CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 115927

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Jeffrey Yuan, Ph.D.
Director, Global Regulatory Affairs
508 Carnegie Center
Princeton, New Jersey 08540

Dear Dr. Yuan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aripiprazole tablet with an ingestible event marker (IEM) from Proteus® (the Proteus Ingestible Sensor).

We also refer to the meeting between representatives of your firm and the FDA on May 5, 2015. The purpose of the meeting was to gain alignment with us on the proposed NDA structure and content, on the handling of packaging and environmental assessment, on the acceptability of the human factors validation data for review, on the proposed labeling, and on the handling of the Otsuka Medical Software in the 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 email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor’s Slide Presentation
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, May 5, 2015 9:00 -10:30 AM (ET)
Meeting Location: White Oak Building 22, Conference Room: 1315
Application Number: IND 115927
Product Name: aripiprazole tablet + ingestible event marker (IEM)
Indication: Schizophrenia
Sponsor/Applicant Name: Otsuka Pharmaceutical Development & Commercialization, Inc.

FDA ATTENDEES
Mitchell Mathis, M.D. Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D. Deputy Director, DPP
Jing Zhang, M.D. Clinical Team Leader
Aisar Atrakchi, Ph.D. Pharmacology/Toxicology Supervisor
David Claffey, Ph.D. CMC Team Leader, Office of Pharmaceutical Quality (OPQ)
Ashley Boam, MSBE Director (acting), Office of Policy for Pharmaceutical Quality (OPQ)
Richard Lostritto, Ph.D. Deputy Director (Acting), Science and Policy
Irene Z. Chan, Pharm.D., BCPS Associate Director, Division of Medication Error Prevention and Analysis (DMEPA)
Loretta Holmes, BSN, Pharm.D. Safety Evaluator, DMEPA
Danielle Harris, Pharm.D., BCPS Team Leader, DMEPA
Ariane Conrad. Pharm.D. FDA/ISMP Safe Medication Management Fellow, DMEPA
Katelyn Brown, Pharm.D. Regulatory Pharmaceutical Fellow, Medication Safety, DMEPA
Patricia Love, M.D. Deputy Director, Office of Combination Products (OCP), Office of Commissioner (OC)
Bindi Nikhar, MD Clinical Associate Director, OCP/OC
Shawn Forrest, MS Branch Chief (Acting), Cardiac Diagnostic Devices Branch, CDRH
Mitchell Shein, MS Deputy Director, Cardiac Diagnostic Devices Branch, CDRH
Luke Ralston Lead Reviewer, 513(g)
Simran Parihar, Pharm.D. Regulatory Health Project Manager, DPP
SPONSOR ATTENDEES

Otsuka Pharmaceutical Co., Ltd
Janet Ahn           Director of Product Management Digital Health
Michael Fahmy, M.S. Director of Labeling, Global Regulatory Affairs
Elora Gupta, Ph.D. Senior Director of Global Regulatory Affairs
Kenji Tomikawa     Manager, Medical Regulatory Affairs
David Unger, Ph.D. Senior Director, Pharmaceutical Technology
Tim Peters-Strickland, M.D. Senior Director, Global Clinical Development
Jeffery Yuan, Ph.D. Director of Global Regulatory Affairs
Henrietta Ukwu, M.D. Senior Vice President of Global Regulatory Affairs
Yukako Tsuzaki, M.A. Language Services Specialist

Proteus Digital Health
George Savage, M.D. Cofounder and Chief Medical Officer
Jafar Shenasa      Head, Regulatory Affairs

1.0 BACKGROUND

The sponsor, Otsuka Pharmaceutical Co., Ltd (Otsuka), is developing a combination drug-device that consists of an aripiprazole tablet plus an embedded ingestible event marker (IEM) from Proteus® (the Proteus Ingestible Sensor), which is also referred to as aripiprazole + IEM, under the Investigational New Drug (IND) 115927. IND 115927 was allowed to proceed on Oct 24, 2013. The purpose of the aripiprazole + IEM tablet is to be used in conjunction with a system to

The sponsor’s agenda for this meeting is to gain concurrence with FDA that adequate evidence is available to file a NDA for TRADEMARK. The proposed claim is “TRADEMARK

The sponsor requests concurrence with the FDA that the preliminary results from the Human Factors Validation study provide sufficient support for the claim that the NDA may be filed and approved. The Human Factors Validation study included 36 patients from three different diagnostic groups (schizophrenia, major depressive disorder, bipolar 1 disorder) who were divided between two conditions of use (assisted and unassisted).

