CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209607Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70663

MEETING MINUTES

Molecular Insight Pharmaceuticals Inc.
C/O Progenics Pharmaceuticals, Inc.
Attention: Jouliana Jean Paul, J.D.
Regulatory Affairs Manager
1 World Trade Center, 47th Floor
47th Floor, Suite J
New York, NY 10007

Dear Ms. Paul:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{131}I Iobenguane.

We also refer to the meeting between representatives of your firm and the FDA on January 17, 2017. The purpose of the meeting was to discuss nonclinical, clinical pharmacology, clinical and statistical issues regarding the proposed NDA.

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, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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:	preNDA
Meeting Date:	January 17, 2017
Application Number:	IND 70663
Product Name:	^{131}I Iobenguane
Indication:	Treatment of iobenguane-avid metastatic or recurrent pheochromocytoma and paraganglioma
Sponsor/Applicant Name:	Molecular Insight Pharmaceuticals (MIP)
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Sharon Sickafuse

FDA ATTENDEES

Office of Hematology and Oncology

Division of Oncology Products 2
Brendan Baggot
Amy Barone, M.D.
Diana Bradford, M.D.
Suzanne, Demko, P.A.-C.
Martha Donoghue, M.D.
Patricia Keegan, M.D.
Sharon Sickafuse, M.S.

Division of Hematology Oncology Toxicology
Whitney Helms, Ph.D.

Office of Biostatistics

Division V
Huanyu (Jade) Chen, Ph.D.

Office of Clinical Pharmacology

Division V
Brian Furmanksi, Ph.D.
Hong Zhao, Ph.D.

SPONSOR ATTENDEES

Stuart Apfel, M.D., Medical Monitor & Safety Officer
Thomas Armor, B.S., CNMT Director, Clinical Imaging
Mark R. Baker, Chief Executive Officer
Ariane Cutulo, RAC, Senior Manager, Product Development
Jouliana Jean-Paul, J.D., Manager, Regulatory Affairs
Jessica Jensen, MPH, Vice President, Clinical Development
(b) (4), MPH, Clinical Consultant
Yakov Rotshteyn, Ph.D., Executive Director, Product Development
Nancy Stambler, Dr.P.H., Executive Director, Biometrics
Vivien Wong, Ph.D., Executive Vice President, Development
(b) (4), Regulatory Consultant

BACKGROUND

On October 21, 2016, Molecular Insight Pharmaceuticals submitted a preNDA meeting request (SDN 224) to discuss the format and content of the clinical and nonclinical sections of a proposed NDA. The meeting package was submitted on December 19, 2016 (SDN 228).

Regulatory

- MIP received orphan drug designation for ^{131}I Iobenguane for the treatment of neuroendocrine tumors on January 18, 2006.
- Fast track designation was granted on March 8, 2006.
- On July 26, 2015, FDA granted a Breakthrough Therapy Designation for ^{131}I Iobenguane for the treatment of patients with iobenguane-avid metastatic and/or recurrent pheochromocytoma and paraganglioma (PPGL) based on preliminary clinical evidence of efficacy obtained in Study MIP1B12B. An Initial Breakthrough Therapy meeting was held on January 22, 2016.
- MIP is proposing to submit a 505(b)(1) NDA in Q2 2017 for approval of this product in the United States. A preNDA CMC meeting occurred on October 6, 2016.
- A WRO letter was issued on September 9, 2016, regarding content and format of the Integrated Summary of Safety, datasets, and presentation of efficacy data.

Nonclinical

MIP plans to submit a series of nonclinical studies to evaluate the pharmacology, safety pharmacology, pharmacokinetics, and toxicity of ^{131}I Iobenguane. MIP states that the pharmacology studies demonstrated the potential utility of ^{131}I Iobenguane as a target for neuroendocrine tumors. An assessment of safety pharmacology consisted of an *in vitro* HERG assay and incorporating cardiovascular parameters into the repeated-dose toxicity study in dogs. MIP evaluated the toxicity of ^{127}I Iobenguane in a 12-day repeated dose toxicity study in rats and in a 28-day repeated dose toxicity study in dogs. MIP states that they have also conducted a full battery of genotoxicity studies with unlabeled iobenguane (MIBG).

Clinical and Statistical

Four clinical trials (MIP-IB11, MIP-IB12, MIP-IB12B, and MIP-IB13) will provide the supporting safety and efficacy data for ^{131}I Iobenguane for the treatment of patients with iobenguane-avid malignant and/or recurrent pheochromocytoma and paraganglioma (PPGL). The patient populations of these trials include adult patients with PPGL (MIP-IB11, MIP-IB12 and MIP-IB12B), adult patients with metastatic carcinoid tumors (MIP-IB11), and pediatric and adult patients with neuroblastoma (MIP-IB13). Dosing regimens differed across trials including dosimetry only (MIP-IB11), single-therapeutic dose and dose-ranging (MIP-IB12 and MIP-IB13), and two therapeutic doses (MIP-IB12B).

MIP-IB12B, a multi-center, open-label, single arm study, is being conducted under a Special Protocol Assessment (SPA) agreement and will provide the efficacy data to support the NDA. Patients with malignant or recurrent PPGL enrolled in this study received one dosimetric dose and up to two 500 mCi therapeutic doses of ^{131}I Iobenguane. Study MIP-IB12 was a single-dose dose-ranging study in patients with PPGL intended to provide supportive safety and efficacy data for the NDA. Study MIP-IB11, a dosimetry-only study without therapeutic dosing in patients with malignant or recurrent PPGL and metastatic only carcinoid, and Study MIP-IB13, a study conducted in patients with neuroblastoma, will provide safety data for the NDA. An expanded access program (EAP) is currently being established under an amendment to the MIP-IB12B protocol.

The statistical analysis plan (SAP V4.0) for Study MIP-IB12B was submitted on May 27, 2016. The full analysis dataset (FAS) includes patients who received an imaging dose and at least one therapeutic dose. The per protocol dataset (PP) comprises patients who received an imaging dose and at least two therapeutic doses, were evaluated at Month-3 and Month-6 for efficacy, and did not have major protocol violations. The primary efficacy endpoint is the proportion of patients with a reduction (including discontinuation) of all anti-hypertensive medications by at least 50% for at least six months following treatment with at least one dose of ^{131}I Iobenguane.

The primary endpoint will be assessed at the time of study completion or discontinuation, whichever occurs first. The 50% reduction is determined separately for each baseline medication, based on the total daily dose of the antihypertensive medication(s) on the day of the first therapeutic dose.

For the primary analysis of the primary endpoint, a point estimate (with a 95% confidence interval, calculated using the Agresti-Coull method) for the proportion of subjects in the FAS with a reduction (including discontinuation) of all antihypertensive medications by at least 50% for at least six months or two cycles will be calculated. This single-arm trial will be considered a success if the lower bound of this two-sided 95% confidence interval exceeds 0.10 (10%).

In Appendix 1 of SAP V4.0, a detailed primary endpoint calculation clarifies the criteria and considerations for meeting the primary endpoint.

