CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214907Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118215

MEETING MINUTES

On Target Laboratories, Inc.
Attention: Kimberly Fabrizio
V.P. of Regulatory Affairs and Quality Assurance
1281 Win Hentschel Blvd.
West Lafayette, IN 47906

Dear Ms. Fabrizio:[1]

Please refer to your investigational new drug application (IND) file for Pafolacianine sodium injection (OTL38 Injection).

We also refer to your September 17, 2020, correspondence, received September 17, 2020, requesting a meeting to discuss the content and format of the NDA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1994.

Sincerely,

{See appended electronic signature page}

Sharon Thomas
Senior Program Management Officer
Division of Imaging and Radiation Products
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www fda.gov/RegulatoryInformation/Guidances/default htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: Friday, November 13, 2020, 1:00 p.m. to 2:30 p.m.

Application Number: IND 118215

Product Name: Pafolacianine sodium injection (OTL38 Injection)

Indication: (b) (4)

Sponsor's Name: On Target Laboratories, Inc.

]

Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

FDA ATTENDEES

Division of Imaging and Radiation Medicine (DIRM)

Libero Marzella M.D., Ph.D., Director, (DIRM)
Alex Gorovets, M.D., Deputy Director, (OSM)
Venkata Mattay, M.D., Ph.D., Clinical Team Leader (DIRM)
Joseph Rajendran, M.D., Clinical Reviewer, (DIRM)
Olayinka Dina, Ph.D., Nonclinical Reviewer, (DIRM)
Adebayo Laniyonu, Ph.D., Nonclinical Supervisor, (DIRM)
Sue-Jane Wang, PhD, Statistics Supervisory Deputy Director, (DBI)
Jyoti Zalkikar, PhD, Statistics Secondary Statistical Reviewer, (DBI)
John Lawrence, PhD, Statistics Primary Statistical Reviewer, (DBI)
Chris Galliford, Ph.D., CMC Reviewer, (DNDP-III)
Danae Christodoulou, Ph.D., CMC Supervisor (DNDP-III)
Christy John, Ph.D., Clinical Pharmacology Team Leader, (OCP)
Sharon Thomas, Regulatory Project Manager, (DIRM)
Kyong Kang, PharmD, Chief, Project Manager, (DIRM)
Miriam Dinatale, D.O. FAAFP, Team Leader (DPURM)
Evangela Covert, BSc, Project Manager (DPURM)
Sun, Wenjie, MD, Clinician (DPURM)
Neil Ogden, PhD, Supervisor- Biologist (CDRH)
Kejing Chen, PhD, Reviewer (CDRH)

SPONSOR ATTENDEES:
Kimberly Fabrizio, VP of Regulatory Affairs and Quality Assurance
Tim Biro, Chief Operating Officer
Janus Tanyi, MD – lead principal investigator
Morave Bear, statistician
(b) (4)

1.0 BACKGROUND

On September 17, 2020 On Target requested a Type B Meeting to discuss the format and content of the upcoming New Drug Application. The meeting was granted on September 24, 2020. FDA sent Preliminary Comments to On Target Laboratories, Inc. on November 11, 2020. On Target Laboratories. On November 12, 2020 On Target Laboratories provided a Response for Clarification regarding Questions 10, 14, 15, 20 and the OSI Request, (ATTACHMENT A). On Target confirmed that no further clarification was required on Questions 1-9; 11-13; 16-19; 21-23. The Sponsor's questions are in italics, FDA's responses in bold font and the Meeting Discussion in ***bold italics.***

2.0. DISCUSSION

Device

Question 1:

(b) (4)

Question 2:

It is the intention for the device manufacturers to submit a 510(k) to CDRH to be reviewed in parallel with the NDA that On Target Laboratories (OTL) will submit to CDER. (b) (4) *Will this approach be acceptable to CDRH?*

FDA Response to Question 2:

Please refer to Response to Question 1. (b) (4)

(b) (4)

Chemistry, Manufacturing and Control

Question 4:

The fourth validation lot was intended to confirm that the impurity variability was controlled in the manufacturing process, by transferring the impurity assay testing to the drug product manufacturing partner versus a third-party contract laboratory. On Target believes that data from the fourth lot supports that there is adequate control in the drug product manufacturing process and that the previous variability observed in the impurity profile for pafolacianine sodium injection was linked to the use of the third-party laboratory. The impurity analysis results across all lots manufactured will be included in Appendix 3.2. Does the Division agree that the reported data demonstrates that impurity levels are controlled, and that the analysis of impurities is controlled and supports a commercial manufacturing process?

FDA Response to Question 4:

Without access to batch data from the fourth manufacturing lot, it would be premature to comment on its acceptability. We refer you to our comments in the written response to your recent inquiry regarding manufactured lots that were OOS. We also remind you that all of the supporting CMC information necessary to support your NDA should be included for review at the time of NDA submission, including all stability data.