No new treatment indication is proposed for the aripiprazole + IEM combination beyond those currently approved for Abilify (aripiprazole) in the adult oral tablet formulation:

- Schizophrenia; acute and maintenance treatment
- Acute treatment of manic and mixed episodes associated with bipolar I disorder, and as monotherapy or adjunctive for maintenance treatment
- Adjunctive treatment of major depressive disorder

The Sponsor states that TRADEMARK is not intended to address the treatment of the disease (i.e., schizophrenia, bipolar I disorder, or MDD), because that has been demonstrated by approval of the aripiprazole oral tablet (NDA 21-436).

Reference ID: 3775040
The sponsor plans not to submit an integrated summary of efficacy or safety in the proposed NDA, since the efficacy and safety of the components have already been demonstrated and the indications for TRADEMARK are the same as those for the Abilify oral tablet in adults. At the Feb 4, 2015 Type C meeting, the sponsor indicated that clinical safety data from trials that used the TRADEMARK product would be provided.

2. DISCUSSION

2.1. General

**Question 1:** As discussed at the 04 Feb 2015 Type C meeting, the TRADEMARK product consists of the following 4 components: aripiprazole + IEM tablet; Proteus Patch + MDDS; Patient Component of the Otsuka Medical Software; and Healthcare Provider and Caregiver Web Portals of the Otsuka Medical Software. Based on previous meetings with the Agency on the TRADEMARK development program and requirements for registration (see minutes from meetings on 29 Sep 2012, 13 Aug 2013, 10 Feb 2014, and 04 Feb 2015) and International Conference on Harmonisation M4 “Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use,” the NDA will consist of chemistry, manufacturing, and control, human factors validation data, safety data from trials using TRADEMARK, and proposed labeling. Appropriate cross-references to the already approved and cleared components of TRADEMARK will be made in the NDA.

The proposed content and structure of the NDA will include a summary of clinical safety and a clinical overview. As previously indicated, the sponsor will cross-reference the Abilify NDAs and Proteus 510(k)s for the efficacy and safety of the drug and device components, as appropriate, and will not provide an integrated summary of efficacy in this NDA.

Does the Agency agree with the proposed structure and table of contents for the NDA?

**FDA Response to Question 1:**

*From clinical point of view, the proposed structure and table of contents for the NDA appears acceptable.*

*We agree with your proposal to cross-reference the drug substance information to NDA 21436, but request that you, at minimum, include the current drug substance specification in Section 3.2.S.*

**Discussion at meeting:** There was no further discussion.

**Question 2:** The TRADEMARK NDA will be reviewed as a non-new molecular entity (NME) original NDA, as confirmed by the FDA at the pre-IND Meeting, 14 Aug 2013.

The program has been granted Fast Track status based on the potential for the integrated system. The sponsor maintains that TRADEMARK fills this serious unmet medical need.

Will the Agency consider an expedited review (Priority Review) of the NDA based on these considerations? It is understood that the official review designation will be granted after NDA submission.

**FDA Response to Question 2:**
*There are approved treatments for all the indications for which this product would be approved. Therefore, this product does not address an unmet medical need and does not qualify for expedited review.*

**Discussion at meeting:** There was no further discussion.

**Question 3:** TRADEMARK consists of both already approved and cleared components (aripiprazole, Proteus IEM, and Proteus Patch) for which safety and efficacy have already been demonstrated. No clinical phase 3 trials are needed for the proposed NDA and the sponsor is not seeking a new indication.

Furthermore, the application will not raise significant public health questions concerning the role of TRADEMARK in diagnosis, cure, mitigation, treatment, or prevention of disease.

