CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213006Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 106410

MEETING MINUTES

Urovant Sciences GmbH
Attention: David N. Hovland, Ph.D.
Global Regulatory Affairs, Urovant Sciences, Inc.
5151 California Ave., Suite 250
Irvine, CA 92617

Dear Dr. Hovland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RVT-901 (vibegron) tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2019. The purpose of the meeting was to discuss the structure and content of a planned New Drug Application (NDA).

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

If you have any questions, please call Nenita Crisostomo, Regulatory Project Manager at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 12, 2019, at 3:00 PM – 4:00 PM
Meeting Location: Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
White Oak Building 22, conference Room 1419
Silver Spring, MD 20903

Application Number: IND 106410
Product Name: RVT-901 (vibegron) tablets

Indication: Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency
Sponsor Name: Urovant Sciences GmbH

Meeting Chair: Mark S. Hirsch, M.D.
Meeting Recorder: Jeannie Roule

FDA ATTENDEES

Audrey Gassman, M.D. – Deputy Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Mark S. Hirsch, M.D. – Medical Team Leader, DBRUP
Nenita Crisostomo – Regulatory Health Project Management, DBRUP
Jeannie Roule - Regulatory Health Project Management, DBRUP
Debuene Chang, M.D. – Medical Officer, DBRUP
Elena Boley, M.D.- Medical Officer, DBRUP
LaiMing Lee, Ph.D. – Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III, Office of Clinical Pharmacology, Office of Translational Sciences
Mukesh Summan, Ph.D., DABT – Pharmacology/Toxicology Supervisor, DBRUP
Laurie McLeod-Flynn, Ph.D. – Pharmacology/Toxicology Reviewer, DBRUP
Mahboob Sobhan, Ph.D. – Associate Director, Division of Biometrics III (DBIII)
Jia Guo, Ph.D. – Statistician, Division of Biometrics III (DBIII)
Mark Seggel Ph.D. - Acting CMC Lead, Office of Pharmaceutical Quality (OPQ), Office of New Drug Products (ONDP), Division of New Drug Products II (DNDPII) Branch V

FDA ATTENDEES (continued)

Roy Blay, Ph.D. – Reviewer, Good Clinical Practice Assessment Branch, Office of Scientific Investigations (OSI)
Oyinlola Fashina, Pharm.D., B.C.P.S., B.C.C.P. – Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Laura Zendel – Risk Management Team Leader, Division of Risk Management, OSE
Mona Patel – Risk Management Analyst, Division of Risk Management, OSE
Preston Dunnmon, M.D.- Medical Officer, Division of Cardiovascular and Renal Products (DCRP)

SPONSOR ATTENDEES

David Hovland, Ph.D. – Senior Vice President, Urovant Sciences, Inc.
Cornelia Haag-Molkenteller, M.D., Ph.D. – Chief Medical Officer, Urovant Sciences, Inc.
Biljana Nadjsombati, Pharm.D. – Vice President, Urovant Sciences, Inc.

1.0 BACKGROUND

On January 29, 2010, Merck submitted IND 106410 for MK-4618 for the treatment of overactive bladder (OAB). An End of Phase 2 (EOP2) meeting was held with Merck on January 18, 2013. On February 28, 2017, the IND sponsorship changed from Merck to Urovant Sciences GmbH (Urovant). A second EOP2 meeting was held with Urovant on July 24, 2017, to discuss revised development plans. A Type C meeting was held on January 18, 2018, to discuss Urovant's planned patient-reported outcomes, Phase 3 statistical analysis plan and proposed labeling. On April 17, 2019, a Type C meeting to discuss the key aspects of the CMC program was cancelled after Preliminary Responses were conveyed to Urovant on April 11, 2019.

This Pre-NDA meeting was requested by Urovant to discuss their planned new drug application.

The meeting information package was submitted by Urovant on May 8, 2019, and the Division conveyed Preliminary Responses on June 5, 2019. On June 10, 2019, Urovant provided an e-Mail response to the Division's Preliminary Responses.

2. DISCUSSION

Urovant's specific questions are presented in **bold** font, the Division's responses are in regular font. Urovant's responses are in ***bold italics*** and the meeting discussions are presented in *italicized* font.

2.1. CMC

Question 1a: Does the Agency agree that the initial NDA submission can include (b) (4)

Division Response: No. The NDA should be complete at the time of submission and include at least 12 months of long-term stability data and 6 months of accelerated stability data from three primary stability batches (refer to ICH Q1A(R2), Stability Testing of New Drug Substances and Products, for recommendations regarding selection of primary stability batches). A stability update may be submitted within 30 calendar days of submission of the original application.

Question 1b: Long-term stability timepoints for the 7-count DP configuration are shifted approximately 2.5 months relative to the 30- and 90-count configurations. If the Agency will not accept (b) (4) **(per Question 1a), does the Agency agree that the initial NDA submission can include 12-month stability data for the 30- and 90-count DP configurations and 9-month stability for the 7-count DP configuratio** (b) (4)

Division Response: No. See our response to Question 1a.

Sponsor Response to Division Response to Questions 1a and 1b: The Sponsor acknowledges the Agency's responses. The drug product stability dataset for the primary stability batches will be complete at the time of NDA submission.

The three primary stability batches of vibegron 75 mg tablets were manufactured as bulk tablet batches and split into sub-batches for the 7-, 30-, and 90-count bottle configurations (same size bottle for all configurations). Therefore, 9 primary stability batches are currently being tested according to the matrixing design stability protocol (summarized in Table 1 below), previously agreed with the Agency (see Preliminary Comments for April 17, 2019 Type C CMC meeting).

To provide a comprehensive stability dataset for the NDA per our agreed matrixing design, the Sponsor will supplement the current stability protocol to include full testing (physico-chemical and microbial) of all 3 batches of the 7-count configuration at 9 months to ensure that a complete long-term stability dataset is available for all 3 configurations at the last timepoint (9 months for 7-count; 12 months for 30- and 90-count) prior to NDA submission (in accordance with ICH Q1D, "Guidance for Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products").

Table 1 Matrixing Design for Long-Term Stability Testing

Timepoint (months)		0	3	6	9	12	18	24	36	48	60
7-count bottle	Batch 1	(b) (4)									
	Batch 2										
	Batch 3										
30-count bottle	Batch 1										
	Batch 2										
	Batch 3										
90-count bottle	Batch 1										
	Batch 2										
	Batch 3										

T = Tested for appearance, assay, related substances, (b) (4) and dissolution;
M=Micro testing; Supplemental testing shown in blue text.

At the time of initial submission, the NDA will include all available data from the 3 primary stability batches in accordance with the supplemented matrixing design protocol. Specifically, this will include 6-month accelerated stability data for the 7-, 30-, and 90-count configurations, 9 months long-term stability data for three batches of the 7-count configuration, and 12 months long-term stability data for 3 batches each of the 30- and 90-count configurations.

The Sponsor does not plan to submit a stability update after 30 days following submission of the original application.

Additional discussion of Question 1 is planned for the meeting.

Discussion at the meeting: The Division explained that the reference to ICH Q1A(R2) for recommendations regarding selection of primary stability batches was included in the response to Question 1a because the Sponsor had referred to drug product stability batches as 'registration,' 'registration verification' and 'verification' batches. The Division further explained that at the time of submission, the primary stability data package should be complete with a minimum of 12 months long term data for 3 batches of drug product in each of the three packaging configurations.

The Sponsor reiterated their original proposal to provide 12-months long term data for three batches of tablets packaged in 30-count and 90-count packaging configurations and 9-months long term data for three batches of tablets packaged in the 7-count configuration in the initial NDA submission. To augment the stability package, the Sponsor proposed submitting full testing data for the three 7-count batches at the 9-month time point. The Sponsor noted that the robust stability of drug substance and drug product had been demonstrated over the long course of development.

The Sponsor and the Division discussed alternatives to ensure that an adequate stability package was submitted to the NDA. The Sponsor proposed to provide the 12-month data for the 7-count packaging configuration within 60 days of NDA submission. The Agency agreed to discuss this proposal internally and would advise the Sponsor in a Post-Meeting Comment in the final meeting minutes.

The Sponsor stated that they will also submit at least 24-months long-term data from four supportive drug product batches. The Sponsor is proposing an expiration dating period of at least 24 months for all three packaging configurations. The Agency noted it could not agree on an expiration dating period at this time. The determination of the expiration dating period will be based on review of the data provided in the NDA.

The Sponsor noted that they plan to submit their NDA by December 2019.

Post-Meeting Comment:
The Division agrees that the Sponsor can submit the 12-month long-term stability data for the three batches of tablets in the 7-count configuration within 60 days of the initial NDA submission.

Question 2: To facilitate Agency consideration of the comprehensive DP stability program for NDA 213006, the Sponsor proposes to submit updated long-term DP stability data for the registration and verification batches (b) (4) **Does the Agency agree?**

Division Response: No. See our response to Question 1a.

Sponsor Response to Division Response to Question 2: The Sponsor acknowledges the Agency's comment. No further discussion required.

2.2 NDA STRUCTURE, SCOPE, AND CONTENT

Question 3: A draft eCTD Table of Contents for NDA 213006 is provided in Appendix 3. Does the Agency agree that the proposed organization of the submission is acceptable?

Division Response: Yes.

Sponsor Response to Division Response to Question 3: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 4: The ISS for NDA 213006 will include the Phase 1 Ambulatory Blood Pressure Monitoring (ABPM) study (URO-901-1001), the Merck Phase 2 study (008), the Kyorin Phase 3 studies (301 and 302), and the pivotal efficacy/safety

study (RVT-901-3003) and its extension study (RVT-901-3004). The ISS pooling and safety analysis will include vibegron doses of 75 mg (the dose intended for registration) and 100 mg (to provide supportive safety data). The draft Statistical Analysis Plan (SAP) for the ISS is included in Appendix 7. Does the Agency agree with the proposed pooling strategies and safety analyses for the ISS?

Division Response: Your proposed pooling strategies and safety analyses for the ISS are reasonable; however, to facilitate our review, we request:

Several additional sections in the ISS:

- A "*75 mg only*" section, consisting of RVT-901-3003 only, RVT-901-3004 only, and RVT-901-3003 and RVT-901-3004 combined,
- A "*Merck Study 008 only*" section, consisting of Merck Study 008-50mg only, Merck Study 008-100mg only, and Merck Study 008-50mg/100mg combined, and
- A "*Kyorin only*" section, consisting of Kyorin 301 only, Kyorin 302 only and Kyorin 301 and 302 combined.

An additional safety analysis that includes the 50mg dose:

- The data from 50mg is important to compare to data from 75mg and 100mg. In your ISS, include a section showing safety data from patients who received 50mg compared to safety data from patients who received 75mg and 100mg.

And for your vital signs data:

- For the ABPM study, also submit the ABPM results as raw datasets.
- For the clinical BP cuff and HR results:

    a. Do not co-mingle the cuff BP and HR data from studies where single random blood pressures were measured along with studies where blood pressures were measured in triplicate and averaged. Instead, identify those studies where blood pressures were measured in triplicate and apply your proposed analytical approach to those studies separately (in addition to the integration you propose).

    b. The timing of blood pressures relative to drug dosing should be reported for all studies being pooled for vital sign analyses. Clarify how you intend to assess maximal vital sign effects in the C_{max} "window" (assuming that there will be some inter-subject variability in the timing of C_{max}), or state that this cannot be done due to random timing of assessments. In the latter scenario, we will have to rely solely on the ABPM study to assess C_{max} effects.

c. Depending on the tolerability of the experimental therapy, the missing at random (MAR) assumption for the MMRM analyses that are planned may not be correct. Clearly identify how many subjects in each treatment group contribute to the MMRM analyses at the timepoints that you plan to analyze. Excessive missingness in the active treatment arms may make interpretation of vital sign trends by MMRM problematic.

Sponsor Response to Division Response to Question 4: The Sponsor acknowledges the Agency's comments. Responses to each of the 3 sections of the Agency's comments are presented below.

- ***Additional sections in the ISS:***

  The Sponsor agrees to the Agency's request to include "75 mg only," "Merck Study 008 only," and "Kyorin only" sections in the ISS SAP. Module 2.7.4 will contain safety summaries from individual studies RVT-901-3003, 008, and 301 and 302. For study RVT-901-3004, the study SAP already contains safety summaries that combine the data from RVT-901-3003 and RVT-901-3004. The Sponsor will add additional adverse events analyses to the ISS SAP to provide the requested safety summaries for RVT-901-3004 only, for Merck study 008 (which will include the 50mg/100mg combined), and for Kyorin 301 and 302 combined.

  The Agency has requested additional sections for individual studies. However, given the limited number of subjects within each individual study, the Sponsor proposes to apply the subgroup analysis specified in the ISS SAP only to the pooled datasets.

  - ***Additional safety analysis that includes the 50 mg dose:***

    The Sponsor agrees to include a section showing the safety data from patients who received 50 mg compared to safety data from patients who received 75 mg and 100 mg. The Sponsor will retain the current pooling strategy for Pools 1-3 and add an additional Pooling strategy, Pool 4, which will include the 50 mg dose group (Table 2). Pool 4 will be used to summarize the adverse event data for the placebo-controlled 4-, 8-, or 12-week randomized, double blind studies.

Table 1: Pooling Strategy for Clinical Safety Data

Pool	Description	Studies Included
1	12-week, randomized, double-blind exposure of placebo, vibegron (75 or 100 mg), or tolterodine	-RVT-901-3003 -Kyorin 301
2	4-, 8-, or 12-week, randomized, double-blind exposure of placebo, vibegron (75, 75+100, or 100 mg), or tolterodine	-RVT-901-3003 -Merck 008 (Parts 1 and 2) -Kyorin 301 -RVT-901-1001
3	Long-term extension dosing of vibegron (75 or 100 mg), or tolterodine	-RVT-901-3003 -RVT-901-3004 -Merck 008 (Parts 1 and 2) -Kyorin 302
4	4-, 8-, or 12-week, randomized, double-blind exposure of placebo, vibegron (50, 75, or 100 mg), or tolterodine	-RVT-901-3003 -Merck 008 (Parts 1 and 2) -Kyorin 301 -RVT-901-1001

Pool 4 will have the following header, including tolterodine:

Preferred Term	Placebo N=xxx n (%) [# AEs]	Vibegron 75mg N=xxx n (%) [# AEs]	Vibegron 50mg N=xxx n (%) [# AEs]	Vibegron 100mg N=xxx n (%)[# AEs]	Tolterodine ER 4mg N=xxx n (%) [# AEs]

- ***Vital Signs Data:***
  - ***For the ABPM study, study URO-901-1001, the Sponsor is planning to submit CDSIC SDTM and ADaM datasets.***
  - ***The Sponsor agrees to not co-mingle the cuff BP and HR rate data from single measurements with triplicate measurements that are averaged.***
  - ***Assessment of the maximal vital sign effect in the C_{max} window will be assessed with the ambulatory blood pressure measurements in study URO-901-1001. The endpoint evaluated is the change from baseline in the maximum of the hourly means in the C_{max} window of 0.5 to 6.5 hours post dose. This study was specifically designed to allow for such an analysis, to adequately characterize the effect of vibegron on BP throughout the day.***
  - ***The Sponsor agrees with the Agency's comment to clearly identify how many subjects in each treatment group contribute to the MMRM analyses at the timepoints that we plan to analyze.***

Additional discussion of the "Additional sections in the ISS" and "Additional safety analysis that includes the 50 mg dose" sections of the Agency's response to Question 4 is planned for the meeting.

Discussion at the meeting: Overall, the above response was acceptable to the Division. However, the Division clarified that the Sponsor should also submit the raw ABPM data. There was additional discussion concerning the handling of missing ABPM data, including whether the MMRM analysis method remained valid when ABPM missing data is not at random. The Division suggested that the protocol should include an alternative analysis plan. The Sponsor acknowledged and stated that they anticipate minimal missing ABPM data due to infrequent premature dropouts from the study. The Division also requested that the sponsor submit the specifics of the methodology used to assess the quality of the ABPM data.

Question 5: Does the Agency agree that an ISE is not necessary?

Division Response: Yes, we agree that section 2.7.3 of your NDA can include individual summaries of the pivotal efficacy/safety study and supportive studies in place of an ISE.

Sponsor Response to Division Response to Question 5: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 6: Datasets for the studies included in the ISS (Refer to Question 9) and clinical pharmacology studies initiated after 2016 will be provided in CDISC format (SDTM IG v3.2, ADaM IG v1.1, and define.xml). For the clinical pharmacology studies initiated before 2016, datasets will be provided in the legacy format (SDS v2.0 and Define.pdf). Does the Agency agree?

Division Response: Yes. We agree with your proposed formats for the submission datasets. Submit the Clinical Pharmacology datasets (e.g., pharmacokinetic concentrations and calculated pharmacokinetic parameters) as xpt files. Submit a table in your NDA outlining the formulation(s) used in each clinical study and clarify how each formulation is bridged to the Phase 3 and to-be-marketed formulations. We remind you that the assays used in your Clinical Pharmacology studies should be demonstrated to be specific, sensitive and reproducible. Refer to the Guidance for Industry: Bioanalytical Method Validation (May 2018). https://www.fda.gov/media/70858/download

Sponsor Response to Division Response to Question 6: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 7: Individual subject Case Report Forms (CRFs) for deaths, other serious adverse events, and withdrawals due to adverse events will be included only for the pivotal efficacy/safety study (RVT-901-3003) and its associated extension study (RVT-901-3004). Does the Agency agree?

