CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204441Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72975

MEETING MINUTES

Otsuka Pharmaceuticals
Attention: Robert Ashworth, Ph.D.
Vice President, Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Ashworth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OPC-41061 (tolvaptan) Tablets.

We also refer to your May 11, 2012 correspondence requesting a Pre-NDA meeting.

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2012. The purpose of the meeting was to discuss any issues related to your 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 call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Copy of eDish Data Requirements

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 19, 2012 11:00 AM – 12:00 PM, EST
Meeting Location: White Oak Bldg 22 Room 1313

Application Number: 072975
Product Name: OPC-41061 (tolvaptan)
Indication: Autosomal Dominant Polycystic Kidney Disease
Sponsor/Applicant Name: Otsuka Pharmaceutical Development & Commercialization

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Anna Park, R.Ph.

FDA ATTENDEES

Division of Cardiovascular and Renal Products

Norman Stockbridge	Director
Stephen Grant	Deputy Director
Aliza Thompson	Clinical Team Leader
Shona Pendse	Clinical Reviewer
Thomas Papoian	Pharmacology Team Leader
Edward Fromm	Chief, Project Management Staff
Anna Park	Regulatory Project Manager

Office of Clinical Pharmacology

Divya Menon-Andersen	Clinical Pharmacology Reviewer
Hobart Rogers	Pharmacogenomics Reviewer

Office of Biostatistics, Division of Biometrics I

James Hung	Director

OTSUKA ATTENDEES

Robert Ashworth	Vice President, Regulatory Affairs
Frank Czerwiec	Senior Director, Global Clinical Development
Taro Iwamoto	President, Representative Director
Holly Krasa	Associate Director, Global Medical Affairs
David Martinko	Associate Director, Program Management

Robert McQuade	Executive Vice President, Global Medical and Regulatory Affairs
Susan Shoaf	Director, Clinical Pharmacology
Takeshi Watanabe	Director, Global Medical and Regulatory Affairs
Chris Zimmer	Senior Director, Global Clinical Development
(b) (4)	(b) (4) Consultant. (b) (4)

BACKGROUND

Tolvaptan is a vasopressin V2 receptor antagonist approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia on May 19 2009 (New Drug Application [NDA] 22-275) and marketed as SAMSCA®. It is being developed by Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) under IND 072975 (b) (4) for the treatment of autosomal dominant polycystic kidney disease (ADPKD). The development program for treatment of ADPKD was granted Fast Track designation on January 20, 2006 and Orphan Drug designation on April 6, 2012.

Otsuka conducted trial 156-04-251,"*A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease."* The sponsor submitted the protocol for this trial for Special Protocol Assessment on August 18, 2005 and a No-Agreement Letter was issued by the Division on September 29, 2005. This pivotal trial data were locked and unblinded on April 12, 2012. Otsuka is now planning to seek approval to market tolvaptan for treatment of ADPKD.

Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by comments from the sponsor (in italics) and any additional discussions that took place during the meeting.

DISCUSSION

Question 1: Would the results of the 156-04-251 trial as summarized here and described in more detail in Section 3.4.3.2 (Efficacy Results) be adequate to support an acceptable NDA filing for the proposed indication?

Preliminary FDA Response: Yes, your results as summarized are adequate to support an acceptable NDA filing. Based on the information contained in your submission, we think key efficacy issues include the robustness of your findings for the renal pain and renal function components of your key secondary endpoint, the amount of missing data, and the nature of the follow up information obtained in study subjects who prematurely discontinued study medication. We are also interested in whether the data suggest that benefit continues to accrue over time and whether effects are seen across the spectrum of renal disease (defined by level of renal impairment and also by kidney size). As indicated in prior correspondence, we do not currently accept changes in kidney volume as a surrogate endpoint and thus will place emphasis on the findings for your key secondary composite endpoint.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: Otsuka inquired if the effect of tolvaptan on total kidney volume (TKV- the primary endpoint of trial 156-04-251) would play a role in the decision whether to approve tolvaptan for this indication. The Division reaffirmed that they consider TKV an unvalidated surrogate, so it would not play a role. The Division indicated it was open to discussing whether the effect of tolvaptan on TKV could be described in section 14 of the label if tolvaptan is approved for this indication.

The Division observed that 14% of placebo subjects and 23% of tolvaptan subjects enrolled in trial 156-04-251 did not complete it. Otsuka was advised that informative censoring is likely to be an important review issue and so should be addressed in detail in the NDA submission. Otsuka was advised also that having vital status on all subjects, including subjects who prematurely discontinued from the trial, is desirable. Otsuka indicated they would try to obtain this information.

The Division inquired about the indication that would be sought by Otsuka. Otsuka indicated they had not decided what indication would be sought but that they planned to seek a broad indication for prevention of progression of ADPKD including in patients with mild disease.