Therefore, based on the FDA's criteria for the need for an advisory committee, the sponsor believes an advisory committee is not needed for TRADEMARK.

Does the Agency agree?

**FDA Response to Question 3:**
*No, we do not agree. During the submission review, we will determine the need for an advisory committee.*

**Discussion at meeting:** FDA clarified that we have not yet identified any issues that would warrant an advisory committee; however, we intend to keep this option open. Whether or not an AC will be necessary is always a matter of review once we receive the NDA submission.
**Question 4:** After review of the regulations and the safety data for TRADEMARK, the sponsor does not believe that there is any risk that requires a Risk Evaluation and Mitigation Strategy (REMS).

Does the Agency agree on the proposed risk management activities?

**FDA Response to Question 4:**
*Given that the system is purported to be physiologically inert and the drug substance is already approved, the Division tends to agree; however, this is ultimately a matter of review.*

**Discussion at meeting:** There was no further discussion.

**Question 5:** For Module 3, Section 3.2.R.2 Method Validation Package, 4 representative sample kits will be assembled per 21 CFR 314.50(e). The sponsor will provide in the sample kit sufficient quantity for the FDA to perform testing of the aripiprazole + IEM tablets.

The Proteus Patch, which is part of the commercial kit, will not be provided in the sample kit as it has been cleared in 510(k) K113070 (DEN120011), K131009, K131524, and K133263.

Does the Agency agree?

**FDA Response to Question 5:**
*This approach appears appropriate to meet requirements under 21 CFR 314.50(e)(i); However, per 21 CFR 314.50(e)(ii), we also request three samples of the finished market package, including the patch, that you intend to commercially distribute.*

**Discussion at meeting:** FDA clarified that the three samples of the finished market package, including the patch, should be included at the time the NDA is submitted.

**Question 6:** The environmental analysis in Module 1, Section 1.12.14 will be conducted for the aripiprazole drug substance only. The device components of the product have already been cleared and are exempted as per 21 CFR 25.34 and will be used as per their intended uses.

Does the Agency agree?

**FDA Response to Question 6:**
*Yes.*
**Discussion at meeting:** There was no further discussion.

**Question 7:** On 27 Jan 2015, the sponsor received the Agency’s review of the human factors validation protocols. Appropriate revisions have been made to the validation protocols and will be addressed in the validation and summary reports. An initial summary from the validation studies is provided below and indicates that TRADEMARK can be safely and correctly used by the intended patient population. An initial summary from the validation studies is provided in the appendices of this briefing book.

Does the summary of the validation trial results support the filing and review of the NDA?

**FDA Response to Question 7:**

**DMEPA response:** To support the filing and review of the NDA, we request that you submit study reports for all HF validation studies. These reports must include:

- the information outlined under Appendix A of FDA’s Draft Guidance for Industry: Applying Human Factors and Usability Engineering to Optimize Medical Device Design;
- raw data collected from each participant, including observed and subjective data;
- a copy of the study protocol implemented;
- a copy of the IFU tested;
- samples of the finished market package, including the patch, that you intend to commercially distribute (see response to question 5 above); and
- agreed upon information as stated in Appendix 3 of your briefing document.

Additionally, if further changes were made to the user-interface (e.g., product design, IFU, other labeling) after completion of the HF validation studies, all changes should be described along with your rationale for implementing these changes and any additional validation data to support the additional changes. In the event that further changes were made to the IFU after completion of the HF validation studies, please submit a side-by-side comparison of the two versions (tested version versus intend-to-market version) that clearly points out where changes were made.

The acceptability of the study results to support safe and effective use of the combination product as well as any claims will be a review issue. Please note that the evaluation of any proposed claims will be based on the totality of data submitted to your NDA.

**Discussion at meeting:** There was no further discussion.

**Question 8:** As a follow up to the 4 Feb 2015 Type C meeting, the sponsor has provided details and supporting rationale on the format of the proposed label along with draft labeling.
Does the Agency agree with the proposed format and labeling?

**FDA Response to Question 8:**

CDFH comment: We recommend cross-referencing a cleared device with an indication that aligns more closely with the proposed indication.