Division Response: No, we do not agree that CRFs for deaths, other SAEs and withdrawals due to AE be included only for the pivotal efficacy/ safety study (RVT-901-3003) and associated extension study (RVT-901-3004). Include CRFs for all deaths, other SAEs and withdrawals due to AEs across all studies conducted during clinical development.

Sponsor Response to Division Response to Question 7: The Sponsor acknowledges the Agency's comment. The NDA will include all requested CRFs. No further discussion required.

Question 8: Narratives for discontinuations due to adverse events (AEs) post-randomization and adverse events of clinical interest (AECI) will be included only for the pivotal efficacy/safety study (RVT-901-3003) and its associated extension study (RVT-901-3004). Does the Agency agree?

Division Response: No, we do not agree that only narratives for discontinuations due to AEs and AECI be included only for the pivotal study RVT-901-3003 and its extension RVT-901-3004. Narratives for SAEs, discontinuations due to AEs and AECI should be included across all studies conducted during clinical development.

Sponsor Response to Division Response to Question 8: The Sponsor acknowledges the Agency's comment. Narratives for SAEs, discontinuations due to AEs, and AECIs (if prospectively defined in study protocols) will be included in the NDA for all studies. No further discussion required.

Question 9: Selected studies supporting NDA 213006 were conducted by Kyorin, the company responsible for development and commercialization of vibegron in Japan (Beova was approved for the treatment of OAB in Japan in September 2018). Original versions of nonclinical and clinical study reports from Kyorin are in Japanese and the Sponsor has translated each final study report into English. The Sponsor proposes to include only the English translated version of each of Kyorin's nonclinical and clinical reports in the submission of NDA 213006. The original Japanese version of each translated report can be made available upon request. Does the Agency agree?

Division Response: Yes. Only English translated reports need be initially submitted to NDA 213006.

Sponsor Response to Division Response to Question 9: The Sponsor acknowledges the Agency's comment. No further discussion required.

2.3 CLINICAL SAFETY

Question 10: At the time of submission of NDA 213006, the Phase 3 clinical studies of vibegron for the treatment of OAB will have been completed. All safety

data from the Phase 3 program for OAB and blinded/unblinded (as appropriate) safety information from the ongoing vibegron studies for other indications and from postmarketing reports for Kyorin's Beova product in Japan will be provided in Section 2.7.4 in the initial submission. For the 120-day safety update, the Sponsor proposes to provide a non-integrated, standalone document (in Module 5) summarizing relevant safety information (blinded/unblinded, as appropriate) from ongoing vibegron studies (b) (4) **and from post-marketing reports for Kyorin's Beova product in Japan. Does the Agency agree?**

Division Response: Your proposal for safety data submission is reasonable. However, in the 120-day safety update, include full reports, not just line listings, for all SAEs and discontinuations due to AEs in ongoing Urovant studies. We remind you that the NDA submission should include all post-marketing reports, such as 15-day reports from Kyorin's Beova product in Japan. Only new post-marketing reports should be included in your 120-day safety update.

Sponsor Response to Division Response to Question 10: The Sponsor acknowledges the Agency's comment. The 120-day safety update will include narratives for all SAEs and discontinuations due to AEs (blinded for treatment allocation) from the ongoing Urovant clinical studies, and CIOMS forms for expedited post-marketing reports from Kyorin's Beova product in Japan. No further discussion required.

2.4 NONCLINICAL

Question 11a: Does the Agency agree with the Sponsor's proposed approach (b) (4)

Division Response: Yes.

Question 11b: Alternatively, would the Agency prefer (b) (4)

Division Response: No.

Sponsor Response to Division Response to Questions 11a and 11b: The Sponsor acknowledges the Agency's comments. No further discussion required.

Question 12: Nonclinical studies supporting NDA 213006 were conducted by the previous Sponsor (Merck) or by Kyorin. Given their legacy nature (majority initiated prior to 2016), currently available datasets are limited to the mouse

(TT12-6031) and rat (TT11-6036) carcinogenicity studies. Furthermore, the datasets are in XPT format. The Sponsor plans to provide datasets in XPT format in the NDA for the mouse and rat carcinogenicity studies. No other nonclinical datasets will be provided. Does the Agency agree?

Division Response: Yes.

Sponsor Response to Division Response to Question 12: The Sponsor acknowledges the Agency's comment. No further discussion required.

2.5 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

Question 13: The Sponsor will provide Office of Scientific Investigations (OSI)-requested Bioresearch Monitoring (BIMO) information for the pivotal efficacy/safety study evaluating once daily 75 mg vibegron (RVT-901-3003) in the NDA, in accordance with current FDA expectations. Does the Agency agree?

Division Response: No. Submit OSI-requested BIMO information also for the extension study RVT-901-3004.

Sponsor Response to Division Response to Question 13: The Sponsor acknowledges the Agency's comment. No further discussion required.

2.6 REGULATORY AFFAIRS

Question 14: Vibegron is a New Chemical Entity (NCE). The Sponsor intends to submit a 505(b)(1) New Molecular Entity NDA (NDA 213006), for vibegron for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency, in accordance with "the Program" under PDUFA (Prescription Drug User Fee Act) VI. Does the Agency agree?

Division Response: Yes.

Sponsor Response to Division Response to Question 14: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 15: The Sponsor believes that vibegron, as an NCE submitted under a 505(b)(1) application, is entitled to a 5-year period of exclusivity. Does the Agency agree?

Division Response: The exclusivity determination is determined after the NDA is approved.

Sponsor Response to Division Response to Question 15: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 16: Given that vibegron is not first-in-class as a beta-3 adrenergic receptor agonist for the treatment of OAB, the Sponsor does not believe that NDA 213006 will require referral for discussion at the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC). Does the Agency agree?

Division Response: No. While we have no current plans to discuss your application at a meeting of the BRUDAC, it is premature to determine the need for a meeting of the BRUDAC prior to the application being submitted and initially reviewed.

Sponsor Response to Division Response to Question 16: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 17: The Sponsor believes that appropriate labeling and routine analysis of spontaneous postmarketing adverse events will be sufficient to ensure that the benefit of vibegron outweighs its risks as a treatment for OAB, and that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary. Does the Agency agree?

Division Response: We have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of vibegron outweigh the risks, and if a REMS is necessary, what the required REMS elements would be. The need for a REMS will be determined during the review of the application. We agree, however, that the NDA does not need to include a REMS proposal at the time of NDA submission.

Sponsor Response to Division Response to Question 17: The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 18: (b) (4) **Does the Agency agree?**

Division Response: No. (b) (4)

Sponsor Response to Division Response to Question 18: The Sponsor acknowledges the Agency's comment. No further discussion required.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 29, 2019, 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 FDA.gov.[1]

4.0 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-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP 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 iPSP, including an iPSP 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*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.
- 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.

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

[5] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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)				

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring*

(BIMO) Inspections for CDER Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

8.0 ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[7]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid[8]

9.0 ACTION ITEMS

The meeting minutes will be conveyed to the Sponsor within 30 days.

10.0 ATTACHMENTS AND HANDOUTS

"Urovant Response to FDA Preliminary Comments for 12Jun2019 Type B Pre-NDA Meeting Sent 10Jun2019" received via e-Mail on June 10, 2019.

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6 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRe quirements/UCM332468.pdf

7 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm

8 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

Urovant Sciences GmbH

IND 106410 Vibegron OAB: Type B Pre-NDA Meeting, June 12, 2019

Meeting Purpose: Discuss Structure and Content of NDA for Vibegron for the Treatment of Overactive Bladder

1. BACKGROUND

Vibegron (Urovant Sciences GmbH [Urovant] product code: RVT-901; also known as URO-901, MK-4618, KRP-114V) is a potent and selective full agonist of the human beta-3 adrenergic receptor (β3-AR) that is currently in Phase 3 clinical development for the treatment of overactive bladder (OAB).

The Sponsor submitted a Type B Pre-NDA meeting request on April 10, 2019. The meeting information package was submitted on May 8, 2019.

The Sponsor's original questions are presented below in *italics*, while the Division's preliminary responses are in presented regular font.

The Sponsor's responses to the Division's preliminary comments appear below in ***bold, italic font.***

2. QUESTIONS AND RESPONSES

2.1. CMC

Question 1a: Does the Agency agree that the initial NDA submission can include (b) (4)

Division Response to Question 1a:

No. The NDA should be complete at the time of submission and include at least 12 months of long-term stability data and 6 months of accelerated stability data from three primary stability batches (refer to ICH Q1A(R2), Stability Testing of New Drug Substances and Products, for recommendations regarding selection of primary stability batches). A stability update may be submitted within 30 calendar days of submission of the original application.

Question 1b: Long-term stability timepoints for the 7-count DP configuration are shifted approximately 2.5 months relative to the 30- and 90-count configurations. If the Agency will not accep (b) (4) *(per Question 1a), does the Agency agree that the initial NDA submission can include 12-month stability data for the 30- and 90-count DP configurations and 9-month stability for the 7-count DP configuration* (b) (4)

Division Response to Question 1b:

No. See our response to Question 1a.

Sponsor Response to Division Response to Questions 1a and 1b:

The Sponsor acknowledges the Agency's responses. The drug product stability dataset for the primary stability batches will be complete at the time of NDA submission.

The three primary stability batches of vibegron 75 mg tablets were manufactured as bulk tablet batches and split into sub-batches for the 7-, 30-, and 90-count bottle configurations (same size bottle for all configurations). Therefore, 9 primary stability batches are currently being tested according to the matrixing design stability protocol (summarized in Table 1 below), previously agreed with the Agency (see Preliminary Comments for April 17, 2019 Type C CMC meeting).

To provide a comprehensive stability dataset for the NDA per our agreed matrixing design, the Sponsor will supplement the current stability protocol to include full testing (physico-chemical and microbial) of all 3 batches of the 7-count configuration at 9 months to ensure that a complete long-term stability dataset is available for all 3 configurations at the last timepoint (9 months for 7-count; 12 months for 30- and 90-count) prior to NDA submission (in accordance with ICH Q1D, "Guidance for Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products").

Table 1 Matrixing Design for Long-Term Stability Testing

Timepoint (months)		**0**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**	**60**
7-count bottle	Batch 1	(b) (4)									
	Batch 2										
	Batch 3										
30-count bottle	Batch 1										
	Batch 2										
	Batch 3										
90-count bottle	Batch 1										
	Batch 2										
	Batch 3										

T = Tested for appearance, assay, related substances, (b) (4) and dissolution; M=Micro testing; Supplemental testing shown in blue text.

At the time of initial submission, the NDA will include all available data from the 3 primary stability batches in accordance with the supplemented matrixing design protocol. Specifically, this will include 6-month accelerated stability data for the 7-, 30-, and 90-count configurations, 9 months long-term stability data for three batches of the 7-count configuration, and 12 months long-term stability data for 3 batches each of the 30- and 90-count configurations.

The Sponsor does not plan to submit a stability update after 30 days following submission of the original application.

Additional discussion of Question 1 is planned for the meeting.

Question 2: To facilitate Agency consideration of the comprehensive DP stability program for NDA 213006, the Sponsor proposes to submit updated long-term DP stability data for the registration and verification batches (b) (4) *Does the Agency agree?*

Division Response to Question 2:

No. See our response to Question 1a.

Sponsor Response to Division Response to Question 2:

The Sponsor acknowledges the Agency's comment. No further discussion required.

2.2. NDA Structure, Scope, and Content

Question 3: A draft eCTD Table of Contents for NDA 213006 is provided in Appendix 3. Does the Agency agree that the proposed organization of the submission is acceptable?

Division Response to Question 3:

Yes.

Sponsor Response to Division Response to Question 3:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 4: The ISS for NDA 213006 will include the Phase 1 Ambulatory Blood Pressure Monitoring (ABPM) study (URO-901-1001), the Merck Phase 2 study (008), the Kyorin Phase 3 studies (301 and 302), and the pivotal efficacy/safety study (RVT-901-3003) and its extension study (RVT-901-3004). The ISS pooling and safety analysis will include vibegron doses of 75 mg (the dose intended for registration) and 100 mg (to provide supportive safety data). The draft Statistical Analysis Plan (SAP) for the ISS is included in Appendix 7. Does the Agency agree with the proposed pooling strategies and safety analyses for the ISS?

Division Response to Question 4:

Your proposed pooling strategies and safety analyses for the ISS are reasonable; however, to facilitate our review, we request:

Several additional sections in the ISS:

- A "75 mg only" section, consisting of RVT-901-3003 only, RVT-901-3004 only, and RVT-901-3003 and RVT-901-3004 combined,
- A "Merck Study 008 only" section, consisting of Merck Study 008-50mg only, Merck Study 008-100mg only, and Merck Study 008-50mg/100mg combined, and
- A "Kyorin only" section, consisting of Kyorin 301 only, Kyorin 302 only and Kyorin 301 and 302 combined.

An additional safety analysis that includes the 50mg dose:

- The data from 50mg is important to compare to data from 75mg and 100mg. In your ISS, include a section showing safety data from patients who received 50mg compared to safety data from patients who received 75mg and 100mg.

And for your vital signs data:

- For the ABPM study, also submit the ABPM results as raw datasets.
- For the clinical BP cuff and HR results:

  a. Do not co-mingle the cuff BP and HR data from studies where single random blood pressures were measured along with studies where blood pressures were measured in triplicate and averaged. Instead, identify those studies where blood pressures were measured in triplicate and apply your proposed analytical approach to those studies separately (in addition to the integration you propose).

  b. The timing of blood pressures relative to drug dosing should be reported for all studies being pooled for vital sign analyses. Clarify how you intend to assess maximal vital sign effects in the C_{max} "window" (assuming that there will be some inter-subject variability in the timing of C_{max}), or state that this cannot be done due to random timing of assessments. In the latter scenario, we will have to rely solely on the ABPM study to assess C_{max} effects.

  c. Depending on the tolerability of the experimental therapy, the missing at random (MAR) assumption for the MMRM analyses that are planned may not be correct. Clearly identify how many subjects in each treatment group contribute to the MMRM analyses at the timepoints that you plan to analyze. Excessive missingness in the active treatment arms may make interpretation of vital sign trends by MMRM problematic.

Sponsor Response to Division Response to Question 4:

The Sponsor acknowledges the Agency's comments. Responses to each of the 3 sections of the Agency's comments are presented below.

- ***Additional sections in the ISS:***

  The Sponsor agrees to the Agency's request to include "75 mg only," "Merck Study 008 only," and "Kyorin only" sections in the ISS SAP. Module 2.7.4 will contain safety summaries from individual studies RVT-901-3003, 008, and 301 and 302. For study RVT-901-3004, the study SAP already contains safety summaries that combine the data from RVT-901-3003 and RVT-901-3004. The Sponsor will add additional adverse events analyses to the ISS SAP to provide the requested safety summaries for RVT-901-3004 only, for Merck study 008 (which will include the 50mg/100mg combined), and for Kyorin 301 and 302 combined.

  The Agency has requested additional sections for individual studies. However, given the limited number of subjects within each individual study, the Sponsor proposes to apply the subgroup analysis specified in the ISS SAP only to the pooled datasets.

- ***Additional safety analysis that includes the 50 mg dose:***

  The Sponsor agrees to include a section showing the safety data from patients who received 50 mg compared to safety data from patients who received 75 mg and 100 mg. The Sponsor will retain the current pooling strategy for Pools 1-3 and add an additional Pooling strategy, Pool 4, which will include the 50 mg dose group (Table 2). Pool 4 will be used to summarize the adverse event data for the placebo-controlled 4-, 8-, or 12-week randomized, double blind studies.

Table 1: Pooling Strategy for Clinical Safety Data

Pool	Description	Studies Included
1	12-week, randomized, double-blind exposure of placebo, vibegron (75 or 100 mg), or tolterodine	-RVT-901-3003 -Kyorin 301
2	4-, 8-, or 12-week, randomized, double-blind exposure of placebo, vibegron (75, 75+100, or 100 mg), or tolterodine	-RVT-901-3003 -Merck 008 (Parts 1 and 2) -Kyorin 301 -RVT-901-1001
3	Long-term extension dosing of vibegron (75 or 100 mg), or tolterodine	-RVT-901-3003 -RVT-901-3004 -Merck 008 (Parts 1 and 2) -Kyorin 302
4	4-, 8-, or 12-week, randomized, double-blind exposure of placebo, vibegron (50, 75, or 100 mg), or tolterodine	-RVT-901-3003 -Merck 008 (Parts 1 and 2) -Kyorin 301 -RVT-901-1001

Pool 4 will have the following header, including tolterodine:

Preferred Term	Placebo N=xxx n (%) [# AEs]	Vibegron 75mg N=xxx n (%) [# AEs]	Vibegron 50mg N=xxx n (%) [# AEs]	Vibegron 100mg n (%) [# AEs]	Tolterodine ER 4mg N=xxx n (%) [# AEs]

- ***Vital Signs Data:***
  - ***For the ABPM study, study URO-901-1001, the Sponsor is planning to submit CDSIC SDTM and ADaM datasets.***
  - ***The Sponsor agrees to not co-mingle the cuff BP and HR rate data from single measurements with triplicate measurements that are averaged.***
  - ***Assessment of the maximal vital sign effect in the C_{max} window will be assessed with the ambulatory blood pressure measurements in study URO-901-1001. The endpoint evaluated is the change from baseline in the maximum of the hourly means in the C_{max} window of 0.5 to 6.5 hours post dose. This study was specifically designed to allow for***

such an analysis, to adequately characterize the effect of vibegron on BP throughout the day.

