CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210854Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126653

MEETING MINUTES

Shionogi Incorporated
Attention: Priyanka Kamath, MS
Manager, U.S. Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Kamath:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for S-033188.

We also refer to the meeting between representatives of your firm and the Division of Antiviral Products (DAVP) on October 31, 2017. The purpose of the meeting was to discuss the results of the completed Phase 2 study 1518T0821 and the Phase 3 study 1601T0831, conducted in influenza subjects who are otherwise healthy to support a New Drug Application (NDA) for the treatment of acute uncomplicated influenza. Specifically, to discuss the acceptability and completeness of the clinical, nonclinical, clinical pharmacology and product quality package, the datasets, pooling of the Phase 2 and Phase 3 data, and priority review designation.

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

If you have any questions, call me at (301) 796-0827 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial 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: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 31, 2017
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: 126653
Product Name: S-033188

Indication: **Treatment of acute uncomplicated influenza**
Applicant Name: **Shionogi Incorporated**

Meeting Chair: Melisse Baylor, MD, Medical Officer
Meeting Recorder: Victoria Tyson

FDA ATTENDEES

Melisse Baylor, M.D., Medical Officer
Mary Singer, M.D., Ph.D., Medical Team Lead
Fraser Smith, Ph.D., Biometrics
Thamban Valappil, Ph.D., Biometrics Team Lead
Su-Young Choi, Pharm D., Ph.D. Clinical Pharmacology
Paula Bielnicka, Clinical Pharmacology Student Intern
Shirley Seo, Ph.D., Clinical Pharmacology Team Lead
Ada Zhuang, Ph.D., Clinical Pharmacology/Pharmacometrics
Chao Liu, Ph.D., Clinical Pharmacology/Pharmacometrics Team Lead
William Ince, Ph.D., Clinical Virology
Anamaris ColbergPoley, Ph.D., Clinical Virology
Michael Thomson, Ph.D., Clinical Virology
Julian O'Rear, Ph.D., Clinical Virology Team Lead
David McMillan, Ph.D., Nonclinical
Rajan Pragani, Ph.D., Product Quality
Stephen Miller, Ph.D., Product Quality Team Lead
Adam Sherwat, M.D., Medical Team Lead
Elizabeth Thompson, MS, Chief Project Management Staff
Poonam Mishra, M.D., MPH, Deputy Director for Safety
Jeffrey Murray, M.D., MPH, Deputy Director
Debra Birnkrant, M.D., Director

John Farley, M.D., Deputy Director, OAP

FDA PARTICIPANT (phone)
Barbara Styrt, M.D., MPH, Medical Officer, OAP

Shionogi ATTENDEES
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Ting Chen, MS, Vice President, US Regulatory Affairs, USA
Ravi Chivkula, MS, Director, Regulatory Affairs-CMC, USA
Ann Howell, Pharm D, MS, Senior Director, US Regulatory Affairs, USA
Priyanka Kamath, MS, Manager, US Regulatory Affairs, USA
Keiko Kawaguchi, MS, Project Statistician Japan
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Takeki Uehara, DVM, Ph.D., Global Project Leader, Senior Director, Project Management, Japan
Masaaki Wada, MS, Senior Director, Chemistry, Manufacturing and Controls, Japan
Toshihiro Wajima, Ph.D., Head of Clinical Pharmacology & Pharmacokinetics, Japan

Hoffmann-La Roche/Genentech ATTENDEES
Barry Clinch, Ph.D., Roche Representative-Group Clinical Science Director
Linda Jack, Ph.D., Roche Representative-Regulatory Franchise Head, Rheumatology & Infectious Disease
Mark Eisner, M.D., MPH, Vice President of Product Development Immunology, Infectious Disease and Ophthalmology, Genentech/Roche

Shionogi PARTICIPANTS (phone)
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Kevin Halloran, MS, Senior Vice President, Regulatory Affairs /Quality, US
Jimmy Chen, Ph.D, Senior Director Pharmaceutical Sciences, US
Fangjun Wu, PhD, Senior Manager Pharmaceutical Sciences, US
Go Kimura, PhD, Director, Section Head Formulation Process Development, Japan
Motoyuki Hagihara, Director Section Head of Process Chemistry Department, API, Japan

1.0 BACKGROUND

S-033188 is an antiviral drug that inhibits influenza virus cap-dependent endonuclease (CEN), thereby disrupting viral replication. Shionogi has completed 11 Phase 1 studies of S-033188 (prodrug) and S-033447 (active form) and two clinical studies (Phase 2 and 3) in patients with acute uncomplicated influenza A and B (Study 1601T0831 and Study 1518T0821).

S-033188 is being developed as 20 mg and 40 mg tablets for a single dose administration based on body weight; 40 mg for patients weighing < 80 kg and 80 mg for patients weighing > 80 kg. An NDA is planned for submission in April 2018, for the treatment of acute uncomplicated influenza virus infection (b) (4) in patients 12 years of age and older.

The DAVP received the Pre-NDA meeting request on August 28, 2017 to discuss the acceptability and completeness of the clinical, nonclinical, clinical pharmacology and product quality package and to discuss the datasets, pooling of the Phase 2 and Phase 3 data, and priority review designation. The meeting was granted on September 14, 2017 and the background package was received on October 2, 2017. DAVP sent Preliminary Comments to Shionogi Incorporated on October 30, 2017. Shionogi responded to the Preliminary Meeting Comments on October 31, 2017. No further discussion was required on Comments, 1, 8, 9, 11, 15, 17, and 18. Shionogi provided responses to Comments 5, 6, 7, 10, (1, 2, and 3), 12, Additional Comments 1, 2 and 3, and to Clinical Virology Comments 1, 3, 4 and 7-18, for clarification/comment.

2. DISCUSSION

2.1. Clinical

Question 2: *Does the Agency agree that the nonclinical and clinical data are supportive of submission of an NDA* (b) (4) *indication proposal, understanding the actual indication will be a review issue?*

FDA Response to Question 2: We have significant concerns about the data provided in support of efficacy against influenza (b) (4). Both nonclinical and clinical data suggest that a higher dose may be needed (b) (4), and consideration should be given to adding a treatment arm to the ongoing Phase 3 high-risk trial to study a higher S-033188 dose.

As you have noted, however, the actual indication will be a review issue, and you should provide strong justification for your proposed indication and dose.

(b) (4)

(b) (4)

Question 3: *Does the Agency agree that the size of the anticipated safety database is sufficient for submitting the proposed NDA?*

FDA Response to Question 3: We do not agree with the size of anticipated safety database for the proposed submission. (b) (4)

(b) (4)

(b) (4)

Post-Meeting Follow-up Comment: *The Division discussed this issue internally and agree that a safety database* (b) (4) *would be acceptable for submission of the NDA.*

Question 4: *Does the Agency agree with the cut-off date and proposed content of the 120-day Safety Update?*

FDA Response to Question 4: As discussed in our response to Question 3, (b) (4) the timing of the safety update should be acceptable.

Discussion: *We generally agree with the proposed timing of the Safety Update, which should include tabular summaries of all adverse events, serious adverse events, Grade 3 and 4 adverse events, Grade 3 and 4 laboratory abnormalities, and adverse events leading to premature study discontinuation. In addition, narratives for all deaths, discontinuations due to adverse events, and serious adverse events should be included in the Safety Update.* (b) (4)

Question 5: *Does the Agency agree with the integration plans for the Phase 2 and Phase 3 data, specifically the groupings for and types of efficacy analyses and safety analyses?*

FDA Response to Question 5: Your plans for pooling of the Phase 2 and 3 safety and efficacy data are acceptable; however, the efficacy and safety data will be reviewed separately for each individual trial for independent evidence of treatment effect. Please also note that whether pooled safety data will be presented in labeling, will be a review issue.

(b) (4)

Analyses of pooled data should also include subset analyses of the primary endpoint and key virologic endpoints based on virus type and subtype as well as resistance.

Shionogi Preliminary Response: *Type I error was not controlled for subgroup analyses of virus subtype in the Phase 2 and 3. We would like to further discuss the need to control Type 1 error in the post-hoc pooled analyses after the Phase 2 and 3 studies have already completed.*

Discussion: *The Division raised concern with pooling the data from the Phase 2 and 3 trials for subjects infected with Type B influenza because of the differences in the pharmacokinetics in Japanese and US patients and questioned the relevance of the data to US patients. The Division reiterated the fact that pooling the Phase 2 and 3 data will be a review issue, and as discussed during the End of Phase 2 Meeting,* (b) (4)

2.2 Clinical Pharmacology

Question 6: *Does the Agency agree that the clinical pharmacology package is sufficient for submission of an NDA?*

FDA Response to Question 6: Overall, the package appears sufficient for submission of an NDA. Please clarify your plan for a hepatic impairment study in subjects with severe hepatic impairment.

Shionogi Response: *We have followed the FDA guidance which indicates no severe hepatic impairment study is needed if no effect was seen in subjects with moderate hepatic impairment. We plan to label as per the FDA guidance recommendation, which would include caution for severe hepatic impairment due to hepatic clearance and lack of data in this population.*

Discussion: *The Division agreed this will be a review and labeling issue.*

Question 7: *Does the Agency agree with the proposed dosing for S-033188 for the treatment of influenza?*

FDA Response to Question 7: The final dose for approval will be a review issue. When submitting your NDA, please specify the lower limit of weight for adolescent patients. (b) (4)

Shionogi Preliminary Response: *The lower limit of weight for adolescent patients was 40 kg in the clinical study and this can be indicated in the label.*

Discussion: *No meeting discussion occurred.*

Question 10: *Does the Agency agree that a high fat food effect study is not required for either the 20 mg or 40 mg tablets?*

FDA Response to Question 10: Conduct of a high-fat food effect study using the to-be-marketed formulation is preferable for the following reasons:

1. There is uncertainty with respect to the magnitude of the effect of high-fat food on the to-be-marketed formulation. We currently do not have data to show that the effect of moderate-fat food can be directly extrapolated to high-fat food.

2. While your subgroup analysis by prandial states in Phase 2 and 3 trials indicates that there is no significant effect of food on efficacy, the data are largely driven by Japanese patients. In Japanese patients, baseline exposure of S-033188 is higher and thus, the effect of food on efficacy could be masked. Also, the types of foods that are typically consumed by people with influenza in Japan are likely different from the US. Non-Asians have lower baseline drug exposures and may consume high fat foods more frequently than Japanese patients.

3. Without results from a high-fat food effect study, labeling language with respect to prandial conditions may become restrictive (e.g., avoid high-fat food or take in fasted state). This is not preferable due to the time that is required for the patient to wait in order to avoid certain foods or reach a fasted state. A prolonged delay in drug administration may decrease the effectiveness of a flu drug.

Shionogi Preliminary Response: *No meeting discussion occurred.*

We have the following questions for clarification:

1. Were the types of meal (high, medium, or low fat) recorded in the eCRF in efficacy trials? How was prandial state captured? Did subjects report the exact timing of meals before and after drug administration in efficacy trials?

Shionogi Preliminary Response: *The types of meals were not recorded. The exact timing of meals both pre- and post-dosing was recorded for both the Phase 2 and Phase 3 study and for analysis data was organized into the following categories: > 4 hours before or after drug administration; between 2 and 4 hours of drug administration; and < 2 hours from drug administration.*

Discussion*: No further discussion was required.*

2. As for the underlying cause of negative food effects on S-033188 absorption, have you determined whether changes in pH due to food intake could be the reason for decreased absorption?

Shionogi Preliminary Response: *The solubility of S-033188 is independent of pH. Dissolution at pH 1.2, pH 4.5, and pH 6.8 are similar, as described in the pre-NDA briefing document pages 46-48. Additional effects on pH changes will be provided with the NDA.*

Discussion*: No further discussion was required.*

3. You stated that S-033188 likely forms chelation. If this is the case, we recommend that you conduct a study evaluating the effects of cation-containing drugs such as MAALOX®, on the absorption of S-033188.

Discussion: *No meeting discussion occurred.*

Shionogi Preliminary Response: *We have completed a nonclinical study in monkeys and the extent of decrease due to minerals is comparable to the food-effect seen in human Phase 1 studies.*

Post-Meeting Follow-up Comment Discussion: *The magnitude of drug-food or contents of food interaction observed in preclinical species may not be directly extrapolated to humans. While it is a review issue, this study alone is unlikely to be able to support the use of S-033188 with cation-containing products.*

Generally speaking, for a drug that forms chelation, the effects of cation-containing products on the absorption of the drug are significant (50-90% reduction) when the two products are simultaneously administered. Therefore, restrictive labeling language may be implemented in the absence of drug interaction data in humans.