Finally, Otsuka stated they plan to propose a new trade name for tolvaptan marketed for treatment of ADPKD. The dose, population treated, and outcomes are so different that they believed having two labels will make the information clearer for prescribers. The Division noted that the main concern about having two trade names for the same drug is patient confusion resulting in taking the same drug twice without realizing it. The Division indicated that the two populations for whom tolvaptan would be indicated are distinct and so Otsuka's proposal seems reasonable.

Question 2: The NDA package is based principally on data from a single pivotal trial providing an average of 2.48 years of tolvaptan exposure in 961 subjects (totaling 2334.5 exposure years, with over 800 patients exposed for 12 months or longer) compared with 2.75 years of placebo exposure in 483 subjects (1305.5 exposure years); many of these subjects have been enrolled in an open-label extension trial planned to provide a minimum of 2 additional years of safety and efficacy data (refer to Section 3.6). Additionally, open-label data on approximately 40 subjects with > 5 years exposure will be provided. Otsuka believes these data meet or exceed the International Conference on Harmonization (ICH) recommendations for support of a chronic treatment indication; does the Division concur?

Preliminary FDA Response: We agree that these data are consistent with the ICH recommendations for support of a chronic treatment indication.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: No additional discussion.

Question 3: The 156-04-251 trial's inclusion and stratification criteria have relied on renal function assessment based on the Cockcroft-Gault estimated CrCl. The second and third efficacy endpoints relied on unadjusted serum creatinine measurements. The NDA data presentation will report these analyses but, for consistency and interpretability, will also describe assessments of renal function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which, as discussed in Section 3.4.2.1.3, provides a more reliable estimate for GFR

across chronic kidney disease (CKD) stages, especially when actual GFR is > 60 mL/min. Does the Division agree with the use of the CKD-EPI estimated glomerular filtration rate (eGFR) formula for the NDA?

Preliminary Response: Yes, we agree with the use of the CKD-EPI formula for the NDA.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: No additional discussion.

Question 4: Otsuka is performing a full risk assessment of the datasets in patients with ADPKD, with a focus on general safety issues as well as potential drug-induced liver injury as described in Section 3.5, after which time the sponsor will determine if a risk evaluation and mitigation strategy (REMS) is required to be submitted with the NDA. Does the Agency agree with the proposed risk assessment approach outlined in the briefing document?

Preliminary FDA Response: Yes, however, there should be further discussion with the Agency regarding the need for a REMS once you have reviewed the data but prior to NDA submission.

In your liver analyses tables of elevated liver tests, please define the period for a concurrent elevation in liver tests (e.g., Does "ALT >3xULN and total bilirubin >2xULN" mean that the total bilirubin elevation occurred on the same day as the ALT elevation or does it mean that the rise occurred within seven days after the ALT elevation?). You should also plan to submit the two liver analyses datasets described below.

- A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, randomization date, study termination date, first medication date, last medication date, the following liver test results, ratios, and date of collection: ALT, AST, total bilirubin, and alkaline phosphatase, and an indicator for central or local lab. All liver test results should be in consistent units. Note that there is a date associated with each lab test, e.g., ALT_date, AST_date.

- A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, the date and results of all laboratory tests done to rule out other causes of drug induced liver injury.

Please also submit SAS transport files for your MedDRA coding dictionaries for the AEs of special interest. The purpose of this dataset is to understand how verbatim AE terms were mapped.

Otsuka's Response:

- *Please confirm that the purpose of the meeting is to discuss the rationale for inclusion/exclusion of a REMS and if necessary, the elements that may be required.*

- *Otsuka proposes to leverage its Fast -Track Status for the meeting and request a 2 week review period for the Briefing Package? Does the Agency agree?*

Additional discussion during the meeting: Otsuka was advised to submit their rationale for the inclusion/exclusion of a REMS and, if deemed necessary, a description of the elements to be included. The Division will review the package and attempt to provide feedback in the requested timeframe. A meeting may or may not be needed.

Question 5: Tolvaptan was previously reviewed by the FDA Cardiovascular and Renal Drug Products' Scientific Advisory Committee following the submission of NDA 22-275 for the treatment of hyponatremia (25 Jun 2008). Does the Division believe there will be questions relating to the tolvaptan NDA for ADPKD that might necessitate a second Scientific Advisory Committee meeting?

Preliminary FDA Response: Yes, we think it is likely that there will be questions pertaining to this new treatment indication for which an Advisory Committee Meeting will be convened.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: The Division indicated that an Advisory Committee Meeting (if convened) would likely be held no later than two months prior to the PDUFA date. The Division requested and the sponsor agreed to provide the names of experts that they had employed as consultants because those individuals will not be available to serve as members of the Advisory Committee.

Question 6: The primary safety and efficacy data of this NDA come from a single 3-year double-blind trial. Otsuka proposes the table of contents (TOC) of clinical tables, mock-up tables for the key efficacy tables, and mock-up tables for the key safety tables as shown in Appendix 4. Is this formatting acceptable to the Division?