**Discussion at meeting:** There was no further discussion.

**Question 9:**

Does the Agency agree with this proposal?

**FDA Response to Question 9:**

At this time, we are not able to determine the potential applicability of enforcement discretion.

In addition, the briefing document indicates that the NDA will cross-reference K113070 (DEN120011), K131009, K131524, and K133263 to support the device functionality. Please confirm whether the most recently cleared version of the device (K133263) is the intended version to be considered in the NDA. In addition in the NDA, please identify and state the relevance of any version to the device intended for the NDA copackage.

**Discussion at meeting:**

- The software is part of the combination product. As such the risks relate to the entire combination and the software is part of the overall review.

- Regarding the cross-referenced 510(k) submissions, Otsuka stated that it will cross reference the most recently applicable cleared version of the Proteus device. Also, during the discussion other versions were mentioned. FDA requested that the NDA
very clearly indicate (and tabulate) what aspects of the 510(k) or 510(k)s are cross-referenced and for what purpose.

- FDA noted that the intended use of the new software is unclear (e.g., what decisions are being made based on seeing the data from the app?). The risk analysis is associated with the display information and the source of the information. The HCP can only access data that the patient has explicitly given him/her permission to access, and the patient can revoke that permission at any time via the app. The Otsuka software is specifically designed for use by mental health patients (i.e., those with schizophrenia, bipolar disorder, etc.).

**Additional Comments Regarding NDA and MAF Content:**

FDA clarified that the MAF should contain data that is confidential trade secret to the NDA holder. At that point, FDA would review the MAF.

Regarding the Otsuka NDA data: the Otsuka data and any common Proteus data known to Otsuka should be in the NDA. Also, the NDA should contain the qualification data for the sensor in aripiprazole.

The comparability protocol for submission to the NDA should provide Otsuka’s proposal for certain anticipated changes that could be made postapproval and the type of reporting (NDA supplement or annual report) proposed for each. Also, for changes made to the Proteus system (e.g., those made in rapid response to the mobile phone operating system updates), the submission should include a proposal for those changes as well.

FDA asked the sponsor to propose a location for the Otsuka Medical Software documentation and Comparability Protocol in the proposed NDA. In a post-meeting email correspondence, the sponsor proposed the following:

- Otsuka proposes to incorporate the documentation for the Otsuka Medical Software into module 1.11.1, Quality Information Amendment of the eCTD structure, alongside the Human Factors Validation and Summary Reports. This
documentation of the software would be in a format similar to what would be provided to CDRH as a MAF (Device Master File).

- Alongside the software documentation, Otsuka also proposes to include the Comparability Protocol in module 1.11.1. As discussed on Tuesday, this protocol will focus primarily on the handling of post approval updates to the Otsuka Medical Software; therefore, it is proposed to be included in the same section as the software documentation.

In a further follow up to this communication, FDA advised the sponsor to link the video file(s) into the backbone, and also provide a PDF file of the video for archival purposes. Acceptable video file formats are .wmv and .mpg, which can be viewed with Windows Media Player, standard on reviewer workstations. Also, video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone. We also noted that the sponsor should include the word "video" in the leaf title of the video file, so reviewers can quickly identify the file.

Labeling – The labeling should specify the compatible mobile devices and include a warning to alert patients not to change their phone operating system (or change phones) without checking with the manufacturer to confirm compatibility. The submission should include data to show lockout from other patches in vicinity (9 f)

Patient labeling is in the form of the help menu and videos on the phone. No printed patient labeling is planned.