- ***The Sponsor agrees with the Agency's comment to clearly identify how many subjects in each treatment group contribute to the MMRM analyses at the timepoints that we plan to analyze.***

Additional discussion of the "Additional sections in the ISS" and "Additional safety analysis that includes the 50 mg dose" sections of the Agency's response to Question 4 is planned for the meeting.

Question 5: Does the Agency agree that an ISE is not necessary?

Division Response to Question 5:

Yes, we agree that section 2.7.3 of your NDA can include individual summaries of the pivotal efficacy/safety study and supportive studies in place of an ISE.

Sponsor Response to Division Response to Question 5:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 6: Datasets for the studies included in the ISS (Refer to Question 9) and clinical pharmacology studies initiated after 2016 will be provided in CDISC format (SDTM IG v3.2, ADaM IG v1.1, and define.xml). For the clinical pharmacology studies initiated before 2016, datasets will be provided in the legacy format (SDS v2.0 and Define.pdf). Does the Agency agree?

Division Response to Question 6:

Yes. We agree with your proposed formats for the submission datasets. Submit the Clinical Pharmacology datasets (e.g., pharmacokinetic concentrations and calculated pharmacokinetic parameters) as xpt files. Submit a table in your NDA outlining the formulation(s) used in each clinical study and clarify how each formulation is bridged to the Phase 3 and to-be-marketed formulations. We remind you that the assays used in your Clinical Pharmacology studies should be demonstrated to be specific, sensitive and reproducible. Refer to the Guidance for Industry: Bioanalytical Method Validation (May 2018). https://www.fda.gov/media/70858/download

Sponsor Response to Division Response to Question 6:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 7: Individual subject Case Report Forms (CRFs) for deaths, other serious adverse events, and withdrawals due to adverse events will be included only for the pivotal efficacy/safety study (RVT-901-3003) and its associated extension study (RVT-901-3004). Does the Agency agree?

Division Response to Question 7:

No, we do not agree that CRFs for deaths, other SAEs and withdrawals due to AE be included only for the pivotal efficacy/ safety study (RVT-901- 3003) and associated extension study (RVT-901-3004). Include CRFs for all deaths, other SAEs and withdrawals due to AEs across all studies conducted during clinical development.

Sponsor Response to Division Response to Question 7:

The Sponsor acknowledges the Agency's comment. The NDA will include all requested CRFs.

No further discussion required.

Question 8: Narratives for discontinuations due to adverse events (AEs) post- randomization and adverse events of clinical interest (AECI) will be included only for the pivotal efficacy/safety study (RVT-901-3003) and its associated extension study (RVT-901-3004). Does the Agency agree?

Division Response to Question 8:

No, we do not agree that only narratives for discontinuations due to AEs and AECI be included only for the pivotal study RVT-901-3003 and its extension RVT-901-3004. Narratives for SAEs, discontinuations due to AEs and AECI should be included across all studies conducted during clinical development.

Sponsor Response to Division Response to Question 8:

The Sponsor acknowledges the Agency's comment. Narratives for SAEs, discontinuations due to AEs, and AECIs (if prospectively defined in study protocols) will be included in the NDA for all studies.

No further discussion required.

Question 9: Selected studies supporting NDA 213006 were conducted by Kyorin, the company responsible for development and commercialization of vibegron in Japan (Beova was approved for the treatment of OAB in Japan in September 2018). Original versions of nonclinical and clinical study reports from Kyorin are in Japanese and the Sponsor has translated each final study report into English. The Sponsor proposes to include only the English translated version of each of Kyorin's nonclinical and clinical reports in the submission of NDA 213006. The original Japanese version of each translated report can be made available upon request. Does the Agency agree?

Division Response to Question 9:

Yes. Only English translated reports need be initially submitted to NDA 213006.

Sponsor Response to Division Response to Question 9:

The Sponsor acknowledges the Agency's comment. No further discussion required.

2.3. Clinical Safety

Question 10: At the time of submission of NDA 213006, the Phase 3 clinical studies of vibegron for the treatment of OAB will have been completed. All safety data from the Phase 3 program for OAB and blinded/unblinded (as appropriate) safety information from the ongoing vibegron studies for other indications and from postmarketing reports for Kyorin's Beova product in Japan will be provided in Section 2.7.4 in the initial submission. For the 120-day safety update, the Sponsor proposes to provide a non-integrated, standalone document (in Module 5) summarizing relevant safety information (blinded/unblinded, as appropriate) from ongoing vibegron studies (b) (4) *and from post- marketing reports for Kyorin's Beova product in Japan. Does the Agency agree?*

Division Response to Question 10:

Your proposal for safety data submission is reasonable. However, in the 120-day safety update, include full reports, not just line listings, for all SAEs and discontinuations due to AEs in ongoing Urovant studies. We remind you that the NDA submission should include all post-marketing reports, such as 15-day reports from Kyorin's Beova product in Japan. Only new post-marketing reports should be included in your 120-day safety update.

Sponsor Response to Division Response to Question 10:

The Sponsor acknowledges the Agency's comment. The 120-day safety update will include narratives for all SAEs and discontinuations due to AEs (blinded for treatment allocation) from the ongoing Urovant clinical studies, and CIOMS forms for expedited post-marketing reports from Kyorin's Beova product in Japan.

No further discussion required.

2.4. Nonclinical

Question 11a: Does the Agency agree with the Sponsor's proposed approach (b) (4)

Division Response to Question 11a:

Yes.

Question 11b: Alternatively, would the Agency prefer (b) (4)

Division Response to Question 11b:

No.

Sponsor Response to Division Response to Questions 11a and 11b:

The Sponsor acknowledges the Agency's comments. No further discussion required.

Question 12: Nonclinical studies supporting NDA 213006 were conducted by the previous Sponsor (Merck) or by Kyorin. Given their legacy nature (majority initiated prior to 2016),

currently available datasets are limited to the mouse (TT12-6031) and rat (TT11-6036) carcinogenicity studies. Furthermore, the datasets are in XPT format. The Sponsor plans to provide datasets in XPT format in the NDA for the mouse and rat carcinogenicity studies. No other nonclinical datasets will be provided. Does the Agency agree?

Division Response:

Yes.

Sponsor Response to Division Response to Question 12:

The Sponsor acknowledges the Agency's comment. No further discussion required.

2.5. Office of Scientific Investigations (OSI) Requests

Question 13: The Sponsor will provide Office of Scientific Investigations (OSI)- requested Bioresearch Monitoring (BIMO) information for the pivotal efficacy/safety study evaluating once daily 75 mg vibegron (RVT-901-3003) in the NDA, in accordance with current FDA expectations. Does the Agency agree?

Division Response:

No. Submit OSI-requested BIMO information also for the extension study RVT-901-3004.

Sponsor Response to Division Response to Question 13:

The Sponsor acknowledges the Agency's comment. No further discussion required.

2.6. Regulatory Affairs

Question 14: Vibegron is a New Chemical Entity (NCE). The Sponsor intends to submit a 505(b)(1) New Molecular Entity NDA (NDA 213006), for vibegron for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency, in accordance with "the Program" under PDUFA (Prescription Drug User Fee Act) VI. Does the Agency agree?

Division Response to Question 14:

Yes.

Sponsor Response to Division Response to Question 14:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 15: The Sponsor believes that vibegron, as an NCE submitted under a 505(b)(1) application, is entitled to a 5-year period of exclusivity. Does the Agency agree?

Division Response to Question 15:

The exclusivity determination is determined after the NDA is approved.

Sponsor Response to Division Response to Question 15:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 16: Given that vibegron is not first-in-class as a beta-3 adrenergic receptor agonist for the treatment of OAB, the Sponsor does not believe that NDA 213006 will require referral for discussion at the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC). Does the Agency agree?

Division Response to Question 16:

No. While we have no current plans to discuss your application at a meeting of the BRUDAC, it is premature to determine the need for a meeting of the BRUDAC prior to the application being submitted and initially reviewed.

Sponsor Response to Division Response to Question 16:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 17: The Sponsor believes that appropriate labeling and routine analysis of spontaneous postmarketing adverse events will be sufficient to ensure that the benefit of vibegron outweighs its risks as a treatment for OAB, and that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary. Does the Agency agree?

Division Response to Question 17:

We have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of vibegron outweigh the risks, and if a REMS is necessary, what the required REMS elements would be. The need for a REMS will be determined during the review of the application. We agree, however, that the NDA does not need to include a REMS proposal at the time of NDA submission.

Sponsor Response to Division Response to Question 17:

The Sponsor acknowledges the Agency's comment. No further discussion required.

Question 18: [redacted] (b) (4) *Does the Agency agree?*

Division Response:

No. [redacted] (b) (4)

Sponsor Response to Division Response to Question 18:

The Sponsor acknowledges the Agency's comment. No further discussion required.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK S HIRSCH
07/10/2019 08:14:28 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106410

MEETING MINUTES

Urovant Sciences GmbH
Attention: Kevin Healy, Ph.D. – Senior Director
Global Regulatory Affairs
320 W. 37th St.
New York, NY 10018

Dear Dr. Healy:

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

We also refer to the meeting between representatives of your firm and the FDA on July 24, 2017. The purpose of the meeting was to discuss your revised development program consisting of planned nonclinical, clinical pharmacology, and Phase 3 clinical studies to complement the data that has been obtained since the January 2013 End of Phase 2 meeting.

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

If you have any questions, please call Nenita Crisostomo, Regulatory Health Project Manager at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
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:	End of Phase 2
Meeting Date and Time:	July 24, 2017, at 2:30 PM – 3:30 PM, Eastern Standard Time
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1421 Silver Spring, MD 20903
Application Number:	IND 106410
Product Name:	RVT-901 (vibegron) tablets
Indication:	Treatment of overactive bladder
Sponsor/Applicant Name:	Urovant Sciences GmbH
Meeting Chair:	Mark S. Hirsch, M.D.
Meeting Recorder:	Nenita Crisostomo, R.N.

FDA ATTENDEES

Audrey Gassman, M.D. Deputy Director, Division of Bone Reproductive and Urologic Products (DBRUP)
Mark S. Hirsch, M.D. – Medical Team Leader, DBRUP
Debuene Chang, M.D. – Medical Officer, DBRUP
Doanh Tran, Ph.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology-3 (DCP-3), Office of Clinical Pharmacology (OCP)
LaiMing Lee, Ph.D. – Clinical Pharmacology Reviewer, DCP-3, OCP
Mark Seggel, Ph.D. – CMC Lead, New Drug Products Branch V, Division of New Drug Products II (DNDPII), OPQ
Kalpana Paudel, Ph.D. – Biopharmaceutics Reviewer, Biopharmaceutics Branch II, ONDQA
Mukesh Summan, Ph.D., DABT – Pharmacology/Toxicology Supervisor, DBRUP
Laurie L. McLeod-Flynn, Ph.D. – Pharmacology/Toxicology Reviewer, DBRUP
Jia Guo, Ph.D. – Biostatistician, Division of Biometrics II (DBII)
Selena Daniels, Pharm.D., M.S. – Team Leader, Clinical Outcome Assessments (COA) Staff, Office of New Drugs (OND)
Sarrit Kovacs, Ph.D. – Reviewer, COA Staff, OND
Kimberly Chiu, Pharm.D. – Project Manager, COA Staff, OND
Preston Dunnmon, M.D. – Medical Officer, Division of Cardiovascular and Renal Products (DCRP)
Jennifer Mercier – Chief, Project Management Staff, DBRUP
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DBRUP

UROVANT SCIENCES GmbH
William T. Symonds, Pharm.D. – Chief Development Officer
Paul N. Mudd Jr, Pharm.D., MBA, VP – Clinical Research
(b) (4) – Consultant (Chief Scientific Officer, (b) (4))
Nate Bennett, Ph.D. – Director of Statistics
Steve Piscitelli, Pharm.D., VP – Clinical Pharmacology
(b) (4) – Consultant (Patient Reported Outcomes Assessment, (b) (4)
(b) (4))
(b) (4) – Consultant (Medical Director, Medical Affairs, (b) (4))
Kevin Healy, Ph.D. – Senior Director, Global Regulatory Affairs

1. BACKGROUND

On January 29, 2010, Merck submitted IND 106410 for MK-4618 for the treatment of overactive bladder (OAB). On January 18, 2013, an End of Phase 2 (EOP2) was held between the Division and Merck. Since that time, several additional studies have been completed, including the Merck Phase 2b Study 008, and in partnership with Kyorin, the Japanese-only, Kyorin Phase 3 Study 301 and its extension, Kyorin Study 302, with a total of approximately 2,625 OAB patients included. The Phase 3 studies proposed at the January 18, 2013, EOP2 meeting were not conducted.

On February 28, 2017, the sponsorship for this IND changed from Merck to Urovant. The vibegron development plans has been revised by Urovant based on the Division's feedback at the January 18, 2013, EOP2 meeting, the totality of safety and efficacy data generated from 2013 to 2016, and currently published information. Urovant requested this meeting to discuss their revised development plans.

The meeting information package was received by the Division on June 23, 2017. The Preliminary Comments were sent to the Sponsor from the Division on July 20, 2017. In turn, the Sponsor sent responses to the Preliminary Comments via email on July 21, 2017.

The Sponsor's specific questions are presented in *italics*, and the Division's responses and additional comments are presented in regular font. The Sponsor's responses are presented in ***bold italics*** and Discussions at the meeting are presented in **bold regular font**.

2. DISCUSSION

Discussion at the meeting: The Division began the discussions by requesting that the Sponsor clarify the dosing schedule used in Kyorin Study 301. The Sponsor stated that, in order to maintain study blinding, the dosing schedule in Study 301 was twice daily, but active vibegron was administered once per day (in the morning) and placebo was administered in the evening.

The Division also requested that the Sponsor clarify whether they had access to the full datasets and study reports for Kyorin Studies 301 and 302. The Sponsor responded that

they had recently obtained full access to all datasets for the 2 studies, as well as full English translations of the study reports.

The meeting transitioned to a discussion of Questions 7 and 8, followed by a discussion of Questions 10 to 13. The Sponsor stated that no additional discussion was necessary for the remainder of the questions.

Question 1: Based on the justification provided in Section 10.4.1.1.3, does the Agency concur with our designation of starting materials (b) (4) *in the synthesis of the active pharmaceutical ingredient?*

Response: We concur with your designation of starting materials (b) (4) in the synthesis of the active pharmaceutical ingredient, with the understanding that your synthetic schemes for the starting materials would be included in the NDA. We remind you that complete evaluations of the synthetic routes and the specifications of the drug substance and the starting materials, as well as your controls on potential genotoxic impurities in the drug substance based upon the synthetic routes, would be conducted at the NDA review stage.

Sponsor Response: No further discussion necessary

Question 2: Does the Agency agree that the proposed specifications for the active pharmaceutical ingredient are adequate to support the Phase 3 program?

Response: The scope of the proposed specification for the active pharmaceutical ingredient appears reasonable to support the Phase 3 program. However, the final acceptance criteria will be an NDA review issue. For example, you have not provided a justification for the limit of the (b) (4) impurity (NMT (b) (4) %), or a comprehensive list of potential impurities in the drug substance. In addition, validation will need to be provided to demonstrate that your methods are capable of analyzing the potential impurities. These pieces of information would be needed in the NDA submission and will be reviewed at that time.

Sponsor Response: No further discussion necessary

Question 3: Does the Agency agree that the proposed specifications for the vibegron drug product, with the planned further development of the dissolution method and acceptance criteria, are adequate to support the Phase 3 program?

Response: Yes, the proposed drug product specification appears adequate to support the Phase 3 program. However, we note that the proposed acceptance criterion of (b) (4) % for total impurities is not justified based on the available data. We recommend tightening the acceptance criterion for total impurities.

Your approach to dissolution method development of the drug product appears reasonable. We recommend that the selection of the specification time point should be where Q= (b) (4)% dissolution occurs. Note that the final determination on the acceptability of the dissolution method and acceptance criterion is a review issue that can be determined during NDA review stage with complete dissolution data (individual, mean +/- SD, mean profile, n=12/batch). However, based on the data submitted so far, it appears that dissolution criterion can be tightened to Q= (b) (4)% at (b) (4) minutes for better quality control. Also pay attention to the discriminating ability of your method in terms of formulation and process variables to reject bad batches.

Sponsor Response: ***No further discussion necessary***

Question 4: Does the Agency agree that the proposed drug substance and drug product stability study designs will be adequate to support submission of an NDA for vibegron?

Response: Yes, the proposed drug substance and drug product stability study designs (stability storage conditions and testing time points) appear adequate to support submission of an NDA.

