CLINICAL STUDY PROTOCOL: OTL-2016-OTL38-006

Title:	A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer
Test Drug:	OTL38 Injection: folate analog ligand conjugated with an indole cyanine-like green dye as a solution in vials containing 1.6 mL at 2 mg/mL
Protocol Identification:	OTL-2016-OTL38-006
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:	Version 1.0, 16 May 2017
Date of Amendments:	Version 2.0, 27 November 2018
[redacted]	[redacted] Signature

CONFIDENTIALITY STATEMENT

The information contained within this report is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of On Target Laboratories, Inc.

CRO 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]

CRO will notify the On Target US Regulatory representative about any SAE/SUSAR/unanticipated ADE report that it receives. In addition, CRO 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.

CRO 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 CRO.

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

CONTACT [redacted] **SAFETY SURVEILLANCE** 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] **Safety Surveillance** MUST BE INFORMED IMMEDIATELY.

Complete a Serious Adverse Event report form within the electronic data capture (EDC) system* and provide any supporting documentation to [redacted] **SAFETY SURVEILLANCE** as described below:

[redacted] **SAFETY SURVEILLANCE:**	**MEDICAL MONITOR**
[redacted]	[redacted]

* In the event the EDC system is unavailable at the time of reporting a paper form will be provided and should be faxed or e-mailed to [redacted] Safety Surveillance.

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] SAFETY SURVEILLANCE 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 (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer
Sponsor	On Target Labs, Inc. [redacted]
Primary Objectives	• To confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery
Secondary Objectives	• To estimate the proportion of folate positive ovarian cancer patients in whom all lesions detected by fluorescent light only are histologically negative, the patient level False Positive Rate (FPRp) • To estimate the Sensitivity and False Positive Rate for OTL38 in combination with fluorescent light with respect to the detection of FR+ ovarian cancer lesions confirmed by [redacted] pathology • To assess the safety of using OTL38 and [redacted] Imaging System or Quest Spectrum Imaging System for intraoperative imaging [redacted]
Exploratory Objectives	• To estimate the lesion inoperability rate for all lesions identified by fluorescent light only. • To describe the diagnostic characteristics of OTL38 in combination with fluorescent light for lesions of various histological and pathological cell types • To assess CA-125 levels before and after surgery • To estimate the plasma pharmacokinetics (PK) of OTL38 in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, [redacted]
Study Design	This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery. [redacted]

	[redacted] Efficacy will be assessed for patients undergoing both normal light and fluorescent light imaging. All patients exposed to OTL38, [redacted] will be followed for safety. The study will consist of a screening period of up to 28 days prior to the scheduled surgery, a diagnosis and treatment period (day of surgery; Day 1), and safety assessment visits on Day 7 (+/-4) and Day 28 (+/-4) after surgery. The study database will be frozen when the last patient completes the Day 28 assessment (which will be considered the study completion date); AEs/ADEs judged by the Investigator to be at least possibly related to study drug will continue to be reported regardless of how much time has elapsed since the last exposure to study drug. [redacted]
Treatment	• OTL38 is a folate analog ligand conjugated with an indole cyanine-like green dye. • Each patient will complete a single dose of 0.025 mg/kg OTL38 at least 1 hour before the initiation of fluorescent imaging. • The imaging systems [redacted] that will be used for the intraoperative visualization of ovarian cancer labeled with OTL38 are not yet approved for use with OTL38, and therefore are considered investigational for purposes of this study.
Study Duration	Patients will complete a single dose of 0.025 mg/kg OTL38 at least 1hour hours before the initiation of fluorescent imaging. Safety assessments will occur on Day 7 (± 4) and Day 28 (± 4). [redacted] levels will be measured at a long-term follow-up visit [redacted] after surgery. [redacted]

Eligibility Criteria	**Inclusion:** 1. Female patients 18 years of age and older 2. Have a primary diagnosis, or at high clinical suspicion, of primary ovarian cancer (of epithelial type), planned for primary surgical cytoreduction, interval debulking, or have recurrent ovarian cancer surgery, and: o Who are scheduled to undergo laparotomy for the debulking surgery OR o Who are scheduled to undergo laparoscopy and pre-authorized to undergo laparotomy for the debulking surgery if cancer is detected on the laparoscopy 3. A negative serum pregnancy test at Screening followed by a negative urine pregnancy test on the day of surgery or day of admission for female patients of childbearing potential 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 for participation in the study 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. Known FR-negative ovarian cancer 3. Planned surgical debulking via laparoscopy or robotic surgery, with no intent of laparotomy. 4. Patients with known ovarian cancer miliary disease determined pre-operatively to be inoperable. 5. Any medical condition that, in the opinion of the investigators, could potentially jeopardize the safety of the patient 6. History of anaphylactic reactions 7. History of allergy to any of the components of OTL38, including folic acid 8. Pregnancy or positive pregnancy test 9. Clinically significant abnormalities on electrocardiogram (ECG) 10. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule 11. Impaired renal function defined as eGFR< 50 mL/min/1.73m^2 12. Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin. 13. Known Stage IV ovarian cancer with brain metastases 14. Received an investigational agent in another clinical trial within 30 days prior to surgery 15. Known sensitivity to fluorescent light

Number of Subjects	A minimum sample size of 100 evaluable patients is required to evaluate the primary efficacy endpoint. [redacted]
Number of Investigator Sites	Up to 16 investigational sites (14 in the United States and 2 ex-U.S. [the Netherlands]).
Assessments	At specified time points as outlined in the schedule of events, patients will undergo the following procedures: collection of informed consent, medical history, demographics, physical exam including weight, vital signs including temperature, and ECG. Patients will also provide samples for clinical chemistry, CBC with differential, and a serum/urine test for women of child-bearing potential. Concomitant medications and adverse events as reported by the patient will be monitored. Blood samples for PK analysis will be drawn from all subjects at sparse time points (30, 60 and 90 minutes) following the start of OTL38 infusion (see Section 6.5). [redacted]
Study Endpoints	**Primary Efficacy:** • Proportion of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by [redacted] that was detected using the combination of OTL38 and fluorescent light but not under normal light or palpation. [redacted]

Secondary Efficacy:

- False Positive Rate at the patient level (FPRp) [redacted]
- Sensitivity or True Positive Rate (TPR) for OTL38 in combination with fluorescent light, [redacted]
- False positive rate (FPR) for OTL38 in combination with fluorescent light, for the purpose of this protocol, [redacted]

[redacted]

[redacted]

[redacted] to evaluable lesion status for:

- Cancer (ovarian or other cell type) that are FR+
- Cytologically abnormal lesions that are FR+

- Proportion of patients in whom the Pre-Fluorescence Surgical Plan was changed based on fluorescent imaging both prior to initiation of the surgical procedure and upon reimaging of the surgical field after the surgical procedure immediately prior to surgical closure.
- CA-125 levels before and after surgery

Safety:

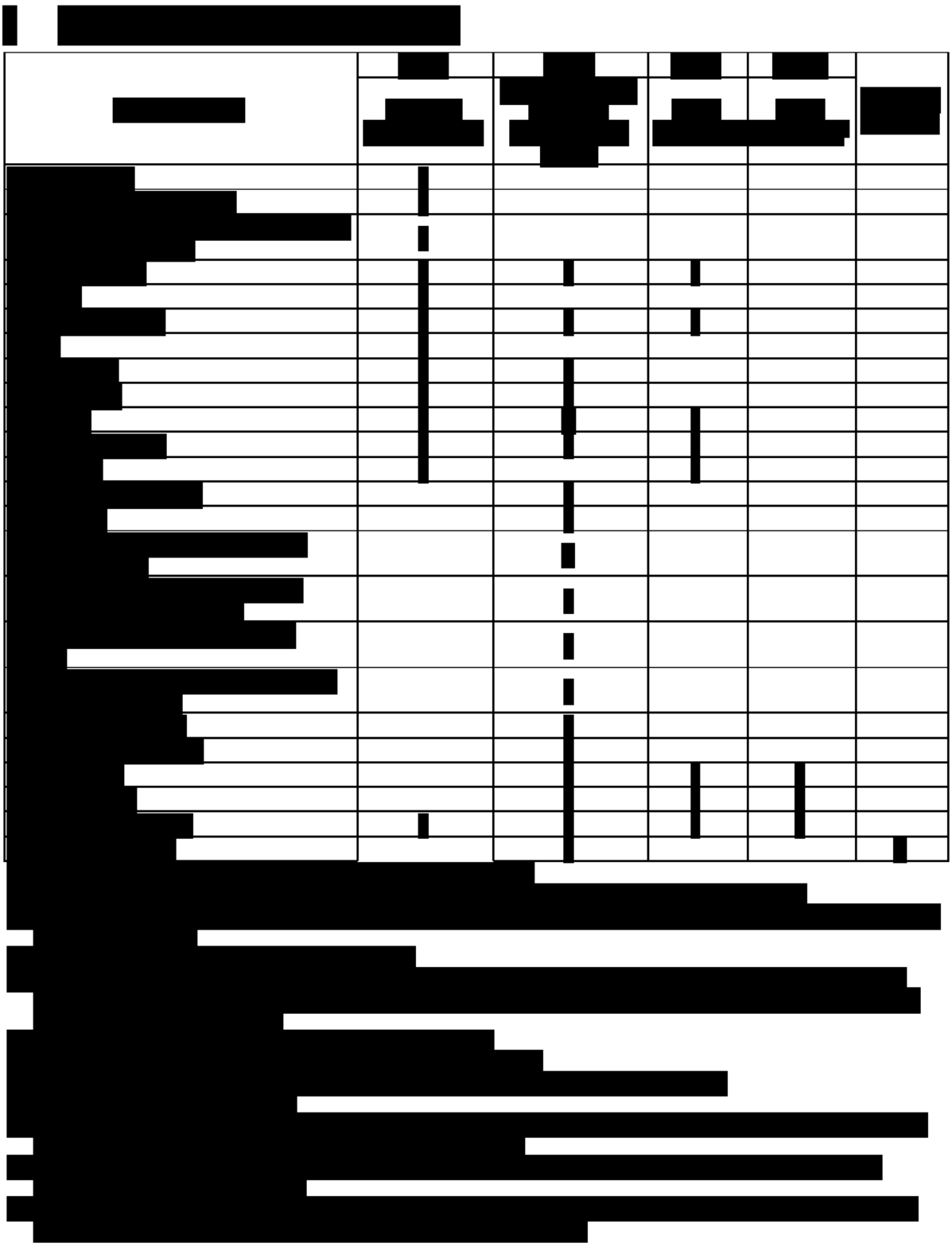
- Incidence rates of treatment-emergent AEs (TEAEs), SAEs, and Adverse Device Effects (ADEs), and changes in clinical laboratory values, vital signs, physical examination, concomitant medications and ECG through Visit 4.