Criteria for Meeting Primary Endpoint:

1. Receive an imaging dose
2. Receive at least one therapeutic dose

3. Have a reduction of each pre-therapeutic dose (baseline) of anti-hypertensive medication by ≥50% for a minimum of six consecutive months beginning during the 12-month Efficacy Phase of the study, during which no new, long-term antihypertensive medication is introduced.

Considerations:

1. The introduction of a new, transient (i.e., duration ≤ 14 days) antihypertensive medication regimen at any point during the study will not disqualify a patient from being able to achieve the primary efficacy endpoint.
2. Conversely, the introduction of a new, long-term (i.e., duration > 14 days) antihypertensive medication regimen after receiving a therapeutic dose will disqualify a patient from being able to achieve the primary endpoint. New long-term antihypertensive medications introduced before Therapeutic Dose #1 is administered are considered part of the baseline antihypertensive medication regimen that must be reduced by at least 50% for achieving primary endpoint.
3. A transient (i.e., duration ≤ 14 days) dose increase of an existing antihypertensive medication regimen at any point during the study will not disqualify a patient from being able to achieve the primary endpoint.
4. Conversely, a long-term (i.e., duration > 14 days) increase in dose of an existing antihypertensive medication regimen after receiving a therapeutic dose will disqualify a patient from being able to achieve the primary endpoint.
5. The introduction of an antihypertensive medication regimen or increase in existing antihypertensive medication regimen that occurs after the patient has already met the primary endpoint (i.e., had a ≥50% reduction of all antihypertensive medications for at least six consecutive months) will not disqualify the patient from achieving the primary endpoint.
6. Only antihypertensive medication prescribed for hypertension should be included for the primary endpoint (e.g. propranolol prescribed for atrial fibrillation will not be included).
7. A month is defined as a 28-days period.
8. A patient must begin the 6-month responder period during the 12-month efficacy evaluation phase and may extend into the long term follow up phase.

The secondary efficacy endpoints include 1) overall response rate, 2) tumor response of complete response, partial response, and mixed response, 3) status of bone lesions using Soloway Scale, and 4) tumor marker responses. Tumors will be measured at baseline and at 3, 6, 9 and 12 months after the first Therapeutic Dose. Overall tumor response at 3, 6, 9 and 12 months per RECIST criteria will be assessed centrally by independent, blinded readers.

Recruitment for study MIP-IB12B ended on December 31, 2015. As of July 2016, 74 patients received at least an imaging dose, 68 patients received at least one therapeutic dose (FAS) and 49 patients received two therapeutic doses. As specified in the analysis plan and in the protocol accepted under the SPA, there are at least 58 evaluable patients in the FAS population. Although 58 patients was the goal, an additional 10 patients were granted approval to participate in the trial because an Expanded Access Protocol (EAP) was not yet available. As a result, the last (68^{th}) patient received the first therapeutic dose in February 2016. A total of 41 patients have

completed their four-year long-term follow-up (LTFU) and, as of July 2016, eight patients are being followed currently. The projected timing for 68 patients to complete the 12-month efficacy evaluation (12 months from first therapeutic dose) is March 2017, at which point a database lock will occur and a clinical study report will be prepared in support of a NDA submission.

In MIP's November 18, 2016, response to FDA's WRO letter of September 9, 2016, they proposed to provide ADaM datasets for studies MIP-IB12B and MIP-IB13, but not for MIP-IB11 and MIP-IB12 as these studies were started in 2006 and 2007, respectively, and were previously completed and submitted to the IND in legacy format. FDA recommended that the Sponsor contact *cder-edata@fda.hhs.gov* to request a waiver to the proposed partial non-CDISC submission for studies MIP-IB11 and MIP-IB12 that are unsupported or retired by December 17, 2016. The request for the waiver was submitted on December 7, 2016.

FDA emailed preliminary comments to MIP on January 12, 2017. MIP responded via email on January 13, 2017, stating that they wished to discuss items #4, 16, 17, 18a, 18b, and 18d.

SPONSOR QUESTIONS AND FDA RESPONSES

Regulatory

1. *Due to the high, unmet medical need for patients with metastatic and/or recurrent pheochromocytoma and paraganglioma (PPGL), and assuming the registrational study MIP-IB12B meets the primary endpoint specified in the SPA, Progenics intends to request Priority Review for NDA 209607. Beyond a summary of the MIP-IB12B data and a summary of AZEDRA benefit-risk considerations, can the Agency identify any additional items to provide that would support the Priority Review request?*

   FDA Response:
   FDA does not anticipate that additional items will be required to support the Priority Review Request based on unmet medical need, Breakthrough Therapy Designation and clinical data provided.

   Discussion:
   MIP did not have any questions or comments.

2. *Progenics proposes to submit the complete NDA in eCTD format on or about June 30, 2017. However, the Nonclinical Study Reports (Module 4) and the Nonclinical Summaries (Modules 2.4 and 2.6) will be completed and available for submission in January 2017. Is the Agency amenable to receiving the nonclinical sections of the NDA, on a rolling basis, in advance of the complete NDA filing?*

   FDA Response:
   Yes.

Discussion:
MIP did not have any questions or comments.

3. *Based on the well-known mechanism of action of MIBG in neuroendocrine tumors and the use of the required dosimetry step as a safety check, as well as the strict in-hospital radiation safety regulations and guidelines governing radiotherapeutics administration, the Sponsor does not plan to include a REMS in the AZEDRA NDA submission. Does the Agency agree?*

FDA Response:
The need for a REMS is not anticipated, however, FDA expects MIP to submit a detailed risk-benefit profile assessment with the original NDA.

Discussion:
MIP did not have any questions or comments.

Safety and Efficacy Assessments

4. *The statistical analysis plan (SAP) for study MIP-IB12B was submitted to the Agency for review on May 27, 2016 (SN0207). For the assessment of primary efficacy endpoint responders, the SAP incorporates important data definitions not detailed in the protocol. Does the Agency agree with the data definitions related to the primary efficacy analysis described in the SAP and highlighted in the Information Package?*

FDA Response:
FDA acknowledges MIP's modifications to the primary efficacy analysis population and the data definitions. A final determination of the most appropriate analysis population and description of clinical benefit will be made during review of the NDA where all data are available. Provide all time to event data, including the duration of response, in weeks instead of "months" defined as a 28 day period.

Discussion:
MIP acknowledged FDA's comments and agreed to provide all time to event data in weeks. MIP will submit the final SAP in February 2017.

MIP proposed the following change to the definition of primary outcome responder (new language is underlined):

(b) (4)

(b) (4)

FDA stated that they are not comfortable with the revised definition at this time because of the possibility that it could result in classification of some patients as responders who would not be appropriate.

FDA noted that changes in tumor size and catecholamine levels as evidence of an antitumor response to ^{131}I Iobenguane will also be considered during review of the NDA.

FDA requested that MIP include definition of the primary endpoint in the SAP instead of in an appendix to SAP. MIP agreed to do so.

5. *At the recommendation of the Agency, Progenics plans to provide an assessment of the extent to which AZEDRA provides a significant advance over alternative (i.e., off-label) therapy of PPGL, along with a summary of the natural history of the diseases. Does the Agency agree that the information to be included, as outlined below is a reasonable plan to provide adequate supportive efficacy information for full NDA (i.e., non-accelerated) approval?*

FDA Response:
The proposed plan appears acceptable to provide adequate supportive efficacy information for the NDA; however, a final determination will be made during review of the NDA.