Additional Chemistry comment:
To facilitate our ongoing review of the IND, please submit a tabulation identifying the vibegron drug product lots (bulk and packaged) used in each clinical study. Include the formulation, manufacturer, manufacturing process and date of manufacture.

Sponsor Response: ***No further discussion necessary***

Nonclinical

Question 5: Does the Agency agree that the nonclinical package is sufficient to support the proposed Phase 3 program as well as the filing of the vibegron NDA?

Response: We agree that the nonclinical package is sufficient to support the proposed Phase 3 program and the filing of an NDA. However, we reserve the right to request additional nonclinical studies if unanticipated toxicity or exaggerated pharmacology is observed in clinical or nonclinical studies.

Sponsor Response: No further discussion necessary.

Clinical Pharmacology

Question 6: During the January 2013 EOP2 meeting, the Agency responses to Question 3 and Question 4 included the following comments "the overall clinical pharmacology program appears adequate...subject to a full review at the time of NDA submission" and "Based on the limited information provided and the sponsor's own assessment of the data, the list of DDI studies appears to be adequate". Furthermore, in response to Question 5, the Agency agreed that no further pharmacodynamic (PD) interaction studies (beyond the planned warfarin studies) are required.

Does the Agency agree that the completed and planned clinical pharmacology studies support NDA filing of vibegron for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency?

Response: Yes. We recommend that the vibegron dose in the proposed clinical pharmacology studies should be the highest to-be-marketed dose and formulation. For a subset of patients in your proposed Phase 3 study, include sufficient blood sampling to characterize the steady state pharmacokinetics of vibegron. Submit in your IND and NDA a table outlining the formulation(s) used in each clinical study and clarify how each formulation is bridged to the Phase 3 and to-be-marketed formulations.

Sponsor Response: No further discussion necessary.

Clinical – Phase 3 Program

Question 7: Does the Agency agree that the totality of evidence to be provided by the five OAB clinical studies (RVT-901-3003 [pivotal safety/efficacy] and RVT-901-3004 [pivotal safety]; supportive studies: Merck Study 008 and Kyorin Studies 301 and 302) are adequate to support submission and allow FDA review of a vibegron NDA for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency?

Response: The completed studies (Merck Study 008 and Kyorin Studies 301, 302), along with your planned studies RVT-901-3003 and RVT 901-3004, could provide sufficient evidence to support submission of an NDA for vibegron for the OAB indication.

We note that several serious cardiovascular adverse events (SAEs) were reported in the already completed Phase 2 and Phase 3 studies, including 4 MACE, one event of loss of consciousness (LOC) in the Merck 008 study, 3 MACE in the Kyorin 3004 study, and one death after an event of fall following suspected alcohol ingestion. Based on the CV AEs, and the apparent effect of vibegron on blood pressure (BP) and heart rate at doses ≥ 100 mg, we continue to be interested in the effect of vibegron on BP and BP-related AEs in your planned Phase 3 studies. You should assess BP at or near the times of maximum plasma concentrations (T_{max}) in those studies, and you should also monitor for BP-related AEs.

There have been other noteworthy AEs in the completed Phase 2 and Phase 3 studies, including urinary tract infection (UTI), one case of neutropenia, and one case each of supraventricular tachycardia (SVT), somnolence, elevated hepatic tests, and increased serum creatinine, all leading to discontinuation of vibegron therapy. These potential safety issues are of interest and should be monitored in your planned studies.

Sponsor Response: The sponsor would like to discuss the collection and characterization of heart rate and blood pressure data in the vibegron clinical program. The sponsor plans to monitor for the noteworthy AEs, including BP-related AE's, mentioned by the Division.

Discussion at the meeting: The Sponsor summarized a plan to measure BP and HR in all patients at all visits in Study 3003. The Sponsor proposed to collect the time of last dose prior to each visit as well as the time of the BP and HR measurements in order to construct

a plot with time post-dose on the x-axis and BP/HR on the y-axis. The Sponsor also proposed to collect BP and HR in the PK subset (25% of patients) at the Week 4 visit, at which time patients will take their dose in the clinic and then will have a PK sample collected and BP and HR measured at least 1 hour or more after dosing. The Sponsor believes this approach may provide the best real-world evidence on the effect of vibegron on BP and HR.

The Division expressed a concern that the Sponsor's proposed approach will not be adequate to define *outlier* blood pressure effects at T_{max}. This concern stems from the following observations:

- **Data in healthy normal subjects appear to demonstrate a dose-dependent increase in HR or BP at vibegron doses greater than 100 mg.**

- **Data from the Study 008 main trial appears to demonstrate that while group mean changes from baseline in HR and SBP/DBP are similar between placebo and vibegron 100 mg and are of small magnitude, for all positive categorical shifts for changes in HR, a higher frequency is reported for vibegron 100 mg compared to placebo across the range of defined shift categories. The observation that small mean changes in HR are accompanied by consistently more frequent positive categorical shifts for HR suggests that negative categorical HR shifts are also occurring more frequently in the vibegron 100 mg treatment arm compared to placebo. The same appears true for DBP categorical shifts in the Study 008 main trial.**

Thus, the Division is concerned that an identifiable subgroup of patients (perhaps those with the lowest weight, or those with the most renal impairment, or those with a baseline blood pressure exceeding 140/90, or the oldest patients) may be experiencing important categorical shifts in HR and BP and these shifts are obscured in the analysis of population means.

Further, the cuff blood pressures that were collected in Study 008, and those that are planned for Studies 3003 and 3004, are not timed to C_{max}, where the largest cardiovascular effects are expected to occur. If the vibegron T_{max} is in the range of 0.8 to 3.0 hours, the Sponsor's proposed approach for assessing vital signs may miss the largest magnitude effects on HR and BP in most subjects.

Potential C_{max}-mediated, drug-related effects on BP and HR are often evaluated in an ambulatory blood pressure monitoring (ABPM) study, which has the ability to evaluate changes in BP and HR within a window of time around the T_{max}. While the Division have held previous discussions with the former IND Sponsor in regard to an ABPM study sample size of approximately 30 patients, there is flexibility in the sample size for the ABPM study, especially if it is performed in a population of subjects that may be most prone to drug effects on BP and HR. Cumulative function distribution (CFD) analyses of the ABPM study data for maximal change from baseline in HR, SBP, and DBP in the T_{max}

window provide for a meaningful assessment of potential drug-related effects on BP and HR.

The Sponsor responded that they understood the Division's concerns and is aligned with the Division's intent to collect BP and HR data around T_{max}. The Sponsor will consider the advice provided at today's meeting and will submit a plan for assessing the potential effect of vibegron on BP and HR in the near future.

Additional comments from the Division of Cardiovascular and Renal Products (DCRP):

1. Regarding your planned assessment for BP effects of vibegron, the data in healthy normal subjects demonstrates a dose-dependent increase in HR or BP at doses above 100 mg. Additionally, data from the Merck Study 008 main trial demonstrates that while group means for changes from baseline in HR and SBP/DBP appear similar between the placebo and vibegron 100mg arms, it is noted that in the all the categorical shift changes for HR occur at a higher frequency in the 100 mg vibegron arm compared to the placebo arm across the range of the defined categories. The same is true for DBP categorical shifts in the main study. This suggests that there may be a sub-population within Merck Study 008 that could be identified as more "at risk" for drug-induced vital sign changes (e.g., the lowest weight quartile and/or the lowest GFR quartile, and/or the highest age quartile, and/or a baseline blood pressure exceeding 140/90).

   Sponsor Response: Urovant appreciates the Agency comments and will investigate the subgroups as suggested. No further discussion necessary.

2. In addition to identifying this subpopulation for analysis from Merck Study 008, we request that you also do cumulative function distribution (CFD) analyses for the maximal change from baseline in HR, SBP, and DBP for placebo, vibegron 100mg, and tolterodine monotherapy from the main phase data of Merck Study 008, both for the overall Merck Study 008 study population, and for the "at risk" sub-population we describe above, however you decide to define that sub-population.

   Sponsor Response: Urovant will investigate the subgroups as suggested. No further discussion necessary.

3. Assuming that the vital signs were randomly acquired relative to drug dosing in Merck Study 008, and assuming this may be the case for other Phase 2 and Phase 3 trials with Week 4 data where placebo and vibegron 100 mg were administered (including the as of yet not submitted Japanese Phase 3 studies), we ask that you integrate all of the vital sign data from these trials to assess for HR/SBP/DBP effects, including your prior analyses of population means and shifts, together with the above-described cumulative function curve (CFC) analyses for change from baseline for these parameters - done separately for the overall integrated population, as well as the "at risk" sub-population, however you define that group.

   Sponsor Response: Urovant will investigate the subgroups as suggested. No further discussion necessary.

4. As best we can tell, the cuff pressures collected in Merck Study 008, and those that are planned for the Urovant Studies 3003 and 3004, are not timed to C_{max}, where the largest HR/SBP/DBP effects are expected to occur. Your plan not to conduct the 30-subject ambulatory BP monitoring (ABPM) study that was discussed at the January 18, 2013, EOP2 meeting precludes the ability to assess vital sign effects at C_{max}. Clarify how you intend to obtain this information if you proceed with your plan to cancel the ABPM study.

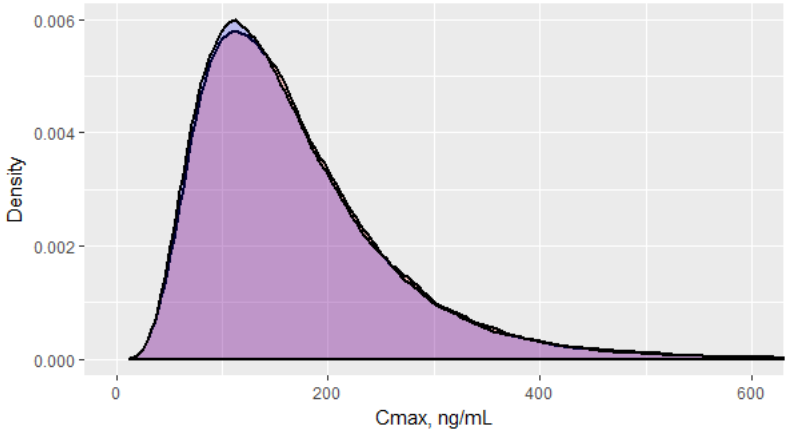
   ***Sponsor Response*: The sponsor would like to discuss the collection and characterization of heart rate and blood pressure data in the vibegron clinical program.**

   Discussion at the meeting: See Discussion above, under Question 7.

5. You posit that due to the non-dose-linearity of vibegron exposure below 100 mg, that subjects receiving 75 mg with the highest exposures should not exceed the C_{max} of the Merck Study 008 safety dataset. Does your modeling of this predicted limit on C_{max} take into consideration that prior studies have not enrolled subjects with moderate renal impairment and Urovant Study 3003 will include these subjects?

   ***Sponsor Response*: Modeling of vibegron C_{max} included exposures from 50, 75 and 100 mg doses. Exposures were further simulated at 1.6-fold the exposures of 75 mg and compared with exposures from 100 mg to estimate C_{max} in subjects with moderate renal impairment based on Study 014 (1.6-fold increase compared to normal renal function). As shown below, the density plots are practically superimposable suggesting that the limit on C_{max} for 75 mg in moderate renal impairment covers C_{max} observed with a 100 mg dose.**

   Density Plots of Simulated Steady-State Vibegron C_{max} for 75 mg in Patients with Moderate Renal Impairment (1.6 fold Higher Exposures) and for 100 mg (blue)



6. Address the apparent inconsistencies in the proposed Phase 3 protocols regarding the patient position from which BP will be measured (e.g., one bullet states that the BP will

be acquired in a semi-recumbent position, but the sub-bullet states that acquisition will take place in the sitting position).

Sponsor Response: This will be corrected in the final protocol prior to submission to the Agency; no further discussion necessary.

7. Clarify that HR will be acquired simultaneously with SBP/DBP, and that the mean of the three readings for each parameter will be used in the analytical dataset.

   Sponsor Response: Urovant confirms that HR will be acquired simultaneously with SBP/DBP, and that the mean of three readings for each parameter will be used in the analytical dataset. No further discussion necessary.

8. Submit the charter for your Clinical Events Committee for the MACCE analysis, to include the definition set reference you are using to define these events.

   Sponsor Response: The charter will be submitted with the final protocol; no further discussion necessary.

Question 8: Does the Agency agree that the target population as defined by inclusion and exclusion criteria in the Phase 3 studies is adequate to demonstrate safety and efficacy of vibegron in the proposed indication?

Response: In general, the inclusion/exclusion criteria appear acceptable to define the target population, with the following caveats:

- For inclusion criteria #7: "*Patient has a history of 24hr urine volume greater than 3000mL or voided volume diary measurement greater than 3000mL during the Run-in Period.*" This would appear to be an exclusion criterion, not an inclusion, criterion.

- We note that you plan to include subjects with BP as high as 180/100 mmHg, require a stable antihypertensive regimen 90 days prior to baseline, and measure antihypertensive medication changes post-randomization as an indicator of study drug effect on BP. Patients with BPs in the range of 180/100 mmHg are not medically stable, and post-randomization antihypertension medication changes that take place to address their hypertension will confound the assessment of study drug effect on BP. We suggest that you consider stipulating that subjects may have had a history of these kinds of blood pressures, but that their hypertension must be medically controlled on a stable antihypertensive regimen at their Baseline visit.

Sponsor Response: We agree that Inclusion criteria #7 should be an exclusion criterion; this will be corrected in the final protocol.

We would like to discuss the BP exclusion at the meeting. The EOP2 Meeting Minutes from January 2013 stated "In order to enroll an appropriate broad target population, we recommend that uncontrolled hypertension (as in exclusion criterion #6) be defined as a

systolic blood pressure (BP) ≥ 180 mm Hg and/or diastolic BP ≥ 100 mm Hg…". We had adopted this criterion to exclude these patients and added further detail to ensure that patients who were enrolled requiring antihypertensive treatment were on stable medication prior to study entry.

Discussion at the meeting: The Division clarified that since the 2013 EOP2 meeting advice, the Division's thinking on this issue has evolved. The Division explained that BP may be uncontrolled in hypertensive patients before clinical trials, and then, once on study, antihypertensive medications are optimized and blood pressure is lowered. This can result in a "parallel study" or "hypertension substudy" in which a significant decrease in BP (e.g., 30 mm Hg) may be due to improved BP management or patient compliance with their antihypertensive medication regimen. This effect can mask a BP increase related to study drug. For this reason, we now emphasize the importance of enrolling medically stable patients, with an upper limit of systolic BP ≥160 mm, rather than ≥180 mm Hg.

The Sponsor stated that they understood the Division's concern and would propose a means to address the concern.

Question 9: During the January 2013 EOP2 meeting, the Agency response to Question 13 regarding the dose selection for the Phase 3 studies included the following comments: "We do not object to the 50 mg and 100 mg doses selected for the Phase 3 studies. We point out the relatively shallow dose response relationship for efficacy, and that many endpoints demonstrated similar efficacy for the 50 mg and 100 mg doses. However, it appears that some endpoints demonstrated better efficacy at the 100 mg dose compared to the 50 mg dose." The Agency also noted some safety considerations, and further commented that "the current dose selection assumes some risk if there is a lack of incremental clinical benefit and also safety concerns for the 100 mg dose." Based upon extensive analyses performed by Urovant across all available clinical data, a single dose level of 75 mg is proposed for the Phase 3 program as described below.

Does the Agency agree with the 75 mg dose rationale for the proposed Urovant Phase 3 program?

Response: While we do not object to your plan for a single daily dose of 75 mg, we encourage you to consider a dose titration regimen instead, with a lower starting dose (e.g., 50 mg) and a maximum dose of 75 mg. Our rationale is that some patients may receive adequate benefit at a lower dose (e.g., 50 mg) without the need to take the higher dose (e.g., 75 mg). The lower starting dose may also be appropriate for special populations (e.g., elderly patients, etc.).

Sponsor Response: No further discussion necessary.

Question 10: The proposed indication is:

> ***[Trademark] is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.***

During the January 2013 EOP2 meeting, the Agency response to Question 10 regarding the co-primary endpoints for the Phase 3 studies included the following comments: "The co-primary endpoints selected for Protocol 019 and Protocol 020, change from baseline to Week 12 in average number of micturitions/day and average number of urge urinary incontinence episodes/day are acceptable for Phase 3 studies designed to support your first proposed indication. We note that your proposed diary asks patients to judge the reason for each leakage episode (urge vs. stress vs. other). We ask that you demonstrate that there is reproducibility and reliability in responding to this question in the diary in the Phase 2 study since it will play a crucial role in tabulating the coprimary endpoint of urge urinary incontinence."

Does the Agency agree that a reduction in overactive bladder symptoms, as measured by the proposed co-primary endpoints (average number of micturitions/day and average number of urgency urinary incontinence episodes/day) for Study RVT-901-3003 support the clinical indication?

Response: Yes. We agree that the co-primary endpoints "*change from baseline to Week 12 in average number of micturitions/day and average number of urge urinary incontinence episodes/day"* are acceptable for the OAB indication.