Pharmacokinetics:

- Primary plasma pharmacokinetic (PK) parameters for OTL38, including systemic clearance (CL), volume of distribution of the central and peripheral compartments (V_c, V_p), and distributional clearance(s) (CL_d), on a population and individual patient level.
- Effects of patient specific covariates (e.g. baseline demographics and laboratory value indicators of renal and hepatic function) upon PK parameters, [redacted]

Statistical Methods	**Analysis of Primary Efficacy Endpoint** The primary analysis of the primary efficacy endpoint (Section 8.2.5.1) 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 patient level False Positive Rate (FPR_p) will be analyzed descriptively, providing the point estimate and the two-sided 95% Wilson (score) confidence interval. [redacted] **Analysis of Safety** For all safety assessments, the baseline value will be the last non-missing value recorded for a particular safety parameter before exposure to study drug. In general, the analysis of safety will be descriptive. **Sample Size Estimation** [redacted]

	[redacted]



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List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AEL	Accessible Emission Limits
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FITC	Fluorescein isothiocyanate
FNR	False Negative Rate
FPR	False Positive Rate
FR	Folate Receptor
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MIL	Miliary disease
mITT	Modified Intent-to-Treat
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
TPR	True Positive Rate
ULN	Upper limit of the normal range
WHO	World Health Organization

3 BACKGROUND INFORMATION

3.1 Background

Ovarian cancer is the twelfth leading cause of cancer death in the United States. Based on data from SEER 18 2006-2012, the overall five-year survival rate is 46.2% and for distant and unstaged disease it is only 24-28% (SEER 2016, Kosary 2007). The standard management of primary ovarian cancer is optimal cytoreductive surgery (usually defined as reduction of residual disease to less than 1 to 2 cm) followed by chemotherapy (Al Rawahi 2013). Experts are advocating complete cytoreductive surgery for tumor debulking as it results in better overall survival than optimal cytoreduction (Shih 2010). Although tumor debulking surgery is the cornerstone of current treatment in patients, the lesions can be diffuse and numerous, of various sizes, and often not readily visible in the surgical field, leading to varying rates of optimal cytoreduction among surgeons (Ibeanu 2010). This is an important factor in the poor prognosis for patients with advanced ovarian cancer. Tumor-specific intraoperative fluorescence imaging may improve staging and debulking efforts in cytoreductive surgery.

3.2 Rationale

Over 90% of ovarian epithelial cancers express folate receptor (FR), a folate binding protein, making this receptor an ideal target for marking most ovarian cancers (Markert 2008, Parker 2005, Ross 1994, Toffoli 1998, Weitman 1992). This also makes FR an ideal target for intraoperative imaging of this cancer, facilitating cytoreduction, and potentially improving outcomes in these patients (Kalli 2008). Chemotherapy does not appear to affect FR expression in ovarian cancer specimens as examined by immunohistochemistry (Crane 2012), so prior treatment is unlikely to affect utility of FRα ligands as imaging agents. Since FRα is normally expressed only in the proximal tubules of the kidneys and in the choroidal plexus, uptake of OTL-0038 in the kidneys is possible. However, the fluorescence signal in the kidneys is expected to be significantly lower than the tumor tissues (Ross 1994). A fluorescent probe targeting FR, Folate-FITC (fluorescein isothiocyanate), has been investigated for use in patients with ovarian cancer (van Dam 2011).

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 FRα will retain folate and any fluorescent labeled folate conjugate and internalize this (Leamon 1993). On Target Laboratories, Inc. has developed OTL0038, a folate analog ligand conjugated with an indole cyanine-like green dye as a tumor-imaging agent in patients with tumors that overexpress FRα. [redacted]

[redacted]

3.3 Investigational Product

The resulting imaging agent, OTL0038 (also known as OTL-0038 or OTL-038), 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 were conducted using 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 intra-operative imaging agent. [redacted]

The data from a Phase 1a study in healthy volunteers supports the safety of OTL38 Injection [redacted]

Recent results from a Phase 2 study demonstrated that OTL38 injection was safe and well-tolerated in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, including interval debulking. [redacted]

Please refer to the Investigator's Brochure for more detail 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 ovarian cancer imaging are:

- Improved staging of the tumor
- Removal of more lesions
- Added assurance of clean margins to excised tumors.

In a preliminary study by van Dam et al (2011), significantly more lesions were detected by surgeons using Folate-FITC than with visual observation alone (34 vs. 7; $p < 0.001$). Lesions as small as 1 mm could be detected and removed. This resulted in better staging of patients as more lesions could be visualized but, more importantly, it resulted in greater tumor debulking. Since the degree of tumor removal directly affects the prognosis, this was a large potential benefit. This would need to be studied with OTL38. Use of OTL38 would not change the surgeon's option to remove additional tissue because of impressions based on experience, visualization, or tactile senses. The smallest detectable tumor using OTL38 in the phase 2 study [redacted] in volume.

4 STUDY OBJECTIVES

4.1 Primary

- To confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery

4.2 Secondary

- To estimate the proportion of folate positive ovarian cancer patients in whom all lesions, without regard to evaluable lesion status, detected by fluorescent light only are histologically negative, the patient level False Positive Rate (FPRp)
- To estimate the Sensitivity and False Positive Rate for OTL38 in combination with fluorescent light with respect to the detection of FR+ ovarian cancer lesions confirmed by [redacted] pathology
- To assess the safety of using OTL38 and [redacted] Imaging System for intraoperative imaging with OTL38

4.3 Exploratory

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

5 STUDY DESIGN

5.1 Overall Investigation Plan

This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery.

All patients participating in the study are expected to receive OTL38 and undergo normal light evaluation; [redacted] All patients will first undergo evaluation by normal light and all suspicious lesions identified under normal white light will be recorded as such. Following normal light assessment, but prior to any surgical removal of lesions or the use of fluorescent light imaging, patients will be randomized to either undergo fluorescent imaging or not. Patients randomized to the no fluorescent imaging group receive the usual standard of care and surgery based on normal light assessment only. Patients randomized to the fluorescent imaging group will undergo assessment with fluorescent light imaging prior to and after surgery. The specific randomized allocation ratio of normal light and fluorescent imaging patients to normal light only patients will remain blinded to the Investigators and their staff.

[redacted]

Efficacy will be assessed for subjects undergoing both normal light and fluorescent light imaging. All subjects exposed to OTL38, regardless of randomized group assignment, will be followed for safety. The study will consist of a screening period of up to 28 days prior to the scheduled surgery, a diagnosis and treatment period (day of surgery; Day 1), and safety assessment visits on Day 7 (+/-4) and Day 28 (+/-4) after surgery. The study database will be frozen when last patient completes the Day 28 assessment (which will be considered the study completion date); AEs/ADEs judged by the Investigator to be at least possibly related to study drug will continue to be reported regardless of how much time has elapsed since the last exposure to study drug. Long-term follow-up data on [redacted] will be collected [redacted] after surgery from available patients.

5.1.1 Study Assessments

The assessments for this study are listed in Section 5.7.

5.1.2 Safety assessment

All AEs deemed to be related to OTL38 and of severity graded as mild, moderate or severe will be monitored. The following definitions of severity will be considered in this determination:

- 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.

Safety assessments will also include changes in labs, vitals, and ECG.

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. Female patients 18 years of age and older
2. Have a primary diagnosis, or at high clinical suspicion, of primary ovarian cancer (of epithelial type), planned for primary surgical cytoreduction, interval debulking, or have recurrent ovarian cancer, and:
   - Who are scheduled to undergo laparotomy for the debulking surgery

   OR

   - Who are scheduled to undergo laparoscopy and pre-authorized to undergo laparotomy for the debulking surgery if cancer is detected on the laparoscopy
3. A negative serum pregnancy test at Screening followed by a negative urine pregnancy test on the day of surgery or day of admission for female patients of childbearing potential
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 for participation in the study 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

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

1. Previous exposure to OTL38
2. Known FR-negative ovarian cancer
3. Planned surgical debulking via laparoscopy or robotic surgery, with no intent of laparotomy
4. Patients with known ovarian cancer miliary disease determined pre-operatively to be inoperable
5. Any medical condition that in the opinion of the investigators could potentially jeopardize the safety of the patient
6. History of anaphylactic reactions
7. History of allergy to any of the components of OTL38, including folic acid
8. Pregnancy or positive pregnancy test
9. Clinically significant abnormalities on the electrocardiogram (ECG)
10. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
11. Impaired renal function defined as eGFR< 50 mL/min/1.73m^2
12. Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin.
13. Known Stage IV ovarian cancer with brain metastases
14. Received an investigational agent in another clinical trial within 30 days prior to surgery
15. Known sensitivity to fluorescent light

5.3 Patient Enrollment

Prior to enrolling patients in the study, Sponsor will require copies of the site's written IRB/IEC approval of the protocol, informed consent forms, and all other applicable material. All patients must provide informed consent before commencement of study-related procedures. All patient who enter the screening period (entry is defined as the point at which the patient signs the informed consent) will receive a unique patient identification number that will be used to identify the patient throughout the clinical study.

The patient identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, even if the patient is rescreened. The patient identification number will not necessarily be the same as the randomization number assigned in the study.

A patient will be considered enrolled when the patient signs the informed consent form and receives the study drug.