Preliminary FDA Response: Yes, your formatting is acceptable. The analysis datasets necessary to derive key tables should also be submitted (e.g., analyses related to efficacy, safety, subject disposition). Your submission should also include a table that lists and hyperlinks to 1) all of the main tables and figures in your Pivotal trial and ISS, 2) the SAS code used to generate the table or figure, and 3) the datasets used to generate the table or figure. In your disposition dataset, information such as last visit date, last contact date, type of contact (phone or clinic visit), patient vital status, last dose date, and reason for discontinuation should be included.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: No additional discussion.

Question 7: The structure of the analysis datasets is provided in Appendix 5. Does the Division agree that the structure of the analysis datasets is acceptable to support filing and approval of the NDA?

Preliminary FDA Response: Yes, the structure of the analysis datasets is acceptable to support filing of the NDA. You should also provide the raw datasets from which your analysis datasets were derived, along with all related program codes. Your definition file should also clearly describe the algorithm used to derive key variables. See also the response to Question 6.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: No additional discussion.

Question 8: For the NDA safety updates, Otsuka proposes to provide only listings and narratives without case report forms (CRFs). Does the Division agree with this proposal?

Preliminary FDA Response: This may be reasonable – however, we would like further information on the data that what will be submitted as part of your safety update.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: The sponsor indicated that the safety update would include safety data from ongoing open-label extension trials. Safety data available as of March 3, 2012 will be submitted with the NDA. The sponsor also agreed to submit CRFs for all events requested by the Division in Comment 6. The sponsor clarified that the NDA will not contain efficacy data from ongoing open-label extension trials.

Question 9: Otsuka proposes that the combined extent of exposure across trials in Module 2.7.4 for trials that included both IR and modified-release (MR) formulations of tolvaptan will present only data for the IR formulation of tolvaptan. Safety data of MR capsules will be summarized in the individual study reports in Module 5 (b) (4)
Trial 156-09-285 included 25 ADPKD subjects, approximately half of whom received the IR formulation. Trial 156-09-290 is ongoing and will not be unblinded for the NDA. Does the Division agree with this proposal?

Preliminary FDA Response: Yes, we agree that Trial 156-09-290 does not need to be unblinded for the purpose of this NDA.

Otsuka's Response: *No further comments at this time.*

Additional discussion during the meeting: No additional discussion.

Other preliminary comments and requests:

1. Please clarify the treatment indication that you will be seeking, and specifically the population in which you seek a claim.
2. In reference to the exposure-response analyses conducted in support of this application, please provide a brief description of the analyses conducted (objectives, response variables, range of data etc.). In addition, please submit the following datasets and codes/scripts in the NDA for reviewers to recreate modeling and simulations:
   - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   - Model code or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
3. Please submit the Clinical Pharmacology Summary according to the format specified in the attachment.

   Otsuka's Response: *A question-based review document has already been completed for tolvaptan as part of the hyponatremia indication. We propose cross-referencing that review and only providing updates relevant to the ADPKD indication.*

   Additional discussion during the meeting: Dr. Menon-Anderson indicated that the proposal was acceptable.

4. Please submit genotype data for PKD1 and PKD2 where available.
5. For all derived (analysis) datasets, please indicate the CRF page/tabulation datasets from which the information was derived.
6. Please submit case report forms (CRFs) for all deaths and dropouts (i.e. subjects who permanently discontinued trial medication) because of serious adverse events. We also request that you submit CRFs for subjects who (1) discontinued tolvaptan because of "loss to follow up", "investigator withdrew subject" and "subject withdrew consent"; (2) experienced a serious liver-related adverse event; and (3) developed clinically significant hypernatremia.

   Otsuka's Response: *Otsuka will provide the requested information for the placebo-controlled, pivotal 156-04-251 trial. Please confirm Otsuka's proposed definition of "clinically significant hypernatremia" as those subjects whose laboratory values exceed pre-specified "Potentially Clinically Significant" criteria or who report an AE of "Hypernatremia" or "Increased Blood Sodium".*

   Additional discussion during the meeting: The Division agreed but clarified that CRFs did not need to be submitted for subjects with minor elevations in serum sodium outside the normal range (i.e., an isolated serum sodium of 147 mEq/L).

7. The adjudication packages (i.e., the documents that were provided to adjudicators) for all potential endpoint events should be submitted with the NDA. The signed form documenting the adjudicator's decision should also be submitted.

   ***Otsuka's Response**:* *No further comments at this time.*

8. Please submit MCP-1, cystatin C and any other supportive biomarker data from placebo-controlled trials.

   Otsuka's Response: *No further comments at this time.*

ATTACHMENTS AND HANDOUTS

We have attached the eDISH specifications for the liver data sets. It is important to note that separate files of the PDF narratives by subject (please provide separate PDF files for each subject instead of combining all subjects into a single PDF file) in SAS version 9.1 or 9.2 for eDISH is needed, as mentioned on the specs, separate from the narratives provided as part of Module 5. We need the SAS data set to be packaged as a zip file and sent on a CD/DVD as SAS 9.1/9.2 can not currently be submitted via Gateway.

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

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

/s/

ANNA J PARK
07/25/2012

NORMAN L STOCKBRIDGE
07/25/2012