2.3 Clinical Virology

Question 12. *Does the Agency agree that 3 months stability data for the S-033447 concentration in the swabs is sufficient for submission of an NDA?*

FDA Response to Question 12: The plan is acceptable from a Virology standpoint. We expect that spiking-in estimated nasal concentrations (including a high concentration as a positive control) of S-033447 to reconstructed samples across a range of virus titers will be adequate to determine if, and at what virus titer, carry-over may be an issue. In any case, we have asked that endpoints based on viral RNA be included in all your key virologic endpoint evaluations (see Additional Comments), where potential drug carryover would be presumed to have no impact.

Shionogi Preliminary Response: *We are planning the study described above and will provide it with the NDA.*

Discussion: *No meeting discussion occurred.*

2.5 Biometrics

Question 13. *Does the Agency agree with the Sponsor's proposal to meet the content requirements for the Integrated Summary of Efficacy and Integrated Summary of Safety in the NDA by providing detailed integrated analyses of all relevant data with appropriate tables and text incorporated from both the clinical study reports and the pooled analyses in Module 2.7.3 and 2.7.4 and the statistical outputs pertaining to the pooled analyses in Module 5.3.5.3?*

FDA Response to Question 13: In general, we agree with your proposal to meet the content requirements of the ISS and ISE in the NDA. The individual pivotal Phase 2 and 3 clinical study reports along with the ISS should also include the following additional safety analyses:

- Laboratory analyses by toxicity scale graded treatment-emergent laboratory abnormalities (e.g., using the Division of AIDS grading table)

- Assessment of hepatic adverse events and laboratory abnormalities (increased ALT, AST, and total bilirubin) and neuropsychiatric adverse events by toxicity grade, timing, age, sex, race, and region

In addition, please include a virology summary with hypertext links to study reports in section 2.7.2.4, Special Studies.

Shionogi Preliminary Response: *In FDA's preliminary response, it is mentioned that the Division agrees with our approach, but then it is mentioned that the ISS should include additional analyses. We would like to clarify/confirm that the Division agrees that only a 2.7.3 and 2.7.4 will be provided, which will include complete summaries of individual data and pooled data. Only statistical outputs and TLFs are included in 5.3.5.3.*

Additionally, we confirm that the additional information requested will be provided in 2.7.4. Because of the low number of hepatic and neuropsychiatric AEs we will describe the requested information (timing, age, sex, race, and region) in the narratives rather than in summary tables.

Discussion: *No meeting discussion occurred.*

Post-Meeting Follow-up Comments: *We agree with your approach (i.e. only 2.7.3 and 2.7.4 will be provided which will include complete summaries of individual and pooled data, and only statistical outputs, tables and figures will be included in 5.3.5.3).*

Question 14. Does the Agency agree with the datasets and programs planned to be submitted with the NDA?

FDA Response to Question 14: In addition to submitting statistical programs for primary/secondary analyses of the primary efficacy endpoint, please submit statistical programs for analyses of secondary efficacy endpoints and for any inferential statistical analyses of safety endpoints. In addition, please submit the programs used to create analysis datasets for the corresponding analyses.

Please provide the treatment-emergent adverse event (TEAE) definition utilized in the pivotal Phase 2 and 3 trials, and include a TEAE flag in the individual trial and pooled ADAE and ADLB datasets.

Please submit the coding dictionary used for mapping investigator verbatim AE terms to preferred terms in the individual trials and ISS.

The pivotal Phase 2 and 3 individual and pooled ADLB datasets should include a laboratory toxicity grade column, a baseline laboratory flag, and a baseline toxicity grade column.

Please also include datasets for the Phase 1 studies and for the Phase 3 pediatric study.

Please submit mock pooled ISS ADAM datasets for CDER review prior to submitting the NDA. This process may help identify and resolve any potential issues of navigability or interpretability that could impact the review of the application.

Please provide virologic datasets for each clinical study that conform to the recommendations sent in previous communications (see comments sent 8/15/2016; we have also included the most recent version of the *Draft Recommendations for Submitting Influenza Virus Resistance Analyses*, appended), including the preliminary meeting comments sent 6/26/2017, based on review of your phase 2 virology datasets submitted 4/26/2017 (6/26/2017 Additional Comment 5). Additionally, (based on review of dataset T0821) values under "EC_{50}" should be numeric and please include a column that indicates the assay used for each measurement (if more than one was used for a given parameter) and columns for the LLOQ and LOD in virologic datasets. We recommend submitting preliminary or mock datasets for feedback in advance of the NDA submission. See Additional Comments for additional data submission recommendations.

Shionogi Preliminary Response: *Shionogi will provide statistical programs for the primary and secondary analyses of the primary efficacy endpoint. In addition, Shionogi will submit the programs used to create analysis datasets for corresponding analyses.*

There are 15 secondary endpoints in the Phase 3 study. Shionogi proposes to provide statistical programs for the following key secondary endpoints only in the Phase 3 study. Is this acceptable to the Division?

- *Proportion of patients positive for influenza virus titer*
- *Change from baseline in virus titer*
- *Time to cessation of viral shedding by virus titer*
- *Time to resolution of fever*

- *Time to return to pre-influenza health status*
- *Incidence of influenza-related complications*

In addition, Shionogi proposes to provide statistical programs for the following key secondary endpoints only in the Phase 2 study.

- *Proportion of patients positive for influenza virus titer*
- *Change from baseline in virus titer*
- *Time to cessation of viral shedding by virus titer – analyzed post-hoc*
- *Time to resolution of fever*
- *Time to resumption of normal activity*
- *Incidence of influenza-related complications*

With regard to safety endpoints, Shionogi proposes to submit statistical programs for TEAEs and TRAEs only in the Phase 3 study. Is this acceptable to the Division?

Discussion: *The Division asked Shionogi to provide the definitions used for treatment-emergent adverse events (TEAE) in the pivotal Phase 2 and 3 trials, and to flag all abnormal TEAEs in the individual trials and pooled ADAE and ADLB datasets.*

Post-Meeting Follow-up Comments: *Although it is acceptable to submit statistical programs for TEAEs and TRAEs for the Phase 3 trial, submission of statistical programs for TEAEs and TRAES in the Phase 3 study is not necessary.*

Please provide the treatment-emergent adverse event (TEAE) definition utilized in the pivotal Phase 2 and 3 trials, and include a TEAE flag in the individual trial and pooled ADAE and ADLB datasets.

Shionogi Preliminary Response: *We would like to clarify FDA's request, specifically we would like to know if:*

- *We should flag all abnormal lab values regardless of association with an AE; or*

We should flag all of those described in the ADLB datasets comment below.

Discussion: *No meeting discussion occurred.*

Post-Meeting Follow-up Comments: *Rather than flagging all abnormal lab values, please flag all Grade 1-4 labs. This approach excludes labs that are outside the normal range (> ULN or < LLN) but are not Graded abnormalities.*

Please submit the coding dictionary used for mapping investigator verbatim AE terms to preferred terms in the individual trials and ISS.

Shionogi Preliminary Response: *The version of MedDRA will be provided with the NDA.*

The pivotal Phase 2 and 3 individual and pooled ADLB datasets should include a laboratory toxicity grade column, a baseline laboratory flag, and a baseline toxicity grade column.

Discussion: *No meeting discussion occurred.*

Shionogi Preliminary Response: *The laboratory toxicity grade and a baseline laboratory flag will be included in the pivotal Phase 2 and 3 individually and pooled ADLB datasets.*

Discussion: *Please also include datasets for the Phase 1 studies and for the Phase 3 pediatric study.*

Shionogi Preliminary Response: *PK datasets for all Phase 1 studies are planned to be provided with the NDA. Shionogi would like to confirm if all safety datasets or only ADLB datasets are requested for all Phase 1 studies. Shionogi would like to confirm that only ADS (analysis datasets) are necessary i.e. not SDTM/ADaM.*

Pediatric data is being provided with the NDA to support safety. Shionogi would like to confirm if the dataset for all safety is requested or only ADLB datasets for the Japanese pediatric study.

Discussion: *No meeting discussion occurred.*

Post-Meeting Follow-up Comments: *Please provide all safety datasets and ADLB datasets for all Phase 1 studies. Analysis datasets (only) are acceptable. For the Japanese pediatric study, please provide all safety datasets, including the ADLB datasets.*

Please submit mock pooled ISS ADAM datasets for CDER review prior to submitting the NDA. This process may help identify and resolve any potential issues of navigability or interpretability that could impact the review of the application.

Shionogi Preliminary Response: *Shionogi will provide mock pooled ISS ADAM datasets to FDA for review and comment prior to submitting the NDA.*

Please provide virologic datasets for each clinical study that conform to the recommendations sent in previous communications (see comments sent 8/15/2016; we have also included the most recent version of the *Draft Recommendations for Submitting Influenza Virus Resistance Analyses*, appended), including the preliminary meeting comments sent 6/26/2017, based on review of your phase 2 virology datasets submitted 4/26/2017 (6/26/2017 Additional Comment 5). Additionally, (based on review of dataset T0821) values under "EC50" should be numeric and please include a column that indicates the assay used for each measurement (if more than one was used for a given parameter) and columns for the LLOQ and LOD in virologic datasets. We recommend submitting preliminary or mock datasets for feedback in advance of the NDA submission. See Additional Comments for additional data submission recommendations.

Discussion: *No meeting discussion occurred.*

Shionogi Preliminary Response: *Shionogi will follow FDA's guidance and advice provided in previous communications.*

Discussion: *No meeting discussion occurred.*

2.6 Regulatory

Shionogi Preliminary Response: *Shionogi would like to discuss this comment with the Division further at the meeting.* (b) (4) *Considering this, we would like to discuss again the necessity for the additional studies.*

(b) (4)

2.7 Chemistry, Manufacturing and Controls

Question 19: *Does the Agency agree that the content of our proposed stability data package is sufficient to support the shelf life of both the 20 and 40 mg tablets? This assumes that all data provided in the NDA submission meets the proposed shelf life specifications.*

FDA Response to Question 19: *Your proposed stability dataset for the initial NDA submission is reasonable. However, please provide the 6-month stability data update for the 40 mg tablet during the NDA review cycle.*

Shionogi Preliminary Response: *We would like to discuss this topic further at the meeting. Specifically, we would like to show what data will be provided and when it will be provided during the review cycle.*

Discussion: *Shionogi presented a table summarizing the batches to be provided and their proposed timeline. In summary, 6 month data on 3 registration batches of 40 mg tablets will be available at 60 days after NDA submission. An additional supportive batch will have a 12 month update at that time. Additional site-specific DP batches (3 for each strength) will have release data in the initial NDA submission and 3 month updates will be available after 60 days. The Division confirmed that these plans are acceptable and clarified that if the 40 mg tablet data are equivalent to the 20 mg tablet data, a single expiration dating period would usually be assigned, using the ICH Q1E approach to analysis for the 20 mg dataset. The Division also indicated that the review team might request additional stability updates during the review, and Shionogi was supportive of this possibility.* (b) (4)

3.0 ADDITIONAL COMMENTS/INFORMATION REQUESTS

Clinical

(b) (4)

Discussion: *The Division stressed the importance* [redacted] (b) (4)

2. You have already submitted Clinical Study Reports (CSRs) for multiple trials to your IND. The results for these trials will also be submitted as part of the NDA. In the NDA submission, for each of these studies, please identify any differences in the CSR submitted to the NDA compared to the CSR submitted to the IND.

Shionogi Preliminary Response: *The CSRs in the NDA are expected to be the same as those previously submitted to the IND. If we find any differences, we will identify them clearly in the NDA.*

Discussion: *No meeting discussion occurred.*

3. With the submission of your NDA, please submit an exposure-response analysis using time to alleviation of symptoms as the measure of response (in addition to change in virus and viral RNA shedding).

Shionogi Preliminary Response: *This exposure-response analysis has been performed and will be part of the NDA.*

Discussion: *No meeting discussion occurred.*

4. With the submission of your NDA, please submit an exposure-response analysis for safety for treatment-emergent adverse events (TEAE), treatment-related AEs, common AEs, and serious adverse events.

Shionogi Preliminary Response: *Because we only have 2 SAEs in the pivotal studies and a low frequency of discrete adverse events was observed, an exposure response analysis TEAE, TRAE and SAEs would not be meaningful. Therefore, Shionogi proposes to summarize exposure data for patients with most frequent (≥ 2%) adverse events only, which include bronchitis, sinusitis, diarrhea and nausea and for patients with SAEs. Does the Division agree with this proposal?*

Discussion: *No meeting discussion occurred.*

Post-Meeting Follow-up Comment: *The Division agrees with this proposal.*

Clinical Virology

Many of the Virology comments below follow-up on comments sent previously and pertain to information that will support data analysis and labeling.