Discussion:
MIP did not have any questions or comments.

6. *Based on agreement and feedback from the Agency in a WRO Type C meeting on September 9, 2016, the Sponsor has prepared the ISS SAP accordingly. Does the Agency agree with the ISS SAP as presented in the Information package*?

FDA Response:
Yes, the ISS SAP appears acceptable.

Discussion:
MIP did not have any questions or comments.

7. *At the recommendation of the Agency, Progenics plans to support the AZEDRA safety database with a thorough literature review addressing the reported toxicity of conventional I-131 iobenguane. Does the Agency agree that the content outline presented below sufficiently encompasses the supplemental safety information in support of NDA submission?*

FDA Response:
The content outline appears acceptable; however, a final determination will be made on review of the information officially submitted to the NDA.

Discussion:
MIP did not have any questions or comments.

Nonclinical

8. Does the Agency agree with the proposed content of Module 4 as outlined in the Information Package?

FDA Response:
In general, the proposed content of Module 4 appears acceptable.

Discussion:
MIP did not have any questions or comments.

Clinical and Statistical

9. Does the Agency agree with the proposed content of Module 5 as outlined in the Information Package?

FDA Response:
The content outline appears acceptable; however, a final determination will be made on review of the information officially submitted to the NDA.

Discussion:
MIP did not have any questions or comments.

10. Progenics plans to submit narratives and case report forms (CRF) for subjects in the clinical program who experienced serious adverse events, discontinuations due to adverse events and deaths. We also plan to submit CRFs for subjects who experienced an adverse event of special interest (AESI), as defined in the individual study reports and in the ISS SAP. CRFs for all other patients will be available upon request. Does the Agency agree with this plan for submission of narratives and CRFs?

FDA Response:
Yes, the plan appears acceptable.

Discussion:
MIP did not have any questions or comments.

11. Progenics plans to submit one study report (pivotal study MIP-IB12B) in granular eCTD format and three study reports (MIP-IB11, MIP-IB12, and MIP-IB13) in legacy electronic format. Does the Agency agree with this approach?

FDA Response:
Yes, the plan appears acceptable; however the request for waiver is under review.

Discussion:
MIP did not have any questions or comments.

12. Does the Agency agree with the proposed content of the Summary of Clinical Efficacy (Module 2.7.3) as outlined in Appendix A?

FDA Response:
The proposed content of the Summary of Clinical Efficacy appears acceptable; however, a final determination will be made on review of the information officially submitted to the NDA.

Discussion:
MIP did not have any questions or comments.

13. Does the Agency agree with the proposed content of the Summary of Clinical Safety (Module 2.7.4) as outlined in Appendix A?

FDA Response:
The proposed content of the Summary of Clinical Safety appears acceptable; however, a final determination will be made on review of the information officially submitted to the NDA.

Discussion:
MIP did not have any questions or comments.

Clinical Pharmacology

14. Does the Agency agree with the proposed content of the Clinical Pharmacology Summary (Module 2.7.2) as described below?

FDA Response:
Yes. In the Summary of Clinical Pharmacology, address the following:

- What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

- How was the potential for ^{131}I Iobenguane to prolong the QT/QTc interval assessed? What are the conclusions and proposed labeling description?

- What are the characteristics of distribution, metabolism and elimination of ^{131}I Iobenguane?

- What influence do intrinsic factors (such as sex, race, weight, disease, organ impairment) have on ^{131}I Iobenguane exposure, efficacy and safety? What dose modifications are recommended?

- What influence do extrinsic factors (such as drug interactions) have on ^{131}I Iobenguane exposure, efficacy, and safety? What dose modifications are recommended?

Discussion:
MIP did not have any questions or comments.

15. *Dosimetry data generated in each clinical study will be provided in their respective Clinical Study Reports. A discussion of dosimetry data will also be included in the Summary of Clinical Pharmacology (Module 2.7.2). Dosimetry raw data and whole body planar images will not be included in the NDA. Does the Agency agree with this approach?*

FDA Response:
The proposal appears acceptable; however, ensure that all datasets are in the SAS transport files (*.xpt) format and description of each data item is provided in a define.pdf file.

Discussion:
MIP did not have any questions or comments.

Safety Update

16. *Does the Agency agree with the proposed timing and content of the post-submission safety update?*

FDA Response:
FDA agrees with MIP's plan to submit the 120-Day post submission safety update to include safety data from the long-term follow-up period of Study MIP-IB12B, as well as safety from the ongoing Expanded Access Study.

Discussion:
MIP stated that the 120-day safety update would be submitted in October with a data cut-off of August 30, 2017. FDA agreed and asked MIP to consider whether a Day 90 submission would be feasible.

MIP asked if FDA wanted to receive topline data after the database lock in March 2017. FDA stated that this is not necessary, unless these topline results are dramatically different from the preliminary data previously discussed.

MIP asked if FDA anticipated the need for an advisory committee. FDA stated that an advisory committee meeting is not currently anticipated, but that a decision will be made after receiving the NDA.

FDA recommended that MIP submit a request for an application orientation meeting at least one month before the planned NDA submission. MIP stated that they would do so.

ADDITIONAL FDA CLINICAL PHARMACOLOGY COMMENTS

17. In the NDA submission, provide the specific activity for ^{131}I Iobenguane and convert the proposed dose from mCi to GBq.

Discussion:
MIP stated that specific activity information at time of calibration (TOC) for all batches used in ^{131}I Iobenguane clinical studies will be provided in Module 2.7.1. FDA stated that this was acceptable.

MIP stated that doses will be indicated in both mCi and GBq in clinical pharmacology related documents where feasible. Conversion to SI units may not be done in documents such as legacy documents and previously submitted reports, etc. FDA provided concurrence with this plan and requested that MIP provide the dose in mass units and in GBq in the clinical pharmacology datasets. MIP agreed to do so.

18. In addition, apply the following advice in preparing the clinical pharmacology sections of the original NDA submission:

a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics studies.

Discussion:
Validation reports for LC/MS/MS bioanalytical methods will be provided, but not for direct gamma counting using an automated well gamma counter. FDA stated that this was acceptable and requested that MIP provide the following information regarding the gamma counter at each clinical site: make and model, limit of quantitation, linear range, and information on the reference standard. MIP agreed to do so and clarified that the dosing solution was used as the reference standard for converting the raw counts to units of radioactivity concentration.

b. Provide complete datasets for all clinical pharmacology and biopharmaceutics studies. The subject's unique ID in the pharmacokinetic datasets should be consistent with those in datasets submitted for clinical review.

Discussion:
MIP stated that datasets will be provided as SAS transport files (*.xpt).

c. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or patients that have been excluded from the analysis should be flagged and maintained in the datasets.