**Additional Discussion at meeting: Video Demonstration**

Following the demonstration provided by Otsuka, the Agency sought clarification regarding app and patch functionality. Otsuka provided the following clarification points:

- The patch battery lasts one week and any data generated after the battery dies are not transmitted.
- The patch “status icon” serves to indicate to the user the quality of the patch connectivity. The icon will display as “red” in the event that the connectivity is poor due to (1) insufficient Bluetooth connectivity, (2) inadequate contact of patch with skin, (3) patch needing replacement or (4) unsuccessful pairing with app. This and other icons were tested in human factors studies for participant knowledge/comprehension.
- The app does not have to be “on” at all times to ensure data collection. Data will transmit when the app is “synced.”
- The HCP/caregiver is unable to access the patient’s information until access is granted by the patient. The patient can deny access at any time. They can also reconnect.
3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 6, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.
Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

### 4.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

5.0 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 PLLR Requirements for Prescribing Information websites including:

- 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 in the PI for human drug and biological products
- 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 42 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

6.0 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.”
<table>
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<th>Site Name</th>
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<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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Corresponding names and titles of onsite contact:

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<th>Site Name</th>
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<th>Onsite Contact (Person, Title)</th>
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Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

7.0 ATTACHMENTS AND HANDOUTS

Sponsor’s Slide Presentation and Demo video

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
06/04/2015
IND 115927

Otsuka Pharmaceutical Company, Ltd.
Attention: Jeffrey Yuan, Ph.D.
Director of Global Regulatory Affairs
508 Carnegie Center
Princeton, NJ 08540

Dear Dr. Yuan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aripiprazole tablet with an ingestible event marker (IEM) from Proteus® (the Proteus Ingestible Sensor).

We also refer to the meeting between representatives of your firm and the FDA on February 4, 2015. The purpose of the meeting was to gain alignment with the Agency on the description of the MIND1 system and its components, on the proposed labeling and instructions for use, and on the handling of post approval changes to the system.

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

If you have any questions, please email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 115927

Proteus Digital Health, Inc.
Attention: Dr. George Savage, MD
Co-founder & Chief Medical Officer
2600 Bridge Parkway, Suite 101
Redwood City, CA 94065

Dear Dr. Savage:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Abilify (aripiprazole) tablets with embedded Proteus Ingestible Event Marker.

We also refer to the meeting between representatives of your firm and the FDA on August 14, 2013. The purpose of the meeting was to discuss the 1) content of the upcoming IND submission; 2) unmet medical need being addressed by this program; 3) stability proposal for aripiprazole tablets with embedded Proteus Ingestible Event Marker; 4) procedural questions on the proposed NDA; and 5) potential labeling for the device/drug combination.

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.

We would also like to call your attention to a guidance released by the FDA on August 14, 2013, pertaining to the development of wireless devices. This guidance may be found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077272.pdf.

If you have any questions, please email, Simran Parihar, PharmD, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
CAPT, USPHS
Director (Acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor’s Slides
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: Wednesday, August 14, 2013, 11:00am-12:00pm (EST)
Meeting Location: White Oak CDER Building #22, Conference Room 1415

Application Number: Pre-IND 115927
Product Name: Aripiprazole Tablets + Ingestible Event Marker (IEM)
Indication: Schizophrenia
Sponsor/Applicant Name: Otsuka Pharmaceutical Co., Ltd & Proteus Digital Health, Inc.

Meeting Chair: Mitchell Mathis, M.D.

FDA ATTENDEES (tentative)

Dr. Robert Temple, M.D. Deputy Director for Clinical Science
Dr. Mitchell Mathis, M.D. Director (acting), Division of Psychiatry Products (DPP)
Dr. Jing Zhang, M.D. Medical Team Leader, DPP
Dr. Gregory Dubitsky, M.D. Medical Reviewer, DPP
Dr. Aisar Atrakchi, Ph.D. Pharmacology/Toxicology Supervisor, DPP
Dr. Imran Khan, Ph.D. Pharmacology/Toxicology Reviewer, DPP
Dr. Chhagan Tele, Ph.D. Pharmaceutical Assessment Team Leader, Office of New Drug Quality Assessment (ONDQA)
Dr. Sandra Suarez, Ph.D. Biopharmaceutics Acting Team Leader, ONDQA
Mr. Frank Lacy Electronics Engineer Reviewer, The Center for Device and Radiological Health (CDRH)
Dr. Hiren Patel, Pharm.D., M.S. Senior Regulatory Project Manager, DPP
Dr. Simran Parihar, Pharm.D. Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Proteus Digital Health
Dr. George Savage, M.D., Co-founder & Chief Medical Officer
Consultant, (b) (4)
Ms. Zahedeh Hatamkhany, BS, Senior Scientist, CMC Regulatory - Combination Products
Mr. Jafar Shenasa, MSc, Senior Director, Regulatory Affairs