Question 5:

On Target has followed International Conference for Harmonization (ICH) Q3B (R2) in setting the reporting criteria for impurities to be any impurity (b) (4) *% would be reported. On Target will include the associated chromatograms with all reported impurities in Appendix 3.3.* (b) (4) *continues to be the only known impurity meeting the reporting requirements and therefore has been fully characterized. Does the Division agree the impurities identified and the associated data are adequate to support an NDA?*

FDA Response to Question 5:

This approach appears to be acceptable. However, the adequacy of your analytical methods will be evaluated when analytical data is provided in the NDA. We refer you to ICH Q6A for additional guidance on specifications and analytical methods.

Question 6:

(b) (4) *. Does the Division agree?*

FDA Response to Question 6:

No, we do not agree (b) (4)

Question 7:

The drug substance manufacturer for pafolacianine sodium is (b) (4) *Due to COVID-19 and the recently released FDA temporary guidance on –* ***"Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency",*** *On Target inquired on their ability to host remote health authority inspections in the event the FDA indicated such a PAI was required. The manufacturer confirmed that they are not able to host a remote audit and would work with the* (b) (4) *to comply with FDA requirements. Does the Division agree that this restriction will not impact the review of the NDA?*

FDA Response to Question 7:

We do not expect that lack of capability to host a remote health authority inspection will impact the review of the NDA.

Per the referenced temporary Guidance, we will use additional tools, where available, to determine the need for an inspection and to support the application assessment, such as reviewing a firm's previous compliance history, using information sharing from trusted foreign regulatory partners through mutual recognition and confidentiality agreements, and requesting records "in advance of or in lieu of" facility inspections or voluntarily from facilities and sites.

Nonclinical

Question 8:

On Target believes that the completed pafolacianine sodium nonclinical studies (pharmacology, pharmacokinetics, and toxicology) support the registration requirements and that no further nonclinical studies will be required prior to NDA submission. Does the Division agree?

FDA Response to Question 8:

Yes, we agree. The completed pharmacology, pharmacokinetics, and toxicology studies are sufficient to support the requirements for the your planned pafolacianine NDA submission.

Clinical Pharmacology

Question 9:

On Target does not plan to conduct additional clinical research in renal and/or hepatic impaired patients, since patients with severe impairment would not be candidates for ovarian cancer surgery and pafolacianine sodium injection has been shown to be safe at doses up to and including 0.2 mg/kg. PK data associated with renal and hepatic organ function from the Phase 3 study will be included in the NDA. Does the Division agree with this plan?

FDA Response to Question 9:

Your PK assessment plan and the proposal not to conduct dedicated studies for renal and hepatic impairment appear reasonable; however, the final determination regarding the need for additional clinical studies will be determined at the time of NDA review.

Question 10:

On Target believes that incomplete or slow recovery of [^{14}C]-OTL-0038-related radioactivity in healthy volunteers is to be expected in the Human ADME study. In addition, the plasma and blood radioactivity data suggest limited metabolites in circulation within 2 hr. of the start of dosing. Does the Division agree the Human ADME study is adequate to support an NDA?

FDA Response to Question 10:

We are concerned that only 34.9 ± 6.31% of injected radioactivity was recovered at approximately one month. We recommend that you describe the metabolism and excretion of OTL-038 and its metabolites and the safety margin of metabolites in non-clinical studies in your NDA application.

Meeting Discussion:

On Target stated that a brief summary of the nonclinical research conducted to characterize the M5 metabolite was completed and provided additional clarification on the human ADME document in the clarification response document. A Human ADME study was conducted to further understand the M5 metabolite in humans, especially from a safety exposure perspective and the full clinical study report will be provided in Module 5 of the NDA and summarized in 2.7.1. Does this help clarify the concerns raised by the reviewers in the Preliminary Response document? The Division responded, "yes" and no further discussion was held.

Clinical

Question 11:

In combination with the safety profile and achievement of the primary endpoint in the SPA conducted Phase 3 trial, does the Division agree this data is sufficient to support a marketing application?

FDA Response to Question 11:

We will make that determination at the time of the NDA filing review.

Question 12:

Does the Division agree based on the efficacy and safety data presented in the Phase 2 and Phase 3 programs that the benefit of this adjunct drug outweighs the risk for patients undergoing Ovarian cancer surgery?

FDA Response to Question 12:

This determination will occur at the completion of our review of the NDA.