Discussion:
MIP did not have any questions or comments.

d. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

Discussion:
MIP stated that geometric means for the PK parameter data will be provided in Modules 2.7.1 and 2.7.2, but will not be available in the previously submitted MIP-IB11 report. FDA stated that this was acceptable.

e. Identify individual patients with dose modifications; the time to the first dose modification; and the reasons for dose modification. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose in the Summary of Clinical Pharmacology.

Discussion.:
MIP did not have any questions or comments.

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 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.

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.

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.

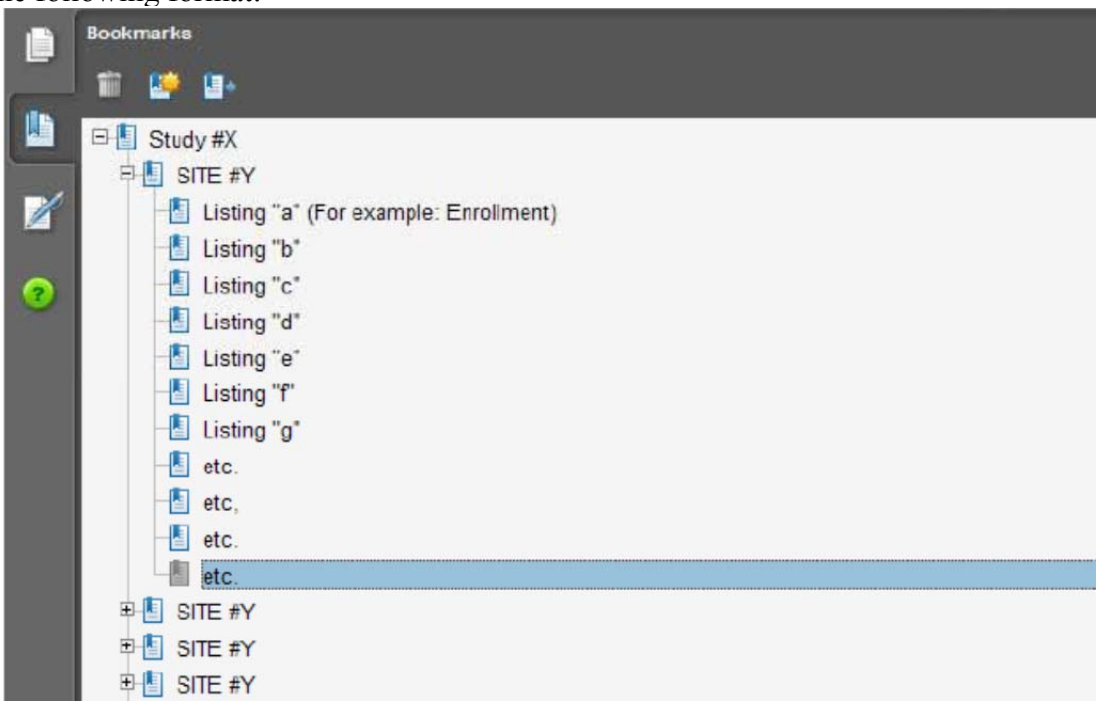
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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

2. 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 Item[1]	STF File Tag	Used For	Allowable File Formats
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.

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

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

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit request for rolling submission.	MIP	ASAP
Submit request for Application Orientation meeting	MIP	4-6 weeks before NDA submission

ATTACHMENT
MIP's presentation

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/s/

SHARON K SICKAFUSE
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND70663

MEETING MINUTES

Molecular Insight Pharmaceuticals, Inc.
Attention: Jouliana Jean-Paul, J.D., Regulatory Affairs Manager
One World Trade Center
47th Floor, Suite J
New York, NY 10007

Dear Ms. Jean-Paul:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MIBG I 131.

We also refer to the meeting between representatives of your firm and the FDA on October 6, 2016. The purpose of the meeting was to seek advice and agreement on the format, content and registration plans for the CMC portions of the planned AZEDRA NDA submission.

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, please contact Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief (Acting)
Office of New Drug Product II, Branch VI
Office of Pharmaceutical Quality
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: B
Meeting Category: Pre-NDA CMC Only

Meeting Date and Time: October 6, 2016 10:00:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22; Room 1419
Silver Spring, Maryland 20903

Application Number: 70663
Product Name: MIBG I 131 (Ultratrace Iobenguane I 131)
Indication: Treatment of Neuroendocrine Tumors
Sponsor/Applicant Name: Molecular Insight Pharmaceuticals, Inc.

Meeting Chair: Danae Christodoulou
Meeting Recorder: Steven Kinsley

FDA ATTENDEES

Danae Christodoulou, Ph.D.	Branch Chief (Acting), ONDP/DNDPII/ Branch VI
Dhanalakshmi Kasi, Ph.D.	Drug Product Reviewer, ONDP/DNDPII/Branch VI
Eldon Leutzinger, Ph.D.	Quality Assessment Lead, ONDP/DNDPII/BranchVI
Derek Smith, Ph.D.	Branch Chief (Acting), OPF/DIA/Branch II
Christina Capacci-Daniel, Ph.D.	Quality Assessment Lead, OPF/DIA/Branch II
Steven Kinsley, Ph.D.	Regulatory Business Process Manager, OPRO/Branch 1

SPONSOR ATTENDEES

(b) (4)	Radiopharmaceutical Manufacturing Consultant
Malini Batheja, Ph.D., RAC	Associate Director, Analytical Sciences
(b) (4)	Regulatory Affairs Consultant
Richard Czarnecky, M.S.	Executive Director, Quality Assurance
Jouliana Jean-Paul, J.D.	Regulatory Affairs Manager
Ed Lee	Director, Regulatory Affairs
Yakov Rotshteyn, Ph.D.	Executive Director, Product Development
Vivien Wong, Ph.D.	Executive Vice President, Development

1.0 BACKGROUND

^{131}I Iobenguane, contains the norepinephrine (NE) transporter substrate MIBG (meta-iodobenzylguanidine). ^{131}I MIBG and ^{123}I MIBG are approved for imaging of tumors of neural crest origin. "Conventional" MIBG preparations contain an excess of unlabeled MIBG which competes for the transporter sites and disrupts the NE uptake mechanism, resulting in increased free NE that leads to an increased risk of cardiovascular adverse reactions, specifically tachycardia and paroxysmal hypertension. MIP states that their product binds to neuroendocrine tumors in an identical method to conventional MIBG. (b) (4)

As discussed at the January 22, 2016 Type B meeting with FDA to discuss development plans under Breakthrough Therapy designation, Molecular Insight Pharmacuetical (MIP) plans to submit a New Drug Application (NDA) for AZEDRA in 2Q 2017. At the request of FDA, a separate Type B pre-NDA meeting request to discuss the Chemistry, Manufacturing and Controls (CMC) sections of the NDA was submitted on July 29, 2016 and the meeting was granted on August 16, 2016.

Progenics accepted the Preliminary Comments and cancelled a previous CMC only meeting (Type C, TCON, October 31, 2013, cancelled Oct. 24, 2013) discussing the acceptance criterion and specifications for radiochemical purity for the Azedra drug product.

The purpose of this meeting is discuss: the proposed format and content of CMC-related information in the NDA submission for Azedra; the commercial readiness of the drug substance (b) (4) and drug product manufactures; and specific issues potentially impacting the manufacture of Azedra drug substance (b) (4) and drug product..