We remind you of our previous concern that the patient voiding diary (PVD) requires patients to make a choice between stress and urge incontinence for each incontinence episode, which may present a challenge for some patients. While your previous results do not suggest widespread difficulty with this part of the voiding diary, if some patients struggle with this choice, there is a risk that your study may not be sensitive to small differences between groups for urge incontinence episodes (UUI), a mandatory co-primary endpoint.

In regard to the patient voiding diary (PVD) and other PROs proposed for use in Phase 3:

1. Submit an Evidence Dossier for our review and comment, as follows:

    a. Submit all qualitative work that has been conducted with patients, including interviewer scripts and patient transcripts, from both the concept elicitation and cognitive debriefing interviews, in support of the patient voiding diary and other patient-reported outcome (PRO) tools that are proposed as pre-specified endpoints in Phase 3. The information in the Evidence Dossier should demonstrate that the concepts included in the PVD and the other PRO tools are important and comprehensive to patients in terms of their OAB symptom experience (Wet and Dry) and that patients are interpreting all instructions, terms, and concepts in consistent ways.
    b. Provide evidence that patients can accurately and reliably select the type of incontinence episode (stress, urge or other) that they experience.
    c. Submit results from all analyses of the PVD and other PRO tools' showing their psychometric properties and performance in the Phase 2 study (Merck Study 008).
    d. Provide a scoring algorithm for the PVD and other PRO tools along with a proposed calculation of the pre-specified endpoint scores.

2. We acknowledge that you are currently in the process of migrating the paper version of the PVD to electronic mode for use in Phase 3, are currently testing the patient instructions and usability of the electronic PVD with patients in order to finalize them for Phase 3, and plan to provide a summary report for review and comment. Clarify whether you plan to conduct usability testing in all languages and within all cultures intended for inclusion in Phase 3.

   We recommend both translation and cultural adaptation of the PVD, including instructions, items/domains, and response options, for multinational studies. Translation and cultural validation adaptation of clinical outcome assessments can affect efficacy findings and it is important to ensure that efficacy assessments are standardized across cultures, languages, and sites. Translation and cultural adaptation includes conducting qualitative work on the instrument within all languages and cultures in which the instrument is to be assessed. We refer you to the ISPOR principles for the translation and cultural validation adaptation process.[1]

3. The Patient Global Impression of Severity, Change, and Control (PGI-Severity, PGI-Change, and PGI-Control, respectively) scales proposed for Phase 3 (Study RVT-901-3003) appear reasonable to serve as anchor scales for anchor-based analysis to help interpret a clinically meaningful within-patient change in PVD and other key PRO item scores from the patient perspective. The anchor scales should be assessed at the same time points as, but completed after, the key PRO tools. We recommend that you also include in Phase 3 the three patient perceived status items that you included in your Phase 2 Study 008 (e.g., frequency of OAB symptoms, accidental urine leakage, and amount of control over OAB symptoms) for the purpose of data comparability.

***Sponsor Response*: The response below includes information relevant to Questions 10-13.**

An extensive background package, including much of the information being requested in support of the PVD, was submitted to the Agency by Merck on January 5, 2007 (Type C Meeting Briefing Document). At the time of NDA filing, we will submit an updated PRO evidence package in which we will reference and supplement the supporting evidence submitted previously by Merck. Additional evidence to be provided will include the methods and results of upcoming patient interviews (including our protocol, interview guide, and transcriptions), as well as further support for the responder definitions, including CDF and PDF curves based on the existing data, as well as CDFs based on the phase 3 data. In addition to testing the usability of the electronic diary, the planned interviews will further explore patients' perceptions of meaningful improvements in each of their OAB symptoms, as well as their ability to distinguish between leakage that is primarily caused by urgency vs. stress. We will also include additional evidence pertaining to the OAB-q in the updated PRO evidence

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

package, with a focus on supporting changes in scores on the coping domain as a key secondary endpoint for the Phase 3 study.

With respect to the questions and suggestions surrounding usability testing (Question 10.2), translation and cultural adaptation of the PVD, we would like to clarify that usability testing of the electronic PVD is planned in the US; however, Merck followed the standard process recommended by Wild and her colleagues (2005) to create culturally appropriate versions of the diary in more than 50 languages. If any additional language versions are required, translation and cultural adaptation will be conducted following the same process.

At the time of final Phase 3 protocol submission, we will also provide the following documents for Agency review: a detailed phase 3 SAP, an abbreviated TPP to lay out claims for the PVD (b) (4) ***and a brief report*** (b) (4) ***This brief report will include a summary of all analyses conducted to date, provide the CDFs and PDFs FDA has requested, and describe relevant methods and results from the patient interviews to be conducted in August 2017.***

Finally, with respect to the third part of the response to Question 10, we seek clarification from the Agency. In particular, given that two patient-perceived status measures are slated for use in the Phase 3 study (PGI-Severity and PGI-Control), in addition to the PGI-Change item, we would like to better understand the recommendation to include three additional status measures from the Phase 2 Study 008 (e.g., frequency of OAB symptoms, accidental urine leakage, and amount of control over OAB symptoms). The ability to compare data from the Phase 3 and Phase 2 studies is referenced. However, we believe the endpoints derived from the PVD offer a clear avenue for comparison. We are particularly concerned about the inclusion of a second item addressing control over OAB symptoms. For easy reference, we have included both sets of items below. We appreciate Agency clarification.

Global Items Slated for Use in Phase 3

Patient Global Impression of Severity (PGI-Severity)
Overall, how would you rate your overactive bladder symptoms now?
☐ None
☐ Mild
☐ Moderate
☐ Severe

Patient Global Impression of Control (PGI-Control)
How well are you able to control your bladder symptoms now?
☐ Not at all
☐ A little bit
☐ Moderately well
☐ Quite well
☐ Very well

Patient Global Impression of Change (PGI-Change)
Overall, compared to the start of the study, how would you rate your overactive bladder symptoms now?
☐ Much better
☐ Moderately better
☐ A little better
☐ No change
☐ A little worse
☐ Moderately worse
☐ Much worse

Patient Perception Items Used to Facilitate Responder Analysis of Phase 2 Data

Patient Perception of Symptom Frequency
Over the past week, how often did you have overactive bladder symptoms?
☐ Never
☐ Rarely
☐ Sometimes
☐ Often
☐ Very often

Patient Perception of Control
Over the past week, how much control did you have over your overactive bladder symptoms?
☐ Complete control
☐ A lot of control
☐ Some control
☐ Only a little control
☐ No control

Patient Perception of Urgency-Related Leakage
Do you experience urine leakage related to the feeling of urgency?
☐ Yes
☐ No

If Yes, how much does it bother you?
☐ Not at all
☐ Slightly
☐ Moderately
☐ Greatly

<u>Discussion at the meeting</u>: The Division advised the Sponsor to provide the following for a thorough FDA review of the claims being sought:

- **Exact copies of all clinical outcome assessments (COAs) used as key endpoints;**

- **Evidence, compiled in a dossier, of the content validity and other measurement properties of the COAs, as well as the conceptual framework and scoring information for the COAs;**
- **Target Product Profile (TPP);**
- **All Phase 2 clinical efficacy data; and**
- **Analytical plans for planned Phase 3 efficacy endpoints**

The Division advised the Sponsor to allow sufficient time for FDA review of these materials so that feedback could be provided to the Sponsor prior to their submission of the Phase 3 protocol.

The Division emphasized the need for the Sponsor to provide evidence from completed studies using the PVD that patients were able to correctly distinguish the type of incontinence episode ("urge", "stress" or "other") that they had experienced. The Sponsor indicated that there was support for this part of the PVD from data generated in Study 008 and further support will be generated in planned qualitative research studies (e.g., in patient interviews).

The Division did not voice major concerns concerning the planned transition from paper voiding diaries to an electronic form, but recommended that the Sponsor should plan to adequately translate and culturally adapt the electronic diaries for use in the planned multinational study. The Division also recommended that the Sponsor implement a back-up plan (e.g. web-based or paper) in case of potential device failure and data loss with e-diaries.

With regards to the Global Impression items that will serve as anchors for the planned analyses intended to support responder definitions for each of the key Phase 3 efficacy endpoints, the Sponsor inquired about the Division's suggestion to include 3 Global items that had been used in the Phase 2 Study 008 in addition to the 3 items that the Sponsor planned for Phase 3. The Sponsor selected the 3 Global items based on their understanding of current FDA standards. The Sponsor inquired whether it was acceptable for them to proceed with the 3 Global Impression items as planned. While the Division acknowledged that the 3 Global Impression items planned for use in Phase 3 are consistent with recent FDA feedback, the Division nonetheless indicated a preference for a recall period of "over the past week" rather than "now" within the context of the OAB condition. For that reason, the Division continued to recommend that the Sponsor administer both the proposed Phase 3 anchor items and the Phase 2 anchor items to allow comparison of the results of responder analyses across the Phase 2 and Phase 3 studies.

Question 11: Does the Agency agree that 'the need to urinate immediately' (urgency urinary episode) can lead to labeling claims as a secondary endpoint in Study RVT-901-3003?

Response: If your qualitative research and clinical study results support content validity, reliability and sensitivity to change of this item, and the endpoint is properly incorporated into the study's statistical plan, and the actual results are clinically compelling, and the results for this endpoint are confirmed by results from this same endpoint in a second clinical study, then "*the*

need to urinate immediately" as a reflection of urinary urgency could lead to labeling claims as a secondary endpoint in Study RVT-901-3003. We encourage you to submit a Targeted Product Profile (TPP), and additional information to justify possible labeling for this secondary endpoint.

***Sponsor Response*: Further to the information provided above in Question 10, Study 008 provided initial efficacy data on "the need to urinate immediately" endpoint and Study RVT-901-3003 will confirm this result for labeling.**

Question 12: Does the FDA agree (b) (4)

Response: No. You have not presented sufficient data (b) (4)

(b) (4) However, to supplement your anchor-based analyses, you should provide both cumulative distribution function (CDF) and probability density function (PDF; also known as a kernel density plot) curves to explore and to derive a number of thresholds for meaningful change. (b) (4)

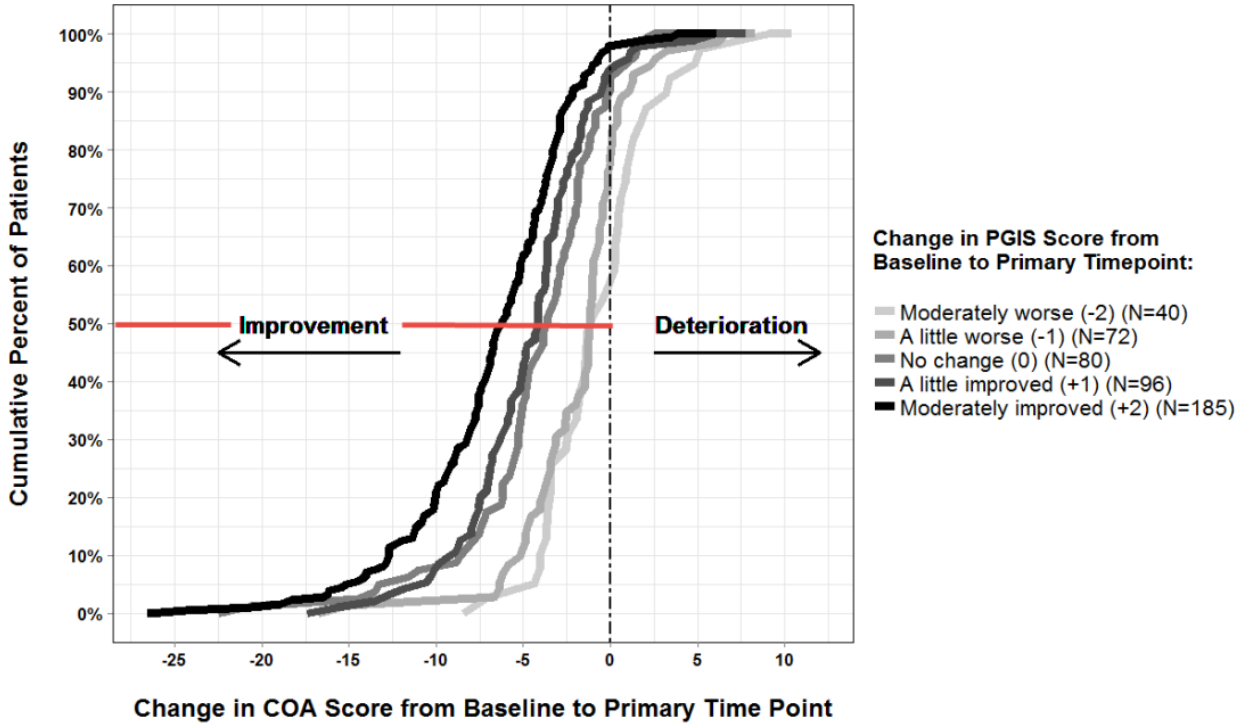
Therefore, submit the following CDF and PDF curves using data from your Phase 2 study (Merck Study 008), including sample sizes and median scores for each CDF and PDF curve:

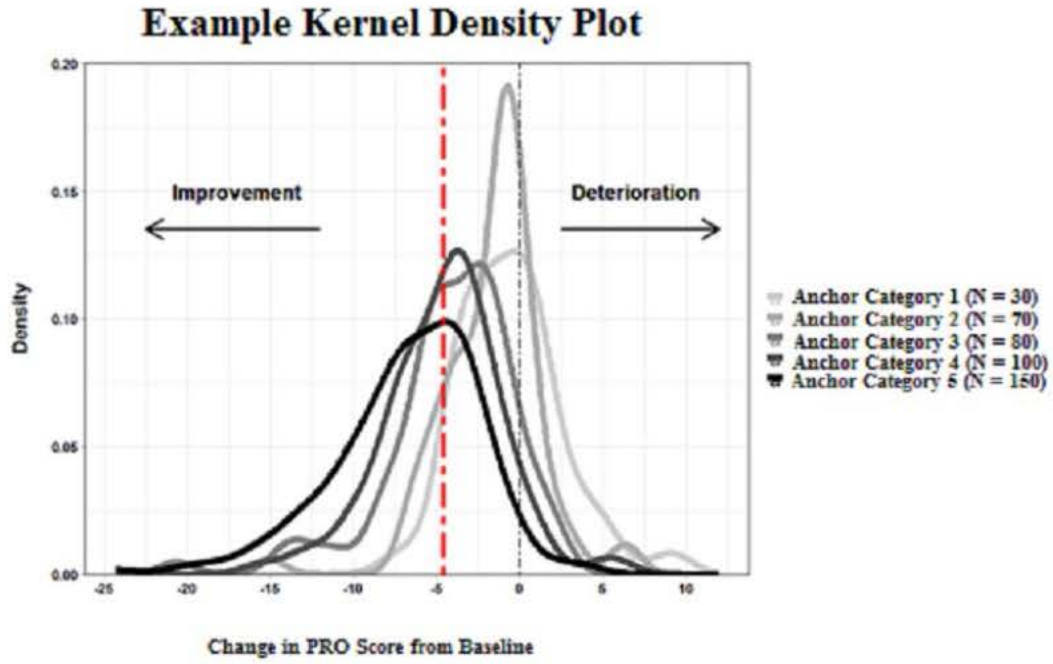
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) for all patients (both treatment and placebo arms pooled) by the anchor item change response options (e.g., very much improved, much improved, etc.) at week 8.
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) for all patients (both treatment and placebo arms pooled) by the anchor item severity response category change scores from baseline (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) with curves for each treatment arm

Examples of CDF and PDF figures are shown below:

EXAMPLE Empirical Cumulative Distribution of Change in COA Score from Baseline to Primary Time Point, by Change in PGIS Score from Baseline to Primary Time Point

Where Change in Score from Baseline to Primary Timepoint = [Score at Primary Time Point] - [Baseline Score]





In summary, for Question 12, we recommend that you work with the COA Staff to establish supportive data for clinically meaningful responder rates, and subsequently incorporate valid secondary endpoints into the statistical analysis plans of your studies as appropriate.

***Sponsor Response*: Please see response to Question 10.**

Question 13: Does the Agency agree that the health-related quality of life (HRQL) total score of the Overactive Bladder Questionnaire (OAB-q) LF (long form) and the coping domain are acceptable as secondary endpoints (b) (4)

Response: On its face, the Coping domain of the OAB-q LF appears reasonable; however, there are some items in the domain that may be insensitive to treatment effects. See our response to Question 10 requesting an Evidence Dossier providing information to demonstrate that the proposed PRO items and domains are well-defined and reliable, reflect clinical benefit to patients (b) (4)

(b) (4)

We encourage you to submit a Targeted Product Profile (TPP), and additional information (b) (4)

We do not agree [redacted] (b) (4)

Finally, we acknowledge that you plan to use the one-week recall version of the OAB-q LF instrument and agree that this recall period is preferable to the original [redacted] (b) (4) recall period.

***Sponsor Response*: Please see response to Question 10.**

Question 14: Urovant plans to test for a statistically significant difference at a two-sided alpha-level of 0.05 for the co-primary endpoints in Study RVT-901-3003, and will test key secondary endpoints hierarchically in support of potential inclusion in the labeling. Given the totality of clinical evidence with vibegron to be provided by the previously discussed five OAB clinical studies, does the Agency agree that the proposed sample size, the approach for the statistical analysis, and testing strategy for controlling the type I error control for the primary and key secondary hypotheses in RVT-901-3003 are appropriate to support submission and FDA review for the planned indication?