5.3.1 Randomization

[redacted] To achieve this safeguard, a blinded randomization of patients to undergo fluorescent imaging or not will occur after normal light assessment, but prior to surgery or fluorescent imaging. The randomization will be generated from a single centralized randomization list. [redacted] The randomization date is to be documented in the patients' medical record and on the enrollment electronic case report form (eCRF).

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 safety assessments during Visits 3 and 4 ([redacted]
- Death
- Other

If a subject is withdrawn at any time, the reason(s) will be recorded on the relevant page of the 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 Study Drug Information and Dosage

5.5.1 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.

5.5.2 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.

5.5.3 Storage and Handling of Test Article

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

[redacted]

5.5.4 Study Drug Administration

OTL38 will be prepared following the Dose Preparation for OTL38 Injection Pharmacy Manual (see Appendix 1). OTL38 will be administered intravenously over approximately 60 minutes. The infusion will be completed at least one hour prior to intraoperative imaging. [redacted]

5.5.5 Camera/Imaging System

The [redacted] imaging systems used in this study are not approved for use with OTL38, and are therefore considered investigational for purposes of this study.

5.5.5.1 Summary of the Camera/Imaging System Requirements

[redacted]

[redacted]

5.5.5.2 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

5.6 Concomitant Medications

5.6.1 Allowed Medications

Necessary supportive measures for optimal medical care will be given throughout the study. Additional care may be administered as indicated by the treating physician and patient's medical need, and after discussion with the medical monitor.

All concomitant medications and supportive therapy administered starting Day 1 prior to the infusion of OTL38 until Visit 4 must be recorded on the appropriate case report form (eCRF).

5.6.2 Prohibited Medications

No other investigational products will be allowed during this study. 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/surgery.

Note that OTL38 should not be mixed with other medicinal products and should not be given simultaneously through the same IV line as another medicine.

[redacted]

5.7 Schedule of Events

5.7.1 Measurement and Evaluations

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

5.7.1.1 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
- Physical examination
- Height and weight

- Concomitant 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

5.7.1.2 Visit 2-Day of Admission (Day 0) or Day of Surgery (Day 1):

- Updated medical history and physical exam
- Concomitant medications assessment
- Urine pregnancy test (for women of childbearing potential)
- [redacted]
- Blood samples for PK assessment are to be drawn at the following timepoints, [redacted]
- AEs recording including during infusion of OTL38
  - During and post-surgery any AEs and ADEs will be recorded.
- Vital signs (temperature, blood pressure, and pulse rate) will be taken at baseline (15 minutes prior to OTL38 infusion), every 15 minutes during infusion (only blood pressure and pulse rate), and then every hour after infusion until surgery is initiated. During and post-surgery these will be recorded per institutional practice.

5.7.1.2.1 Intra-operative Procedures

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

- **FOR ALL PATIENTS UNDERGOING FLUORESCENT IMAGING FOLLOW**

[redacted]

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

[redacted]

[redacted]

5.7.1.3 Visit 3 (Day 7 [± 4]):

- Safety assessments will be scheduled for Day 7 (± 4) on site.
- AEs, ADEs, and concomitant medication information will be recorded.
- Physical exam, ECG, clinical laboratory and vital sign assessments will be performed.

5.7.1.4 Visits 4 (Day 28 [±4]):

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

5.7.1.5 Follow-up [redacted]

- Follow-up clinic visit will be scheduled for [redacted]

5.7.2 Interim Analysis

No interim analysis is planned.

[redacted]

5.7.3 Surgical Reporting Schematic

[redacted]

5.7.4 Post-Surgery Questionnaire

After each surgery, the Investigator will fill out the questionnaire per Appendix 3E.

5.7.5 Pathology Samples

All excised lesions will be processed as outlined in Section 5.7.1.2.1. Please refer to the site Manual for additional details.

5.7.6 Pharmacokinetic Samples

The PK blood samples will be processed to plasma, stored, and shipped appropriately to the indicated bioanalytical laboratory.

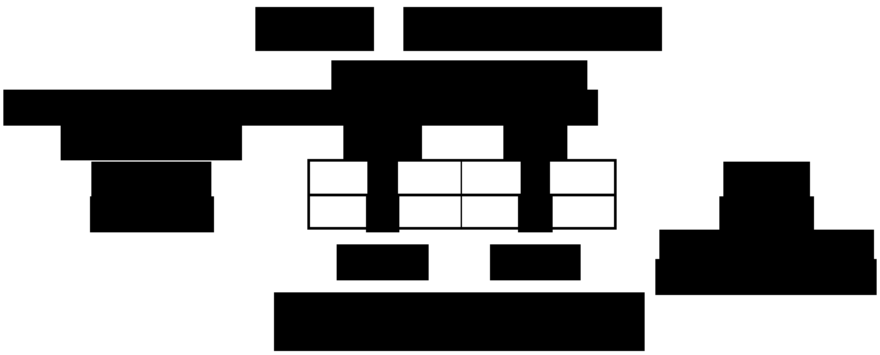
6 STUDY ENDPOINTS

6.1 Primary Efficacy

- Proportion of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by [redacted] pathology (Standard of truth) that was detected using the combination of OTL38 and fluorescent light but not under normal light or palpation. [redacted]

6.2 Secondary Efficacy

- False Positive Rate at the patient level (FPRp) [redacted]
- Sensitivity or True Positive Rate (TPR) for OTL38 in combination with fluorescent light, [redacted]
- False positive rate (FPR) for OTL38 in combination with fluorescent light, for the purpose of this protocol, [redacted]



6.3 Exploratory Efficacy

- [redacted]

[redacted]

6.4 Safety

- Incidence rates of treatment-emergent AEs (TEAEs), SAEs, and Adverse Device Effects (ADEs), and changes in clinical laboratory values, vital signs, physical examination, concomitant medications and ECG through Visit 4.

6.5 Pharmacokinetics

- Primary plasma pharmacokinetic (PK) parameters for OTL38, including systemic clearance (CL), volume of distribution of the central and peripheral compartments (V_c, V_p), and distributional clearance(s) (CL_d), on a population and individual patient level.
- Effects of patient specific covariates (e.g. baseline demographics and laboratory value indicators of renal and hepatic function) upon PK parameters, reported as coefficients demonstrating significance at the alpha level of 0.05.

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.

An adverse device effect (ADE) is defined as any untoward and unintended response to a medical device, in this study, the camera/imaging system. This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, as well as any adverse 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.

A suspected ADE is a subset of all ADEs for which there is a reasonable possibility (ie, 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.

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)]

7.2 Reporting of Adverse Events

7.2.1 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 (including ADEs) 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 (including ADEs) beginning 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 (including ADEs) 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 (including ADEs) 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.

7.2.2 Laboratory Abnormalities

To the extent possible, all 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 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 and interventions 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.

7.2.3 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 7.5

below. 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 AEs must be submitted to the IRB/EC in an annual report.

7.2.4 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 3 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.

7.2.5 Disease Progression

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

7.2.6 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.

7.3 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

7.4 Classification of Adverse Events by Relationship to Study Drug Administration

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

Definitely 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

Probably Related: An adverse event that has a timely relationship to the administration of the study drug and follows a known pattern of response, but for which a potential alternative cause may be present

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

7.5 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

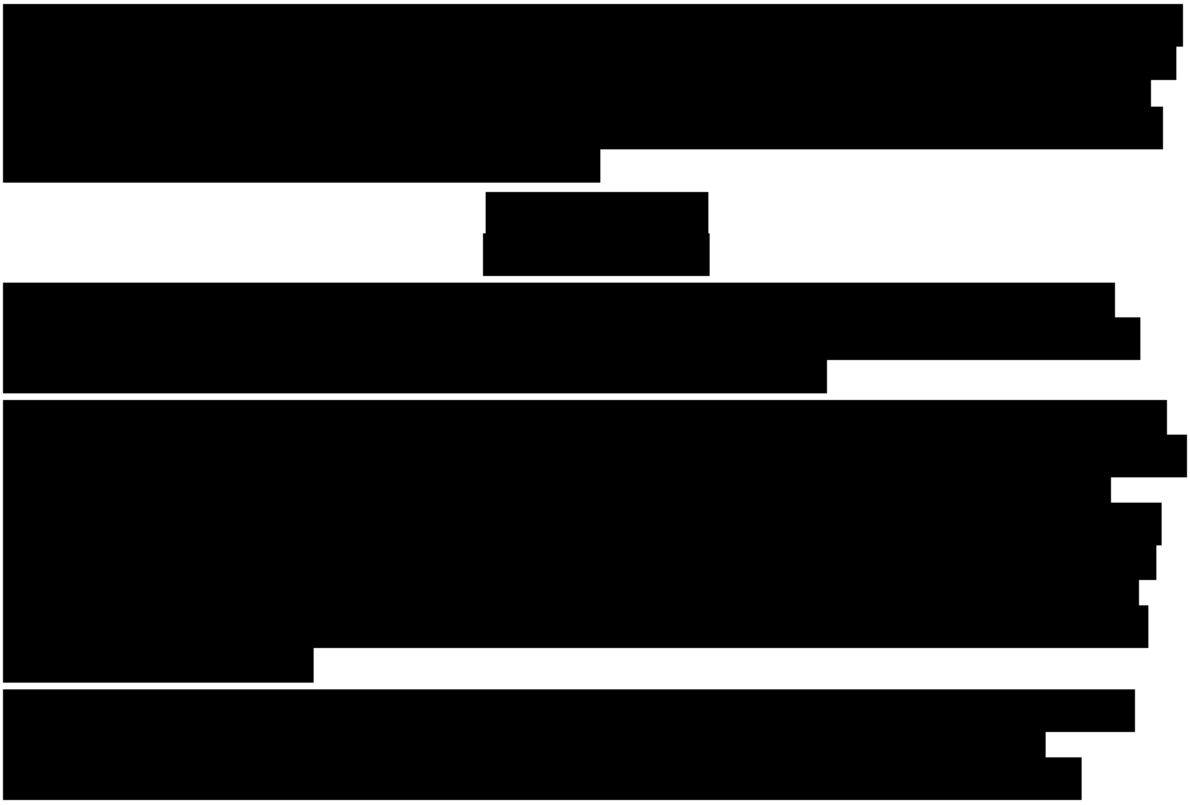
8.1 Data Recording and CRF Processing

With the exception of Pre-Fluorescence Surgical Plans and Surgical Reporting Schematics that will be paper-based, site personnel will be responsible for entering all other data into the Electronic Data Capture (EDC) system, that 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.