FDA sent Preliminary Comments to Molecular Insight Pharmaceuticals, Inc. on September 27, 2016.

2. DISCUSSION

(b) (4)

Question 1.
At the Agency's request (January 22, 2016 Type B Meeting), the (b) (4) *specification has been amended to include limits for* (b) *impurities, as well as individual unknown impurities, for the NDA submission. Does the Agency agree with the revised* (b) (4) *specification for the NDA submission?*

FDA Response to Question 1:

FDA acknowledges revision of the (b) (4) specification. We remind you that impurity limits will be assessed during the NDA review. Provide mass dose information for your drug product in the NDA submission.

Discussion: **There was no discussion on Question 1.**

Question 2.

(b) (4)

FDA Response to question 2:

FDA agrees with your approach. Note that the shelf life of the (b) (4) will be assessed during NDA review based on real time stability data and ICH Q1E recommendations.

Discussion: **There was no discussion on Question 2.**

Drug Product (AZEDRA Iobenguane I 131 Injection)

Question 3.
Manufacturing of the finished drug product (FDP) for the registration clinical trial MIP-IB12B was performed at the (b) (4) *. For commercial manufacturing, the Sponsor plans to utilize a new FDP manufacturer,* (b) (4) *the Sponsor believes that it is not necessary to submit bridging data from the clinical trial manufacturing process to the commercial product. Does the Agency agree?*

Question 4.
Does the Agency agree that the described drug product manufacturing process and specifications at (b) (4) *will adequately support commercial production of drug product?*

FDA Response to question 3 &4:

FDA agrees with your approach. However in your NDA submission, provide release and stability test results for the validation batches and executed batch records from both sites

to assess comparability. Include information on the synthesis equipment at both sites. Clarify if the (b) (4) site will be used to manufacture commercial product.

Sponsor Comments: ***Does the Agency agree that this is the information needed for assessment of comparability?***

- (b) (4) ***will not be used to manufacture commercial Product.*** (b) (4) ***will be the only commercial manufacturer included in the NDA.***

- ***In our NDA submission, we propose to provide:***

  – Release and stability test data, executed batch records, as well as information on the synthesis equipment (b) (4) ***for the 3 validation batches performed at*** (b) (4)
  – Release and stability data and executed batch records of the three recent clinical batches that were placed on stability at (b) (4) ***and were used in the registrational study (MIP-IB12B)***

Discussion: **FDA acknowledged that** (b) (4) **will be the only commercial manufacturer included in the NDA submission. FDA agreed with the proposed submission plan for release and stability data and executed batch records for the three validation batches produced at** (b) (4)**. In addition, the sponsor stated that they will include in the application additional release and stability data and executed batch records for clinical lots produced at** (b) (4)**. FDA agreed.**

Question 5.
Does the Agency agree with the proposed Media Fill Test (process simulation) prior to manufacture of the registration batches of AZEDRA injection at the commercial facility?

FDA Response to question 5:

Yes. FDA agrees with the proposed media fill validation testing to be performed prior to the manufacture of the registration batches at the commercial facility. However, the details of the media fills, (b) (4) are subject to review during an on-site inspection of your facility.

Discussion: **There was no discussion on Question 5.**

Question 6.
Does the Agency agree with the proposed FDP Site Validation Master Plan?

FDA Response to question 6:
The FDA does not approve facility and equipment validation plans, nor process validation plans. The actual protocols, acceptance criteria and study outcomes (as applicable) will be evaluated during an on-site inspection of your manufacturing facilities. The product and manufacturing processes design will be evaluated during the NDA review cycle. It is your company's

responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

For additional information on process validation including the design and qualification of facilities and equipment during Process Validation Stage 2A, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

For further information on Agency's drug compliance and pre-approval inspection programs please refer to the following links on FDA's website:

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm

Additionally, manufacturing firms can request a pre-operational review (POR) of a facility in advance of any submission. The purpose of a POR is to provide comments on plans for construction of new or modifications of facilities prior to commercial production. The POR team includes CDER Facility Reviewers and/or Field Investigators. Elements of equipment and material flow, manufacturing suite design, and other operational or CGMP concerns can be discussed. The POR however does not approve validation or qualification plans or the results of these studies.

For additional information regarding pre-operational reviews or pre-operational visits of manufacturing facilities, please refer to ORA field management directive-135, linked below. In requesting a POR or pre-operational visit (POV), please consult the relevant FDA district office and copy CDER OPQ (CDER-OPQ-Inquiries@fda.hhs.gov) for reviewer participation.

- http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm096042.htm

Discussion: **There was no discussion on Question 6.**

Question 7.
Does the Agency agree on the proposed FDP registration stability plan to support the NDA submission?

FDA Response to question 7:

Yes. FDA agrees with your approach. In addition, provide in use stability data for AZEDRA injection for the infusion time period at room temperature as part of the NDA submission.

Sponsor Commens: ***Does the Agency agree that this information provides sufficient data to support in use stability, and no additional studies are required?***

Pharmacy Manual for MIP-IB12B instructs the clinical sites to administer AZEDRA to patients within 8 hours from the time the frozen drug product is removed from ≤ -70°C storage

- ***The infusion typically lasts for approximately 30 minutes at a flow rate of 100mL/min***

- ***The 8 hours period was based on stability testing performed with AZEDRA in the product vial stored frozen for 9 days, removed from freezer, stored at room temperature for up to12 hours (6 hr and 12 hr time points)***

- ***Thus, we believe the 12 hour room temperature stability data in the product vial covers the in use stability***

Discussion: **Molecular Insights Pharmaceuticals (MIP) verified that Azedra is kept at cold storage and thawed prior to dosing. The stability data is based on the thawed 8 hours in use period. MIP stated that Azedra may be diluted up to 40% (worst case scenario) with saline solution, based on the activity assay of the sample prior to administration. FDA stated that the in use stability conditions should simulate conditions of use based on the instructions given on the packaging insert. FDA understands that the worst case scenario for radiolysis is the concentrated solution, but the maximum dilution should be included. MIP clarified that the drug is not intended for use in children, i.e., no low weight patients.**

Question 8.

AZEDRA will be infused to patients out of the original containers; thus, an extractable/leachable study at room temperature for 24 hours for the primary container/container closure will be performed. Since standard infusion components (such as needles and tubing) routinely available in hospitals for IV administration of parenteral therapeutics will be used, and the infusion time will be short (approximately 30 minutes), the Sponsor believes it is adequate to perform an extractable/leachable study of the primary product container/container closure only. Does the agency agree with this approach?

FDA Response to question 8:

Yes, FDA agrees with the plan of providing extractables/leachables study data at ambient room temperature for 24 hours for the primary container/container closure using (b) (4) formulation of AZEDRA. Clarify if the container/closure components are resistant to radiolysis in your NDA submission.

Sponsor Comments: Does the Agency agree the available information sufficiently supports the conclusion that the container closure components are resistant to radiolysis?