Response: In general, we agree with the proposed sample size, and the approach for the statistical analysis in the study protocol. The secondary efficacy endpoints that are intended for labeling purposes need to be discussed with the Division and agreed upon in advance, and also need to be pre-specified in the statistical analysis plan with appropriate plan for multiplicity control of type I error. See our previous responses to Questions 11, 12 and 13.

***Sponsor Response*: No further discussion necessary.**

Question 15: The planned NDA submission is intended to be a complete dataset, with no new patient exposures in the 120-day safety update. Does the Agency agree that the total population exposure anticipated for the application, including the projected long-term safety exposure to vibegron in the clinical program, is adequate to support filing of the vibegron NDA?

Response: The regulatory decision whether to file an NDA takes place after FDA's preliminary review of a submitted application. A 120-day safety update is required. However, barring unforeseen adverse events or other factors that would affect the need for additional studies, the total population exposure, including long-term exposure, anticipated at time of NDA submission would appear adequate.

***Sponsor Response*: No further discussion necessary.**

Question 16: The tolterodine used in the Phase 3 program will be a generic tolterodine product sourced from [redacted] (b) (4) *the European Union (EU). Given that Urovant is not seeking an anti-muscarinic combination therapy indication, and is not intending to rely on the data from the tolterodine arm to establish*

the safety or efficacy of the planned vibegron indication, does the Agency object to the use of the EU-sourced tolterodine in the Phase 3 program?

Response: We do not object to your plan to use an EU-sourced generic tolterodine in the Phase 3 program. A BE study between the US–approved tolterodine ER 4 mg (Detrol LA) and an EU-sourced generic tolterodine will not be required as long as the safety and efficacy of vibegron + tolterodine ER or tolterodine ER alone is not being relied upon for comparative safety and efficacy assessment.

From the Clinical perspective, however, it may be appropriate and perhaps more valuable to incorporate a mirabegron control arm rather than a tolterodine control arm, especially in light of questions concerning the effect of vibegron on vital signs.

Sponsor Response: No further discussion necessary.

Question 17: The Sponsor will remap the legacy QTc Phase 1 study (Merck Study 012) and the Phase 2b study (Merck Study 008 including extension) to current CDISC Study Data Tabulation Model (SDTM) standards. The remaining 15 Phase 1 studies will have data submitted in legacy format. Does the Agency agree with the proposed remapping strategy?

Response: We request that you submit the complete electronic datasets, including raw and calculated pharmacokinetic data, for all Clinical Pharmacology studies, including the Merck Study 012 (the TQT study).

Sponsor Response: No further discussion necessary.

Question 18: The sixteen (16) clinical pharmacology CSRs, and the CSR for the Phase 2b Merck Study 008, were recently submitted to IND 106410 (SN 0104 and SN 0105). These CSRs were generated by the previous sponsor and follow the traditional Merck format, and Urovant has coordinated with Merck to ensure that the submissions are as complete and reviewer-friendly as possible. The CSRs include summary tables and figures as well as legacy datasets; not all individual subject listings are included. Are these study reports without complete listings acceptable for submission of an NDA, or should a comprehensive set of listings be generated for every CSR that is included in the planned NDA submission?

Response: We request that you submit the complete electronic datasets, including raw and calculated pharmacokinetic data, for the completed Phase 2b study and for all clinical pharmacology studies. In addition, we request a complete study report for the Merck Study 008, to include a comprehensive set of line listings.

Sponsor Response: No further discussion necessary.

3. 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 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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 iPSP, including an iPSP 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.

Discussion at the meeting: Regarding a pediatric study plan (iPSP) , the Division stated that the age range for inclusion of pediatric patients in clinical studies for the treatment of neurogenic detrusor overactivity (NDO) is now 2 years old and above, instead of the previous 5 years old and above. The Sponsor acknowledged.

4. 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.pd

f), 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

5. 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.

6. 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).

7. ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

8. ATTACHMENTS AND HANDOUTS

"Response to Preliminary Comments" was received from Urovant via email on August 21, 2017.

1. SUMMARY

Urovant Sciences GmbH (Urovant) has an End of Phase 2 Type B meeting scheduled with the Agency on July 24, 2017. The Agency provided Preliminary Meeting Comments on 20 July 2017. In order to support an efficient meeting, Urovant's responses to the Agency's Preliminary Comments are provided below.

During the meeting on Monday, no further discussion is needed for the CMC questions (#1-4), the Nonclinical Question (#5), the Clinical Pharmacology Question (#6) or Clinical Questions 9, 14-18.

Urovant would like to focus the meeting discussion on Clinical Questions 7, 8, and 10-13.

2. RESPONSE TO PRELIMINARY MEETING COMMENTS

The sponsor's questions as presented in the meeting information package submitted June 23, 2017 are presented in italics, followed by the Division's responses and additional comments in regular font. The sponsor's response is denoted with bold font.

Chemistry, Manufacturing, and Controls

Question 1: Based on the justification provided in Section 10.4.1.1.3, does the Agency concur with our designation of starting materials (b) (4) *in the synthesis of the active pharmaceutical ingredient?*

Response: We concur with your designation of starting materials (b) (4) in the synthesis of the active pharmaceutical ingredient, with the understanding that your synthetic schemes for the starting materials would be included in the NDA. We remind you that complete evaluations of the synthetic routes and the specifications of the drug substance and the starting materials, as well as your controls on potential genotoxic impurities in the drug substance based upon the synthetic routes, would be conducted at the NDA review stage.

Sponsor Response: No further discussion necessary.

Question 2: Does the Agency agree that the proposed specifications for the active pharmaceutical ingredient are adequate to support the Phase 3 program?

Response: The scope of the proposed specification for the active pharmaceutical ingredient appears reasonable to support the Phase 3 program. However, the final acceptance criteria will be an NDA review issue. For example, you have not provided a justification for the limit of the (b) (4) impurity (NMT (b) (4) %), or a comprehensive list of potential impurities in the drug substance. In addition, validation will need to be provided to demonstrate that your methods are

capable of analyzing the potential impurities. These pieces of information would be needed in the NDA submission and will be reviewed at that time.

Sponsor Response: No further discussion necessary.

Question 3: Does the Agency agree that the proposed specifications for the vibegron drug product, with the planned further development of the dissolution method and acceptance criteria, are adequate to support the Phase 3 program?

Response: Yes, the proposed drug product specification appears adequate to support the Phase 3 program. However, we note that the proposed acceptance criterion of (b) (4)% for total impurities is not justified based on the available data. We recommend tightening the acceptance criterion for total impurities.

Your approach to dissolution method development of the drug product appears reasonable. We recommend that the selection of the specification time point should be where Q= (b) (4)% dissolution occurs. Note that the final determination on the acceptability of the dissolution method and acceptance criterion is a review issue that can be determined during NDA review stage with complete dissolution data (individual, mean +/- SD, mean profile, n=12/batch). However, based on the data submitted so far, it appears that dissolution criterion can be tightened to Q= (b) (4)% at (b) (4) minutes for better quality control. Also pay attention to the discriminating ability of your method in terms of formulation and process variables to reject bad batches.

Sponsor Response: No further discussion necessary.

Question 4: Does the Agency agree that the proposed drug substance and drug product stability study designs will be adequate to support submission of an NDA for vibegron?

Response: Yes, the proposed drug substance and drug product stability study designs (stability storage conditions and testing time points) appear adequate to support submission of an NDA.

Additional Chemistry comment:

To facilitate our ongoing review of the IND, please submit a tabulation identifying the vibegron drug product lots (bulk and packaged) used in each clinical study. Include the formulation, manufacturer, manufacturing process and date of manufacture.

Sponsor Response: No further discussion necessary.

Nonclinical

Question 5: Does the Agency agree that the nonclinical package is sufficient to support the proposed Phase 3 program as well as the filing of the vibegron NDA?

Response: We agree that the nonclinical package is sufficient to support the proposed Phase 3 program and the filing of an NDA. However, we reserve the right to request additional nonclinical studies if unanticipated toxicity or exaggerated pharmacology is observed in clinical or nonclinical studies.

Sponsor Response: No further discussion necessary.

Clinical Pharmacology

Question 6: During the January 2013 EOP2 meeting, the Agency responses to Question 3 and Question 4 included the following comments "the overall clinical pharmacology program appears adequate...subject to a full review at the time of NDA submission" and "Based on the limited information provided and the sponsor's own assessment of the data, the list of DDI studies appears to be adequate". Furthermore, in response to Question 5, the Agency agreed that no further pharmacodynamic (PD) interaction studies (beyond the planned warfarin studies) are required.

Does the Agency agree that the completed and planned clinical pharmacology studies support NDA filing of vibegron for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency?

Response: Yes. We recommend that the vibegron dose in the proposed clinical pharmacology studies should be the highest to-be-marketed dose and formulation. For a subset of patients in your proposed Phase 3 study, include sufficient blood sampling to characterize the steady state pharmacokinetics of vibegron. Submit in your IND and NDA a table outlining the formulation(s) used in each clinical study and clarify how each formulation is bridged to the Phase 3 and to-be-marketed formulations.

Sponsor Response: No further discussion necessary.

Clinical – Phase 3 Program

Question 7: Does the Agency agree that the totality of evidence to be provided by the five OAB clinical studies (RVT-901-3003 [pivotal safety/efficacy] and RVT-901-3004 [pivotal safety]; supportive studies: Merck Study 008 and Kyorin Studies 301 and 302) are adequate to support submission and allow FDA review of a vibegron NDA for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency?

Response: The completed studies (Merck Study 008 and Kyorin Studies 301, 302), along with your planned studies RVT-901-3003 and RVT 901-3004, could provide sufficient evidence to support submission of an NDA for vibegron for the OAB indication.

We note that several serious cardiovascular adverse events (SAEs) were reported in the already completed Phase 2 and Phase 3 studies, including 4 MACE, one event of loss of consciousness (LOC) in the Merck 008 study, 3 MACE in the Kyorin 3004 study, and one death after an event of fall following suspected alcohol ingestion. Based on the CV AEs, and the apparent effect of vibegron on blood pressure (BP) and heart rate at doses ≥ 100 mg, we continue to be interested in the effect of vibegron on BP and BP-related AEs in your planned Phase 3 studies. You should assess BP at or near the times of maximum plasma concentrations (Tmax) in those studies, and you should also monitor for BP-related AEs.

There have been other noteworthy AEs in the completed Phase 2 and Phase 3 studies, including urinary tract infection (UTI), one case of neutropenia, and one case each of supraventricular tachycardia (SVT), somnolence, elevated hepatic tests, and increased serum creatinine, all leading to discontinuation of vibegron therapy. These potential safety issues are of interest and should be monitored in your planned studies.

Sponsor Response: The sponsor would like to discuss the collection and characterization of heart rate and blood pressure data in the vibegron clinical program. The sponsor plans to monitor for the noteworthy AEs, including BP-related AE's, mentioned by the Division.

Additional comments from the Division of Cardiovascular and Renal Products (DCRP):

1. Regarding your planned assessment for BP effects of vibegron, the data in healthy normal subjects demonstrates a dose-dependent increase in HR or BP at doses above 100 mg. Additionally, data from the Merck Study 008 main trial demonstrates that while group means for changes from baseline in HR and SBP/DBP appear similar between the placebo and vibegron 100mg arms, it is noted that in the all the categorical shift changes for HR occur at a higher frequency in the 100 mg vibegron arm compared to the placebo arm across the range of the defined categories. The same is true for DBP categorical shifts in the main study. This suggests that there may be a sub-population within Merck Study 008 that could be identified as more "at risk" for drug-induced vital sign changes (e.g., the lowest weight quartile and/or the lowest GFR quartile, and/or the highest age quartile, and/or a baseline blood pressure exceeding 140/90).

   Sponsor Response: Urovant appreciates the Agency comments and will investigate the subgroups as suggested. No further discussion necessary.

2. In addition to identifying this subpopulation for analysis from Merck Study 008, we request that you also do cumulative function distribution (CFD) analyses for the maximal change from baseline in HR, SBP, and DBP for placebo, vibegron 100mg, and tolterodine monotherapy from the main phase data of Merck Study 008, both for the overall Merck Study 008 study population, and for the "at risk" sub-population we describe above, however you decide to define that sub-population.

   Sponsor Response: Urovant will investigate the subgroups as suggested. No further discussion necessary.

3. Assuming that the vital signs were randomly acquired relative to drug dosing in Merck Study 008, and assuming this may be the case for other Phase 2 and Phase 3 trials with Week 4 data where placebo and vibegron 100 mg were administered (including the as of yet not submitted Japanese Phase 3 studies), we ask that you integrate all of the vital sign data from these trials to assess for HR/SBP/DBP effects, including your prior analyses of population means and shifts, together with the above-described cumulative function curve (CFC) analyses for change from baseline for these parameters - done separately for the overall integrated population, as well as the "at risk" sub-population, however you define that group.

Sponsor Response: Urovant will investigate the subgroups as suggested. No further discussion necessary.

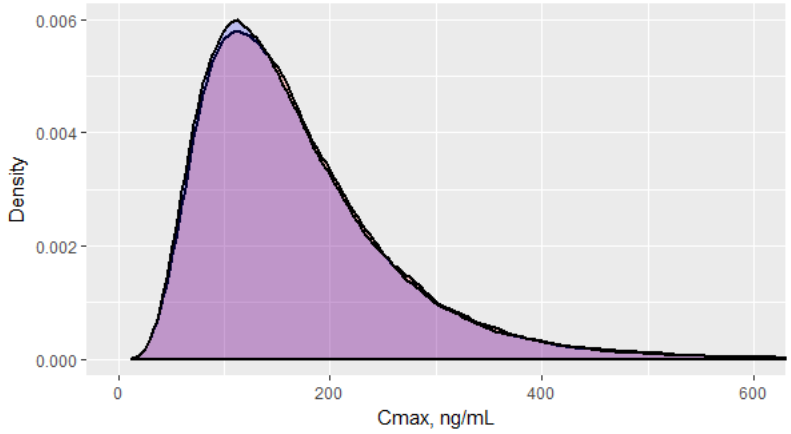
4. As best we can tell, the cuff pressures collected in Merck Study 008, and those that are planned for the Urovant Studies 3003 and 3004, are not timed to Cmax, where the largest HR/SBP/DBP effects are expected to occur. Your plan not to conduct the 30-subject ambulatory BP monitoring (ABPM) study that was discussed at the January 18, 2013, EOP2 meeting precludes the ability to assess vital sign effects at Cmax. Clarify how you intend to obtain this information if you proceed with your plan to cancel the ABPM study.

   Sponsor Response: The sponsor would like to discuss the collection and characterization of heart rate and blood pressure data in the vibegron clinical program.

5. You posit that due to the non-dose-linearity of vibegron exposure below 100 mg, that subjects receiving 75 mg with the highest exposures should not exceed the Cmax of the Merck Study 008 safety dataset. Does your modeling of this predicted limit on Cmax take into consideration that prior studies have not enrolled subjects with moderate renal impairment and Urovant Study 3003 will include these subjects?

   Sponsor Response: Modeling of vibegron C_{max} included exposures from 50, 75 and 100 mg doses. Exposures were further simulated at 1.6-fold the exposures of 75 mg and compared with exposures from 100 mg to estimate C_{max} in subjects with moderate renal impairment based on Study 014 (1.6-fold increase compared to normal renal function). As shown below, the density plots are practically superimposable suggesting that the limit on C_{max} for 75 mg in moderate renal impairment covers C_{max} observed with a 100 mg dose.

Density Plots of Simulated Steady-State Vibegron C_{max} for 75 mg in Patients with Moderate Renal Impairment (1.6 fold Higher Exposures) and for 100 mg (blue)



6. Address the apparent inconsistencies in the proposed Phase 3 protocols regarding the patient position from which BP will be measured (e.g., one bullet states that the BP will be acquired in a semi-recumbent position, but the sub-bullet states that acquisition will take place in the sitting position).

   Sponsor Response: This will be corrected in the final protocol prior to submission to the Agency; no further discussion necessary.

7. Clarify that HR will be acquired simultaneously with SBP/DBP, and that the mean of the three readings for each parameter will be used in the analytical dataset.

   Sponsor Response: Urovant confirms that HR will be acquired simultaneously with SBP/DBP, and that the mean of three readings for each parameter will be used in the analytical dataset. No further discussion necessary.

8. Submit the charter for your Clinical Events Committee for the MACCE analysis, to include the definition set reference you are using to define these events.

   Sponsor Response: The charter will be submitted with the final protocol; no further discussion necessary.

Question 8: Does the Agency agree that the target population as defined by inclusion and exclusion criteria in the Phase 3 studies is adequate to demonstrate safety and efficacy of vibegron in the proposed indication?