Question 13:

*On Target plans to submit the Phase 1 Clinical Study Reports ((b) (4) 1321-A and (b) (4) 1321-B) and the Phase 2 Clinical Study (OTL-2014-OTL38-003) as Legacy Study Reports. These studies were all initiated prior to the 2016 guidance. All reports will be submitted in the NDA per the ICH E6 Guidelines.**Error! Bookmark not defined.** Does the Division agree this will be an acceptable submission plan?*

FDA Response to Question 13:

This proposal is acceptable.

Question 14:

The Phase 3 data will be submitted according to the current CDISC standards; however, the Phase 2 study will be submitted as a legacy study with SAS Transport files only. On Target

believes that the efficacy results can adequately be summarized in the 2.7.3 Clinical Summary of Efficacy, based on the Special Protocol Agreement Phase 3 study, the multisite Phase 2 study, and the Phase 1b, and a more extensive Integrated Efficacy Report with an integrated dataset should not be required. Does the Division agree?

FDA Response to Question 14:

Your proposed data submission approach for phase 2 and phase 3 studies is acceptable. However, an integrated summary of efficacy will be required of an NDA submission.

Meeting Discussion:

The Division agreed that provided On Target followed the required content requirements for the Efficacy Summaries especially in regard to summarizing the strengths and weaknesses between the clinical studies as well as examining differences across subgroups such as sex, age, gender. The Division was fine with presenting the Efficacy in the 2.7.3 Summary of Efficacy and noting the additional analysis in the Module 5 ISE. It was confirmed that integrated efficacy datasets will not be expected in Module 5.

Question 15:

The safety profile for pafolacianine sodium injection will be comprised of all clinical studies conducted to date and all ongoing data collected through 31AUG2020. The safety profile of OTL is consistent across all studies in Phase 1, 2 and 3 in both the Ovarian and Lung Cancer studies. There have been no SAEs or Deaths reported that were related to the drug and the reported TEAEs were mild to moderate and resolved. The most common TEAEs reported across the clinical programs will be available in Appendix 5. On Target plans to submit a full summary of safety data in the 2.7.4 Clinical Summary of Safety only and a more extensive Integrated Safety Report with an integrated dataset should not be required. Does the Division agree with this plan?

FDA Response to Question 15:

An integrated summary of safety will be required.

Meeting Discussion:

The Division discussed that they were moving toward stratification of data versus pooling. On Target explained that the pooled integrated safety results would be presented by 2 pooled groups. One pooled group would include the two ovarian studies (Phase 2 and Phase 3), and exclude the lung trial, while the second pooled group would include all three studies. The integrated safety datasets would also allow the selection of individual study data, or other combinations of study data, for further analysis if desired. The Division agreed the Integrated Safety Data Pooling would be an acceptable approach. The Division also agreed that a Simple ISS format could be utilized as they did not want information duplicated across the sections.

Question 16:

On Target has not had any drug or device related Serious Adverse Events or Deaths reported in any US clinical study. Does the Division agree that if we continue to not have any drug or device related SAEs in the US studies that additional safety narratives would not be required in the 2.7.4 Summary of Safety, as all reported safety events will be adequately summarized in the respective clinical study reports for the non-drug related SAEs?

FDA Response to Question 16:

We agree that you do not need to provide safety narratives.

Question 17:

Does the Division agree that the data obtained in the SPA Phase 3 clinical study and the Phase 2 clinical study will be sufficient to support the NDA with an indication of use for adult patients with (b) (4) *ovarian cancer as an adjunct for intraoperative identification of malignant* (b) (4) *lesions* (b) (4)

FDA Response to Question 17:

The indication for use will be determined during the review of the NDA.

Regulatory

Question 18:

On Target plans to include any final designation letters or waivers in Module 1 of the NDA, which were acquired through the IND 118215; however we will not include supportive communications submitted in the IND leading up to the final FDA decisions (i.e. meeting minutes, meeting request, Fast Track Designation requests, etc.). Section 17.3 contains a proposed table of the communications that will be included in the NDA. Does the Division Agree?

FDA Response to Question 18:

This proposal is generally acceptable.

Question 19:

Pafolacianine will be dispensed directly to hospitals and administered by licensed medical staff, and therefore, there is no requirement for label comprehension studies. Does the Division agree?

FDA Response to Question 19:

Your approach seems reasonable. The acceptability of labeling will be a review issue.

Question 20:

Currently, On Target intends to submit the NDA fully (modules 1-5); however, if there is an unexpected delay in the clinical data analysis would the Division agree to allow On Target to submit a rolling submission containing Module 3 and 4 initially?

FDA Response to Question 20:

We would be interested in learning from you about the potential unexpected delay in the clinical data analysis. In general, you can submit a request for a rolling submission. We note that the start of an NDA review time will depend on the completion date of the rolling submission.

Meeting Discussion:

On Target explained that based on the decisions made regarding the previous clarification requests that a rolling submission would not be required and On Target Laboratories could commit to submitting an NDA in December. The FDA thanked On Target for the information regarding the submission plan, and the plan to submit the full NDA in December.