Type 1 borosilicate glass vials

– Well accepted to be resistant to radiolysis

– Type 1 borosilicate glass is also used in the packaging of 131-I sodium iodide solution with total radioactivity up to (b) (4) ***per vial***

– AZEDRA uses (30 mL) type 1 borosilicate glass vials supplied by (b) (4) ***as are many*** (b) (4) ***products with much higher total radioactivity***

- ***20 mm*** (b) (4) ***stoppers from*** (b) (4)

– Can withstand up to (b) (4) ***(supplier documentation)***

– The calculated radiation exposure level to the stopper from the leading edge of the AZEDRA therapeutic drug product of (b) (4) ***mCi is estimated to be*** (b) (4) ***rads at 24 hours***

Discussion: **FDA agrees. Justification and documentation for the packaging components should be included in the NDA application.**

Question 9.
The Sponsor will use (b) (4) *of non-GMP grade material (as proposed at the January 22, 2016 Type BMeeting). Does the Agency agree with this change?*

FDA Response to question 9:

Yes, FDA agrees. You have mentioned that impurities present in your older process interfere (b) (4) impurity analysis in your NDA submission for further evaluation.

Discussion: **There was no discussion on Question 9.**

General and/or Regulatory

Question 10.
As the active drug substance, iobenguane I-131, is (b) (4) *as well as the finished drug product, will be described in the 32P module. Does the Agency agree with this approach? Does the Agency agree with the proposed Module 3 table of contents?*

FDA Response to question 10:

Yes we agree.

Discussion: **There was no discussion on Question 10.**

3.0 Other Important Information

In addition, we note that a multidiscipline pre-submission meeting will be requested. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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.

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.				

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/applicants 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/applicants 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).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items

6.0 ATTACHMENTS AND HANDOUTS

The following slides were present at the meeting.

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/s/

DANAE D CHRISTODOULOU
10/11/2016

CDER Breakthrough Therapy Designation Determination Review Template

(This template was provided by the CDER Breakthrough Thearapy program manager and will serve as the Clinical Review for DOP2. The MPC meeting was conducted virtually and BT Designation was granted on July 26, 2015)

IND/NDA/BLA #	IND 070663
Request Receipt Date	June 4, 2015
Product	Azedra™Ultratrace® (Iobenguane Iodine-131)
Indication	Iobenguane-avid, metastatic or recurrent, pheochromocytoma and paraganglioma (PPGL)
Drug Class/Mechanism of Action	Iobenguane Iodine-131 [Meta-iodo-benzyl guanidine (MIBG) I 131] is a radioconjugated drug comprised of a substrate that binds to the norepinephrine reuptake receptor linked to the Iodine-131 isotope
Sponsor	Molecular Insight Pharmaceuticals, Inc
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	August 3, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   The proposed indication for ultratrace iobenguane 131I is for the treatment of patients with iobenguane avid metastatic and/or recurrent pheochromocytoma/paraganglioma (PPGL).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐ Undetermined

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:
If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

N/A

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Disease Background:

Pheochromocytomas/paragangliomas (PPGLs) are neuroendocrine tumors with an incidence of two to eight cases per million per year in the United States[1]. Pheochromocytoma arise from adrenomedullary chromaffin cells that commonly produce one or more catecholamines: epinephrine, norepinephrine, and dopamine. Paragangliomas are derived from extra-adrenal chromaffin cells and characterized by either parasympathetic-associated chromaffin tissues (most commonly along cranial and vagus nerves) or sympathetic-associated chromaffin tissues (often designated as extra-adrenal pheochromocytomas). Approximately 80-85% of chromaffin cell tumors are pheochromocytomas; 15-20% of chromaffin cell tumors are paragangliomas.

PPGLs are diagnosed most frequently in adults between 40 and 50 years of age and typically manifest with clinical signs and symptoms, such as headache, palpitations, and diaphoresis, and life-threatening hypertensive crisis. Hypertension is the most common sign observed in more than 95% of functional tumors. Surgical resection is curative. In patients with unresectable primary tumors, surgical debulking may be indicated to reduce tumor burden which may decrease catecholamine levels. Control of hypertension is critical in malignant PPGL due to life-threatening acute hypertensive emergencies, as well as clinical consequences of long-lasting hypertension, which may result in devastating effects on multiple body systems leading to death if untreated. A small reduction in blood pressure in hypertensive patients is thought to reduce cardiovascular complications and improve overall survival[2].

In addition to complications of hypertension, another major cause of death in patients with PPGLs is metastatic disease. Approximately 10-20% of PPGLs are malignant, defined by the World Health Organization classification as the presence of distant metastases, not local invasion. Clinical manifestations of malignant PPGL are similar to those of benign tumors, including hypertension, headache, sweating and palpitations. Malignant PPGLs are generally resistant to chemotherapy; treatment is primarily aimed at palliative control of symptoms. Survival for patients with metastatic PPGL is less than 2 years.

Drug Mechanism of Action:

The small molecule meta-iodobenzylguanidine (MIGB) is a substrate for the norepinephrine reuptake transporter(NET). PPGL exhibits high levels of expression of NET on the cell surface. Azedra, a radioconjugated drug comprised of MIBG linked to the iodine-131 isotope, binds to the NET expressed on PPGL and results in tumor cell death by localized irradiation.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary efficacy endpoint used in this trial was the proportion of patients with a reduction (including discontinuation) of all antihypertensive medications by at least 50% for at least 6 months. The 50% reduction was determined separately for each baseline antihypertensive medications, based on the total daily dose on the day of the first therapeutic dose of Azedra. The design and planned analysis of the protocol supporting this trial, including the primary endpoint, was agreed upon in a special protocol assessment (SPA) agreement on March 5, 2009. Secondary endpoints included safety, tumor response according to RECIST 1.1. criteria, and changes in use of concomitant analgesic and pain medication.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
DOP2 agrees that a durable reduction in hypertension, a major cause of morbidity and mortality in patients with malignant PPGLs, is a clinically meaningful endpoint that directly measures the clinical benefit of the drug. The secondary endpoints of response rate will provide evidence of direct anti-tumor activity of Azedra and will provide supportive evidence that the effects on hypertension result from decreased tumor burden rather than an effect solely on catecholamine levels.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

N/A

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

There are no FDA-approved therapies for the treatment of iobenguane avid metastatic and/or recurrent PPGL in the United States. Standard of care for locally unresectable PPGLs includes radiation therapy with alpha blockade with or without alpha-methytyrosine, beta blockade, and cytoreductive resection[3]. For patients with distant metastasis, the following is additionally recommended: clinical trial, systemic chemotherapy (e.g. dacarbazine, cyclophosphamide, vincristine), or 131I-MIBG (requires prior positive MIBG scan with dosimetry)[3].

MIBG is used for both imaging and treatment purposes. The radioisotope of iodine I-123 (AdreView™, manufactured by GE Healthcare) is approved in the US for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests.

In addition, I-131-MIBG has been compounded and used extensively under IND has been studied extensively for the treatment and imaging of neuroendocrine tumors, predominanty neuroblastoma but also pheochromocytoma with, 38 active or completed trials for patients with neuroendocrine tumors on www.clinicaltrials.gov. The most common adverse reactions reported include dizziness, rash, pruritus,

flushing, and headache, bleeding at the site of injection, hypersensitivity reactions (rare), and hypertension (transient).