Additional analyses recommended for the NDA submission:

1. Please confirm that viruses resistant to S-033188 are sensitive to approved anti-influenza antivirals.

Shionogi Preliminary Response: *Oseltamivir acid susceptibility of viruses harboring a treatment-emergent amino acid substitution detected in all S-033188 clinical studies are being evaluated and these data will be submitted with the NDA.*

Discussion: *No meeting discussion occurred.*

2. Regarding sequence analyses of PB1 and PB2 (in addition to PA) in subjects who exhibit a reduced response to treatment or rebound, please provide the specific criteria for selecting these subjects. We note that in study 1518T0821, PB1 and PB2 were sequenced for reduced-responders regardless of their PA sequencing results, and additional substitutions were identified in virus with known PA resistance substitutions. However, in your resistance analysis plan for phase 3 studies (and the phase 2 hospitalized study), you state that only subjects who do not have virus with a PA substitution that confers resistance will be evaluated for variation in PB1 and PB2. We ask that you include in your NDA application, sequence analyses of the PB1 and PB2 genes of virus from all subjects who meet the criteria for a reduced response, regardless of the findings in the PA gene. We note that resistance in influenza B virus has yet to be sufficiently characterized, and resistance may be conferred by alternative pathways outside of PA. The Division may request that systematic sequencing of PB1 and PB2 genes from S-033188-treated subjects be carried out post-marketing, should data included in the NDA be insufficient to make an adequate determination as to the relative contribution of PB1 and PB2 genes to resistance.

Discussion: *The Division reiterated the concern that PB1 and PB2 have not been adequately evaluated as to their potential roles in mediating susceptibility to S-033188. The sponsor provided an update of their resistance analysis for all clinical studies to be included in their NDA submission (slides 34-60).*

Post-Meeting Follow-up Comments:

a. We appreciate the rigorous and comprehensive analysis of resistance focusing on the PA gene that you are undertaking for your NDA; however, PB1 and PB2 genes have not been adequately evaluated with regard to their involvement in reducing susceptibility to S-033188, as sequence analyses of these genes was not reported in your cell-culture selection studies, and only a limited sampling of subjects from phase 2 and phase 3 studies were evaluated for the emergence of PB1 and/or PB2 variants, limiting the opportunity to observe PB1 or PB2 substitutions that may have emerged in more than one instance. In addition, there were subjects with apparent virus rebound in the phase 3 study in whom known resistance substitutions were not identified in PA. While substitutions in PA may be the primary drivers of resistance, more data are necessary to allow an evaluation of the potential for substitutions in PB1 and PB2 to affect susceptibility, alone or in combination with PA substitutions.

We therefore recommend that you include in your NDA submission sequence analysis of PB1 and PB2 genes, in addition to PA, at baseline, the time of peak rebound (if applicable), and the last evaluable time point in subjects who exhibit a reduced response to treatment in phase 3 studies. The criteria for a reduced response should not only capture subjects who experience virus rebound, but also those who fail to initially respond to treatment or have prolonged shedding. Phenotypic analysis of substitutions identified in PB1 or PB2 should be prioritized based on the criteria outlined in additional comment number 4. Whether additional resistance analyses (including additional phenotypic analyses) that may be needed meet the criteria for a post-marketing requirement or post-marketing commitment will be determined after review of the data submitted with the NDA.

b. In subset analyses evaluating the impact of resistance on clinical and virologic outcomes, please use endpoints (including time points) where a signification difference was demonstrated between active treatment and placebo. We note that in your analyses presented on slide 51, there was no significant

difference between S-033188 treatment and placebo in the incidence of influenza symptoms after Day 5 or the incidence of fever after Day 5.

3. PA substitutions E199G and K362R were selected in cell culture passaging in the presence of S-033447 (study S-033188-EB-208-N), but were not unambiguously evaluated for their impact on susceptibility in cloned virus. These substitutions should be evaluated for their impact on S-033447 susceptibility in cloned virus. Please note that these substitutions will be considered for inclusion in the label as "selected in cell culture."

Shionogi Preliminary Response: *A/H3N2 viruses were used in the S-033188-EB-208-N study, thus A/H3N2 virus harboring the mutation was prepared by reverse genetics (=cloned virus) and drug susceptibility was tested in plaque reduction assay. The result showed the fold change of E199G and K362R was 4.46 and 1.25, respectively. The report will be submitted with the NDA.*

Discussion: *No meeting discussion occurred.*

4. In clinical resistance analyses, amino acid substitutions should be further evaluated phenotypically in cloned virus if they a) are treatment emergent in more than one subject (including substitutions that may be present at baseline but increase in frequency at later time points), b) emerge at highly conserved sites, including unusual substitutions at polymorphic sites or changes that require >1 nucleotide change, c) emerge at sites that would be predicted to impact PA activity or drug susceptibility based on cell culture data or structure, d) are treatment-emergent or present at baseline (and differ from the subject population baseline consensus sequence) in subjects who have a reduced response to treatment. Examples include I38M, identified in study 1601T0822 as treatment emergent in multiple subjects (a) and at a site predicted to impact drug susceptibility (c), and E23K, identified in study 1518T0821 at a position proximal to the drug-binding site (c). Substitutions falling into any of these categories will be considered for inclusion in the label.

Shionogi Preliminary Response: *The requested analyses have been or will be conducted and included with the NDA.*

Discussion: *No meeting discussion occurred.*

(b) (4)

6. Please consider sequencing the PB1 and PB2 genes of available viruses selected in cell culture and animals in the presence of S-033188/S-033447, in studies that evaluated resistance to these compounds.

Discussion: *Please refer to the Discussion for Comment 2.*

7. It is unclear whether you intend to sequence NA and HA from subjects who received oseltamivir in studies 1601T0831 and 1601T0832. Such data would be of interest in comparing relative rates of resistance between S-033188 and oseltamivir, and may be requested by the Division as a post-marking analysis.

Shionogi Preliminary Response: *We have no plans to conduct this study at this time.*

Discussion: *No meeting discussion occurred.*

8. Please be sure to preserve clinical samples from all treatment arms for potential post-marketing analyses.

Shionogi Preliminary Response: *We are retaining all samples with the exception of those obtained from Germany which according to local regulations must be discarded immediately after conclusion of the clinical study.*

Discussion: *No meeting discussion occurred.*

The following information was requested previously and should be included in the NDA submission:

9. We have not received a description and performance information for the ViroSpot assay, making it difficult to interpret results derived from this assay. We have recommended that phenotypic resistance be evaluated for cloned virus in well characterized phenotypic assays that can reproducibly detect small but potentially relevant changes in EC_{50} values.

Shionogi Preliminary Response: *We will provide a validation report with the NDA. However, we used the ViroSpot assay only for baseline variants monitoring. Phenotypic resistance analysis was performed using cloned virus generated by reverse genetics, and plaque reduction assay was employed as FDA recommended.*

Discussion: *No meeting discussion occurred.*

10. Information requested in the preliminary comments sent 6/26/2017 regarding the Type C meeting to discuss trials in hospitalized subjects should be included in your NDA submission for acute, uncomplicated influenza. Specifically, please include the requested assay methods and performance characteristics (6/26/2017, Additional Comments 2 and 3). All assay validation reports should be

submitted for virologic assays used in supportive and pivotal clinical studies and should include the LLOQ, LOD and other performance characteristics along with primer sequences for RT-PCR assays. Please provide information that indicates the limit of detection of minor variants in virus mixtures in your sequencing assay.

We also requested evaluations of the impact on S-033188 susceptibility of specific amino acid substitutions identified in clinical study 1518T0821 (6/26/2017, Additional Comment 4). These substitutions were either linked to reduced susceptibility in cell culture or were identified in subjects who exhibited reduced response to treatment.

Shionogi Preliminary Response: *We will submit these with the NDA as FDA requested.*

Discussion: *No meeting discussion occurred.*

11. Please evaluate the impact of PA I38T/F/M substitutions on sensitivity to S-0331447 in influenza B virus, as indicated in your responses to Division comments that we received 5/27/2016.

Shionogi Preliminary Response: *The requested analysis has been conducted. B/Maryland/1/59 virus harboring the mutation was prepared by reverse genetics (=cloned virus) and drug susceptibility was tested in plaque reduction assay. The results show that, the fold change of I38T/F/M was 5.76, 2.39 and 8.04, respectively. The report will be submitted with the NDA.*

Discussion: *No meeting discussion occurred.*

12. Please provide details regarding the methods used to prepare viral RNPs for evaluating S-033447 inhibition of CEN activity.

Shionogi Preliminary Response: *The method is described in a published manuscript which will be provided with the NDA.*

Discussion: *No meeting discussion occurred.*

Additional data analyses and dataset recommendations for the NDA:

13. Virologic endpoint analyses based on both virus and viral RNA should be included in your final analysis. It is not clear at this point which correlates better with clinical endpoints.

Shionogi Preliminary Response: These analyses have been performed and will be included with the NDA.

Discussion: *No meeting discussion occurred.*

14. Subset analyses should include resistance status (pre-existing and treatment-emergent), as well as virus type and subtype. In your datasets, please include the identity of the type B virus lineage (Yamagata or Victoria), if available.

Shionogi Preliminary Response: *We will perform the requested subset analysis and provide with the NDA, with the exception of including the influenza type B lineage which we have not distinguished in the clinical studies.*

Discussion: *No meeting discussion occurred.*

15. Please submit a combined dataset of all viruses evaluated for susceptibility to S-033447/S-033188 in cell culture, including their EC_{50} and EC_{90} values. In addition to standard strain information, such as strain name and subtype, please include the influenza type B lineage (Yamagata or Victoria).

Shionogi Preliminary Response: *We will provide the requested datasets with the NDA.*

Discussion: *No meeting discussion occurred.*

16. Please determine the frequency of polymorphisms for all positions at which treatment-emergent amino acid substitutions are identified. Provide the frequencies within type A viruses, within key type A subtypes, and within type B viruses and type B lineages. Please include in viral sequence analysis datasets a column that indicates common polymorphisms (≥1%) observed at each position in order of decreasing frequency for the respective virus type/subtype.

Shionogi Preliminary Response: *We will perform the requested analysis on the PA gene only and provide with the NDA.*

Discussion: *The Division requested that a table be provided for all treatment-emergent substitutions (e.g. those indicated on slide 55) that shows the percent identity at each position, that indicates substitutions requiring 2 base changes in the codon, and identifies any of the substitutions in the list that have not been observed in circulating viruses at that position.*

17. We note that in the phenotypic resistance analysis in study 1601T0822, the reference strain A/Victoria/361/2011(H3N2) was used for both H1N1 and H3N2 viruses. Please use influenza A subtype-specific references when evaluating fold changes to a reference in phenotypic assessments and as references for sequence analysis. Please use reference strains that are closely related to the strains circulating during the clinical studies. Phenotypic resistance analysis reports should include the fold-change observed for the positive controls in the assay.

Shionogi Preliminary Response: *The requested additional analyses will be conducted and the results will be provided with the NDA for the Phase 3 OwH study and the Japanese pediatric study, but not for the Phase 2 study as the H1N1 reference strain was not used in this study*.

Discussion: *No meeting discussion occurred.*

Hospitalized study recommendation:

18. Please collect data on the identity of non-influenza virus coinfections in your hospitalized influenza studies.

Shionogi Preliminary Response: *We will collect this information in our planned study.*

Discussion: *No meeting discussion occurred.*

4.0 ADDITONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 14, 2017, 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 VI. 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 and, where applicable, the development of a Formal Communication Plan. 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.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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.

We reference your agreed iPSP dated May 5, 2017. Please include your agreed iPSP, along with any requests for waivers and deferrals, with your original marketing application submission.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

PROPRIETARY NAME REQUEST

If you intend to have a proprietary name for this product, we recommend you submit a request for a proposed proprietary name review as soon as possible. If you require information on submitting a request for proprietary

name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies

of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.				

