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, 4^{7th} 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
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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

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