The pharmacy compounded prepartions of I-131 MIBG are typically administered with a large amount of unlabeled (cold) MIBG. In contrast, Molecular Insight Pharmaceuticals, Inc states that Azedra contains virtually no unlabeled MIBG, which offers two advantages over pharmacy compounded/ investigational MIBG. First, Molecular Insight Pharmaceuticals, Inc states that the unlabeled MIBG competes for the transporter sites and disrupts the norepinephrine re-uptake leading to increase in circulating norepinephrine. The increase in circulating norepinephrine can lead to an increased risk of cardiovascular side effects such as paroxysmal hypertension . Molecular Insight Pharmaceuticals, Inc also states that because Azedra has no unlabeled molecules, the delivery of radioactivity to the tumor is much higher, resulting in more efficient tumor destruction capability.

The following table lists the all other commercial INDs (excluding IND 70663) and all active research INDs for treatment of pheochromocytoma identified in DARRTS.

Application Type/Number	Application SubType	Product Name	Submitter	Responsible Organization	Current Status
					(b) (4)

There have been more than 20 expanded access INDs (predominantly single patient INDs) submitted to FDA for I-131 MIBG for the treatment of pheochromocytoma.

Approved drugs which have been used off-label for treatment of PPGL include cyclophosphamide, vincristine, and dacarbazine. Molecular Insight Pharmaceuticals has summarized the reported treatment effects of chemotherapy and I-131 MIBG on control of hypertension, objective response rate, and survival. (Table adapted from Breakthrough Request submitted by Molecular Insight Pharmaceuticals).

Summary of Largest Clinical Studies with Targeted Radiotherapy and Chemotherapy in Malignant PPGL

	Chemotherapy Cyclophosphamide (C), Vincristine (V), Dacarbazine (D), Doxorubicin (Dx)		Targeted Radiotherapy [131I] Metaiodobenzylguanidine (MIBG)	
Reference	**Averbuck et al. (1988)[b] [29]**	**Ayala-Ramirez et al. (2012)[11]**	**Krempf et al. (1991)[30]**	**Gonias et al. (2009)[24]**
Methodology	Prospective pilot	Retrospective	Prospective	Prospective
No. of evaluable patients	N=18	N=52	N=15	N= 49
Treatment activity	C= 750 mg/m^2, D1 V= 1.4 mg/m^2, D1 D= 600 mg/m^2, D1-D2	C= 600-750 mg/m^2 D= 750-1000 mg/m^2 +/-V= 1-2 mg/m^2 +/-Dx= 60-75 mg/m^2	80-250 mCi (mean, 200 mCi)	492-1160 mCi (median, 818 mCi)
Median no. cycles; treatment regimen	18; Q21D	6.9; Q21-28D	4 (range: 2-11)	1 (range: 1-3)
Blood Pressure Control	No formal evaluation was conducted. Improvement in performance status and blood pressure was observed in patients with biochemical response. Reduction in antihypertensive medications was noted in 4 patients and discontinuation was reported in 1 subject. Duration of control is unreported.	Thirty-one patients (59.6%) had clinical evidence of excessive catecholamine secretion, adrenergic symptoms, and hypertension, and had received antihypertensive medication prior to chemotherapy. Among the 31, 6 patients (19%) achieved a reduction in antihypertensive medications by at least >50% following their first chemo regimen. Three of those 6 patients discontinued all antihypertensive medications (9.7% overall). Duration of control is unreported	No formal evaluation was conducted; Improvement in clinical status and blood pressure was noted in 7 subjects (47%). Discontinuation of antihypertensive medications was reported in 4 subjects (26%). Duration of control is unreported.	Unreported
Tumor Response Rate; criteria	55%; mWHO	25%; criteria not standardized	33%; WHO criteria	27%; RECIST criteria
Survival	3.3 years; median survival from on-study date	51%; 5-year OS rate from diagnosis	Unreported	64%; 5-year OS rate from diagnosis
Safety profile	Toxicity was mild to moderate with myelosuppression, peripheral neuropathy, and gastrointestinal toxicity most commonly reported. Four episodes of hypotension and 1 episode of transient hypertension, was observed following dosing.	Safety findings not reported.	Minimal safety findings reported. Most significant toxicity noted was pancytopenia.	Primary toxicity was hematologic. The most serious grades 3 to 4 nonhematologic toxicities were pulmonary; including acute respiratory distress syndrome (n = 2), bronchiolitis obliterans organizing pneumonia (n = 2), pulmonary embolism (n = 1), fever with neutropenia (n = 7), acute hypertension (n = 10), infection (n = 2), myelodysplastic syndrome (n = 2), and hypogonadism (n = 4).

a Prospective studies were selected when available
b Original study published by Averbuch et al. in 1988 reported on n = 14 patients and updated by Huang et al. in 2008[31]

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

There are no other drugs which have requested breakthrough therapy designation for the same or a very similar indication.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

10. Information related to the preliminary clinical evidence:

a. There is a single clinical trial supporting the BTDR, Trial MIP1B12B, however there the Azedra clinical development program in malignant PPGL consists of two Phase 1 studies (Study MIP-IB11 and MIP-IB12) and the ongoing, single arm trial, Study MIP-IB12B, described in this request. Study MIP-IB11 is a Phase 1 study evaluating the safety, distribution metabolism, and radiation dosimetry of Azedra in patients with malignant PPGL or metastatic carcinoid. Study MIP-IB12 is a Phase 1 study evaluating the maximum tolerated dose, dosimetry, safety, and efficacy of Azedra in patients with malignant PPGL.

Trial MIP-1B12B

The Breakthrough Therapy Designation request is based on preliminary data generated from the ongoing study MIP-IB12B in patients with metastatic and/or recurrent PPGL. Study MIP-IB12B is an open-label, single arm, activity estimating, multicenter study conducted in patients at least 12 years or older with a documented diagnosis of PPGL confirmed by histology or by a physician using supportive data (e.g. abnormal MIBG, elevated tumor markers). The study consists of a screening/dosimetry phase, a 12-month efficacy phase, and a four-year long-term follow-up phase. Approximately 75 patients are expected to enroll to ensure that 58 patients are evaluable for safety and efficacy. Eligible patients receive two doses of Azedra (500 mCI, or 8mCI/kg for patients <62.5 kg, per dose), three months apart, administered after an imaging dose and dosimetry. Under the SPA, the primary endpoint for this study is the proportion of patients with a reduction (including discontinuation) of all antihypertensive medications by at least 50% for at least six months. Secondary endpoints include safety, tumor response according to RECIST criteria, bone lesion status, tumor markers, change in quality of life (QOL), performance status, change in analgesics and pain medications, and overall survival.

Study MIP-IB12B was initiated in June 2009; enrollment was suspended in September 2010 for financial reasons; however study sites remained open and follow-up activities continued per protocol. In December 2014, after MIP was acquired by Progenics and sufficient funding was secured, the study was resumed enrollment. The results supporting this request are from an ad hoc analysis performed prior to the acquisition of MIP by Progenics.