Question 21:

On Target is following the July 2020 FDA Guidance titled "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format." On Target intends to include animal data collected in our nonclinical research studies within the Special Population subheading Pregnancy section as pafolacianine sodium injection should not be administered to pregnant women undergoing ovarian cancer surgery. Does the Division agree that providing the data in the Special Population section of the label is sufficient?

FDA Response to Question 21:

We recommend that if there are concerns regarding use of this product in pregnant women and/or in females of reproductive potential, the human risk statement regarding the use of pafolacianine in pregnancy should be included in 8.1 Pregnancy, Risk Summary, and the details of the embryo-fetal development studies should be described under 8.1, Data-Animal Data. Additionally, depending on the level of concern regarding the embryo-fetal development studies, you should also consider including this information in other sections of labeling (e.g., Warnings and Precautions). We also recommend that you include a review of all available published literature regarding pafolacianine use in pregnant and lactating women and the effects of pafolacianine on male and female fertility (include search parameters and a copy of each reference publication) as well as any reports of exposure of pafolacianine to pregnant and lactating women during clinical development to support your proposed labeling for use of pafolacianine in pregnant and lactating patients (as described in the FDA Guidance "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format").

Question 22:

On Target collected PK data on all subjects in our Phase 3 study and intends to conduct a population PK analysis of the data pertaining to mild and moderate renal and hepatic impairment. Patients with severe organ impairment would not be candidates for ovarian cancer surgery and were therefore excluded from the Phase 3 study. On Target intends to include this PK analysis in the Pharmacokinetic Section of the label. Does the Division agree this is sufficient providing the analysis supports there are no renal or hepatic safety concerns or dosing adjustments with administration of the drug?

FDA Response to Question 22:

Your proposed strategy appears reasonable. However, as stated in our response to Question 10, the need for additional studies and the need for dosing adjustment recommendations, or lack thereof, will be determined at the time of NDA review.

Question 23:

On Target intends to submit draft and annotated proposed labeling in Module 1 of the NDA. Does the Division agree that the Structured Product Labeling submission can be submitted after final label negotiations are completed and not required in the initial NDA?

FDA Response to Question 23:

Yes, we agree.

3.0 IMPORTANT MEETING INFORMATION:

THE CONTENT OF A COMPLETE APPLICATION

The application will be subject to "the Program" under PDUFA VI.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Information on the Program is available at FDA.gov.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30,

2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along

with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[4]

Pre-Meeting Communications:

FDA provided an email response prior to the meeting on November 13, 2020 to this request for clarification as follows:

- **The answer to the sponsor's question is a simple "yes" with the recommendation that the subject data listings be bookmarked by: study (highest level), site (next highest), subject (low level), and data type (lowest level; efficacy data, adverse event data, protocol violations, treatment assignment, subject discontinuations, and concomitant medication use). The data types need not be listed in any specific order, as long as all data in each type are grouped together. All sponsor proposals are acceptable.**

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/RegulatoryInformation/Guidances/default htm.
[3] https://www fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www fda.gov/media/85061/download

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[5]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[6] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we

[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] https://www fda.gov/media/88173/download
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default htm

encourage you to send us samples for validation following the instructions at FDA.gov.[8] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[9] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[10] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[11]

NEW CHEMICAL ENTITY (NCE)

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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[8] https://www fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] https://www.fda.gov/media/88173/download
[10] https://www fda.gov/ForIndustry/DataStandards/StudyDataStandards/default htm
[11] https://www fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[12] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[13]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the

[12] https://www fda.gov/media/84223/download
[13] https://www fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[14] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[15]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master**

14 http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default htm
15 https://www fda.gov/media/109533/download

File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[16]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[17]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol

16 http://www.fda.gov/ectd
17 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- There were no additional issues identified that required further discussion.

5.0 ACTION ITEMS

- Sponsor to submit the NDA when ready.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor's slides (ATTACHMENT A)

(b) (4)

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON P THOMAS
12/01/2020 07:34:32 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118215

MEETING MINUTES

On Target Laboratories, LLC
Attention: Raymond C. Lamy, M.S.
Regulatory Consultant for On Target Laboratories, LLC
372 W. Dominguez Road
Palm Springs, CA 92262

Dear Mr. Lamy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTL38 Injection.