Otsuka Pharmaceuticals
Dr. Daniel Salazar, Ph.D., Senior Vice President of Translational Medicine and Think Team
1.0 BACKGROUND

Proteus Digital Health (Proteus) and Otsuka Pharmaceutical Development and Commercialization (Otsuka) are jointly developing a combination drug-device product consisting of the atypical antipsychotic aripiprazole (marketed as Abilify tablets) with an embedded, ingestible event marker (IEM). After entering the stomach, this device is capable of automatically forwarding recorded data via a secure Bluetooth connection to a compatible computing device, such as a tablet computer or smartphone, which then processes the data using an software application. The user will have the ability to store, display, and transmit data via a cloud-based application to health care providers.

The intended use of this product is

The Proteus Ingestible Sensor was cleared for marketing by the Center for Devices and Radiological Health (CDRH) in July 2012 as K113070, with subsequent versions cleared as K131009 (May 2013) and as K131524 (June 2013). Thus, the components of this combination product consist of an approved small molecule (aripiprazole) with a cleared medical device (Proteus Ingestible Sensor or IS). The term IEM will be used for general references to the embedded ingestion device whereas IS will be used only for specific references to the 510(k) cleared Proteus Ingestible Sensor. The MIND1 (Medical Information Device) program consists of the aripiprazole + IEM combination, wearable sensor, However, MIND1 does not represent the proposed tradename, which will be addressed at a later date.

A face-to-face meeting was held between the Division of Psychiatry Products (DPP) and representatives of Proteus and Otsuka on September 26, 2012, to discuss the proposed development plan, required data and the administrative path for approval of this combination product, and product labeling. Specific questions regarding comparative dissolution and stability testing were addressed by the Office of New Drug Quality Assessment (ONDQA) review staff.
Also, it was also pointed out by the sponsor's consultant.

Please see the Meeting Minutes dated October 4, 2012, for details of the entire meeting discussion.

The objective of this meeting is to discuss the following topics:

- contents of the upcoming IND submission.
- unmet medical need addressed by this program.
- stability proposal for the combination product.
- procedural questions regarding the planned NDA.
- labeling considerations for the combination product.

No new clinical data will be generated during this development program and, thus, no clinical protocol will be included in the IND application. It is not expected that the pharmacological, toxicological, or physiochemical properties of Abilify will be affected by embedding the cleared IS. A proposed Table of Contents for the IND application is provided and consists almost entirely of Module 3 (Quality), with preclinical and clinical data cross-referenced to the Abilify NDA (#21-436).

The sponsor plans to base the NDA on technical details and functionality of the drug-device combination. The application is deemed to represent a non-NME NDA. The NDA will include 6 months of real-time stability data at the time of filing, with a total of 12 months of real-time data provided within the first half of the NDA review cycle. Otsuka has provided the initial 6 months of real-time and accelerated stability data from six development batches to assess 1) the physical properties of the combination tablet, 2) drug stability, 3) IEM functionality, and 4) drug dissolution and release. Findings suggest that the aripiprazole-IEM tablets are directly comparable to the marketed Abilify tablets and there is no interaction between the IEM and aripiprazole when combined. From a marketing perspective, Otsuka is considering changing the amount of color and deboss for the combination tablets to facilitate the differentiation of the IEM tablets from Abilify tablets during marketing.
No additional therapeutic indication will be sought with the aripiprazole-IEM tablet NDA. The sponsor proposes the following changes to Abilify labeling if the combination tablet is approved for marketing in the U.S.:

<table>
<thead>
<tr>
<th>Section</th>
<th>Proposed Additional Text</th>
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<tbody>
<tr>
<td>Highlights</td>
<td></td>
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<tr>
<td>Indications and Usage</td>
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<td>Dosage and Administration</td>
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2. DISCUSSION