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of

the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other

sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.

b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

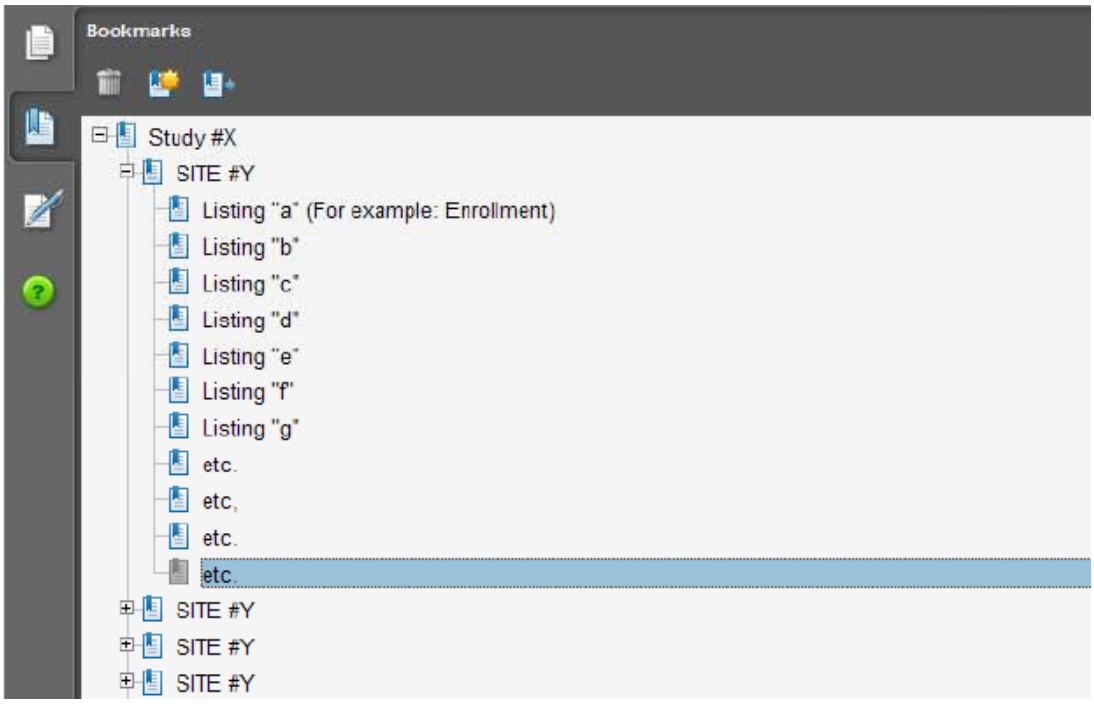
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

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

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

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



III. Request for Site Level Dataset:

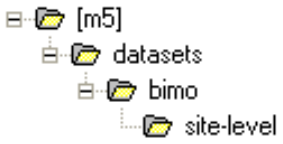
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide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

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

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

DSI Pre-NDA Request Item1	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

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Division asked Shionogi to include baseline phenotypic analysis, combined with baseline genotypic analysis in the NDA submission.	Shionogi	NDA submission
The Division requested that a table be provided for all treatment-emergent substitutions (e.g. those indicated on slide 55) that shows the percent identity at each position, that indicates substitutions requiring 2 base changes in the codon, and identifies any of the substitutions in the list that have not been observed in circulating viruses at that position.	Shionogi	NDA submission

6.0 ATTACHMENTS AND HANDOUTS

Attachment 1: Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format
Attachment 2: Draft Recommendations for Submitting Influenza Virus Resistance Analyses (version 03/23/17).
Attachment 3: Shionogi Preliminary Responses and Slides

Attachment 2

Draft Recommendations for Submitting Influenza Virus Resistance Analyses (version 03/23/17).

One dataset should combine subject data, virologic data, and viral genotypic and phenotypic resistance data. For each study, we recommend constructing datasets as SAS Transport Files (.xpt). A record should be included for all scheduled virus samples regardless of whether they were successfully collected or are negative for virus, RNA or other analytes. Each data category should contain a single metric, statistic or category with uniform format and units. Datasets for separate clinical studies should all contain the same data categories using the same format so they can be easily merged. Please consult the Division on formats that can be used for submitting information not covered in this guidance, such as genotypic data from next-generation sequencing (NGS) platforms or immunological (e.g., anti-influenza virus antibody, cytokine) data.

The Division may request that data also be submitted according to a vertical template format currently being developed for submission of viral drug resistance data from clinical trials. The purpose of the new template is to harmonize variables with current SDTM and ADaM standards, which will aid in the review of genotypic and phenotypic drug resistance data and facilitate the merging of multiple SDTM domains and ADaM derived variables. The vertical format also streamlines and simplifies reporting of genotypic resistance data, reduces the number of columns in transport datasets relative to previous resistance data templates, and allows for relatively straightforward reporting of next generation sequencing summary analysis data and supporting information. Note that if NGS data are being collected for submission, DAVP currently is also requesting submission of raw data for independent analysis and has additional instructions for submission of these data. The Division will provide a new template along with requests that data be submitted in the vertical format. The Division requests that resistance data continue to be submitted as described in this document or as agreed upon during consultation with the Division.

Headings and categorical data can be given as abbreviated and standardized names to fit the SAS format as long as a full description is provided in the submission (e.g., in a separate definition file).

I. **Information to Include in Each Virus Sample Record**[1]

I. Subject data and Sample data (one metric per column):

- **Subject identification number** (ID number should be unique among all clinical studies of the product).
- **Country** (If in US, include CDC region).
- **Season** (hemisphere/country and year).
- **Study design** (e.g. therapeutic or prophylactic), if multiple designs are used.
- **Treatment group** (e.g., specific dose, active control, placebo).
- **Whether or not the primary efficacy endpoint was achieved** (Y or N)
- **Primary clinical endpoint metric** (e.g. symptoms severity score, time to resolution of symptoms, etc.)
- **Symptom onset, date and time** (therapeutic trials).
- **Alleviation of symptoms**, **date and time** (therapeutic trials).
- **Treatment initiation, date and time** (therapeutic trials).
- **Termination of treatment**, **date and time** (therapeutic trials).
- **Relevant plasma pharmacokinetic data** (e.g. AUC, C_{min} and C_{max}).
- **Relevant bronchoalveolar or nasal lavage/swab pharmacokinetic data.**

- **Virus sample collection date and time.**
    - **Virus sample sequence according to schedule** (e.g., baseline, treatment day 0, day 2 post end-of-treatment. Multiple virus samples from the same visit should be numbered, e.g. baseline 1, baseline 2).
    - **Method of virus sample collection** (e.g., nasopharyngeal swab or nasal wash. In most studies, it is anticipated that all samples used for virologic analysis will be obtained using the same methodology that will be described in the protocol and study report. If there is a reason for use of more than one method in the same study, discussion with the Division is recommended.)
    - **Previous therapeutic products used to treat the current infection**, if any.
    - **Concomitant therapeutic products**, and dosage information.
    - **Indication if data were censored** (yes or no).
    - **Reason for censorship** (e.g., discontinuation because of adverse event).
    - **Other infectious agents detected** (yes or no, or not tested).
    - **Identity of other agents detected**

II. Virologic Data:

Virologic data include information about the identity (influenza virus type and subtype) and quantity of the virus in samples. The protocol and study report should include a detailed description of assay methodology and explanation of units of measurement for any qualitative or quantitative assays. Supporting information should be provided to allow review of assay performance; however, use of a specified assay in an antiviral product trial does not constitute FDA review, approval, or endorsement of the assay.

- **Viral titer** in sample $(TCID_{50}/mL)^2$.
- **Viral RNA** in sample $(units/mL)^2$.
- **Virus type/subtype**.
- **Method used to determine virus type/subtype** (e.g., rapid antigen testing, RT-PCR or nucleotide sequence analysis. The specific assay used should be identified for each sample, if not uniform and identified in the protocol).
- **Rapid diagnostic test result** (e.g. positive or negative; the specific assay used should be identified for each sample).
- **Whether or not virologic data were obtained for a given sample** (Y or N).

III. Genotypic Data:

Viral genotypic data are used to evaluate sequence changes in the viral genome that may be associated with drug treatment. Genotypic data should be provided for (at a minimum) baseline virus samples from all subjects and for virus samples collected at other time points specified in the protocol (see the example in Table 1).

Viral genotypic data should be derived directly from virus in subject samples, without any intervening cell culture amplification step. A detailed description of assay methodologies for genotyping of virus from subject samples should be included in the study report,

describing sample manipulations, amplification procedures (RT-PCR), and the sequencing or other genotyping technology used. If Sanger sequencing fails to detect resistance-associated substitutions in subjects who do not appear to respond to treatment or who experience prolonged shedding, more sensitive methods capable of detecting minor variants should be used.

Genotype information for all the relevant coding regions should be provided. Typically, reporting of the inferred amino acid sequence and substitutions is adequate.

Genotypic data should be provided in the following format for each sample evaluated:

- Datasets should contain the reference amino acid sequence. The reference sequence used should be identified by name and GenBank® accession number. Known polymorphic amino
- acid residues should be identified and their frequencies relative to the reference sequence reported.
- The target gene should be identified in a separate column if multiple genes were sequenced
- Samples associated with the detection of emergent variants should be flagged.
- One amino acid per column or row with the gene and amino acid position indicated; the reference amino acid position should be used as the column header.
- Any substitutions identified should be reported using the single-letter abbreviation (e.g. K, for lysine).
- For all positions with mixtures of amino acid substitutions, all amino acids (including the reference when detected in the mixture) should be listed separated by "/". Otherwise, only changes from the reference sequence should be indicated (i.e., blank cell or absence of data for a position indicates no change relative to the reference sequence). Each position should be represented in all datasets, even if no substitutions were detected at the position. Known polymorphic amino acid residues should be identified, for example with an asterisk in the heading or in the reference amino acid sequence.
- The name of nucleotide sequence analysis site (e.g., central laboratory, CRO) should be indicated if more than one was used.
- Indicate the sequence analysis method used (e.g. Sanger sequencing, Illumina deep sequencing). Details of these methods should be provided in the study report submission.
- Indicate if genotypic data were obtained directly from the patient sample or after cell culture expansion.

IV. Phenotypic Data:

The purpose of phenotypic analysis is to determine if viral isolates or variants have reduced susceptibility to the drug. Phenotypic data should be provided for virus in (at a minimum) baseline samples, and samples collected at the appropriate predetermined time points, for subjects who do not appear to respond to treatment or who experience prolonged shedding. Sponsors are strongly encouraged to collect and store virus samples for later analysis should additional phenotypic analyses be necessary. If, in consultation with the Division, it is determined that the genetic pathways to resistance are well established, phenotypic analysis may not be necessary.

Phenotypic analysis should include biological (e.g. virus entry and replication in cell culture) assays to measure drug activity, and both the 50% and 90% effective concentrations (EC, for antiviral activity in cell culture) and inhibitory concentrations (IC, for enzymatic and other biochemical assays) should be reported. Variants containing suspected resistance-associated amino acid substitutions should be evaluated for changes in EC values compared to a reference strain virus, and results for post-baseline viral variant should also be compared to those of the subject's baseline variant. The reference strain name and GenBank® accession numbers should be provided. When possible, a biological clone (e.g. generated by plaque purification or endpoint dilution) or a molecular clone should be used in phenotypic assays to evaluate the susceptibility of specific variants. Please include the following phenotypic information for each record (see the example in Table 2):

1. *Susceptibility to investigational drug and approved drugs or other drugs in the same class*
   - EC_{50} and EC_{90} values of candidate product against the reference strain (the reference strain should be a widely available standard lab strain (e.g. A/Puerto Rico/8/1934, A/California/4/2009).
   - EC_{50} and EC_{90} values of the candidate product against virus isolated (and preferably cloned) from subject samples (including the baseline sample).
   - Include a flag column that indicates whether or not phenotypic data were obtained for a given sample (yes or no).

II. **Other Considerations:**

- Resistance data may be submitted in a single dataset that combines subject and virologic data or in multiple datasets (e.g., one for genotypic data, one for phenotypic data); please consult the Division for recommendations specific for your submission.
- Resistance datasets should be accompanied by study reports that provide detailed descriptions of assay methodologies and performance parameters (e.g., sensitivity, specificity, etc.). However, the approved use of a specified assay in an antiviral product trial does not constitute FDA review, approval, or endorsement of the assay for use elsewhere.

III. **Table 1: Example of Partial Genotype Information Display**

ID	Sample[2]	Day[3]	SubFL[4]	Type	273[5]	274	275	276	277
A Reference[1]					N	Y	H	Y	E
B Reference[1]					V	E	H	T	E
Sub0001	BL	1		H1N1			Y		
Sub0001	Day 3	3		H1N1			Y		
Sub0003	BL	1		H3N2					
Sub0003	Day 3	3	Y	H3N2					D
Sub0006	BL	1		H1N1			H/Y		
Sub0006	Day 3	3	Y	H1N1			Y		
Sub0010	BL	1		B					
Sub0010	Day 3	3		B					
Sub0010	Week 1	8		B					

[1] Influenza type A (human H1N1 or H3N2) or type B virus gene X (e.g. neuraminidase) reference sequence, which should be a specified (accession number), published (in a publicly-available database with unconditional access, such as GenBank®) reference sequence representative of circulating strains.
[2] Study visit; BL = Baseline visit. A separate column should include the sample date and time.
[3] Study day numbering should be clearly indicated in the protocol and should be relative to treatment initiation (e.g. Day -1, Day 0, Day 1, etc.).
[4] Flag for samples with virus expressing treatment-emergent substitutions.
[5] Amino acid position numbering should be specified (e.g. N2, H3).