We also refer to the meeting between representatives of your firm and the FDA on October 11, 2016. The purpose of the meeting was to review the proposed Phase 3 clinical study protocol and statistical analysis plan in preparation for a Special Protocol Assessment (SPA) submission and in addition to specifically discuss the camera imaging system.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Modupe Fagbami
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Others (EOP2 -Device and Pre SPA)
Meeting Date and Time:	October 11, 2016 at 3:00 pm
Meeting Location:	WO, Building 22, Room 1315
Application Number:	IND 118215
Product Name:	OTL38
Indication:	Intra-operative detection of folate receptor positive lesions during surgical resection in ovarian cancer patients (diagnostic for the management of ovarian cancer)
Sponsor Name:	On Target Laboratories, LLC
Meeting Chair:	Louis Marzella, M.D., Ph.D., Director, DMIP
Meeting Recorder:	Modupe Fagbami, Regulatory Project Manager, DMIP

FDA ATTENDEES

Louis Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Ira Krefting, M.D., Safety Deputy Director, DMIP
Nushin Todd, M.D., Ph.D., Associate Director, DMIP
Phillip Davis, M.D., Medical Officer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Christy John, Ph.D., Clinical Pharmacology Reviewer, DCPV
Jyoti Zalkikar, Ph.D., Statistics Team Leader, Division of Biometrics II DBV
Anthony Mucci, Ph.D., Biostatistics Reviewer, Division of Biometrics II DBV
Kejing Chen, Ph.D., Lead Reviewer, General Surgery Devices Branch 1, DSD/CDRH
Neil Ogden, M.S., B.M.E., Chief, General Surgery Devices Branch 1, DSD/CDRH
Modupe Fagbami, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Timothy G. Biro, R.Ph., M.B.A., Chief Operating Officer, On Target Laboratories, LLC
Leslie M. Randall, M.D., Clinical Investigator, University of California, Irvine Medical Center
Janos L. Tanyi, M.D., Ph.D., Clinical Investigator, the Hospital of the Univ of Pennsylvania
(b) (4)

Aaron J. Blouin, Director, Clinical Operations, On Target Laboratories, LLC
(b) (4)

BACKGROUND

The Sponsor, On Target Laboratories, LLC submitted a Type B meeting request on August 3, 2016, to review the proposed Phase 3 clinical study protocol and statistical analysis plan in preparation for a Special Protocol Assessment (SPA) submission and in addition to specifically discuss the camera imaging system for their product OTL38. OTL38 is a folate type ligand conjugated with an indole cyanine green type dye as a solution in vials containing 1.6 ml at 2 mg/ml. Single-dose, infused IV 1-(b) (4) hours prior to surgery, intended dose 0.025 mg/kg.

The purposes of this Type B meeting are to:

- Review the proposed Phase 3 clinical study protocol and statistical analysis plan in preparation for a Special Protocol Assessment (SPA) submission.
- Review the existing camera imaging systems supporting the development and use of OTL38 for the proposed indication.
- Understand FDA's position for the formal and final classification of OTL38 with the camera imaging system(s)
- Obtain the Division's feedback on the proposal for the Phase 3 clinical study for evaluating the camera imaging system(s) for use with OTL38.

These objectives are critical when contemplating a development path for OTL38 and the camera imaging system(s) (b) (4)

FDA sent Preliminary Comments to On Target Laboratories, LLC, On Friday, October 7, 2016.

DISCUSSION

Summary

Four imaging devices, (b) (4) (b) (4) and (b) (4) could be used in this study with OTL0038 for the next phase:

(1) About (b) (4) this is an investigational device (b) (4) (b) (4)

(2) About the other three devices (b) (4) (b) (4)

A. DEVICE

A summary of the camera imaging systems used in OTL38 clinical studies is included in Serial No. 0017, Module 3.2.P.7 (aka "3.2.D" device information). A description of the proposed regulatory pathway (b) (4) The synopsis for the proposed Phase 3 clinical study is in Section **Error! Reference source not found.**.

(b) (4)

Meeting Discussion: There was no further discussion on this item at the meeting

2. Similar to the approach used in the ongoing Phase 2 clinical study, On Target intends to conduct the proposed Phase 3 clinical study with one of the camera imaging systems (b) (4) used in the Phase 2clinical study to evaluate its use with OTL38 in the Phase 3study. In addition, On Target is considering using a second camera imaging system in the Phase 3 study, and will provide all documentation for the system in the final Phase 3 protocol IND submission package. Does the Division agree with this strategy?

FDA Response:

Yes, we agree. In Phase2 study, you used (b) (4) and (b) (4) as investigational devices. In the subject preIND submission, you mentioned VisionSense, Artermis, (b) (4) devices in the preIND file. Similar to the Phase 2 study, you should provide detailed information for all the investigation devices to be used in the next phase and risk analysis addressing potential risks with this type of light-emitting devices.