8.2 Statistical Methods

This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery. The primary objective of the study is to confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian.

8.2.1 Sample Size



[redacted]

8.2.2 Analysis Sets

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

Full Analysis Set (FAS): The FAS for the primary analysis of the primary endpoint will include subjects exposed to OTL38 and randomized to undergo fluorescent imaging (OTL38+Imaging) who:

- Were evaluated under both normal light and fluorescent light imaging, and
- Had [redacted] pathology and histology confirmation (positive for FR+ Ovarian Cancer) for at least one lesion detected under normal light or fluorescent light imaging

[redacted]

Per Protocol Analysis Set (PPAS): The per protocol analysis set will include all patients meeting the FAS criteria in addition the following criteria:

- Meeting all the inclusion and none of the exclusion criteria
- Having no major protocol deviations

[redacted]

Safety Analysis Set (SAS): The safety analysis set will include all patients exposed to OTL38.

[redacted]

Pharmacokinetic Analysis Set: Every patient receiving a full dose of OTL038 and with one or more measurable drug-plasma concentrations will be included in the PK Analysis Set.

8.2.3 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: < 70 Yrs. Vs. ≥ 70 Yrs.
- Race/Ethnicity
- Study Center

[redacted]

8.2.4 Subject Demographics, Baseline Disease Status, and Disposition

Descriptive statistics for subject demographics, baseline disease status, and subject disposition will be provided. Demographics will be grouped by subjects exposed to OTL38, subjects exposed to OTL38 and randomized to not undergo fluorescent light imaging (normal light only), subjects exposed to OTL38 and randomized to undergo fluorescent light imaging (normal light plus fluorescent light imaging), and overall randomized groups. If all subjects exposed to OTL38 are subsequently randomized, the separate category for subjects exposed to OTL38 may be omitted.

8.2.5 Efficacy Evaluations

8.2.5.1 Primary Analysis for the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be a one-sample test for a proportion via an exact binomial test using a two-tailed alpha level of 0.05. [redacted]

8.2.5.2 Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity analyses for the primary efficacy endpoint will be conducted separately for the Per-Protocol analysis sets. [redacted]

8.2.5.3 Analytic Methods for Secondary Efficacy Endpoints

The patient level False Positive Rate (FPR_p) will be analyzed descriptively, providing the point estimate and the two-sided 95% Wilson (score) confidence interval. [redacted]

8.2.5.4 Analytic Methods for Other Endpoints

Sensitivities, FPRs, PPVs and inoperability rates for FR+ with ovarian cancer and other disease+/test+ configurations will be estimated following similar analytic approaches to that outlined above for the secondary efficacy endpoints. The FAS will be used for these analyses, but will be modified for the lesion type requirement as appropriate, without regard to the evaluable status of the lesions.

For other endpoints reflecting the proportion of subjects with at least one additional lesion detected by OTL38 in combination with fluorescent light not detected by normal light, but for other cell types and FR outcomes, the point estimates and exact 95% CIs for the observed proportions will be provided. [redacted]

Other endpoints estimating the mean number of additional evaluable fluorescent light positive lesions (of a specific type) not detected by normal light, will be estimated [redacted] The point estimate for the average number of additional lesions will be provided along with the 95% CIs.

[redacted]

Descriptive summary statistics for [redacted] pre-surgery (baseline), post-surgery, and the change from pre-surgery will be calculated along with the percent change. In addition, the number and percent of patients whose post-surgery [redacted] have increased, decreased, or remained the same as pre-surgery levels will also be provided. This analysis will use all patients with non-missing [redacted]

8.2.6 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. For all safety assessments, the baseline value will be the last non-missing value recorded for a particular safety parameter before exposure to study drug. 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.

8.2.6.1 Adverse Events

Adverse events occurring prior to exposure to OTL38 administration will be provided 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 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 potential ADEs will also be provided.

8.2.6.2 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. 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.

8.2.6.3 Pharmacokinetics

The pharmacokinetics of OTL38 will be estimated by fitting compartmental pharmacokinetic models to the serial plasma concentration-time (Ct) data using established methods including maximum likelihood parameter estimation and nonlinear mixed-effects (NLME) modeling approaches, with the patient serving as the random effect. Various structural PK and error models will be fit to data using a qualified, standard software package. Primary PK parameters will be estimated at the population level and for individual patients as post-hoc empirical Bayesian estimates (EBEs). The actual primary parameters may vary depending on the supported model, but are likely to include systemic clearance (CL), volumes of distribution of the central and peripheral compartment(s) (V_c, V_p), distributional clearance (CL_d), or derivatives thereof. Inter-patient variability in select PK parameters will be assessed as part of the model, as will the residual error. Secondary parameters may include, but are not limited to: model predicted maximum concentration (C_{max}), time of C_{max} (T_{max}), area under the concentration-time curve (AUC) to the last time point (AUC_{last}) and to infinity (AUC_{inf}), and the terminal elimination half-

life ($T_{1/2}$). The model predicted Ct profiles and observed Ct data will be presented as figures for the population and individual level. Individual primary EBE and secondary parameters will be presented as listings at the patient level.

Potential covariates explaining inter-subject PK variability, and their influence upon PK parameters, will be initially screened using a two-stage approach with standard parametric statistical tests on the individual patient EBEs, focusing on CL. Covariates of interest will include baseline demographic values (e.g. height, weight, age, BSA, BMI, race), and laboratory values predictive of renal or hepatic function (e.g. BUN, creatinine, calculated creatinine clearance or GFR, AST, ALT, alkaline phosphatase, albumin, and total bilirubin). If warranted, a single stage approach with direct incorporation of covariates into the NLME PK model may be undertaken using a forward addition - backward deletion method at an alpha level of 0.05.

The final model PK parameter estimates, and any bootstrapped results, will be reported as a table, including the estimates, their standard errors, or confidence intervals. The covariate coefficient estimates, their standard errors, and the associated P values for those significant at the alpha level of 0.05 will be tabulated. Relationships between covariates and PK parameters will be graphically presented as figures. Additional details will be found in the PK analysis plan (PKAP).

8.2.6.4 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.

8.2.6.5 Physical Examination

Physical examination results will be provided in line listings only.

8.2.6.6 Electrocardiogram

Electrocardiogram results will be provided in line listings only.

8.2.6.7 Pathology and Immunohistochemistry

Pathology and immunohistochemistry results will be provided in line listings.

8.2.6.8 Imaging System

Times on and off for the imaging system for each subject will be provided in line listings.

8.2.6.9 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 that started, or were

continuing, during or after administration of the study drug. Prior medications will include all recorded medications that started and 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.

8.3 Handling of Missing Data, Subject Withdrawals, and Treatment Failures

For the primary efficacy endpoint, all subjects included in the FAS will be included in the primary analysis.

For secondary and exploratory efficacy endpoints, patient inclusion for the analysis of a specific endpoint will depend on the lesion type or patient subgroup under specific consideration.

In general, missing safety data will not be imputed with the possible exception of missing or partial dates. Details will be included in the SAP.

8.4 Interim Analyses

No interim analyses are planned. [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 patients must be maintained. Patients will be identified by their initials and an assigned patient number on eCRFs, and other documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the patient (e.g., the signed informed consent document), 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, but also reserves the right to a 30-day window to review the publication for regulatory compliance as well as for protection of its intellectual property.

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 (OTL38) for Intra-operative Imaging of Folate Receptor- Positive Ovarian Cancer", 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 patients.