IV. Table 2: Example of Partial Phenotype Information Display

ID	Sample[1]	Day[2]	EC_{50} value	FC from Ref[3]	FC from BL[4]
Reference			0.025		
Sub0001	BL	1	0.015	0.6	
Sub0001	Day 3	3	0.23	0.9	1.5
Sub0003	BL	1	0.045	1.8	
Sub0003	Day 3	3	0.44	17.6	9.8
Sub0006	BL	1	0.028	1.12	
Sub0006	Day 3	3	0.11	4.4	3.9
Sub0010	BL	1	0.011	0.44	
Sub0010	Day 3	3	0.13	5.2	12
Sub0010	Week 1	8	0.52	20.8	47

[1] Study visit; BL = Baseline visit. A separate column should include the sample date and time.
[2] Study day numbering should be clearly indicated in the protocol and should be relative to treatment initiation (e.g. Day
-1, Day 0, Day 1, etc.).
[3] Fold-Change (FC) in EC_{50} value from the reference virus.
[4] Fold-Change (FC) in EC_{50} value from the Baseline isolate.

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[1] In the SAS transport files, headings and categorical data can be given abbreviated and standardized names to fit the SAS format as long as a full description (e.g., define file) is provided in the submission.

[2]If a sample is positive for virus but a measurement is below the assay's lower limit of quantification (<LLOQ), then report as target detected (TD) or as a predefined value that falls between the LLOQ and the limit of detection (LOD). If a sample is negative for virus, then report the results as target not detected (TND) or as a predefined value that falls below the LOD.

Question 1: *Does the Agency agree that the efficacy data from the Phase 2 and Phase 3 studies in patients with influenza who are otherwise healthy are sufficient for submission of an NDA?*

FDA Response to Question 1: In general, the efficacy data from the Phase 2 and Phase 3 studies appear to be sufficient for submission of an NDA.

Shionogi Preliminary Response:

No additional discussion needed.

Question 2: *Does the Agency agree that the nonclinical and clinical data are supportive of submission of an NDA* (b) (4) *indication proposal, understanding the actual indication will be a review issue?*

FDA Response to Question 2: We have significant concerns about the data provided in support of efficacy against influenza (b) (4) Both nonclinical and clinical data suggest that a higher dose may be needed (b) (4) and consideration should be given to adding a treatment arm to the ongoing Phase 3 high-risk trial to study a higher S-033188 dose.

As you have noted, however, the actual indication will be a review issue, and you should provide strong justification for your proposed indication and dose.

Shionogi Preliminary Response:

We would like to discuss this topic further at the meeting.

Question 3: *Does the Agency agree that the size of the anticipated safety database is sufficient for submitting the proposed NDA?*

FDA Response to Question 3: We do not agree with the size of anticipated safety database for the proposed submission. (b) (4)

(b) (4)

Shionogi Preliminary Response:

We would like to discuss this topic further during the meeting.

Question 4: *Does the Agency agree with the cut-off date and proposed content of the 120-day Safety Update?*

FDA Response to Question 4: As discussed in our response to Question 3, (b) (4) [redacted] the timing of the safety update should be acceptable.

Shionogi Preliminary Response:

This question may be discussed further at the meeting as it relates to the discussion for Question 3.

Question 5: *Does the Agency agree with the integration plans for the Phase 2 and Phase 3 data, specifically the groupings for and types of efficacy analyses and safety analyses?*

FDA Response to Question 5: Your plans for pooling of the Phase 2 and 3 safety and efficacy data are acceptable; however, the efficacy and safety data will be reviewed separately for each individual trial for independent evidence of treatment effect. Please also note that whether pooled safety data will be presented in labeling, will be a review issue.

(b) (4) [redacted]

Analyses of pooled data should also include subset analyses of the primary endpoint and key virologic endpoints based on virus type and subtype as well as resistance.

Shionogi Preliminary Response:

Type I error was not controlled for subgroup analyses of virus subtype in the Phase 2 and 3. We would like to further discuss the need to control Type 1 error in the post-hoc pooled analyses after the Phase 2 and 3 studies have already completed.

Question 6: *Does the Agency agree that the clinical pharmacology package is sufficient for submission of an NDA?*

FDA Response to Question 6: Overall, the package appears sufficient for submission of an NDA. Please clarify your plan for a hepatic impairment study in subjects with severe hepatic impairment.

Shionogi Preliminary Response:

We have followed the FDA guidance which indicates no severe hepatic impairment study is needed if no effect was seen in subjects with moderate hepatic impairment. We plan to label as per the FDA guidance recommendation, which would include caution for severe hepatic impairment due to hepatic clearance and lack of data in this population.

Question 7: *Does the Agency agree with the proposed dosing for S-033188 for the treatment of influenza?*

FDA Response to Question 7: The final dose for approval will be a review issue. When submitting your NDA, please specify the lower limit of weight for adolescent patients. (b) (4)

Shionogi Preliminary Response:

The lower limit of weight for adolescent patients was 40 kg in the clinical study and this can be indicated in the label.

Question 8: *Does the Agency agree with the request for a biowaiver for conducting a 40 mg BE study?*

FDA Response to Question 8: We agree that you can include a request to waive the requirement for conducting a BE study between the 20 mg and 40 mg tablets (Biowaiver Request) in the NDA submission for the proposed 40 mg strength which has not been studied clinically, provided that you have satisfactorily demonstrated proportional similarity in the composition for the active and inactive ingredients across both strengths (20 and 40 mg), the same dosage form, same release mechanism and same manufacturing process, and comparable in-vitro dissolution data for both strengths, as well as providing evidence of pharmacokinetic (PK) linearity over the proposed dose range. The biowaiver request will be evaluated during the NDA review based on the totality of the submitted data. Be advised that dissolution profile comparisons between the higher 40 mg and lower 20 mg strengths should be conducted in three different media (i.e., pH 1.2, 4.5, 6.8) and the proposed medium (if different) using the same dissolution testing conditions. If addition of a surfactant to the dissolution media or if other adjustments to the testing conditions (e.g. volume) are necessary, a detailed justification should be included.

Shionogi Preliminary Response:

No additional discussion needed.

Question 9: *Should the Agency deny the requested biowaiver for a clinical BE study of the 40 mg tablet, would it be acceptable to submit the study report for the BE study within 30 days of the NDA submission date?*

FDA Response to Question 9: As a definitive determination on the acceptability of the biowaiver is not made until the time of NDA submission, you may decide to conduct a

BE trial ahead of this decision. If this is the case, the full clinical and bioanalytical study reports will need to be contained within the original NDA submission. It will not be acceptable to submit it within 30 days of the NDA submission date.

Shionogi Preliminary Response:

No additional discussion needed.

Question 10: *Does the Agency agree that a high fat food effect study is not required for either the 20 mg or 40 mg tablets?*

FDA Response to Question 10: Conduct of a high-fat food effect study using the to-be marketed formulation is preferable for the following reasons:

1. There is uncertainty with respect to the magnitude of the effect of high-fat food on the to be-marketed formulation. We currently do not have data to show that the effect of moderate-fat food can be directly extrapolated to high-fat food.
2. While your subgroup analysis by prandial states in Phase 2 and 3 trials indicates that there is no significant effect of food on efficacy, the data are largely driven by Japanese patients. In Japanese patients, baseline exposure of S-033188 is higher and thus, the effect of food on efficacy could be masked. Also, the types of foods that are typically consumed by people with influenza in Japan are likely different from the US. Non- Asians have lower baseline drug exposures and may consume high fat foods more frequently than Japanese patients.
3. Without results from a high-fat food effect study, labeling language with respect to prandial conditions may become restrictive (e.g., avoid high-fat food or take in fasted state). This is not preferable due to the time that is required for the patient to wait in order to avoid certain foods or reach a fasted state. A prolonged delay in drug administration may decrease the effectiveness of a flu drug.

Shionogi Preliminary Response:

No additional discussion needed.

We have the following questions for clarification:

1. Were the types of meal (high, medium, or low fat) recorded in the eCRF in efficacy trials? How was prandial state captured? Did subjects report the exact timing of meals before and after drug administration in efficacy trials?

Shionogi Preliminary Response:

The types of meals were not recorded. The exact timing of meals both pre and post-dosing was recorded for both the Phase 2 and Phase 3 study and for analysis data was organized into the following categories: > 4 hours before or after drug administration; between 2 and 4 hours of drug administration; and < 2 hours from drug administration].

2. As for the underlying cause of negative food effects on S-033188 absorption, have you determined whether changes in pH due to food intake could be the reason for decreased absorption?

Shionogi Preliminary Response:

The solubility of S-033188 is independent of pH. Dissolution at pH 1.2, pH 4.5, and pH 6.8 are similar as described in the pre-NDA briefing document pages 46-48. Additional effects on pH changes will be provided with the NDA.

3. You stated that S-033188 likely forms chelation. If this is the case, we recommend that you conduct a study evaluating the effects of cation-containing drugs such as MAALOX®, on the absorption of S-033188.

Shionogi Preliminary Response:

We have completed a nonclinical study in monkeys and the extent of decrease due to minerals is comparable to the food-effect seen in human Phase 1 studies.

Question 11: *Does the Agency agree that the nonclinical package is sufficient for submission of an NDA?*

FDA Response to Question 11: Yes, we agree that your nonclinical package appears sufficient to support an NDA for the currently proposed indication. However, please note that any changes in clinical use (b) (4) may result in the need for additional nonclinical studies. Please also refer to our response to Question 16.

Shionogi Preliminary Response:

No additional discussion needed.

Question 12: *Does the Agency agree that 3 months stability data for the S-033447 concentration in the swabs is sufficient for submission of an NDA?*

FDA Response to Question 12: The plan is acceptable from a Virology standpoint. We expect that spiking-in estimated nasal concentrations (including a high concentration as a positive control) of S-033447 to reconstructed samples across a range of virus titers will be adequate to determine if, and at what virus titer, carry-over may be an issue. In any case, we have asked that endpoints based on viral RNA be included in all your key virologic endpoint evaluations (see Additional Comments), where potential drug carryover would be presumed to have no impact.

Shionogi Preliminary Response:

We are planning the study described above and will provide it with the NDA.

Question 13: *Does the Agency agree with the Sponsor's proposal to meet the content requirements for the Integrated Summary of Efficacy and Integrated Summary of Safety*

in the NDA by providing detailed integrated analyses of all relevant data with appropriate tables and text incorporated from both the clinical study reports and the pooled analyses in Module 2.7.3 and 2.7.4 and the statistical outputs pertaining to the pooled analyses in Module 5.3.5.3?

FDA Response to Question 13: In general, we agree with your proposal to meet the content requirements of the ISS and ISE in the NDA. The individual pivotal Phase 2 and 3 clinical study reports along with the ISS should also include the following additional safety analyses:

- Laboratory analyses by toxicity scale graded treatment-emergent laboratory abnormalities (e.g., using the Division of AIDS grading table)
- Assessment of hepatic adverse events and laboratory abnormalities (increased ALT, AST, and total bilirubin) and neuropsychiatric adverse events by toxicity grade, timing, age, sex, race, and region

In addition, please include a virology summary with hypertext links to study reports in section 2.7.2.4, Special Studies.

Shionogi Preliminary Response:

In FDA's preliminary response, it is mentioned that the Division agrees with our approach, but then it is mentioned that the ISS should include additional analyses. We would like to clarify/confirm that the Division agrees that only a 2.7.3 and 2.7.4 will be provided, which will include complete summaries of individual data and pooled data. Only statistical outputs and TLFs are included in 5.3.5.3.

Additionally, we confirm that the additional information requested will be provided in 2.7.4. Because of the low number of hepatic and neuropsychiatric AEs we will describe the requested information (timing, age, sex, race, and region) in the narratives rather than in summary tables.

Question 14: *Does the Agency agree with the datasets and programs planned to be submitted with the NDA?*

FDA Response to Question 14: In addition to submitting statistical programs for primary/secondary analyses of the primary efficacy endpoint, please submit statistical programs for analyses of secondary efficacy endpoints and for any inferential statistical analyses of safety endpoints. In addition, please submit the programs used to create analysis datasets for the corresponding analyses.

Shionogi Preliminary Response:

Shionogi will provide statistical programs for the primary and secondary analyses of the primary efficacy endpoint. In addition, Shionogi will submit the programs used to create analysis datasets for corresponding analyses.

There are 15 secondary endpoints in the Phase 3 study. Shionogi proposes to provide statistical programs for the following key secondary endpoints only in the Phase 3 study. Is this acceptable to the Division?

- Proportion of patients positive for influenza virus titer
- Change from baseline in virus titer
- Time to cessation of viral shedding by virus titer
- Time to resolution of fever
- Time to return to pre-influenza health status
- Incidence of influenza-related complications

In addition, Shionogi proposes to provide statistical programs for the following key secondary endpoints only in the Phase 2 study.

- Proportion of patients positive for influenza virus titer
- Change from baseline in virus titer
- Time to cessation of viral shedding by virus titer – analyzed post-hoc
- Time to resolution of fever
- Time to resumption of normal activity
- Incidence of influenza-related complications

With regard to safety endpoints, Shionogi proposes to submit statistical programs for TEAEs and TRAEs only in the Phase 3 study. Is this acceptable to the Division?

Please provide the treatment-emergent adverse event (TEAE) definition utilized in the pivotal Phase 2 and 3 trials, and include a TEAE flag in the individual trial and pooled ADAE and ADLB datasets.