Meeting Discussion: There was no further discussion on this item at the meeting

3. (b) (4)

4. On Target proposes to collect the data on the individual camera imaging system(s) ultimately used in the proposed Phase 3 clinical study. Does FDA agree (b) (4)

FDA Response:

It will depend on how variable the outcomes are when different imaging systems are used with OTL39. We understand that the four cited devices have similar near-infrared imaging working mechanism and the imaging effects when they are used with OTL39 may be the same or similar. However, performance data should be collected and analyzed to demonstrate whether the visualizations are the same. Please submit literature data or bench testing data that would demonstrate how similar/different imaging devices performance are when OTL38 is used as a drug agent. In addition, we notice that in the ongoing Phase 2

study, two imaging devices ((b) (4) and (b) (4) devices) were proposed to be used in the trial. We recommend you summarize any differences these two devices have had in the trial, and, if any, justify why the differences do not affect the final clinical decision.

Sponsor Clarification:

On Target will continue to collect and analyze performance data on all imaging camera devices used in the Phase 3 study. On Target has no need for further discussion

Meeting Discussion:

FDA reiterated the original response and the Sponsor agreed with the approach.

Additional imaging devices added to the program should have similar performance as the other cameras. Sponsor to collect data on performance of cameras used in the Phase 2 studies

Please see Post Meeting Notes.

5. (b) (4)

FDA Response:

It will depend on the final marketing application structure. (b) (4)

Sponsor Clarification:

(b) (4)

6. If only one camera imaging system is utilized in the proposed Phase 3 clinical study to support the OTL38 NDA, will other camera imaging systems be able to pursue Section 510(k) for commercial use with OTL38?

FDA Response:

(b) (4)

If it is determined that the data obtained in the Phase 3 study with the single device could support use with comparable imaging devices, and the drug label is left open to convey this (*i.e.*, use with imaging device that has certain attributes, rather than that the drug can only be used with a specific imaging device), then other camera imaging systems may be able to pursue a 510(k) claiming use with OTL38.

Sponsor Clarification:

(b) (4)

(b) (4) *On Target has no need for further discussion.*

Meeting Discussion:

(b) (4)

(b) (4)

Please see additional Post meeting Notes:

B. CLINICAL

The proposed Phase 3 clinical study protocol and statistical analysis plan are provided in Section 10.2.4. The proposed protocol is for 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 (Protocol No. OTL-2016-OTL38-006).

Introductory Comments

We encourage you in your efforts to establish the performance characteristics and safety profile of OTL38 in patients scheduled for surgery for confirmed or suspected ovarian cancer. Our comments and recommendations below will allow further refinement of the protocol to ensure clinically useful data is obtained during the conduct of your proposed phase 3 study.

7. Does the FDA agree with the overall design of the proposed Phase 3 study, including study objectives and eligibility criteria

FDA Response:

Please note that we request you provide data to support a (b) (4) **for OTL38 assisted surgery and recommend the inclusion of patients across cancer stages and surgical approaches (primary, secondary debulking) in the phase 3 study population.**

Please see our below comments regarding the efficacy endpoints and statistical analyses

We recommend that the protocol be revised to include sampling for pharmacokinetics in all patients and analyses of correlations between clinical outcomes and drug concentrations (e.g., clearance). Analysis of the correlations between patient characteristics (e.g., gender, patient size, renal status, hepatic status) and drug concentrations should also be performed. Sparse pharmacokinetic sampling may be sufficient to allow the analyses.

Sponsor Clarification:

Patients with ovarian cancer typically present for surgical treatment (the time they could enroll in the proposed Phase 3 study) with late stage disease. On Target anticipates that patients enrolling in the proposed study would be Stage 3 or 4. The patient population for the study will be representative of a typical ovarian cancer patient population in the United States. Included in this study will be primary, interval, and secondary debulking surgeries.
While On Target will perform analyses of the correlations between patient characteristics and drug concentrations, it is important to recognize that patients with impaired cardiac, renal and hepatic functions are rarely surgical candidates, and therefore would not eligible for the proposed Phase 3 study.

If the Division agrees with these statements, then On Target has no need for further discussion

Meeting Discussion:

The Agency reiterated that the Sponsor should collect data supporting a (b) (4) ***for OTL38 assisted surgery, and that the study design will include primary, interval, and secondary debulking patient populations. The Agency also emphasized that the additional lesions identified by OTL38 and included in the primary efficacy analyses must be lesions for which identification with OTL38 imparts added value and results in additional tumor being removed and hence improved surgical debulking. The Clinical Reviewer provided the example of a lesion not being seen under normal light conditions but located within tissue planned for resection that was then identified with OTL38. This type scenario would not add value to the procedure since the lesion was already located within the tissue planned for resection.***

The Agency recommended, conducting PK sampling during the phase 3 study and also separate mass-balance study of OTL38 prior to submitting the NDA. The Sponsor concurred to these.