2.1. Proposed IND and NDA Application Content

**Question 1:** The potential NDA for the aripiprazole + IEM combination will be based on the technical details and functionality of the drug-device combination. In accordance with approved labeling of the Proteus Ingestible Sensor, the proposed labeling will include [blacked out] and not seek any new therapeutic indications. This proposed labeling is consistent with the guidance the FDA provided ahead of the 26 September 2012 Type C meeting, where the agency stated in the preliminary comments for the meeting “Yes, it will be acceptable to add a claim for the [blacked out] to the existing Abilify labeling.” Thus, the current development program does not include any clinical studies related to the assessment of effectiveness of the combination. Given the nature of this filing and the desire for Otsuka to have additional discussions related to the manufacturing process and the results from ongoing long term stability study with the FDA, Otsuka proposes [blacked out].

Does the FDA agree?

**FDA Response to Question 1:** No. Please be advised that prior to submission of an NDA for the aripiprazole+IEM combination product, human factors studies will be required to support the usability of your product by patients with schizophrenia as well as healthcare providers.

To be sure that there are no unique risks associated with using your product, you should perform a comprehensive risk analysis. This analysis will allow you to identify the use-related risks associated with your drug-device combination. A comprehensive risk analysis should include a comprehensive evaluation of all the steps involved in using your device...
(e.g., based on a task analysis or known problems), the errors that users might commit or the
tasks they might fail to perform, the potential negative clinical consequences of use errors
and task failures, the risk-mitigation strategies you employed to reduce any moderate or high
risks to acceptable levels, and the method of validating the risk mitigation strategies. This
information is needed to ensure that all potential risks involved in using your product have
been considered and adequately mitigated and the residual risks are acceptable (i.e., not
easily reduced further and outweighed by the benefits of the device). Based on this use-
related risk analysis, you will have a better idea of the extent to which simulated use testing
is required. The risk analysis will also guide you in the design of a human factors validation
study protocol for your product.

Validation under clinical conditions must be conducted and will involve actual use
conditions and should include representative users. The clinical environments that will be
used in the evaluation should be representative of the actual use environment and the
validation testing process should affect the clinical environment and use conditions as little
as possible.

Validation performed under clinical conditions should be preceded by appropriate
simulated-use testing to ensure that the device is sufficiently well designed to be safe in
actual use (to the degree afforded by simulated-use testing).

Guidance on human factors procedures to follow can be found in Medical Device Use-
Safety:
Incorporating Human Factors Engineering into Risk Management, available online at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/uc
m094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might
also be useful in understanding our current thinking and our approach to human factors. It is
titled, Applying Human Factors and Usability Engineering to Optimize Medical Device
Design and can be found online at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/uc
m259748.htm.

Discussion at Meeting: There was no further discussion.

Question 2: Does the proposed Table of Contents (TOC) for the IND application meet the
Division’s requirements for review and approval of the application?

FDA Response to Question 2: Yes.

Discussion at Meeting: There was no further discussion.
2.2. **Unmet Medical Need**

**Question 3:** Does the FDA agree to the justification that aripiprazole + IEM and its ability to ...(b)(4) and by extension drive enhanced patient compliance address an unmet medical need as outlined in the recently issued FDA draft guidance (June 2013) entitled “Expedited Programs for Serious Conditions – Drugs and Biologics?”

**FDA Response to Question 3:** The determination of whether the aripiprazole-IEM tablet addresses an unmet medical need will be made following submission of an expedited program designation request from you, as described in the draft guidance. In order to evaluate your request, it is necessary that you describe precisely how the MIND1 system will be utilized ...(b)(4). For example, ...(b)(4)

Also, with the recent approval of Abilify Maintena, clinicians now have the option to address non-compliance in aripiprazole-treated patients with this once-monthly injectable formulation of aripiprazole. Your request should describe the advantages and disadvantages of the MIND1 system compared to the use of Abilify Maintena ...(b)(4)

**Discussion at Meeting:** The sponsor indicated that they will submit a formal request for Fast Track designation. They presented information to support their contention that the aripiprazole-IEM combination product satisfies an unmet medical need including: ...(b)(4)
2.3. Stability

*Question 4*: Since Otsuka believes that aripiprazole + IEM meets a significant unmet medical need and available data show no impact on product quality, Otsuka plans to submit 6 months stability data from Primary Batches at the time of NDA filing. Otsuka also plans to update the stability data package with 12 month data from the Primary Batches within the first half of the review period.