Shionogi Preliminary Response:

We would like to clarify FDA's request, specifically we would like to know if:

- We should flag all abnormal lab values regardless of association with an AE; or
- We should flag all of those described in the ADLB datasets comment below.

Please submit the coding dictionary used for mapping investigator verbatim AE terms to preferred terms in the individual trials and ISS.

Shionogi Preliminary Response:

The version of MedDRA will be provided with the NDA.

The pivotal Phase 2 and 3 individual and pooled ADLB datasets should include a laboratory toxicity grade column, a baseline laboratory flag, and a baseline toxicity grade column.

Shionogi Preliminary Response:

The laboratory toxicity grade and a baseline laboratory flag will be included in the pivotal Phase 2 and 3 individually and pooled ADLB datasets.

Please also include datasets for the Phase 1 studies and for the Phase 3 pediatric study.

Shionogi Preliminary Response:

- PK datasets for all Phase 1 studies are planned to be provided with the NDA. Shionogi would like to confirm if all safety datasets or only ADLB datasets are requested for all Phase 1 studies. Shionogi would like to confirm that only ADS (analysis datasets) are necessary i.e. not SDTM/ADaM.

  Pediatric data is being provided with the NDA to support safety. Shionogi would like to confirm if the dataset for all safety is requested or only ADLB datasets for the Japanese pediatric study.

Please submit mock pooled ISS ADAM datasets for CDER review prior to submitting the NDA. This process may help identify and resolve any potential issues of navigability or interpretability that could impact the review of the application.

Shionogi Preliminary Response:

Shionogi will provide mock pooled ISS ADAM datasets to FDA for review and comment prior to submitting the NDA.

Please provide virologic datasets for each clinical study that conform to the recommendations sent in previous communications (see comments sent 8/15/2016; we have also included the most recent version of the *Draft Recommendations for Submitting Influenza Virus Resistance Analyses*, appended), including the preliminary meeting comments sent 6/26/2017, based on review of your phase 2 virology datasets submitted 4/26/2017 (6/26/2017 Additional Comment 5). Additionally, (based on review of dataset T0821) values under "EC50" should be numeric and please include a column that indicates the assay used for each measurement (if more than one was used for a given parameter) and columns for the LLOQ and LOD in virologic datasets. We recommend submitting preliminary or mock datasets for feedback in advance of the NDA submission. See Additional Comments for additional data submission recommendations.

Shionogi Preliminary Response:

Shionogi will follow FDA's guidance and advice provided in previous communications.

Question 15: *Does the Agency agree that S-033188 will likely meet the criteria for priority review, understanding that the decision will be made after the NDA application has been submitted?*

FDA Response to Question 15:

The decision to grant priority review designation is made after NDA submission and prior to filing.

Shionogi Preliminary Response:

No additional discussion needed.

(b) (4)

Shionogi Preliminary Response:

Shionogi would like to discuss this comment with the Division further at the meeting. (b) (4) Considering this, we would like to discuss again the necessity for the additional studies.

Question 17: *Does the Agency agree with the proposed rationale and justification for the designation of* (b) (4) *as the regulatory starting materials for the commercial manufacture of S-033188 Drug Substance?*

FDA Response to Question 17: Your proposal for using (b) (4) as the regulatory starting materials appears reasonable based on the current data. However, it is difficult to assess the starting material impact on the quality of the drug substance without being provided the current drug substance specification and batch analysis data in this meeting package. We have the following additional comments:

(b) (4)

4. In your NDA submission, all facilities involved in GMP manufacturing of the drug substance should be listed and must be ready for inspection at the time of NDA submission.

Shionogi Preliminary Response:

No additional discussion needed.

Question18: Does the Agency agree that the proposed dissolution media is adequate for QC release and stability testing of 20 and 40 mg tablets?

FDA Response to Question 18: FDA cannot make a detailed assessment of the adequacy of the proposed in vitro dissolution method under an IND meeting. You can provide a detailed dissolution method development report in a future IND amendment (with a cover letter indicating that you are requesting feedback from the Division of Biopharmaceutics) or in the NDA submission. Note that FDA will finalize the assessment of the proposed dissolution acceptance criterion only during the NDA review.

Please refer to the following general guidelines on the data and information required to be included in a dissolution method development report:

Shionogi Preliminary Response:

No additional discussion needed.

Question 19: *Does the Agency agree that the content of our proposed stability data package is sufficient to support the shelf life of both the 20 and 40 mg tablets? This assumes that all data provided in the NDA submission meets the proposed shelf life specifications.*

FDA Response to Question 19: Your proposed stability dataset for the initial NDA submission is reasonable. However, please provide the 6-month stability data update for the 40 mg tablet during the NDA review cycle.

Shionogi Preliminary Response:

We would like to discuss this topic further at the meeting. Specifically we would like to show what data will be provided and when it will be provided during the review cycle.

Additional comments:

(b) (4)

(b) (4)

2. You have already submitted Clinical Study Reports (CSRs) for multiple trials to your IND. The results for these trials will also be submitted as part of the NDA. In the NDA submission, for each of these studies, please identify any differences in the CSR submitted to the NDA compared to the CSR submitted to the IND.

Shionogi Preliminary Response:

The CSRs in the NDA are expected to be the same as those previously submitted to the IND. If we find any differences, we will identify them clearly in the NDA.

3. With the submission of your NDA, please submit an exposure-response analysis using time to alleviation of symptoms as the measure of response (in addition to change in virus and viral RNA shedding).

Shionogi Preliminary Response:

This exposure-response analysis has been performed and will be part of the NDA.

4. With the submission of your NDA, please submit an exposure-response analysis for safety for treatment-emergent adverse events (TEAE), treatment-related AEs, common AEs, and serious adverse events.

Shionogi Preliminary Response:

Because we only have 2 SAEs in the pivotal studies and a low frequency of discrete adverse events was observed, an exposure response analysis TEAE, TRAE and SAEs would not be meaningful. Therefore, Shionogi proposes to summarize exposure data for patients with most frequent ($\geq$ 2%) adverse events only, which include bronchitis, sinusitis, diarrhea and nausea and for patients with SAEs. Does the Division agree with this proposal?

Clinical Virology

Many of the Virology comments below follow-up on comments sent previously and pertain to information that will support data analysis and labeling.

Additional analyses recommended for the NDA submission:

1. Please confirm that viruses resistant to S-033188 are sensitive to approved anti-influenza antivirals.

Shionogi Preliminary Response:

Oseltamivir acid susceptibility of viruses harboring a treatment-emergent amino acid substitution detected in all S-033188 clinical studies are being evaluated and these data will be submitted with the NDA.

2. Regarding sequence analyses of PB1 and PB2 (in addition to PA) in subjects who exhibit a reduced response to treatment or rebound, please provide the specific criteria for selecting these subjects. We note that in study 1518T0821, PB1 and PB2 were sequenced for reduced-responders regardless of their PA sequencing results, and additional substitutions were identified in virus with known PA resistance substitutions. However, in your resistance analysis plan for phase 3 studies (and the phase 2 hospitalized study), you state that only subjects who do not have virus with a PA substitution that confers resistance will be evaluated for variation in PB1 and PB2. We ask that you include in your NDA application, sequence analyses of the PB1 and PB2 genes of virus from all subjects who meet the criteria for a reduced response, regardless of the findings in the PA gene. We note that resistance in influenza B virus has yet to be sufficiently characterized, and resistance may be conferred by alternative pathways outside of PA. The Division may request that systematic sequencing of PB1 and PB2 genes from S-033188-treated subjects be carried out post-marketing, should data included in the NDA be insufficient to make an adequate determination as to the relative contribution of PB1 and PB2 genes to resistance.

Shionogi Preliminary Response:

Shionogi would like to discuss this point with the Division further at the meeting.

3. PA substitutions E199G and K362R were selected in cell culture passaging in the presence of S-033447 (study S-033188-EB-208-N), but were not unambiguously evaluated for their impact on susceptibility in cloned virus. These substitutions should be evaluated for their impact on S-033447 susceptibility in cloned virus. Please note that these substitutions will be considered for inclusion in the label as "selected in cell culture."

Shionogi Preliminary Response:

A/H3N2 viruses were used in the S-033188-EB-208-N study, thus A/H3N2 virus harboring the mutation was prepared by reverse genetics (=cloned virus) and drug susceptibility was tested in plaque reduction assay. The result showed the fold change of E199G and K362R was 4.46 and 1.25, respectively. The report will be submitted with the NDA.

4. In clinical resistance analyses, amino acid substitutions should be further evaluated phenotypically in cloned virus if they a) are treatment emergent in more than one subject (including substitutions that may be present at baseline but increase in frequency at later time points), b) emerge at highly conserved sites, including unusual substitutions at polymorphic sites or changes that require >1 nucleotide change, c) emerge at sites that would be predicted to impact PA activity or drug susceptibility based on cell culture data or structure, d) are treatment-emergent or present at baseline (and differ from the subject population baseline consensus sequence) in subjects who have a reduced response to treatment. Examples include I38M, identified in study 1601T0822 as treatment

emergent in multiple subjects (a) and at a site predicted to impact drug susceptibility (c), and E23K, identified in study 1518T0821 at a position proximal to the drug-binding site (c). Substitutions falling into any of these categories will be considered for inclusion in the label.

Shionogi Preliminary Response:

The requested analyses have been or will be conducted and included with the NDA.

Shionogi Preliminary Response:

We would like to discuss this topic further at the meeting.

6. Please consider sequencing the PB1 and PB2 genes of available viruses selected in cell culture and animals in the presence of S-033188/S-033447, in studies that evaluated resistance to these compounds.

Shionogi Preliminary Response:

We would like to discuss this topic further at the meeting.

7. It is unclear whether you intend to sequence NA and HA from subjects who received oseltamivir in studies 1601T0831 and 1601T0832. Such data would be of interest in comparing relative rates of resistance between S-033188 and oseltamivir, and may be requested by the Division as a post-marking analysis.

Shionogi Preliminary Response:

We have no plans to conduct this study at this time.

8. Please be sure to preserve clinical samples from all treatment arms for potential postmarketing analyses.

Shionogi Preliminary Response:

We are retaining all samples with the exception of those obtained from Germany which according to local regulations must be discarded immediately after conclusion of the clinical study.

The following information was requested previously and should be included in the NDA submission:

9. We have not received a description and performance information for the ViroSpot assay, making it difficult to interpret results derived from this assay. We have

recommended that phenotypic resistance be evaluated for cloned virus in well characterized phenotypic assays that can reproducibly detect small but potentially relevant changes in EC50 values.

Shionogi Preliminary Response:

We will provide a validation report with the NDA. However, we used the ViroSpot assay only for baseline variants monitoring. Phenotypic resistance analysis was performed using cloned virus generated by reverse genetics, and plaque reduction assay was employed as FDA recommended.

10. Information requested in the preliminary comments sent 6/26/2017 regarding the Type C meeting to discuss trials in hospitalized subjects should be included in your NDA submission for acute, uncomplicated influenza. Specifically, please include the requested assay methods and performance characteristics (6/26/2017, Additional Comments 2 and 3). All assay validation reports should be submitted for virologic assays used in supportive and pivotal clinical studies and should include the LLOQ, LOD and other performance characteristics along with primer sequences for RT-PCR assays. Please provide information that indicates the limit of detection of minor variants in virus mixtures in your sequencing assay.

    We also requested evaluations of the impact on S-033188 susceptibility of specific amino acid substitutions identified in clinical study 1518T0821 (6/26/2017, Additional Comment 4). These substitutions were either linked to reduced susceptibility in cell culture or were identified in subjects who exhibited reduced response to treatment.

Shionogi Preliminary Response:

We will submit these with the NDA as FDA requested.

11. Please evaluate the impact of PA I38T/F/M substitutions on sensitivity to S-0331447 in influenza B virus, as indicated in your responses to Division comments that we received 5/27/2016.

Shionogi Preliminary Response:

The requested analysis has been conducted. B/Maryland/1/59 virus harboring the mutation was prepared by reverse genetics (=cloned virus) and drug susceptibility was tested in plaque reduction assay. The results show that, the fold change of I38T/F/M was 5.76, 2.39 and 8.04, respectively. The report will be submitted with the NDA.

12. Please provide details regarding the methods used to prepare viral RNPs for evaluating S-033447 inhibition of CEN activity.

Shionogi Preliminary Response:

The method is described in a published manuscript which will be provided with the NDA.

Additional data analyses and dataset recommendations for the NDA:

13. Virologic endpoint analyses based on both virus and viral RNA should be included in your final analysis. It is not clear at this point which correlates better with clinical endpoints.

Shionogi Preliminary Response:

These analyses have been performed and will be included with the NDA.