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

12 REFERENCES

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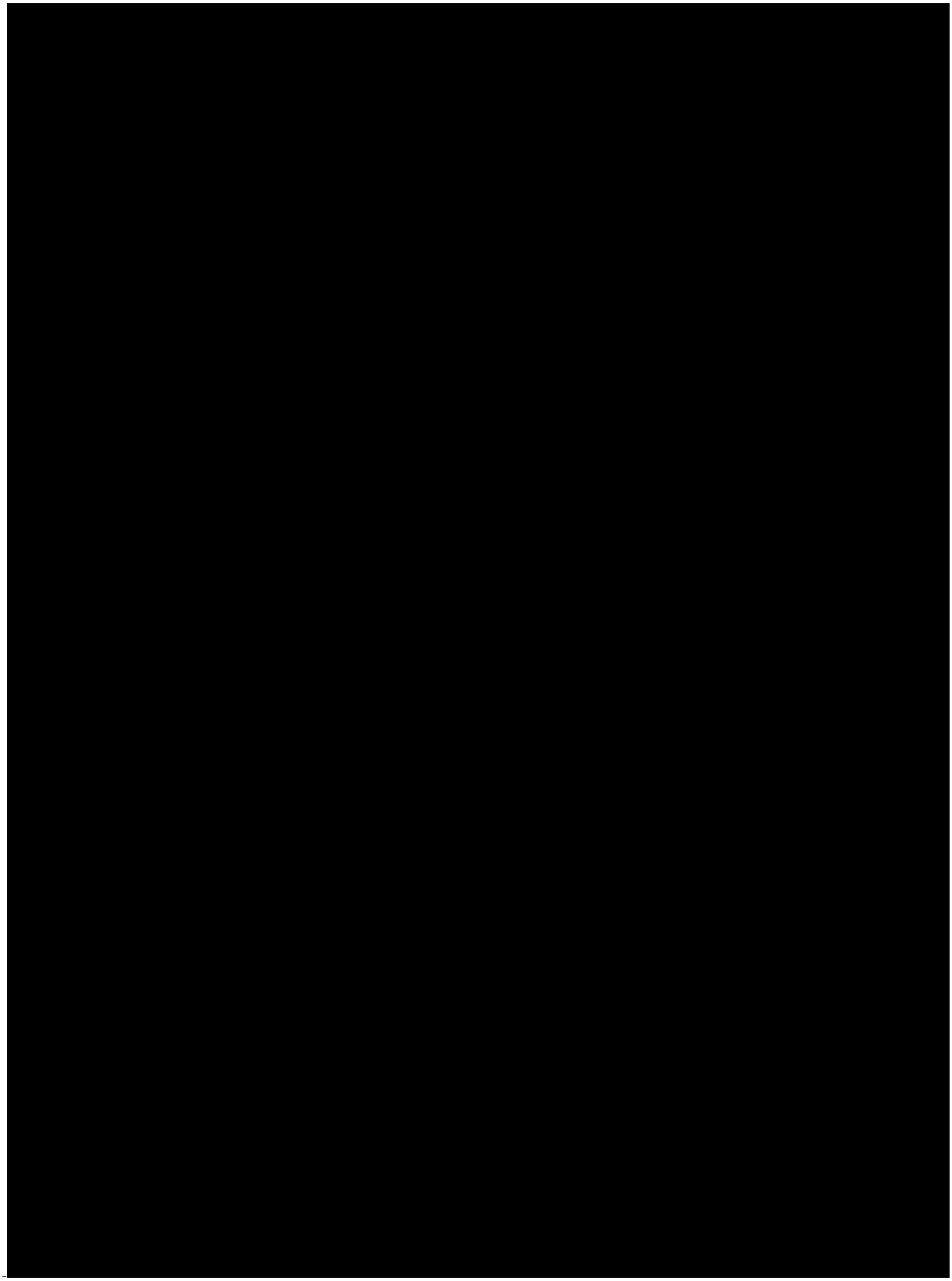
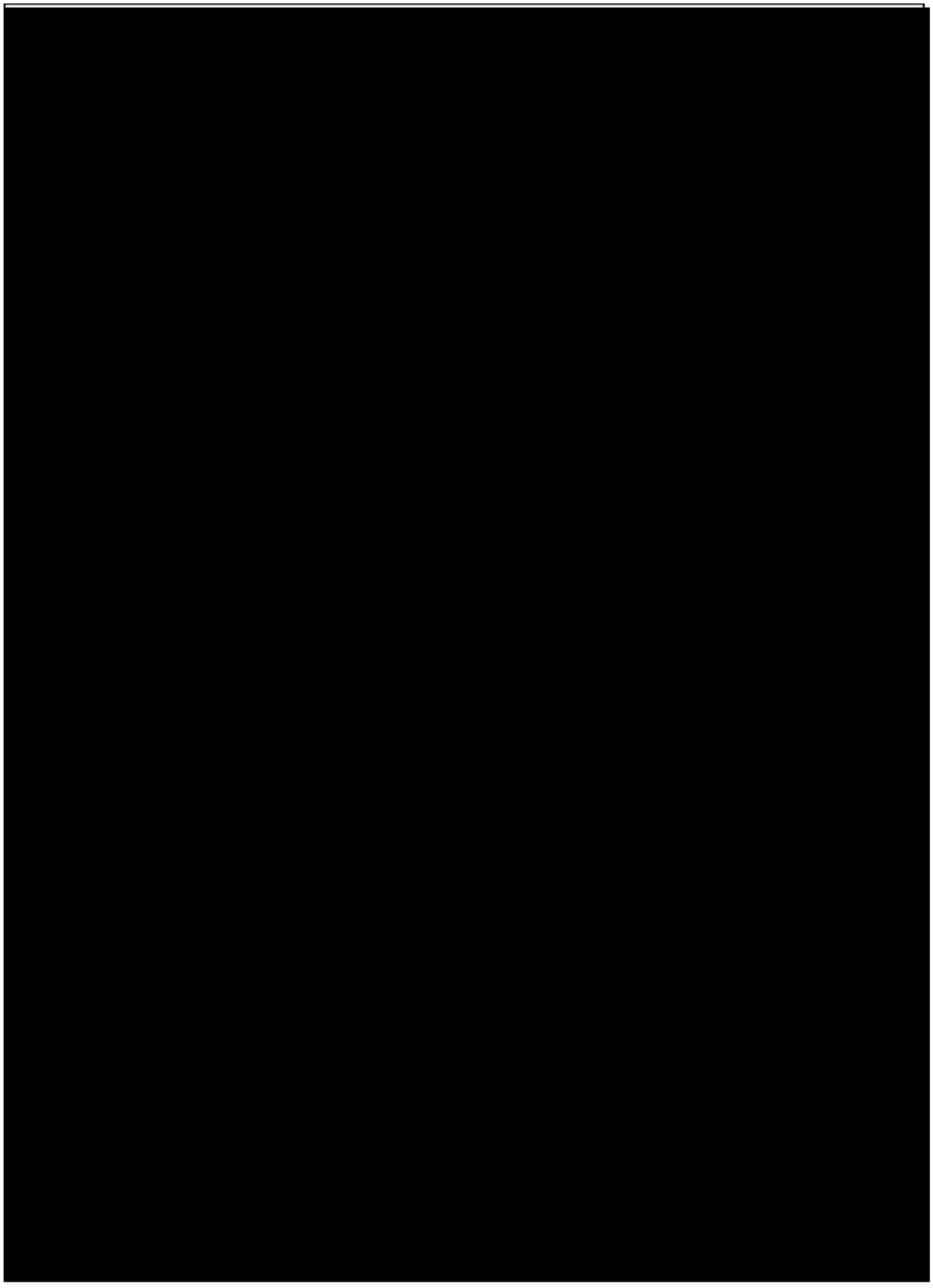
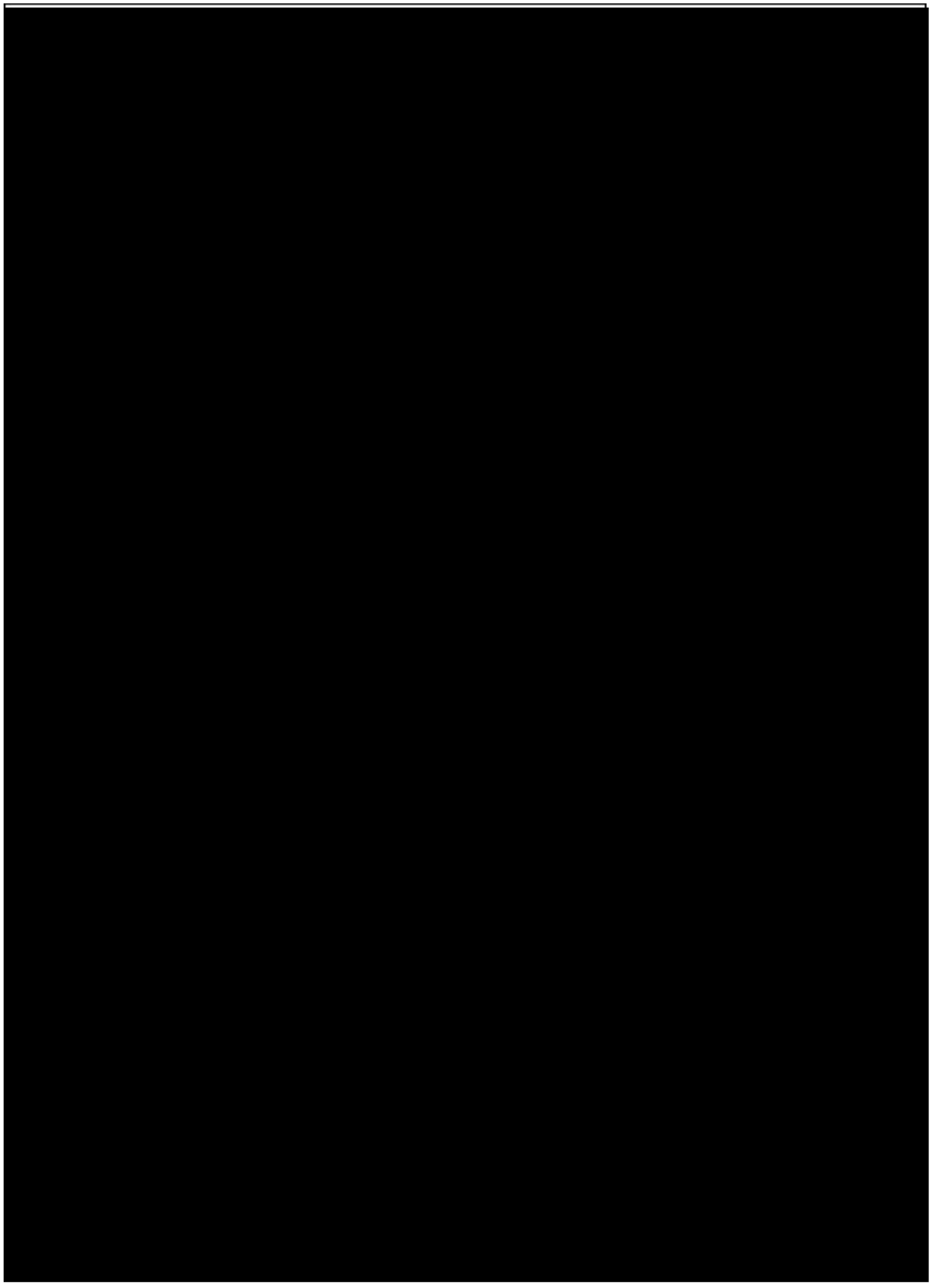
APPENDIX 1. OTL38 DOSE PREPARATION MANUAL







