, and race/ethnicity. Baseline characteristics will include, but are not limited to [redacted] Summaries will be tabulated for subjects for each analysis set. Individual demographic and baseline characteristics data will also be presented in line listings.

11 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug is administered as a single infusion. The number of subjects signing the ICF but not receiving study drug will be presented in the disposition summary. For subjects exposed to study drug, the proportion of subjects not receiving their full dose will be tabulated and the actual dose received for all subjects will be listed in the study drug administration line listing. Additionally, if applicable, the number of subjects randomized to [redacted] who did not do so will be tabulated.

12 EFFICACY EVALUATIONS

For the efficacy endpoints defined below, [redacted]

12.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of FAS subjects who have a CSE. [redacted]

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[redacted]

12.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. Sensitivity and False Positive Rate [redacted]

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[redacted]

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12.3 Exploratory Endpoints

12.4 Safety Endpoints

Safety analyses will be conducted using the SfAS.

1. Incidence rates of treatment-emergent adverse events (TEAEs) defined as adverse events (AEs) starting, or worsening, on or after exposure to study drug. See Section 7.1 of the protocol.
2. Incidence rates of Adverse Device Effects (ADEs) defined as any untoward and unintended response to a medical device, in this study, the camera/imaging system. See Section 7.2.1 of the protocol.
3. Summary statistics for chemistry and hematology parameters. Urinalysis results will be presented in line listings only.
4. Summary statistics for vital signs.
5. Summary statistics for physical examination results.
6. Summary statistics for Electrocardiograms (ECGs).

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7. Pathology and Immunohistochemistry results will be included in line listings only.
8. Summary statistics for on and off times overall imaging systems and for each imaging system will be provided. Data will also be presented in line listings.
9. Pregnancy test results will be presented in line listings only.
10. Incidence rates for concomitant medications defined as all medications started, or continuing, during or after exposure to study drug. Prior medications will be presented in line listings only. See Section 5.7 of the protocol.

13 STATISTICAL ANALYSIS METHODS FOR EFFICACY

The primary analysis of the primary efficacy endpoint will be conducted using the FAS. Analyses of secondary and exploratory efficacy endpoints will use the FAS with additional, or modified, criteria as appropriate for the particular secondary or exploratory endpoint considered.

[redacted]

13.1 Analytic Methods for the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint, CSE, [redacted]

[redacted]

13.1.1 Sensitivity Analyses for the Primary Efficacy Endpoint

In addition to the primary efficacy analysis described above, a sensitivity analysis consisting of descriptive summaries [redacted] will also be provided. [redacted]

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[redacted]

13.1.2 Description of Subgroups to be Analyzed

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

- Age:
  - [redacted]
  - [redacted]
  - [redacted]
- Race
- Ethnicity
- [redacted]
- Study Center

[redacted]

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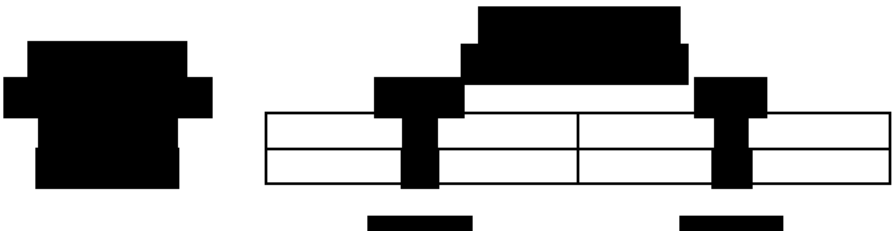
[redacted]

13.2 Analytic Methods for Secondary Efficacy Endpoints

[redacted]



[redacted]

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[redacted]

13.2.1 [redacted]

[redacted]

13.3 Analytic Methods for Exploratory Endpoints

[redacted]

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13.4 Handling of Missing Data and Subject Withdrawals

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

[redacted]

13.5 Investigator Post-Surgery Questionnaire

Any data from the Investigator Post- Surgery Questionnaire used to derive the efficacy endpoints described above will be entered into the Clinical Trial Database (CTDB) and included in line listings.

14 SAFETY EVALUATIONS

14.1 Overview of Safety Analysis Methods

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.

In general, the analysis of safety will be descriptive. No data will be imputed except for partial dates if required to determine if an adverse event is treatment emergent or a medication concomitant with exposure to study drug.

As noted above, the baseline value used for the analysis will be considered the last non-missing value recorded for a particular safety parameter before exposure to study drug. However, where relevant, a change from screening to pre-infusion will also be included in the presentations.

14.1.1 Imputation of Partial Adverse Event Dates

[redacted]

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[redacted]

14.2 Extent of Exposure

Study drug will be administered as a single infusion. A summary of the number of subjects exposed to study drug and any subjects not receiving their full dose will be described. [redacted]

14.3 Adverse Events

Adverse events that are not treatment-emergent, those occurring after signing the ICF but prior to exposure to OTL38 administration, will be provided in line listings. Treatment emergent adverse events (TEAEs) will be summarized via the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term using subject incidence rates. Data will be tabulated by severity, physician assessment of relationship to study drug, serious TEAEs, and TEAEs leading to death or early study withdrawal. Further description of TEAEs may be defined by temporal onset to study drug infusion and/or by event incidence. Additional summaries of TEAEs identified as potential ADEs will also be provided for those subjects exposed to imaging.