14. Subset analyses should include resistance status (pre-existing and treatment-emergent), as well as virus type and subtype. In your datasets, please include the identity of the type B virus lineage (Yamagata or Victoria), if available.

Shionogi Preliminary Response:

We will perform the requested subset analysis and provide with the NDA, with the exception of including the influenza type B lineage which we have not distinguished in the clinical studies.

15. Please submit a combined dataset of all viruses evaluated for susceptibility to S-033447/S-033188 in cell culture, including their EC50 and EC90 values. In addition to standard strain information, such as strain name and subtype, please include the influenza type B lineage (Yamagata or Victoria).

Shionogi Preliminary Response:

We will provide the requested datasets with the NDA.

16. Please determine the frequency of polymorphisms for all positions at which treatment emergent amino acid substitutions are identified. Provide the frequencies within type A viruses, within key type A subtypes, and within type B viruses and type B lineages. Please include in viral sequence analysis datasets a column that indicates common polymorphisms (≥1%) observed at each position in order of decreasing frequency for the respective virus type/subtype.

Shionogi Preliminary Response:

We will perform the requested analysis on the PA gene only and provide with the NDA.

17. We note that in the phenotypic resistance analysis in study 1601T0822, the reference strain A/Victoria/361/2011(H3N2) was used for both H1N1 and H3N2 viruses. Please use influenza A subtype-specific references when evaluating fold changes to a reference in phenotypic assessments and as references for sequence analysis. Please use reference strains that are closely related to the strains circulating during the clinical studies. Phenotypic resistance analysis reports should include the fold-change observed for the positive controls in the assay.

Shionogi Preliminary Response:

The requested additional analyses will be conducted and the results will be provided with the NDA for the Phase 3 OwH study and the Japanese pediatric study, but not for the Phase 2 study as the H1N1 reference strain was not used in this study.

Hospitalized study recommendation:

18. Please collect data on the identity of non-influenza virus coinfections in your hospitalized influenza studies.

Shionogi Preliminary Response:

We will collect this information in our planned study.

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

/s/

VICTORIA L TYSON
11/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126653

MEETING MINUTES

Shionogi, Incorporated
Attention: Machiko Sumi
Director, US Regulatory Affairs-Global Development Projects
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Sumi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for S-033188.

We also refer to the meeting between representatives of your firm and the FDA on August 17, 2016. The purpose of the meeting was to discuss the results of the Phase 2 dose finding and proof-of-concept study (1518T0821) completed in Japan and the design of the Phase 3 studies that will be conducted in otherwise healthy subjects and subjects at high risk for influenza complications. Specifically, to obtain feedback on the study designs, endpoints, statistical methodology, and the updated virology assessment plans. Shionogi plans to initiate the proposed Phase 3 clinical trials in November 2016.

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

If you have any questions, call me at (301) 796-0827 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Shionogi Slide Presentation

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 17, 2016, 1:00-2:30 pm
Meeting Location: White Oak Campus, Building 22, Room 1309

Application Number: IND 126653
Product Name: S-033188
Indication: Treatment of uncomplicated acute (b) (4) influenza (b) (4) in patients 12 years of age and older (b) (4)
Applicant Name: Shionogi, Incorporated

Meeting Chair: Melisse Baylor, MD, Medical Officer
Meeting Recorder: Victoria Tyson, RPM

FDA ATTENDEES

Division of Antiviral Products

Melisse Baylor, Medical Officer
Mary Singer, Medical Team Leader
William Ince, Clinical Virology Reviewer
Takashi Komatsu, Clinical Virology Reviewer
Julian O' Rear, Clinical Virology Team Leader
Su-Young Choi, Clinical Pharmacology Reviewer
Shirley Seo, Clinical Pharmacology Team Leader
Jeffry Florian, Pharmacometrics Team Leader
Pritam Verma, Nonclinical Reviewer
Hanan Ghantous, DABT, Nonclinical Team Leader
Fraser Smith, Biometrics Reviewer
Thamban Valappil, Biometrics Team Leader
Adam Sherwat, Medical Team Leader
Stephanie Troy, Medical Officer
Aimee Hodowanec, Medical Officer
Peter Miele, Medical Officer
Elizabeth Thompson, CPMS
Jeffrey Murray, Deputy Director
Debra Birnkrant, Director

Office of Antimicrobial Products
Barbara Styrt, Associate Director for Medical Countermeasures
Edward Cox, Director

SPONSOR ATTENDEES
Juan Camilo Arjona Ferreira, Senior Vice President, Clinical Development
Marc Lesnick, Senior Vice President, US Regulatory Affairs
Simon Portsmouth, Medical Director
Amrik Shah, Senior Director, Head of Biometrics
Kazuhiro Hatanaka, Head of Global Development
Keiko Kawaguchi, Project Statistician
Takao Shishido, Virologist, Section Head of Infectious Diseases
Akira Naito, Virologist, Department Head of Infectious Diseases
Machiko Sumi, Regulatory Affairs
Takeki Uehara, Global Project Leader
Toshihiro Wajima, Senior Director, Head of Clinical Pharmacology & Pharmacokinetics
Ming Ewe, Director, EU Regulatory Affairs
Stephen Mathews, Senior EU & RoW Regulatory Program Manager, Roche, UK
Barry Clinch, Principal Clinical Development Scientist, Roche, UK
Andrew Kenwright, Senior Statistical Scientist, Roche, UK

1.0 BACKGROUND

S-033188 is a prodrug converted by hydrolysis to S-033447 that inhibits influenza cap-dependent endonuclease activity. The drug product is provided in 10 mg and 20 mg film-coated tablets. Shionogi is developing S-033188 as a single-dose treatment for acute uncomplicated (b) (4) influenza (b) (4) in patients 12 years of age and older (b) (4)

Two Phase 1 studies have been completed: 1510T0811, "A Randomized, Double-blind, Single Ascending Dose and Multiple-Ascending Dose, Placebo-Controlled Study to Investigate the Safety, Tolerability and Pharmacokinetics of S-033188 in Healthy Male Adult Subjects," and 1512T0813, entitled "A Phase 1 Study to Evaluate the Relative Bioavailability of S-033188 20 mg Tablets and Suspension and the Effect of Food on the Pharmacokinetics in Healthy Adult Subjects." Two Phase 1 drug-dug interaction (DDI) studies and a thorough QT study are underway in the US and Japan and a Phase 1 mass balance study is planned to begin in 2016 in the United Kingdom.

Shionogi has completed the Phase 2 dose finding and proof-of-concept study 1518T0821, a randomized, double-blind, multicenter, placebo-controlled study designed to evaluate the efficacy and safety of S-033188 in patients with influenza virus infection. Four-hundred patients (100 per arm) 20-64 years of age who presented within 48 hours of symptoms onset, tested positive for influenza on a RIDT, and were not considered at high risk for complications were randomized to receive the 10 mg, 20 mg, 40 mg S-033188 or placebo. The primary endpoint of the study was time to alleviation of influenza symptoms (TTAS), defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms.

The purpose of this meeting was to discuss the results of the completed Phase 2 study and the design of the Phase 3 studies planned for initiation in November 2016. One of the Phase 3 studies will be conducted in subjects who are otherwise healthy, and the other study will be conducted in subjects at high risk for influenza complications. Shionogi would like to obtain feedback on the study design, endpoints, statistical analysis plan and the updated virology assessment plans. If the planned Phase 3 studies are successful, Shionogi plans to submit a New Drug Application (NDA) in the first half of 2018 for the following Indication:

> *Treatment of uncomplicated acute* (b) (4) *influenza* (b) (4) *in patients 12 years of age and older* (b) (4)

FDA sent Preliminary Comments to Shionogi, Incorporated on August 12, 2016, and updated comments (nonclinical) on August 15, 2016. Shionogi provided a response to the Preliminary Meeting Comments on Monday, August 15, 2016 and presented slides during the meeting. The discussion during the meeting focused on Questions 1, 2, 3, 10, 12, 13 and 15.

2. DISCUSSION

Question 1: *Does the Division agree with 40 mg (taken without regard to food) as the selected dose to proceed with into Phase 3 studies for the treatment of acute uncomplicated influenza?*

FDA Response to Question 1: We are concerned with your proposed dose considering a 50% reduction in the exposure of S-033447 in U.S. subjects as compared to Japanese subjects. In addition, there are significant food effects and decreases in S-033188 exposure with increasing weight. Furthermore, the subset analysis indicates that the 40 mg dose may have had reduced activity against type B virus infections, compared to type A infections, in study 1518T0821. In light of these issues, please comment on whether a higher S-033188 dose(s) should be evaluated in the proposed trials.

Discussion: Dose and Body Weight: *Shionogi asked the Division if the proposed Phase 3 clinical trials would be placed on clinical hold or if it would be a review issue if they decide to proceed with the 40 mg dose. The Division responded that it would be a review issue. Based on concerns with the decreased exposures observed with higher subject weights in the Phase 2 proof-of-concept dose finding study, Shionogi is considering evaluation of weight-based dosing in the Phase 3 trials; 40 mg for lighter weight subjects and 80 mg for heavier weight subjects. The Division encouraged Shionogi to study weight-based dosing and asked Shionogi to submit updated modeling and simulation data that includes different cut-off points based on weight, for review and comment. Shionogi will submit the data within the next few weeks.*

Safety: *Shionogi asked the Division if an NDA safety database of approximately 1500 subjects who received either the 40 mg or the 80 mg dose of S-033188 would be acceptable given that the exposure at the two doses would be similar. The Division responded that although this would be*

a review issue, in general, the safety database proposed should be acceptable if the exposures are similar for the two dosing groups and the safety is comparable for the two subgroups.

Question 2: *Does the Division agree with the Otherwise Healthy Phase 3 Study design for acute uncomplicated influenza* (b) (4) *12 years of age and older?*

FDA Response to Question 2: Although, we agree with the general study design of the Otherwise Healthy Phase 3 trial as described in the concept sheet, we have some concerns about the proposed dose of S-033188 in this Phase 3 trial (See FDA Response to Question 1). Please comment on the possibility of studying a higher dose such as 80 mg in this trial (in addition to the proposed 40 mg dose or instead of the 40 mg dose). In addition, we have the following comments on this study:

- Please clarify whether current or past smoking will be used as a stratifying factor.

Shionogi Response: Data on current smoking habits will be collected. Smoking will not be a stratification factor for the Phase 3 studies because in our Phase 2 study, smoking was not a prognostic factor for clinical response.

- Please see the response to Question 12 regarding the use of RIDTs. Only influenza cases confirmed by a central lab-based RT-PCR assay should be included in the Intent-to-Treat-Infected population.

Shionogi Response: As described on Page 39 and 44 of the briefing book, the ITTI will only include patients who are confirmed via RT-PCR.

- Please provide additional information on the statistical methods that will be used to determine if S-033188 is superior to placebo and oseltamivir.

Shionogi Response: The stratified G. Wilcoxon test will be performed to show superiority to placebo and oseltamivir as the primary analysis with the p-value.

- Please also see responses to questions 12 and 15

Please note that our comments cannot be considered final until review of the complete study protocol.

Discussion: *Please see the discussion under Question 3.*

Question 3: *Does the Division agree that the statistical methods and tests that will be conducted for the Otherwise Healthy Phase 3 Study are acceptable?*

FDA Response to Question 3: We reviewed the statistical methods and tests and have the following comments and requests for additional information:

1. The stratifying factors should be pre-specified in the statistics section of the protocol and should not be refined based on blind review of the data before database lock.

Shionogi Response:

- Based on the Phase 2 study data, we will pre-specify stratifying factors in the Phase 3 OwH study. However we are concerned that prognostic factors in primary endpoint may be changed due to influenza season (e.g. virus type).

- We propose that the stratification factors may be refined based on a blinded data review. If the stratifying factors in the primary analysis are modified by the blinded review, we will perform both the modified primary analysis and the original analysis in order to confirm the robustness of primary analysis.

- In addition, the statistician will not access potentially unblinding data such as virology prior to SAP finalization.

Discussion: *The Division advised Shionogi to prespecify all of the statistical elements related to the primary efficacy analysis and to include all of this information in the statistical analysis section of the protocol. The Division also informed Shionogi that no modifications to the primary analysis should be made after the study data have been obtained.*

Shionogi agreed to prespecify the primary analysis and to conduct a blinded review of all of the data. Shionogi stated the Japanese regulatory authority had approved modification of the primary efficacy analysis after review of the blinded data and that Shionogi would produce different statistical analysis plans for Japan and for FDA. The Division advised Shionogi to submit the statistical analysis plan that includes the primary efficacy analysis and specific details on how they will maintain the blind; and which data will be masked. This information should be included in the protocol as well.