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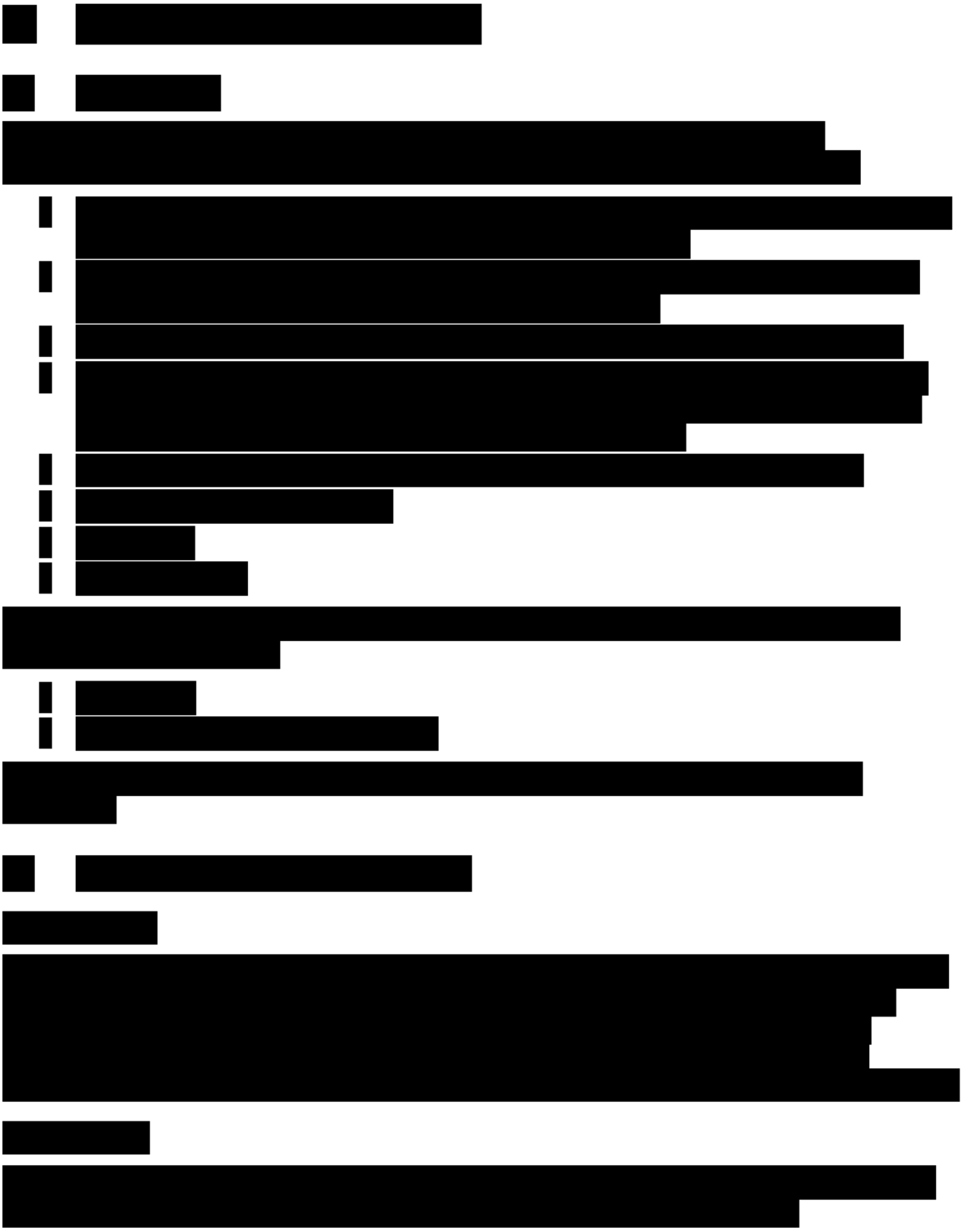

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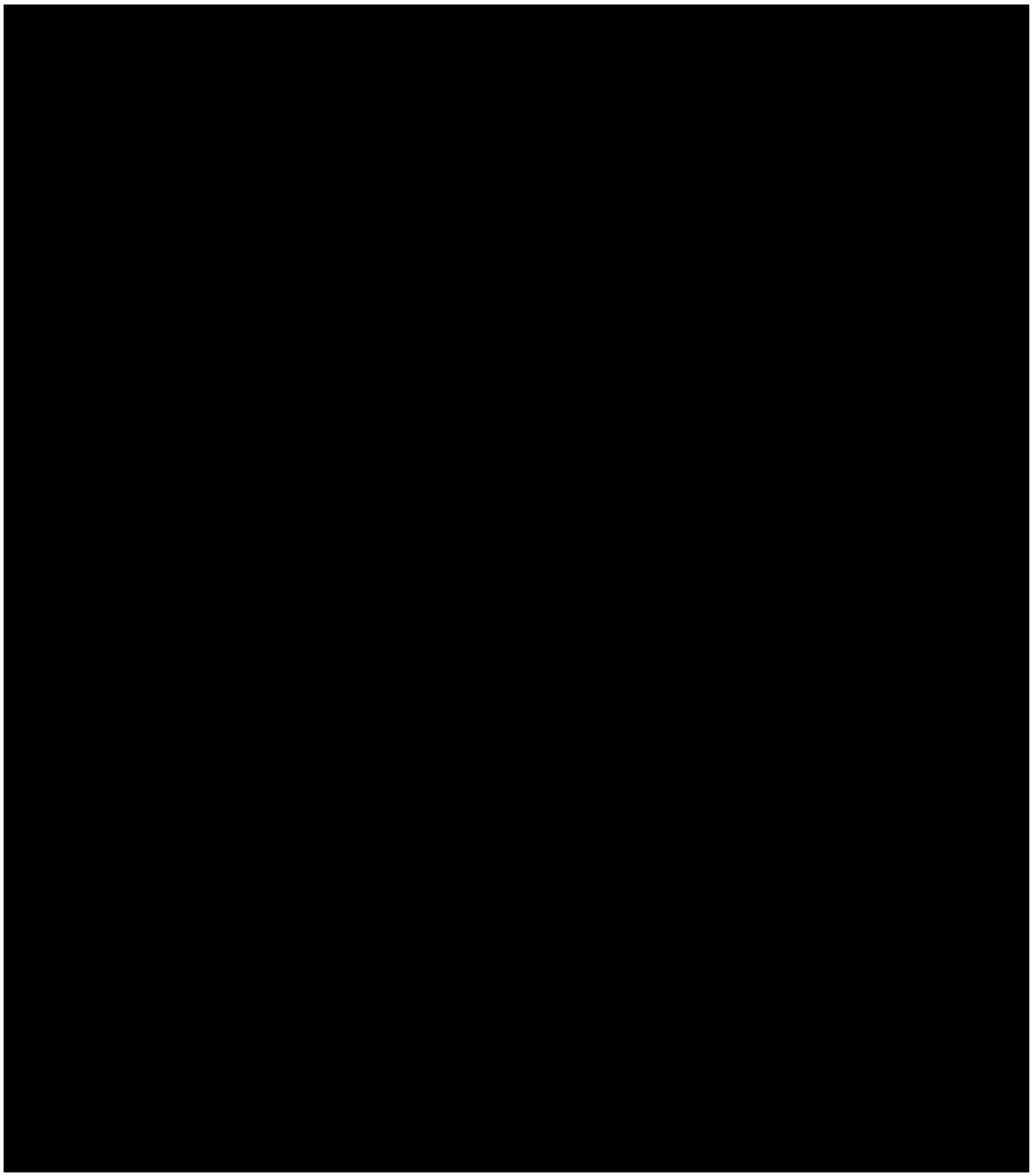

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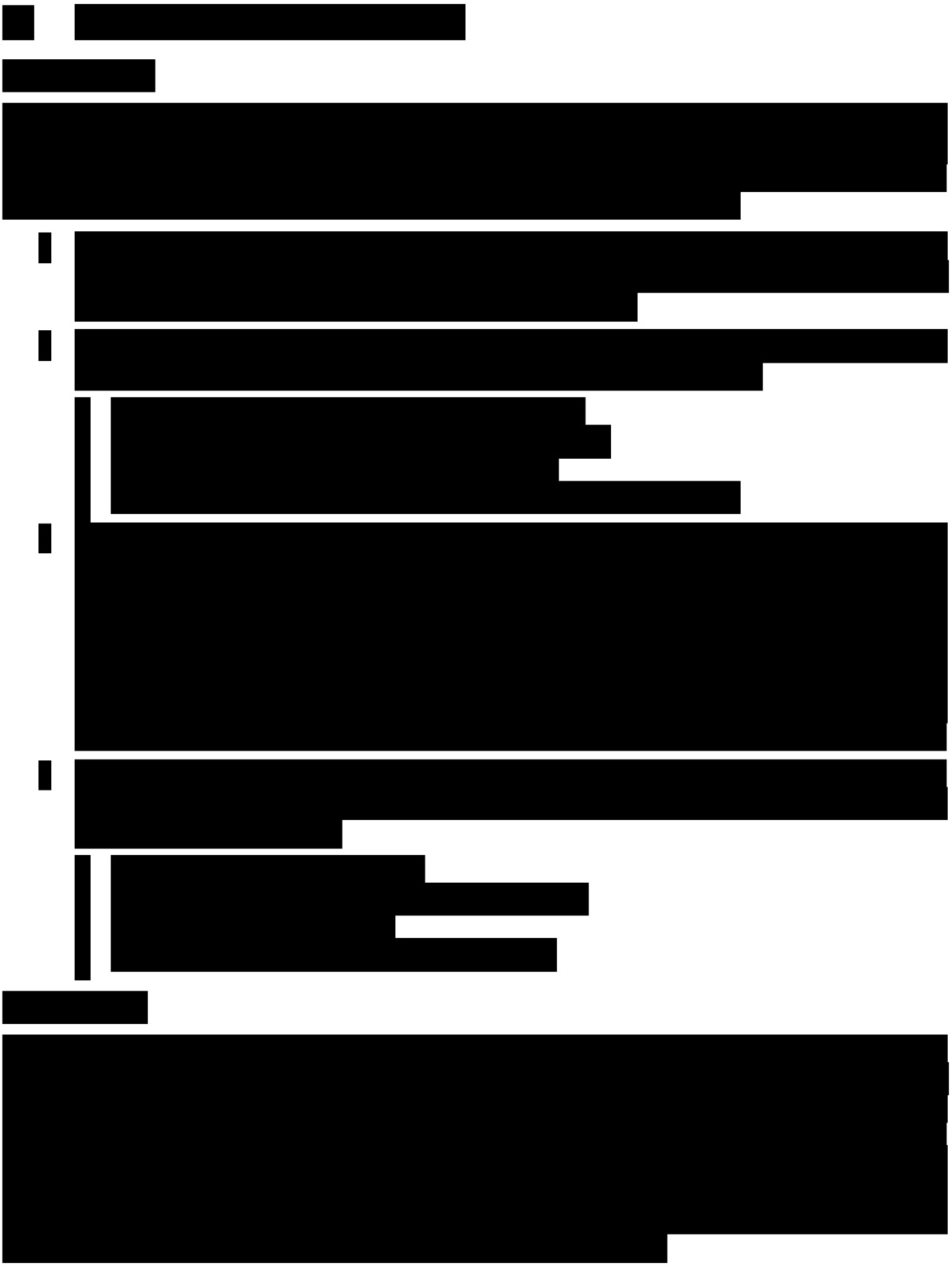