The Agency recommended additional studies on patients withrenal or hepatic impairment, or a phase 1 study in renal impaired, otherwise healthy individuals for labeling purposes. The Sponsor, cited the exclusion criteria in the Phase 3 protocol, that patients with impaired cardiac, renal and hepatic functions are rarely surgical candidates, and therefore will not be eligible for the proposed Phase 3 study.

8. Does the FDA agree with the primary and secondary efficacy endpoints for the proposed Phase 3 study?

FDA Response:

Your proposed primary and secondary efficacy endpoints should be designed to assess the ability of OTL38 imaging procedure to identify additional lesions and/or additional areas of the primary tumor(s) that are clinically useful i.e. result in optimal debulking or no residual disease. We encourage you to revise the protocol so that the primary

endpoint analysis does not include the identification of additional lesion(s) or parts of the primary tumor(s) that are not clinically meaningful (e.g. seeing additional metastatic deposits in patients with already visually identified miliary disease). You might consider including co-primary endpoints that are relevant to specific regions of the surgical field as related to the primary tumor

Please also address the issue of individual surgeon practice so that lesions identified by OTL38 that might be attached/embedded in tissue which would be removed as part of routine practice (even if not identified visually) by some, but not all, surgeons are not included in the analysis.

We encourage you to obtain follow up information (e.g. imaging studies, CA-125 levels) on patients to assess adequacy of resection.

Sponsor Clarification:

Metastatic deposits in patients with visually identified miliary disease were not included in primary endpoint analyses in the Phase 2 ovarian study (informational only). Miliary disease will also not be included in primary endpoint analyses of the proposed Phase 3 study.

Consistent with the Phase 2 ovarian study, the analyses of the primary efficacy endpoint will be all tissue excised and confirmed as cancer (by blinded central pathology). On Target will provide a sensitivity analysis based on excluding lymph nodes because of differing individual surgical practices between investigators. Surgeons consider this the only varying surgical procedure between investigators.

If the Division agrees with these statements, then On Target has no need for further discussion.

Meeting Discussion:

The Agency asked the sponsor to confirm that data exists supporting that optimal debulking is a clinically meaningful patient outcome. The sponsor cited studies associating improved patient survival with optimal tumor debulking surgery for ovarian cancer patients.

FDA recommended defining endpoints that capture clinically meaningful outcomesconsistent with achievement of optimal debulking. FDA recommended and the sponsor agreed that miliary disease will not be included in the efficacy analyses. The sponsor agreed to revised and clearly define their proposed primary and secondary endpoints for the Phase 3 protocol. and only include the types of lesions as accepted as clinically meaningful. Sponsor will revise the protocol and add relevant definitions.

. The Agency recommended endpoints based on resecting fluorescent nodules identified outside the planned (under normal light) resection area that are clinically meaningful.

The Agency agreed that performing CA-125 levels 6 months after the procedure to evaluate surgical success would be useful.

9. Does the FDA agree with the statistical analysis plan for the proposed Phase 3 study?

FDA Response:

You state that in your completed phase 2 study 48.1% of subjects had at least one additional cancer lesion identified by fluorescence that were not seen under normal light conditions. Yet you propose a success threshold proportion of 10% of patients having additional lesions identified under fluorescence (that were not seen under normal light) for your primary endpoint analysis in the planned phase 3 study. We recommend setting a success threshold based on data from your phase 2 studies and one that is clinically meaningful and justified.

We also recommend including a complementary endpoint in place that controls for "overcalling". This could be the patient-level False Positive Rate:FP = Proportion of patients, all of whose OTL38 additional lesions are histology Negative.

Sponsor Clarification:

On Target believes that a success threshold proportion of 10% of patients having additional lesions identified under fluorescence (that were not seen under normal light) for primary endpoint analyses is clinically meaningful and justified based on the following references (provided along with this document in the e-mail):

Bristow et al. Journal of Clinical Oncology, Vol 20, No 5 (March 1), 2002: pp 1248-1259.

CDER; Application No. 022555Orig1s000; Statistical Review(s), page 4.

CDER; Application No. 022555Orig1s000; Summary Review, page 5.

Dr. Janos Tanyi and Dr. Leslie Randall, the principle investigators for the proposed Phase 3 study, concur that a success threshold proportion of 10% of patients (based on the literature citations) is clinically meaningful.

If the Division agrees with this, then On Target has no need for further discussion.

Meeting Discussion:

The Agency agreed with Sponsor's proposed 10% threshold might be a clinically meaningful threshold for assessment of the Phase 3 primary efficacy endpoint. As discussed above the outcome will require support from secondary analyses consistent with achievement of optimal debulking as a result of additional detections.