Response: In general, the inclusion/exclusion criteria appear acceptable to define the target population, with the following caveats:

- For inclusion criteria #7: "*Patient has a history of 24hr urine volume greater than 3000mL or Voided Volume diary measurement greater than 3000mL during the Run-in Period.*" This would appear to be an exclusion criterion, not an inclusion, criterion.
- We note that you plan to include subjects with BP as high as 180/100 mmHg, require a stable antihypertensive regimen 90 days prior to baseline, and measure antihypertensive medication changes post-randomization as an indicator of study drug effect on BP. Patients with BPs in the range of 180/100 mmHg are not medically stable, and post-randomization antihypertension medication changes that take place to address their hypertension will confound the assessment of study drug effect on BP. We suggest that you consider stipulating that subjects may have had a history of these kinds of blood pressures, but that their hypertension must be medically controlled on a stable antihypertensive regimen at their Baseline visit.

Sponsor Response: We agree that Inclusion criteria #7 should be an exclusion criterion; this will be corrected in the final protocol.

We would like to discuss the BP exclusion at the meeting. The EOP2 Meeting Minutes from January 2013 stated "In order to enroll an appropriate broad target population, we recommend that uncontrolled hypertension (as in exclusion criterion #6) be defined as a systolic blood pressure (BP) ≥ 180 mm Hg and/or diastolic BP ≥ 100 mm Hg…". We had adopted this criteria to exclude these patients and added further detail to ensure that patients who were enrolled requiring antihypertensive treatment were on stable medication prior to study entry.

Question 9: During the January 2013 EOP2 meeting, the Agency response to Question 13 regarding the dose selection for the Phase 3 studies included the following comments: "We do not object to the 50 mg and 100 mg doses selected for the Phase 3 studies. We point out the relatively shallow dose response relationship for efficacy, and that many endpoints demonstrated similar efficacy for the 50 mg and 100 mg doses. However, it appears that some endpoints demonstrated better efficacy at the 100 mg dose compared to the 50 mg dose." The Agency also noted some safety considerations, and further commented that "the current dose selection assumes some risk if there is a lack of incremental clinical benefit and also safety concerns for the 100 mg dose." Based upon extensive analyses performed by Urovant across all available clinical data, a single dose level of 75 mg is proposed for the Phase 3 program as described below.

Does the Agency agree with the 75 mg dose rationale for the proposed Urovant Phase 3 program?

Response: While we do not object to your plan for a single daily dose of 75 mg, we encourage you to consider a dose titration regimen instead, with a lower starting dose (e.g., 50 mg) and a maximum dose of 75 mg. Our rationale is that some patients may receive adequate benefit at a lower dose (e.g., 50 mg) without the need to take the higher dose (e.g., 75 mg). The lower starting dose may also be appropriate for special populations (e.g., elderly patients, etc.).

Sponsor Response: No further discussion necessary.

Question 10: The proposed indication is:

> ***[Trademark] is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.***

During the January 2013 EOP2 meeting, the Agency response to Question 10 regarding the co-primary endpoints for the Phase 3 studies included the following comments: "The co-primary endpoints selected for Protocol 019 and Protocol 020, change from baseline to Week 12 in average number of micturitions/day and average number of urge urinary incontinence

episodes/day are acceptable for Phase 3 studies designed to support your first proposed indication. We note that your proposed diary asks patients to judge the reason for each leakage episode (urge vs. stress vs. other). We ask that you demonstrate that there is reproducibility and reliability in responding to this question in the diary in the Phase 2 study since it will play a crucial role in tabulating the coprimary endpoint of urge urinary incontinence."

Does the Agency agree that a reduction in overactive bladder symptoms, as measured by the proposed co-primary endpoints (average number of micturitions/day and average number of urgency urinary incontinence episodes/day) for Study RVT-901-3003 support the clinical indication?

Response: Yes. We agree that the co-primary endpoints "*change from baseline to Week 12 in average number of micturitions/day and average number of urge urinary incontinence episodes/day"* are acceptable for the OAB indication.

We remind you of our previous concern that the patient voiding diary (PVD) requires patients to make a choice between stress and urge incontinence for each incontinence episode, which may present a challenge for some patients. While your previous results do not suggest widespread difficulty with this part of the voiding diary, if some patients struggle with this choice, there is a risk that your study may not be sensitive to small differences between groups for urge incontinence episodes (UUI), a mandatory co-primary endpoint.

In regard to the patient voiding diary (PVD) and other PROs proposed for use in Phase 3:

1. Submit an Evidence Dossier for our review and comment, as follows:

    a. Submit all qualitative work that has been conducted with patients, including interviewer scripts and patient transcripts, from both the concept elicitation and cognitive debriefing interviews, in support of the patient voiding diary and other patient-reported outcome (PRO) tools that are proposed as pre-specified endpoints in Phase 3. The information in the Evidence Dossier should demonstrate that the concepts included in the PVD and the other PRO tools are important and comprehensive to patients in terms of their OAB symptom experience (Wet and Dry) and that patients are interpreting all instructions, terms, and concepts in consistent ways.
    b. Provide evidence that patients can accurately and reliably select the type of incontinence episode (stress, urge or other) that they experience.
    c. Submit results from all analyses of the PVD and other PRO tools' showing their psychometric properties and performance in the Phase 2 study (Merck Study 008).
    d. Provide a scoring algorithm for the PVD and other PRO tools along with a proposed calculation of the pre-specified endpoint scores.

2. We acknowledge that you are currently in the process of migrating the

paper version of the PVD to electronic mode for use in Phase 3, are currently testing the patient instructions and usability of the electronic PVD with patients in order to finalize them for Phase 3, and plan to provide a summary report for review and comment. Clarify whether you plan to conduct usability testing in all languages and within all cultures intended for inclusion in Phase 3.

We recommend both translation and cultural adaptation of the PVD, including instructions, items/domains, and response options, for multinational studies. Translation and cultural validation adaptation of clinical outcome assessments can affect efficacy findings and it is important to ensure that efficacy assessments are standardized across cultures, languages, and sites. Translation and cultural adaptation includes conducting qualitative work on the instrument within all languages and cultures in which the instrument is to be assessed. We refer you to the ISPOR principles for the translation and cultural validation adaptation process.

3. The Patient Global Impression of Severity, Change, and Control (PGI-Severity, PGI- Change, and PGI-Control, respectively) scales proposed for Phase 3 (Study RVT-901- 3003) appear reasonable to serve as anchor scales for anchor-based analysis to help interpret a clinically meaningful within-patient change in PVD and other key PRO item scores from the patient perspective. The anchor scales should be assessed at the same time points as, but completed after, the key PRO tools. We recommend that you also include in Phase 3 the three patient perceived status items that you included in your Phase 2 Study 008 (e.g., frequency of OAB symptoms, accidental urine leakage, and amount of control over OAB symptoms) for the purpose of data comparability.

Sponsor Response: The response below includes information relevant to Questions 10-13.

An extensive background package, including much of the information being requested in support of the PVD, was submitted to the Agency by Merck on January 5, 2007 (Type C Meeting Briefing Document). At the time of NDA filing, we will submit an updated PRO evidence package in which we will reference and supplement the supporting evidence submitted previously by Merck. Additional evidence to be provided will include the methods and results of upcoming patient interviews (including our protocol, interview guide, and transcriptions), as well as further support for the responder definitions, including CDF and PDF curves based on the existing data, as well as CDFs based on the phase 3 data. In addition to testing the usability of the electronic diary, the planned interviews will further explore patients' perceptions of meaningful improvements in each of their OAB symptoms, as well as their ability to distinguish between leakage that is primarily caused by urgency vs. stress. We will also include additional evidence pertaining to the OAB-q in the updated PRO evidence package, with a focus on supporting changes in scores on the coping domain as a key secondary endpoint for the Phase 3 study.

With respect to the questions and suggestions surrounding usability testing (Question 10.2), translation and cultural adaptation of the PVD, we would like to clarify that usability testing of the electronic PVD is planned in the US; however, Merck followed the standard process recommended by Wild and her colleagues (2005) to create culturally appropriate versions of the diary in more than 50 languages. If any additional language versions are required, translation and cultural adaptation will be conducted following the same process.

At the time of final Phase 3 protocol submission, we will also provide the following documents for Agency review: a detailed phase 3 SAP, an abbreviated TPP to lay out claims for the PVD (b) (4) **and a brief report** (b) (4) **This brief report will include a summary of all analyses conducted to date, provide the CDFs and PDFs FDA has requested, and describe relevant methods and results from the patient interviews to be conducted in August 2017.**

Finally, with respect to the third part of the response to Question 10, we seek clarification from the Agency. In particular, given that two patient-perceived status measures are slated for use in the Phase 3 study (PGI-Severity and PGI-Control), in addition to the PGI-Change item, we would like to better understand the recommendation to include three additional status measures from the Phase 2 Study 008 (e.g., frequency of OAB symptoms, accidental urine leakage, and amount of control over OAB symptoms). The ability to compare data from the Phase 3 and Phase 2 studies is referenced. However, we believe the endpoints derived from the PVD offer a clear avenue for comparison. We are particularly concerned about the inclusion of a second item addressing control over OAB symptoms. For easy reference, we have included both sets of items below. We appreciate Agency clarification.

Global Items Slated for Use in Phase 3

Patient Global Impression of Severity (PGI-Severity)

Overall, how would you rate your overactive bladder symptoms now?

☐ None

☐ Mild

☐ Moderate

☐ Severe

Patient Global Impression of Control (PGI-Control)

How well are you able to control your bladder symptoms now?

☐ Not at all

☐ A little bit

☐ **Moderately well**

☐ **Quite well**

☐ **Very well**

Patient Global Impression of Change (PGI-Change)

Overall, compared to the start of the study, how would you rate your overactive bladder symptoms now?

☐ **Much better**

☐ **Moderately better**

☐ **A little better**

☐ **No change**

☐ **A little worse**

☐ **Moderately worse**

☐ **Much worse**

Patient Perception Items Used to Facilitate Responder Analysis of Phase 2 Data

Patient Perception of Symptom Frequency

Over the past week, how often did you have overactive bladder symptoms?

☐ **Never**

☐ **Rarely**

☐ **Sometimes**

☐ **Often**

☐ **Very often**

Patient Perception of Control

Over the past week, how much control did you have over your overactive bladder symptoms?

☐ **Complete control**

☐ **A lot of control**

☐ **Some control**

☐ **Only a little control**

☐ **No control**

Patient Perception of Urgency-Related Leakage

Do you experience urine leakage related to the feeling of urgency?

☐ **Yes**

☐ **No**

If Yes, how much does it bother you?

☐ **Not at all**

☐ **Slightly**

☐ **Moderately**

☐ **Greatly**

Question 11: Does the Agency agree that 'the need to urinate immediately' (urgency urinary episode) can lead to labeling claims as a secondary endpoint in Study RVT-901-3003?

Response: If your qualitative research and clinical study results support content validity, reliability and sensitivity to change of this item, and the endpoint is properly incorporated into the study's statistical plan, and the actual results are clinically compelling, and the results for this endpoint are confirmed by results from this same endpoint in a second clinical study, then "*the need to urinate immediately*" as a reflection of urinary urgency could lead to labeling claims as a secondary endpoint in Study RVT-901-3003. We encourage you to submit a Targeted Product Profile (TPP), and additional information to justify possible labeling for this secondary endpoint.

Sponsor Response: Further to the information provided above in Question 10, Study 008 provided initial efficacy data on "the need to urinate immediately" endpoint and Study RVT-901-3003 will confirm this result for labeling.

Question 12: Does the FDA agree (b) (4)

Response: No. You have not presented sufficient data (b) (4)

(b) (4) However, to supplement your anchor-based analyses, you should provide both cumulative distribution function (CDF) and probability

density function (PDF; also known as a kernel density plot) curves to explore and to derive a number of thresholds for meaningful change. (b) (4)

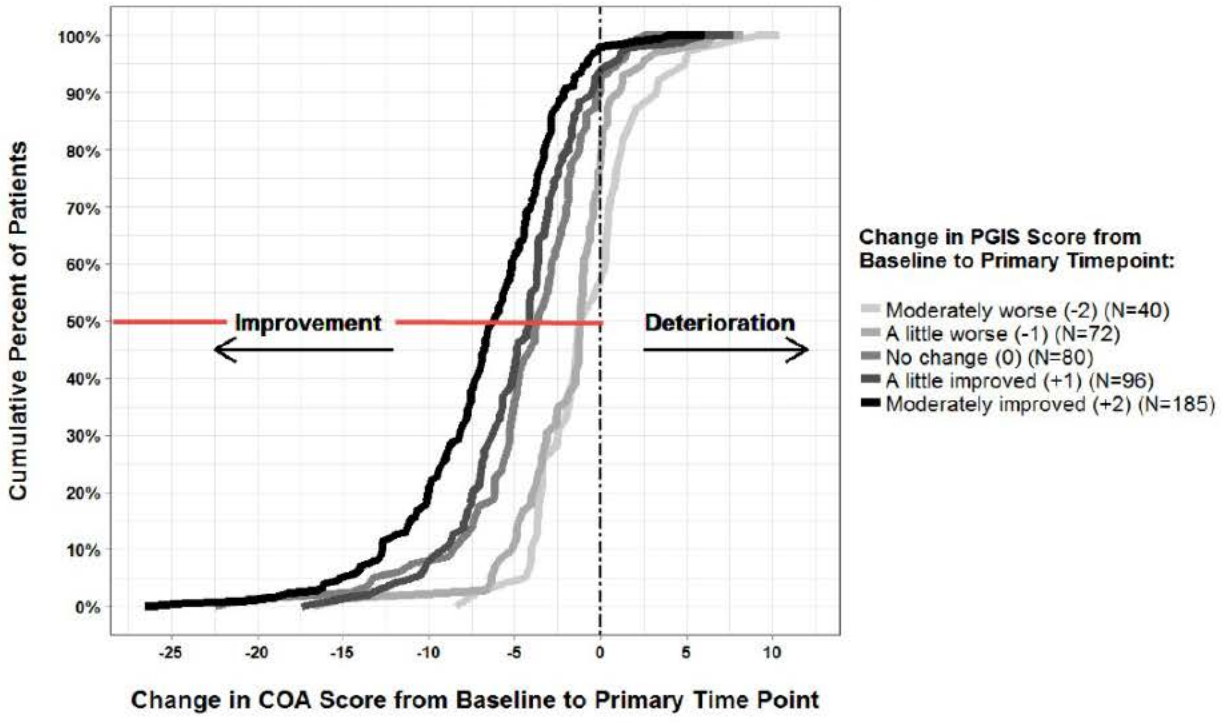
Therefore, submit the following CDF and PDF curves using data from your Phase 2 study (Merck Study 008), including sample sizes and median scores for each CDF and PDF curve:

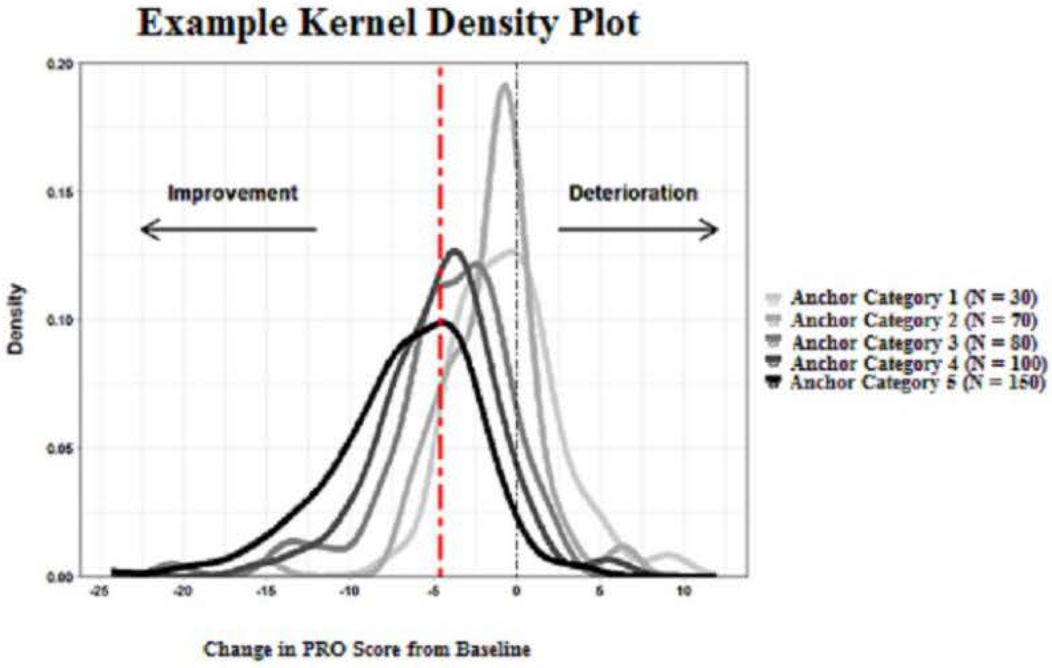
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) for all patients (both treatment and placebo arms pooled) by the anchor item change response options (e.g., very much improved, much improved, etc.) at week 8.
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) for all patients (both treatment and placebo arms pooled) by the anchor item severity response category change scores from baseline (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)
- CDFs and PDFs of change scores from baseline (PRO endpoint of interest) with curves for each treatment arm

Examples of CDF and PDF figures are shown below:

EXAMPLE Empirical Cumulative Distribution of Change in COA Score from Baseline to Primary Time Point, by Change in PGIS Score from Baseline to Primary Time Point

Where Change in Score from Baseline to Primary Timepoint = [Score at Primary Time Point] - [Baseline Score]





In summary, for Question 12, we recommend that you work with the COA Staff to establish supportive data for clinically meaningful responder rates, and subsequently incorporate valid secondary endpoints into the statistical analysis plans of your studies as appropriate.