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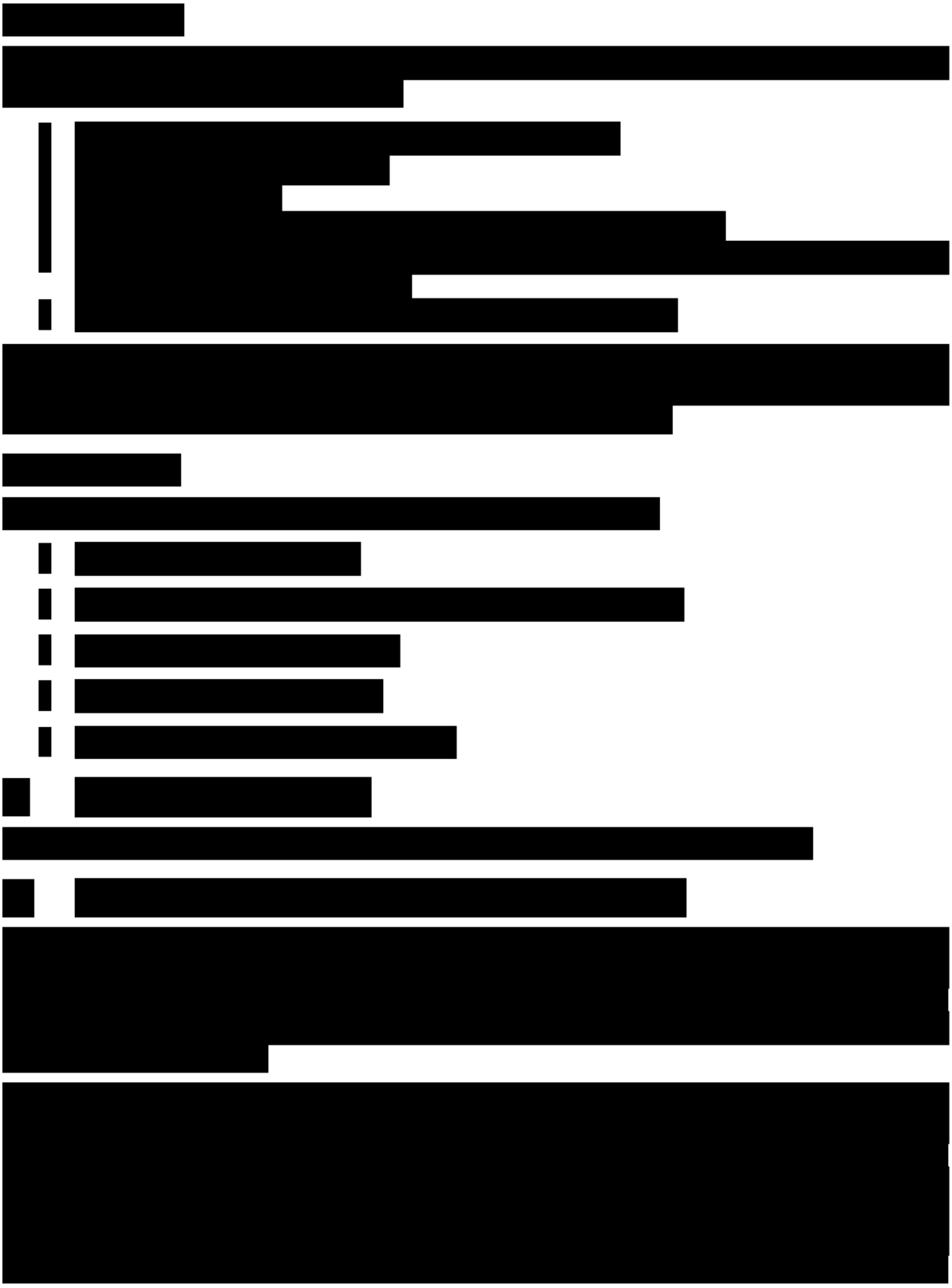