To further support this, Otsuka has included the initial 6 months of real time and accelerated stability from development batches in this document. The process changes associated with manufacturing of aripiprazole + IEM will not affect the drug release characteristics of the formulation.

Does the Agency agree that the proposed stability data package provided at time of NDA submission is sufficient for review?

*FDA Response to Question 4*: At the time of NDA submission you need to provide a minimum of 12 months controlled room temperature and 6 months of accelerated stability data for three batches of each strength.

With regard to your Ingestible Event Marker (IEM):

- Please provide this data for our consideration.
- We understand that upon ingestion,

*Discussion at Meeting*: We reiterated that, at the time of an NDA submission, we require 6 month of accelerated and 12 months of long term of stability data for 3 batches of each strength of registration batches packaged in the to be marketed container closure system.
**Question 5:** In order to differentiate aripiprazole + IEM tablets from the marketed Abilify® (aripiprazole) tablets, Otsuka is considering changing the color and deboss for the commercial aripiprazole + IEM tablets. Since the stability of the aripiprazole + IEM tablets will be established with the proposed stability data package, Otsuka is proposing to submit batch release data and dissolution profile comparison to establish comparability between the aripiprazole + IEM tablets that are on long term stability (LTSS) and the proposed commercial aripiprazole + IEM tablets in the NDA at submission. Otsuka considers this data package as adequate to support approval of the proposed commercial tablets in the NDA.

Does the Agency agree?

**FDA Response to Question 5:** The FDA agrees that dissolution profiles comparisons in the QC method for the approved tablet are appropriate to support the proposed changes in color and debossing for your proposed drug product/device combination.

We remind you that, to support the approval of the proposed drug product/device combination, dissolution profile comparisons with f2 statistical testing using the QC method and in at least three additional media (e.g. 0.1 N HCl, and USP buffer media at pH 4.5, and 6.8) for at least three batches of the proposed drug product/device combination versus the approved product are needed as stated in meeting minutes dated Oct 04, 2012 (refer to this meeting minutes for additional data requested).

**Discussion at Meeting:** The sponsor inquired whether it would be acceptable to submit dissolution profile comparisons with f2 statistical testing in three media for one batch (not three batches) of the proposed drug product/device combination versus the approved product. The FDA stated that in order to increase the confidence of the outcome of the analysis, and given that a biowaiver of the BA/BE requirements was under consideration, the use of three batches rather than one to establish the bridge was recommended. The sponsor agreed to provide dissolution profile comparisons from at least three batches of the proposed drug product/device combination versus the approved product in three different media.

2.4. **Procedural**

**Question 6:** At the September 26, 2012 meeting, the FDA stated that an NDA would need to be submitted for the aripiprazole + IEM. Since both Abilify® (aripiprazole) and the Proteus Ingestible Sensor device are approved products and no new indication is being sought, the NDA for the combination would be a ‘Non-NME original NDA’ (per PDUFA V Reauthorization Performance Goals and Procedures (Fiscal Years 2013 through 2017).

Does the Agency concur?

**FDA Response to Question 6:** Yes.

**Discussion at Meeting:** There was no further discussion.
2.5. Proposed Labeling

**Question 7:** Does the FDA concur with the proposed labeling updates?

**FDA Response to Question 7:** Specific labeling language will be a matter for review during our examination of your NDA. Please be advised that because labeling will not specifically include a claim of (b)(4), any advertising or promotional material will not be permitted to state or imply such a claim.

**Discussion at Meeting:** There was no further discussion.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.


**Discussion at Meeting:** The sponsor stated that they intend to submit a PSP within 10 days of submitting their IND application, which is slated for November 2013. The PSP will request a deferral of pediatric trials. The FDA concurred with this plan.
4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slides prior to the meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
08/19/2013

Reference ID: 3359371