The results presented below are based on patients enrolled as of September 2010, who had received any part of Azedra (imaging or therapeutic dose), with a data cut-off date of April 2012. There were 44 patients who received an imaging dose of Azedr, 41 patients received at least one therapeutic dose, and 34 patients received both therapeutic doses. Of the 41 patients who received at least one therapeutic dose of Azedra, 13 patients (31.7%; 95% CI 0.161-0.472) had a sustained reduction in antihypertensive medication of at least 6 months. Six of the 41 patients (15%) were able to discontinue use of anti-hypertensive medication entirely for at least six months. In an exploratory analysis, 61% of the patients who received at least one therapeutic dose of Azedra, had a reduction of their antihypertensive medications by at least 50% for any duration.

Of the 41 patients who received at least one therapeutic dose of Azedra, 34 had target lesions measurable by RECIST. Basedon the April 2012 cut-off, 14 of those 34 patients (41%) had a partial response (PR), 19 (56%) had stable disease (SD)and one patient had progressive disease. Of the 33 patients that had a partial response or stable disease, 12 met the primary endpoint, sustaining a reduction of antihypertensive medication by at least 50% for duration of greater than 6 months (7 PR, 5 SD).

b. Include any additional relevant information. Consider the following in your response:

DOP2 considers the data provided in this request preliminary clinical evidence of a substantial improvement over available therapies. Malignant PPGLs are serious conditions with no available therapy. Management of malignant PPGLs requires controlling endocrine activity and decreasing tumor burden to improve morbidity and mortality. At the time of the ad hoc analysis,approximately one-third of the patients (13 of 41 patients) had evidence of a durable reduction in anti-hypertensive medications. Furthermore, seven of these patients had a partialtumor response on imaging suggesting that the Azedra has anti-tumor activity and is not only decreasing circulating catecholamines. The clinical relevance of this data would be further supported by individual patient level data, such as cardiovascular comorbidities that developed while on study in responders and nonresponders (requested byDOP2 but not received to date).

Other factors regarding the clinical development program that were taken into considerationwere :

- Ad hoc analysis: DOP2 recognizes that the analysis submitted for support of this BTD request was an unplanned ad hoc analysis, however, the percentage of patients who have who have achieved durable and substantial reductions in anti-hypertensive medications supported by objective tumor responsesprovides preliminary clinical evidence that I-131 MIBG may provide a substantial improvement in disease-related morbidity in this population with no treatment options.

- Single arm trial: DOP2 recognizes that Study MIP-IB12B is a single-arm study and will not provide data regarding overall survival or progression-free, however, a randomized controlled trial would be impractical given the rarity this disease.

- Natural history of the disease: Given the rarity and heterogeneity of this disease, it is challenging to identify a large case series which carefully document the natural history of hypertension control in this population. Based on limited reported clinical experience however, it does not appear that patients who require anti-hypertension medications are able to substantially reduce those medications without some anti-neoplastic intervention (e.g. chemotherapy, radioactive iodine, etc.).

Safety data:

In trial MIP-1B12B, the most commonly reported treatment emergent adverse events (TEAEs) in patients who received at least one dose of Azedra (>10%) were gastrointestinal (nausea, vomiting, constipation, and sialadenitis), hematologic (thrombocytopenia, leukopenia, neutropenia, and anemia) nervous system disorders (dizziness, headache, and dysgeusia), fatigue and anorexia. The most commonly reported serious adverse events (SAEs) were thrombocytopenia (four subjects, 9.1%); disease progression (three subjects, 6.8%); and constipation, dyspnea, or myelodysplastic syndrome (two subjects each, 4.5%). No patients were discontinued due to SAEs except for one SEA that resulted in death (myelodysplastic syndrome). Azedra is also being studied in patients with high-risk, relapsed refractory neuroblastoma. To date, 15 patients have enrolled, with no dose-limiting toxicities reported. The hematologic toxicities observed with Azedra are similar to those observed with other chemotherapeutic and investigational radionuclide therapies, including myelodysplastic syndrome.

The non-hematologic toxicity profile observed with Azedra was favorable compared to other therapies. Conventional 131I-MIBG use has been associated with serious non-hematologic toxicities including respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, pulmonary embolism and hypertension. Cardiovascular toxicities have been observed with CVD treatment including hemodynamic instability and a "catecholamine storm" manifested by sudden onset of extreme tachycardia, severe hypertension or both. These cardiovascular and pulmonary toxicities were not seen following Azedra treatment. Specifically, there were no reports of hypertensive crisis and few reports of hypertension in the study MIP-IB12B.

Discussion
DOP2 has concluded that the safety profile with Azedra is acceptable in light of the serious nature of the disease and lack of satisfactory alternative therapy. The risks are reasonable in light of the preliminary evidence of clinical acivity. DOP2 recommends approval of this request for Breakthrough Therapy Designation.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Malignant PPGLs are serious and life threatening conditions with no available therapy. The data provided in this request show preliminary clinical evidence of clinical benefit based on control of the signs and symptoms of catecholamine secretion, decreased tumor burden, and an acceptable toxicity profile. For these reasons, DOP2 recommends granting this breakthrough request.

☐DENY:

Provide brief summary of rationale for denial: N/A

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

DOP2 has recommended that additional patients be enrolled in Study MIP-IB12B to provide a more precise assessment of the treatment effect and durability of the effect. .DOP2 believes that the clinical outcomes being assessed are direct clinical benefit and that treatment effect can be evaluated by comparison to external controls and the natural history of this disease, given the lack of satisfactory alternative therapies. Thus, DOP2 is not recommending that additional, randomized, internally controlled trials be conducted.

The chemistry of this molecule is relatively simple and will likely not represent significant challenges for this prodcut. The greatest challenges with development of I-131 MIBGare the rarity of the disease and the extensive use in expanded access programs and potentially outside of INDs (pharmacy compounding) which has undermined enrollment of patients in clinical trials conducted by the pharmaceutical industry. While such use may inform the the understanding of toxicity, it has undermined the careful and systematic collection of efficacy, long-term safety and dosimetric characterization of the product, a requirement for radiolabelled drug products.

Azedra is also being developed for the treatment of neuroblastoma. Currently there is one ongoing investigation, MIP 1B13, an activity estimating study of Azedra in patients with relapse/refractory high-risk neuroblastoma.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

N/A

13. List references, if any:

1) PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US). Pheochromocytoma and Paraganglioma Treatment-for health professionals (PDQ®). Patient version; [updated 2015 July 10; cited 2015 July 15]. Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032652/

2) Ayala-Ramirez, M., Feng, L., Habra, M. A., Rich, T., Dickson, P. V., Perrier, N., .. Jimenez, C. (2012). Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas. *Cancer, 118*(11), 2804-2812.

3) NCCN Guidelines Version 1.2015 Pheochromocytoma/Paraganglioma © National Comprehensive Cancer Network, Inc. 2011, All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN Guidelines®, NCCN COMPENDIUM® and NCCN TEMPLATES® are trademarks owned by the National Comprehensive Cancer Network, Inc."

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?
YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

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07/28/2015

SUZANNE G DEMKO
07/28/2015

PATRICIA KEEGAN
07/29/2015