2. Please provide the following details in the statistics section of the protocol pertaining to the covariates you plan to include in your primary efficacy analysis:

   a. The definition of composite symptom scores and the cut-off you plan to use to dichotomize this covariate in your phase three trials.

   b. Geographic regions you plan to use as stratification factors

Discussion: *Shionogi plans to use the covariates, baseline symptom score and region, for the primary and additional secondary analyses. The Division raised concerns with this approach and informed Shionogi that analysis using baseline symptom score could be used as a secondary analyses and to stratify the primary analysis only based on region. The Division raised concern*

with this approach because the composite scores would include several different symptoms which may not all be present at baseline in all patients and the relative importance of each may differ. The Division advised Shionogi to use the same factors for the analysis that were considered for stratification at randomization and to submit the details in the statistical methods section of the protocol.

3. The primary analysis should be robust for early discontinuations. For example, rather than censoring subjects at the time of discontinuation from the study, a sensitivity analysis could assume that all subjects who discontinue early and still have influenza should impute the time to resolution of symptoms as 14 days.

Shionogi Response:

We agree with the proposed sensitivity analysis with the following modification:

- Patients who discontinue up to Day 5 and still have influenza will be censored
- This is because treatment of oseltamivir is 5 days, a minimum of 5 days is required for both arms to complete treatment.
- For patients who discontinue after Day 5 and still have influenza, TTAS of the patients will be imputed as 14 days.

Discussion: *The Division informed Shionogi these analyses can be submitted as a supportive or secondary analysis.*

4. Please perform the log-rank test as a sensitivity analysis. As the Wilcoxon test assigns more weight to early event times than to late times, it is less sensitive than the log-rank test to differences that occur at later points in time. Since there may be issues with lack of proportional hazards, the log rank test will not be used for the primary efficacy analysis.

Shionogi Response: Generally, we agree with this sensitivity analysis in principle. However, it is not clear for us how the log-rank test is appropriate in a setting where early separation among treatments is desirable and expected.

Discussion: *The Division explained that unlike the Wilcoxon test, the log-rank test places equal weight on all subjects and can be used for sensitivity analysis and that the log-rank test evaluates the robustness of the drug treatment.*

5. The log-rank and Wilcoxon tests do not test for equality of medians but for equality of distributions. Another test should also be performed to compare the median number of days to resolution of symptoms in the two treatment groups.

Shionogi Response: The median time of TTAS within each treatment group and the difference in median time between S-033188 vs Placebo and S-033188 vs Oseltamivir will be calculated.

- The Wilcoxon test does not test for equality of medians but for equality of distributions.

- Therefore it is the Sponsor's position that an additional test for comparing the medians may lead to a result that is inconsistent with the result of the primary analysis, which we believe to be the more appropriate analysis.

Discussion: *Shionogi will propose using boot strap median analysis and will submit the statistical analysis plan to the IND for review. The Division also mentioned that the Hodges-*

Lehmann test is a nonparametric approach that can be used to compute the difference in median treatment effects and Shionogi agreed to consider this analysis.

Question 12: *Understanding that the Prescribing Information will ultimately depend on the final data, including the types of patients enrolled in the studies, are there any other approval or labeling implications of conducting the Phase 3 studies using positive RIDTs as an inclusion criterion?*

FDA Response to Question 12: Clinical Virology: Regarding the use of RIDTs, our primary concern is that influenza A and B subtypes/lineages and particularly vulnerable and at-risk patient populations will not be adequately represented in your clinical trials; you will need to demonstrate efficacy for all the virus types/subtype and patient populations for which you are seeking an indication. Lack of adequate representation may result in a lack of support for an indication covering the diversity of influenza viruses responsible for seasonal epidemics. As we have alluded to previously, the use of rapid antigen tests in particular have resulted in under-enrollment of influenza type B-infected subjects in some clinical trials, resulting in a lack of data upon which to base an indication (see RAPIVAB™ prescribing information).

We understand that the ratios of influenza A and B subtypes/lineages fluctuate from season to season, and will thus affect the proportions of subtypes and lineages in your pivotal trials; however, we note that while your enrollment percentages for type B viruses in clinical trial 1518T0821 were 21-24%, the surveillance data reported by the Japanese National Institute of Infectious Diseases and the WHO for the 2015/2016 influenza season in Japan show that type B viruses constituted > 40% of influenza viruses sampled. This would indicate that you may have under-enrolled subjects with type B virus infections in your trial, consistent with the previously-identified limitations of rapid antigen tests in detecting type B viruses. This adds to our concern that certain demographic groups, and type B virus infections in particular, may be inadequately represented in your Phase 3 trials, should a rapid antigen test be used to exclude subjects.

As you have pointed out, RIDTs are not as widely used in the U.S. as in other countries. In the U.S., diagnosis of influenza is commonly based on clinical symptoms consistent with influenza combined with evidence that influenza is circulating in the community. Therefore, the study population defined by the result of an RIDT may not reflect the U.S. study population in which S-033188 will be used.

Please take the above concerns into account when considering the size of the planned clinical trials, enrollment criteria and the choice of the RIDT; however, we strongly recommend that subjects be enrolled based on clinical symptoms if influenza is suspected, regardless of the RIDT result, and particularly if influenza virus is known to be circulating in the area. Please include language in your inclusion criteria that provides this option.

Please identify the RIDT(s) you will use in your clinical trials and, if not FDA-cleared, provide performance characteristics. We recommend FDA-cleared RT-PCR-based RIDTs, which may be more sensitive, specific and robust in clinical practice, but you should carefully review their performance characteristics as well.

As noted previously, the Intent-to-Treat-Infected population should be composed of subjects with influenza virus infections confirmed using the specified central lab RT-PCR assay.

Shionogi Response: Shionogi would like to discuss the use of RIDTs and inclusion criteria, as well as potential impact on the product labeling, at the meeting. The Clearview Exact A and B® RIDT will be used in this study, which is FDA approved, and which has high sensitivity for B virus.

Discussion: *In Japan, a positive RIDT was required for enrollment due to usual health care practice in Japan; Shionogi will explore modifying the protocol so that subjects in Japan will also be enrolled based on symptoms, regardless of the RIDT result, as in the U.S. In the U.S., although an RIDT will be used (the Clearview Exact A and B® RIDT test), subjects will be enrolled based on symptoms, regardless of the RIDT result, consistent with guidance from the FDA and CDC and as is the standard practice in the U.S. The Division advised Shionogi to send all samples, positive and negative by RIDT, to the central laboratory for RT-PCR testing for all consenting subjects, including subjects who meet all inclusion criteria except for a positive*

RIDT. The purpose of this recommendation is to account for the degree potential bias in the RIDT, which may skew enrollment when used to exclude subjects.

Question 13: *Does the Division agree that the completed and planned clinical pharmacology studies are adequate to support an NDA submission?*

FDA Response to Question 13: The proposed plan is acceptable except for the timing of the food effect study. We recommend conducting a food effect study prior to the initiation of Phase 3 trials. If a significant impact of a high fat food on S-033447 exposure is observed in U.S. subjects, the results may impact the design of the Phase 3 trials.

Discussion: *The Phase 2 proof-of-concept study was conducted without regard to food and Shionogi plans to proceed with the proposed Phase 3 trials without regard to food. Shionogi will initiate the food effect study by the end of 2016 and will have the results by May 2017.*

The Division asked Shionogi about the purpose of conducting a drug interaction trial with S-033188 and oseltamivir. Shionogi stated that a clinical trial using the combination of S-033188 and oseltamivir in seriously ill patients with influenza infection is planned. However, detailed information regarding the study design is not available yet.

Question 15: *Does the Division agree with the revised virology assessment plans, including the analytical methods for the evaluation of resistance to be utilized for the Phase 3 studies?*

FDA Response to Question 15: Clinical Virology: We generally agree with your resistance analysis plan, which should identify substitutions that emerge (grow out) in treated patients (compared to baseline), and baseline viruses with reduced susceptibility; however, we would like to clarify several points.

Shionogi Responses:
We agree to conduct phenotypic analysis using cloned variants. We would like to make sure it is acceptable to conduct genotypic assessment for only the S-033188-treated group.

Discussion: *Shionogi presented a summary of the preliminary resistance analysis from the Phase 2 proof-of-concept trial (1518T0821) and detected 5 resistance-associated substitutions from 300 subjects, including at baseline in a subject with a relatively reduced response to treatment and in the last evaluable time point in subjects in which virus rebound was observed.*

The Division raised the possibility that resistant variants could be selected at early time points resulting in reduced response to treatment, but that as drug exposures declined, wild-type variants could re-emerge, and thus resistant variants may not be detected in the last evaluable sample in some cases where resistance is suspected. Therefore, earlier time points may need to be sequenced in these cases. Shionogi confirmed that all samples from subjects would be cryopreserved for potential future analysis.

The Division advised Shionogi to include a subset of placebo samples in their genotypic resistance analysis to account for variability in the viral PA gene in samples from untreated subjects.

In addition, the Division asked Shionogi to submit the resistance analysis report for study 1518T0821, including virology datasets.

Post Meeting Additional Comments:

1. Shionogi may wish to consider including a subset of subjects from the oseltamivir arms, in addition to a subset of subjects from the placebo arm, in their genotypic analysis of the PA gene. These subjects may provide a better control for the virus population dynamics encountered in subjects on antiviral treatment.

2. Please evaluate the impact of the substitutions at A36 and T38 on susceptibility when introduced into an influenza type B virus clone.

3. To clarify our preliminary response to Question 15, item 8, we recommend you consider accounting for not only influenza type A and B virus co-infections, but also co-infections with respiratory viruses from other virus families.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (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.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

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

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

SUBMISSION FORMAT REQUIREMENTS

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

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.

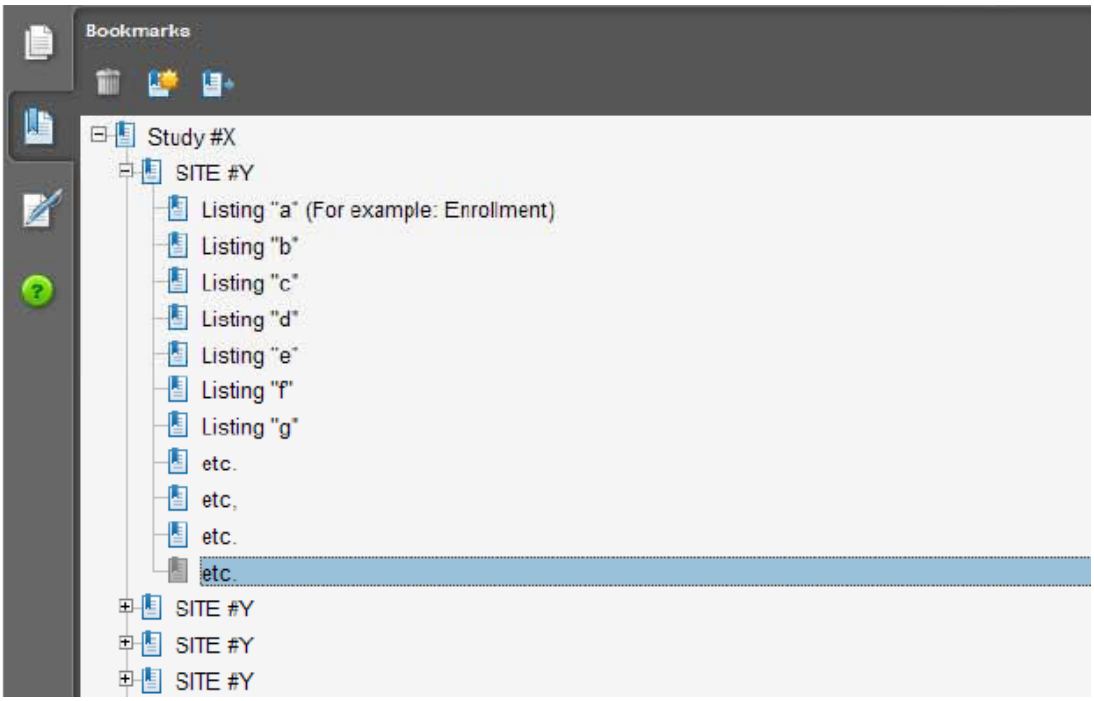
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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 Item1	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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The inclusion of a superiority claim in the Clinical Trials section of the Package Insert based on the results of the proposed Phase 3 trials.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit updated modeling and simulation data that	Shionogi	September 1, 2016

includes different cut off points based on weight, for review and comment.		
Send all samples, positive and negative, to the central laboratory for RT-PCR testing, including subjects who meet all inclusion criteria except RIDT.	Shionogi	
Submit the statistical analysis plans for the Phase 3 trials in the protocol that includes the primary efficacy analysis and specific details on how the blind will maintained.	Shionogi	
Include a subset of placebo samples in the genotypic resistance analysis to account for variability in the viral PA gene in samples from untreated subjects.	Shionogi	
Submit the resistance analysis report for trial 1518T0821 including virology datasets.	Shionogi	

6.0 ATTACHMENTS AND HANDOUTS

20 Page(s) has 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/

VICTORIA L TYSON
09/02/2016