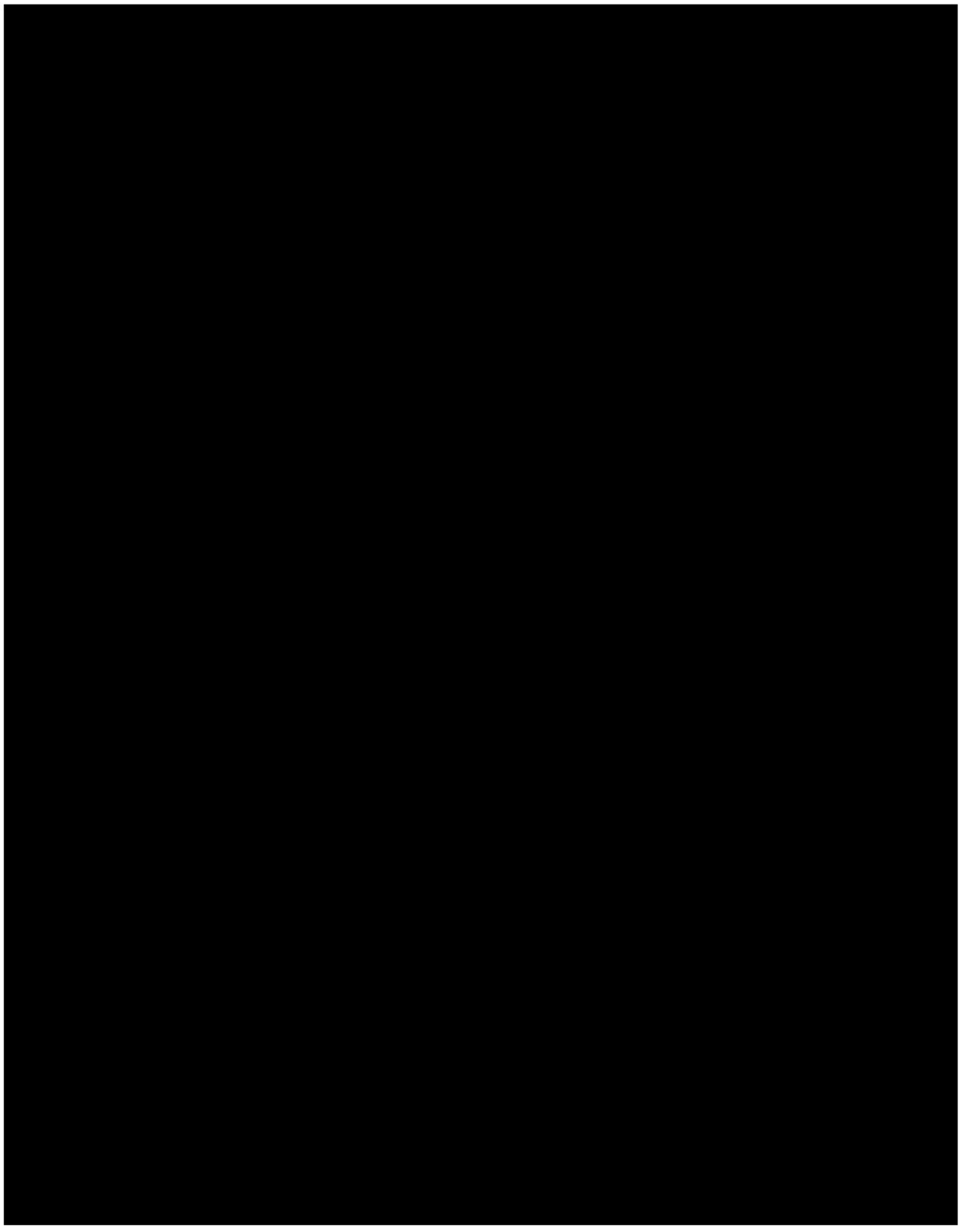

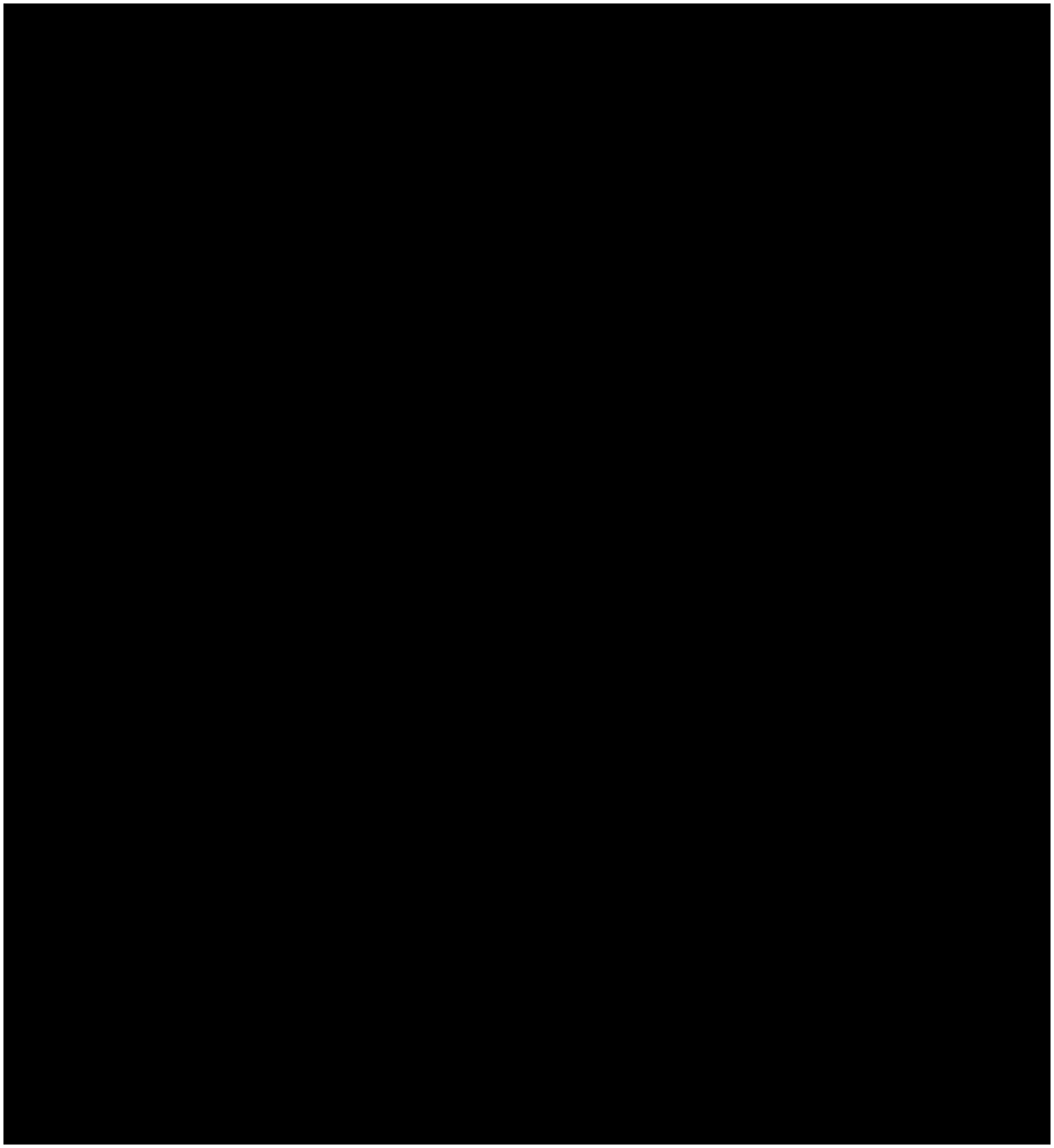

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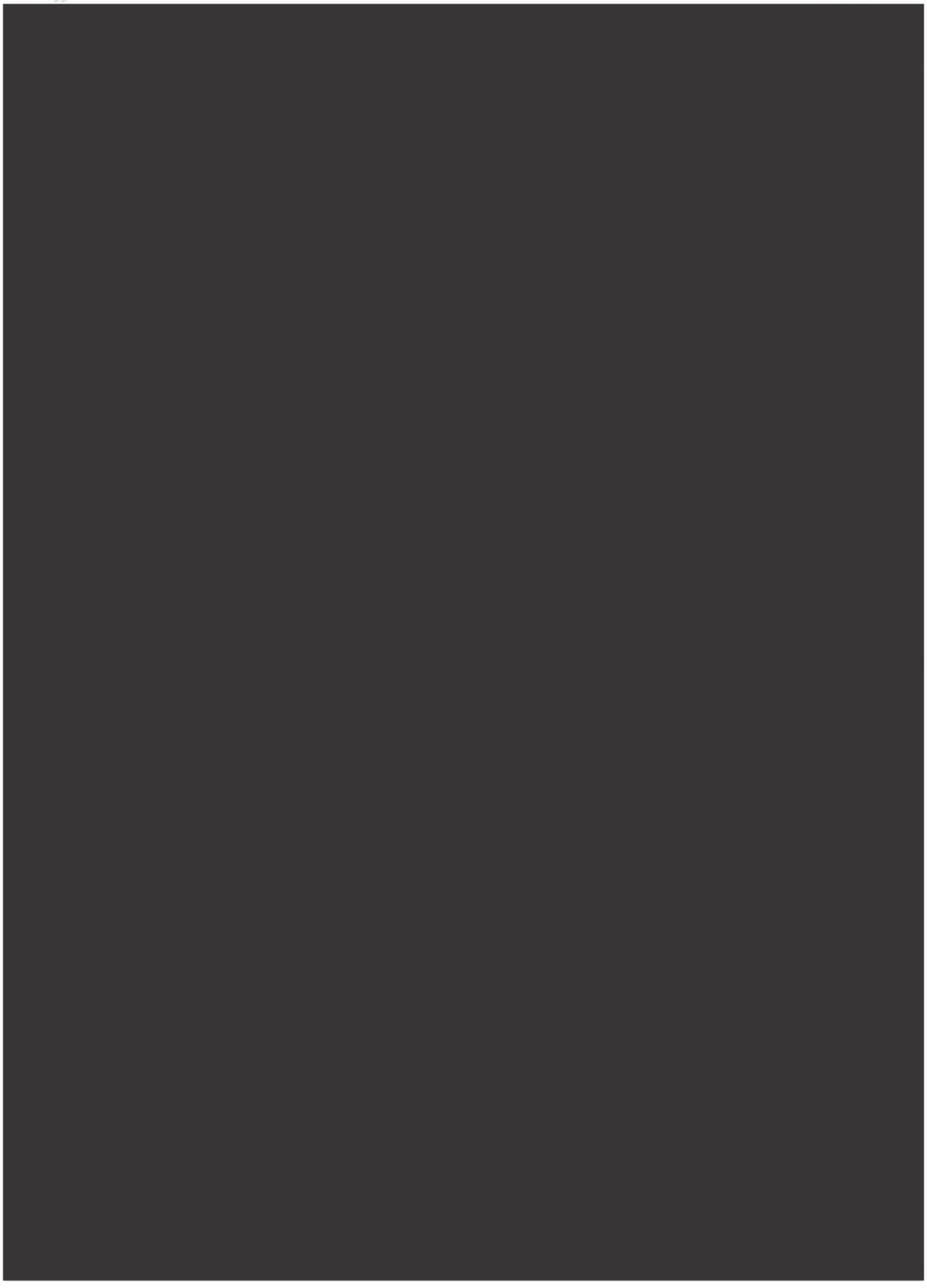

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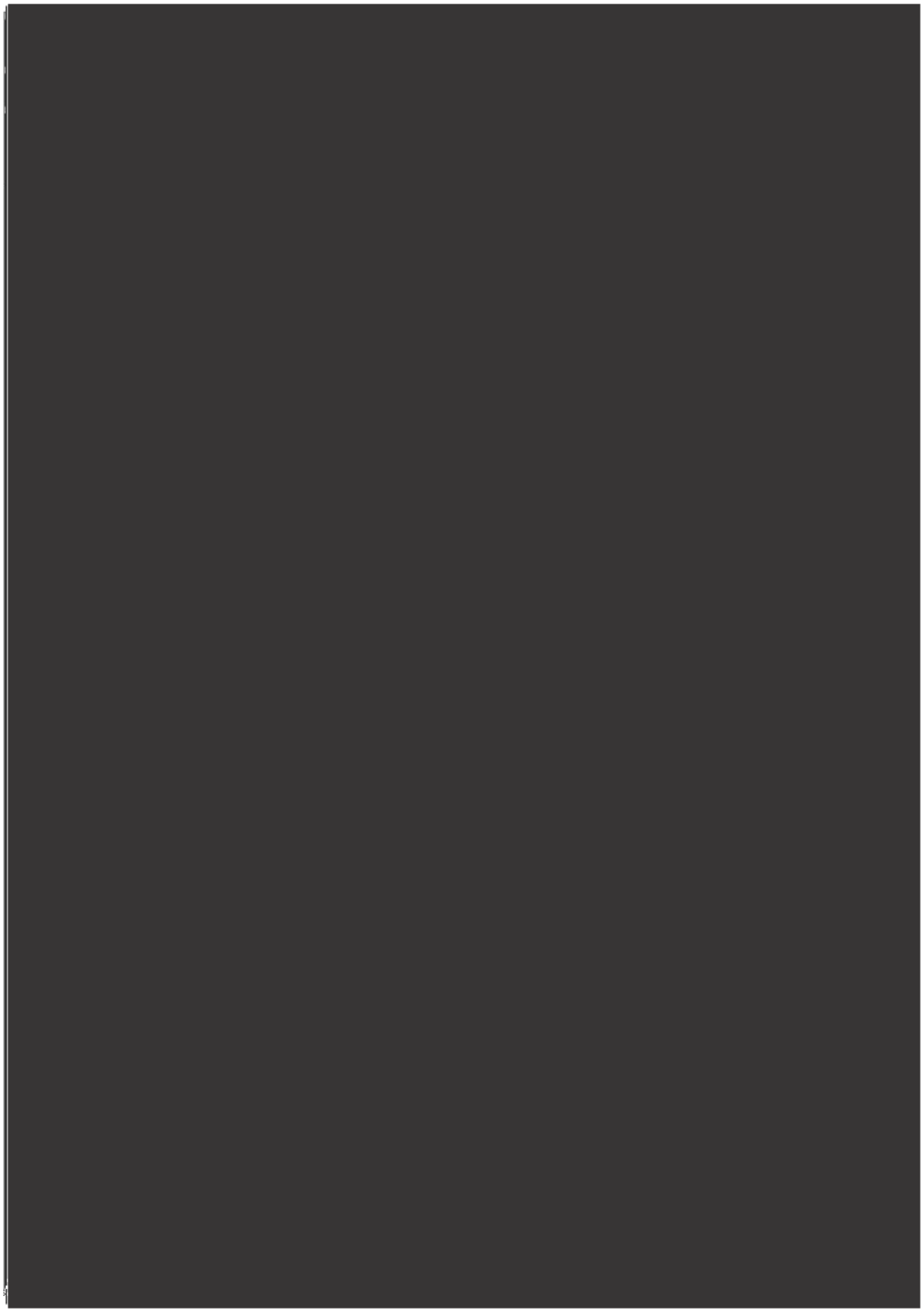

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