The Agency questioned the use of the lower limit of the 99% confidence interval calculated from the Phase 2 study to estimate the sample size to assess the Phase 3 primary efficacy endpoint, the proportion of patients having additional lesions identified under fluorescence (that were not seen under normal light). The issue appeared to arise from a desire to confirm the point estimate from the Phase 2 study in the Phase 3 study.;

Upon completion of the proposed Phase 3 study, the safety database for OTL38 will consist of a minimum of 399 subjects exposed to the product, of which a minimum of 393 subjects will have been administered a dose at or above the dose proposed for approval under a future NDA. Of the total number exposed, 166 of the 399 subjects were ovarian cancer patients and 160 of the 393 subjects receiving a dose at or above the dose proposed for approval under a future NDA were ovarian cancer patients (**Error! Reference source not found.**).

10. Does the FDA agree that the proposed safety database is of sufficient size to support a future NDA submission?

FDA Response:

The described safety database appears acceptable.

Meeting Discussion: There was no further discussion on this item at the meeting

On Target may decide to add an additional imaging device at some point after the start of the proposed Phase 3 study. The second imaging device will have similar performance characteristics to the (b) (4) with respect to excitation of OTL38 and capturing the emissions of the excited dye. Therefore, the Sponsor believes that the two imaging devices are substantially equivalent and that the addition of the second device would not impact the proposed clinical study design or planned data analyses.

11. Does the FDA agree that the addition of the second device would not impact the proposed clinical study design or planned data analyses?

FDA Response:

Please refer our response to Question 4.

Meeting Discussion: There was no further discussion on this item at the meeting

C. REGULATORY

The purpose of the meeting is to discuss the Phase 3 clinical study protocol in anticipation of submission of a request for Special Protocol Assessment (SPA).

12. Does the FDA agree with the submission of the proposed Phase 3 protocol for SPA?

FDA Response:

We encourage you to submit a SPA protocol for review.

Meeting Discussion: There was no further discussion on this item at the meeting

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because none of the criteria apply at this time to your application, you are exempt from these requirements. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD

submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018.** Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd**.**

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.
The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

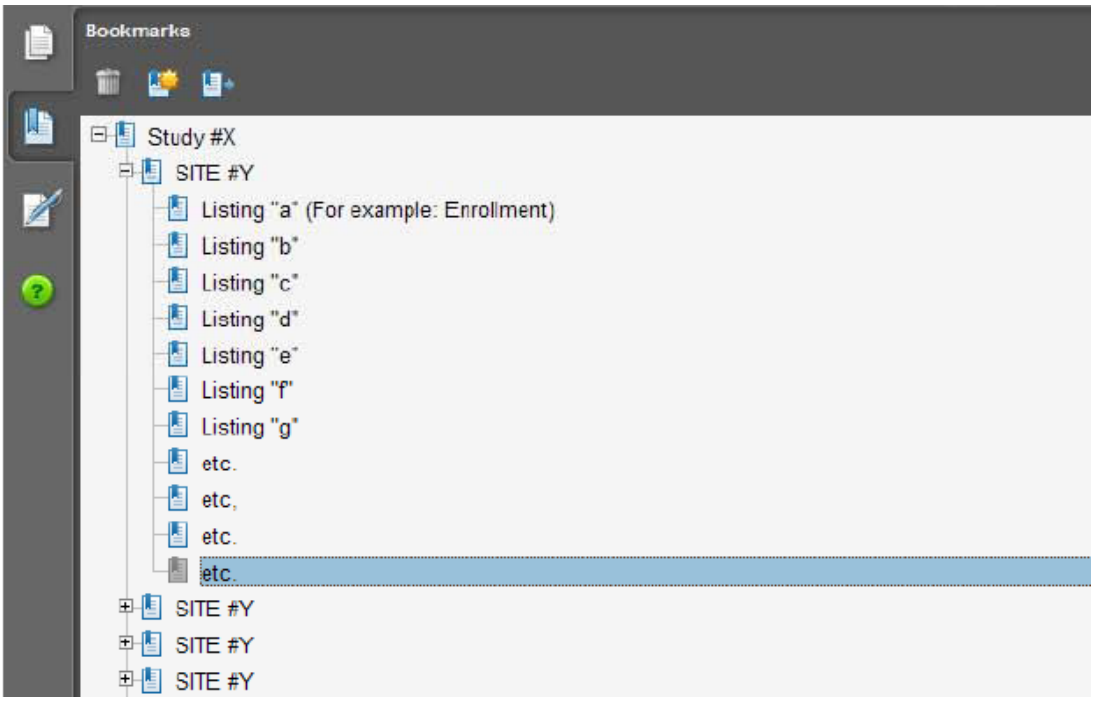
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request	STF File Tag	Used For	Allowable File Formats

Item[1]			
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MODUPE O FAGBAMI
05/09/2017
Revised Meeting Minutes to update FDA list of Attendees.