Treatment-emergent AEs will be summarized for all subjects in the Safety Analysis Set (SfAS). Summary tables will reflect the number and percent of subjects experiencing at least 1 TEAE in each system organ class and preferred term. The overall number and percent of subjects

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experiencing any treatment-emergent AE will also be provided. All percentages will use the number of subjects in the SfAS set as the denominator. An exception will be the presentation of ADEs which will use all subjects undergoing fluorescent light imaging as the denominator. If a subject has more than one AE within a system organ class, the subject will be counted only once in that system organ class. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term.

Treatment-emergent AEs will also be summarized by the maximum relationship to study drug as determined by the Principal Investigator as well as the maximum severity of the event. Relationship to study drug will be scored as Related, Possibly Related, or Not Related. Related AEs will be classified as those scored as Related or Possibly Related. Severity will be rated as per CTCAE v5.0:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling;
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE

If a subject experiences more than 1 AE within system organ class or preferred term, that subject will be counted only once for that event under the maximum severity or most related category within the relevant category. In the event that the relationship to study drug or the severity of the event is missing, for tabulation purposes the maximum relationship will be assumed, and a Grade 3 (Severe) level of severity will be assumed.

Adverse Events of Special Interest (AESIs) will be captured and analyzed. An AESI is defined as an infusion related reaction and will be identified through the following mechanisms to include all AEs that meet the following criteria:

- AE that are not considered procedural in nature (Procedural complications and administration related problems will be excluded and defined as any AE with a preferred term of “procedural complication” or “infusion site discomfort” will be excluded.)

AND meets at least one of the following:

- AE that resulted in interruption of study drug infusion in the study drug administration data (study drug administration CRF; was infusion interrupted = yes; reason for interruption = AE)
- AE that resulted in study drug interruption or study drug withdrawal in the AE data (all AEs with an action taken with study drug =drug interrupted, or drug withdrawn)
- AE that started during the study drug infusion as per the recoded start time (AEs with a start date of Study Day 1 AND a start TIME within the infusion window as defined as start time >

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infusion start time and ≤ infusion stop time; AEs that have the same start time as the study drug infusion will not be counted)

• AE presumed to start during the study drug infusion as per the recorded start/stop dates and assigned relatedness (AEs without a recorded start time, that have both a start date and stop date of Study Day 1, and are indicated as Related or Possibly Related for their relationship to OTL38 Infusion)

- AE that started during the study drug infusion as per the recoded start time which abate after infusion being stopped or reduced.

Incidence of TEAEs will be summarized by age group, race, and gender if there are sufficient numbers of subjects within these subgroups. Otherwise only line listings will be provided.

All AEs will be presented in data listings for subjects. If required, the line listings will distinguish between adverse events occurring after signing the ICF but prior to exposure to study drug, and TEAEs. If a partial date was imputed, the line listings will include both the observed and imputed date. Imputations for missing relationships and severities of AEs will not be included in the line listings.

14.4 Deaths, Serious Adverse Events and Adverse Events

Treatment-emergent serious AEs (SAEs), TEAEs leading to early study withdrawal, and TEAEs resulting in death (included in the serious definition) will be summarized for all subjects in the SfAS. Summary tables will reflect the number and percentage of subjects experiencing at least 1 TEAE in each system organ class and preferred term within each AE subset (serious, leading to early study withdrawal, or death). In addition, the number of subjects experiencing any TEAE in the respective subset will be reported.

Adverse events leading to early study withdrawal, AEs resulting in death, and SAEs will also be presented in data listings.

14.5 Clinical Laboratory Evaluations

The analysis of laboratory parameters will include descriptive statistics for the baseline and all post-baseline visits as well as the changes from baseline at each visit. Baseline distributions and shifts from baseline to each post-baseline study visit for categorical lab parameters will also be provided. Where relevant, as noted above, changes from baseline summaries will include a change from screening to pre-infusion.

Urinalysis data 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.

14.6 Vital Signs, Physical Exams and ECGs

The analysis of vital signs and physical exams will be summarized via descriptive statistics similar to that described above for clinical laboratory evaluations. Vital signs and physical exams will

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also be included in line listings and flagged for abnormal values. Aggregate results for ECGs with regard to normal/abnormal and clinically significant yes/no designations will be presented. ECG data will also be provided in line listings.

14.7 Pathology and Immunohistochemistry

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

14.8 Imaging System

Times on and off for in situ use of the imaging system will be included in the line listings for each subject. Aggregate mean "on" times (in situ), will also be tabulated overall and by imaging system. Also see Section 14.2, Extent of Exposure.

14.9 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 exposure to the study drug. Prior medications will include all recorded medications and supplements that started and stopped prior to exposure to 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 SfAS as the denominator. Prior medications will be presented in line listings only. Concomitant medications will also be provided in line listings.

14.10 Pregnancy Test Results

Pregnancy test result data will be presented in line listings only.

15 INTERIM ANALYSES AND DATA MONITORING

There are no planned interim analyses. [redacted]

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16 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL OR STATISTICAL ANALYSIS PLAN

Any changes to the planned analyses outlined in the SAP not already documented via amendment prior to undertaking any analyses will be described in the CSR.

17 RANDOMIZATION PLAN

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[redacted]

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18 REFERENCES

Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed. Hoboken (NJ): John Wiley & Sons; 2011.