Sponsor Response: Please see response to Question 10.

Question 13: Does the Agency agree that the health-related quality of life (HRQL) total score of the Overactive Bladder Questionnaire (OAB-q) LF (long form) and the coping domain are acceptable as secondary endpoints (b) (4)

Response: On its face, the Coping domain of the OAB-q LF appears reasonable; however, there are some items in the domain that may be insensitive to treatment effects. See our response to Question 10 requesting an Evidence Dossier providing information to demonstrate that the proposed PRO items and domains are well-defined and reliable, reflect clinical benefit to patients (b) (4)

(b) (4)

(b) (4) We encourage you to submit a Targeted Product Profile (TPP), and additional information (b) (4)

We do not agree (b) (4)

Finally, we acknowledge that you plan to use the one-week recall version of the OAB-q LF instrument and agree that this recall period is preferable to the original (b) (4) recall period.

Sponsor Response: Please see response to Question 10.

Question 14: Urovant plans to test for a statistically significant difference at a two-sided alpha-level of 0.05 for the co-primary endpoints in Study RVT-901-3003, and will test key secondary endpoints hierarchically in support of potential inclusion in the labeling. Given the totality of clinical evidence with vibegron to be provided by the previously discussed five OAB clinical studies, does the Agency agree that the proposed sample size, the approach for the statistical analysis, and testing strategy for controlling the type I error control for the primary and key secondary hypotheses in RVT-901-3003 are appropriate to support submission and FDA review for the planned indication?

Response: In general, we agree with the proposed sample size, and the approach for the statistical analysis in the study protocol. The secondary efficacy endpoints that are intended for labeling purposes need to be discussed with the Division and agreed upon in advance, and also need to be pre-specified in the statistical analysis plan with appropriate plan for multiplicity control of type I error. See our previous responses to Questions 11, 12 and 13.

Sponsor Response: No further discussion necessary.

Question 15: The planned NDA submission is intended to be a complete dataset, with no new patient exposures in the 120-day safety update. Does the Agency agree that the total population exposure anticipated for the application, including the projected long-term safety exposure to vibegron in the clinical program, is adequate to support filing of the vibegron NDA?

Response: The regulatory decision whether to file an NDA takes place after FDA's preliminary review of a submitted application. A 120-day safety update is required. However, barring unforeseen adverse events or other factors that would affect the need for additional studies, the total population exposure, including long-term exposure, anticipated at time of NDA submission would appear adequate.

Sponsor Response: No further discussion necessary.

Question 16: The tolterodine used in the Phase 3 program will be a generic tolterodine product sourced from (b) (4) the European Union (EU). Given that Urovant is not seeking an anti-muscarinic combination

therapy indication, and is not intending to rely on the data from the tolterodine arm to establish the safety or efficacy of the planned vibegron indication, does the Agency object to the use of the EU-sourced tolterodine in the Phase 3 program?

Response: We do not object to your plan to use an EU-sourced generic tolterodine in the Phase 3 program. A BE study between the US–approved tolterodine ER 4 mg (Detrol LA) and an EU-sourced generic tolterodine will not be required as long as the safety and efficacy of vibegron + tolterodine ER or tolterodine ER alone is not being relied upon for comparative safety and efficacy assessment.

From the Clinical perspective, however, it may be appropriate and perhaps more valuable to incorporate a mirabegron control arm rather than a tolterodine control arm, especially in light of questions concerning the effect of vibegron on vital signs.

Sponsor Response: No further discussion necessary.

Question 17: The Sponsor will remap the legacy QTc Phase 1 study (Merck Study 012) and the Phase 2b study (Merck Study 008 including extension) to current CDISC Study Data Tabulation Model (SDTM) standards. The remaining 15 Phase 1 studies will have data submitted in legacy format. Does the Agency agree with the proposed remapping strategy?

Response: We request that you submit the complete electronic datasets, including raw and calculated pharmacokinetic data, for all Clinical Pharmacology studies, including the Merck Study 012 (the TQT study).

Sponsor Response: No further discussion necessary.

Question 18: The sixteen (16) clinical pharmacology CSRs, and the CSR for the Phase 2b Merck Study 008, were recently submitted to IND 106410 (SN 0104 and SN 0105). These CSRs were generated by the previous sponsor and follow the traditional Merck format, and Urovant has coordinated with Merck to ensure that the submissions are as complete and reviewer-friendly as possible. The CSRs include summary tables and figures as well as legacy datasets; not all individual subject listings are included. Are these study reports without complete listings acceptable for submission of an NDA, or should a comprehensive set of listings be generated for every CSR that is included in the planned NDA submission?

Response: We request that you submit the complete electronic datasets, including raw and calculated pharmacokinetic data, for the completed Phase 2b study and for all clinical pharmacology studies. In addition, we request a complete study report for the Merck Study 008, to include a comprehensive set of line listings.

Sponsor Response: No further discussion necessary.

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

/s/

MARK S HIRSCH
08/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106410

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Beatriz Rocha, M.D., Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-200
Rahway, NJ 07065

Dear Dr. Rocha:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-4618, a beta-3 adrenergic receptor agonist.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2013. The purpose of the meeting was to discuss the results of your Phase 2b dose-finding study and the path forward in planning the Phase 3 study.

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

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	January 18, 2013, at 11:00 A.M. – 12:30 P.M., Eastern
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1415 Silver Spring, MD 20903
Application Number:	IND 106410
Product Name:	MK-4618, agonist of beta3 adrenergic receptor
Indication:	Treatment of overactive bladder
Sponsor/Applicant Name:	Merck Sharp & Dohme Corp.
Meeting Chair:	Mark S. Hirsch, M.D.
Meeting Recorder:	Nenita Crisostomo, R.N.

FDA ATTENDEES

Hylton V. Joffe, M.D., M.M.Sc. – Director, Division of Reproductive and Urologic Products (DRUP)
Mark S. Hirsch, M.D. – Medical Team Leader, DRUP
Hae Young Ahn, Ph.D. – Deputy Director, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)
Sayed (Sam) Al Habet, RP.h., Ph.D. – Senior Clinical Pharmacology Reviewer, DCPIII, OCP
Chongwoo Yu, Ph.D. – Acting Clinical Pharmacology Team Leader, DCPIII, OCP
Jiang Liu, Ph.D. – Pharmacometrics Reviewer, Division of Pharmacometrics (DPM), OCP
Kelly Kitchens, Ph.D. – Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)
John Duan, Ph.D. – Biopharmaceutics Reviewer, ONDQA
Laurie L. McLeod-Flynn, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Mahboob Sobhan, Ph.D. – Biostatistics Team Leader, Division of Biometrics II (DBII)
Xin Fang, Ph.D. – Biostatistician, DBIII
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP

MERCK SHARP & DOHME CORP.

Beatriz Rocha, M.D., Ph.D. – Director, Regulatory Affairs
Lina Al Juburi, PharmD, M.S. – Director, US Regulatory Policy
Martin Himmel, M.D., M.P.H. – Executive Director, Regulatory Affairs
Sean Curtis, M.D. – Vice President, Project Leadership
Tara Frenkl, M.D, M.Sc. – Senior Principal Scientist, Clinical Research
Sauzanne Khalilieh, M.D. – Director, Clinical Research
David Cutler, M.D. – Distinguished Scientist, Clinical Pharmacology
Stuart A. Green, M.D. – Vice President, Clinical Research Therapeutic Area Head, Respiratory & Immunology

MERCK SHARP & DOHME CORP. (continued)
Wendy Ankrom Comisar, Ph.D. – Associate Director, PPDM Development
Suvajit Samanta, Ph.D. – Principal Scientist, Biostatistics
Richard Anthony Entsuah, Ph.D. – Executive Director, Biostatistics
William Hanley, Ph.D. – Director, Clinical PK/PD
Cathy Anne Pinto, Ph.D., M.S. – Associate Principal Scientist, Epidemiology
Béatrice Jeannine Sacre-Salem D.V.M. – Senior Principal Scientist, Nonclinical Safety Assessment
Mohamed Elkhoga, M.Sc. – Associate Director, CMC
Dennis Zaller, Ph.D. – Executive Director, Biology-Discovery

BACKGROUND

MK-4618 is a beta-3 adrenergic receptor (β3-AR) agonist intended for the treatment of overactive bladder (OAB). The investigational new drug application (IND) for MK-4618 was submitted on January 29, 2010, to evaluate the safety, tolerability and pharmacokinetics of MK-4618 in the Japanese population. According to the Sponsor, this population was specifically chosen for the opening IND study in order to comply with regulatory requirements in Japan and to generate data in Japanese patients so that they could be included in Phase 2 studies. The Sponsor subsequently conducted multiple Phase 1 and Phase 2 studies. The Sponsor now seeks FDA's feedback regarding the proposed Phase 3 development program for MK-4618 for the treatment of OAB.

DISCUSSION

PRE-CLINICAL QUESTIONS

Pharmacology

Question 1: Does the Agency agree with the proposed studies for the conduction of isolated receptor binding affinity experiments using beta3-AR from Dutch belted rabbits?

FDA Response to Question 1: Yes. However, the current measures to protect trial participants of childbearing potential should remain in clinical protocols until the sensitivity of the rabbit model pharmacology to MK-4618 has been characterized in your planned studies, demonstrating a NOAEL at adequate multiples of the drug's pharmacology in rabbits.

Discussion: ***The Sponsor stated that an isolated rabbit bladder strip study did not demonstrate receptor sensitivity to MK-4618. Therefore, the Sponsor proposed to conduct an isolated receptor binding affinity study to address the Division's concern. The Division agreed that the isolated receptor binding affinity experiments alone would be an adequate estimate of rabbit sensitivity to MK-4618 at beta3-ARs.***

Question 2: Does the Agency agree that the completed, ongoing, and proposed safety pharmacology, repeat-dose toxicology, genotoxicity, carcinogenicity, and developmental and reproductive toxicology programs are sufficient to support the proposed Phase III program as well as the filing and registration of MK-4618?

FDA Response to Question 2: Yes, we concur with the nonclinical development plan but reserve the right to request additional nonclinical studies if unanticipated toxicity or exaggerated pharmacology is observed in clinical or nonclinical studies.

CLINICAL QUESTIONS

Clinical Pharmacology

Question 3: Does the Agency agree that the clinical pharmacology program (completed, ongoing and planned studies) is sufficient to support filing and registration of MK-4618?

FDA Response to Question 3: Based on the limited information and review time, the overall clinical pharmacology program appears adequate. However, it should be emphasized that everything will be subject to full review at the time of NDA submission. Therefore, it is impossible at this time to agree that the submitted information is fully satisfactory from the clinical pharmacology perspective. The sponsor should be reminded that critical studies should be conducted with the final to-be-marketed formulation, unless no substantial changes to formulations have been introduced during the development.

Question 4: Does the agency agree that the totality of the preclinical metabolism/transporter data in conjunction with the planned clinical drug-drug interaction (DDI) studies and ongoing/planned clinical ADME and bioavailability studies are sufficient to characterize potential pharmacokinetic interactions when MK-4618 is administered with other medications?

FDA Response to Question 4: Based on the limited information provided and the sponsor's own assessment of the data, the list of DDI studies appears to be adequate (also see our response to Question 3).

Question 5: Does the Agency agree that, aside from the evaluation of the effects of MK-4618 on Prothrombin Time/International Normalized Ratio (PT/INR) in the planned warfarin study, no further PD interaction studies are required to support filing and registration?

FDA Response to Question 5: Yes we agree (also see our response to Question 3).

Question 6: Does the Agency agree (b) (4)

FDA Response to Question 6: No, at this time we do not agree. This is a review issue (also see our response to Question 3).

Question 7: Does the Agency agree that the proposed Population PK plans in Phase III are adequate to characterize PK in the target patient population, and that plans for unblinding of PK data for development of a PopPK model during Phase III are acceptable?

FDA Response to Question 7: We agree with your proposed Population PK plans, however, your plan to unblind the PK data prior to database lock for the Phase III studies raises concerns as a potential source of bias, and requires additional discussion.

Discussion: The Sponsor explained that they needed six weeks to build the compartmental analysis, therefore, they planned to hire an external vendor who would be unblinded to the PK data. In addition, two persons from Merck would be appointed to work with the vendor in entering the data. Persons working on the compartmental analysis would be blinded to the safety and efficacy data. The Division agreed to consider this further and provide an opinion in a Post-Meeting Note.

Post-Meeting Note: The Sponsor's plan is acceptable.

Question 8: Assuming that additional bridging data (venous DBS/ fingerstick DBS vs. plasma) in the TQT study in healthy-volunteers at therapeutic and supra-therapeutic exposures demonstrate a predictive correlation, does the Agency concur it is sufficient to support using DBS as an alternative matrix in patients for future studies?

FDA Response to Question 8: The lack of a fully linear relationship between the drug concentrations obtained from matched plasma samples and dried blood spots (DBS) samples suggests that further investigation is warranted. You should continue to collect both plasma samples and DBS samples in future trials. We remind you that the comparison between the pharmacokinetic (PK) profiles for individual patients obtained from DBS and plasma is critical in understanding the correlation between the two sampling methods. You should submit the PK profiles for individual patients obtained from both DBS and plasma samples from Protocol 015 and from your proposed TQT study in addition to the correlation analysis prior to finalizing your bioanalytical strategy for the proposed Phase 3 trial(s) for further consideration/discussion.

Clinical Development

Question 9: Assuming that a favorable benefit/risk profile emerges as a result of the Phase III studies, does the Agency agree that the proposed Phase III clinical program is adequate to support registration of MK-4618 for the proposed indications?

[Trademark] is indicated for the treatment of Overactive Bladder with symptoms of urge urinary incontinence, urgency, and frequency.

(b) (4)

FDA Response to Question 9: We agree that primary evidence of efficacy of MK-4618 for the treatment of patients with OAB should come from 2 randomized 12 week placebo-controlled Phase III studies (Protocols 019 and 020).

However, additional discussion is needed in regard to the proposed indication (b) (4)

Discussion: (b) (4)

Question 10: Does the Agency agree that a reduction in OAB symptoms, as measured by the primary and key secondary endpoints for each study in the proposed Phase III program support the clinical indication and subsequent label efficacy claim for OAB, including onset of action as early as Week 2?

Proposed indication:
[Trademark] is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

(b) (4)

FDA Response to Question 10: The co-primary endpoints selected for Protocol 019 and Protocol 020, change from baseline to Week 12 in average number of micturitions/day and average number of urge urinary incontinence episodes/day are acceptable for Phase 3 studies designed to support your first proposed indication. We note that your proposed diary asks patients to judge the reason for each leakage episode (urge vs. stress vs. other). We ask that you demonstrate that there is reproducibility and reliability in responding to this question in the diary in the Phase 2 study since it will play a crucial role in tabulating the co-primary endpoint of urge urinary incontinence.

Discussion: ***The Division expressed concern that patients may be unable to accurately and reliably select the type of incontinence episode they experienced. The Sponsor expressed***

confidence in this part of the patient diary, stating that results from Phase 2 demonstrated that this information was accurately and reliably captured. The Division encouraged the Sponsor to submit this information for a formal consultative assessment by the Study Endpoints and Labeling Development (SEALD) team prior to implementation in the phase 3 trials, particularly because this relates to a key efficacy endpoint.

A claim of efficacy at two weeks is possible if adequately supported by a pre-specified statistical analysis plan of the Phase 3 efficacy data.

(b) (4)

Discussion: ***The Sponsor asked for clarification as to whether co-primary endpoints were required for the combination study. The Division responded that co-primary endpoints were preferred.***

Question 11: Does the Agency agree that the target population as defined by inclusion and exclusion criteria in the Phase III study protocols is representative of the OAB population that would receive the drug after Marketing Authorisation approval and thus adequate to demonstrate safety and efficacy of MK-4618 in the proposed indication?

FDA Response to Question 11: Yes. We note and agree that the proportion of the Phase III study population that will be OAB dry is limited to 25% and that the proportion of men will be limited to 15%. In order to enroll an appropriate broad target population, we recommend that uncontrolled hypertension (as in exclusion criterion #6) be defined as systolic blood pressure (BP) ≥ 180 mm Hg and/or diastolic BP ≥ 100 mm Hg, not as systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 100 mm Hg and we do not recommend (b) (4) The remainder of the inclusion and exclusion criteria is acceptable.

We note that the exclusion (b) (4) Please provide a rationale for this exclusion criterion.

Question 12: (b) (4) *does the Agency agree* (b) (4)

FDA Response to Question 12: No. (b) (4)

(b) (4)

Question 13: Does the Agency agree with the doses selected for the Phase III studies?

FDA Response to Question 13: We do not object to the 50 mg and 100 mg doses selected for the Phase 3 studies. We point out the relatively shallow dose-response relationship for efficacy, and that many endpoints demonstrated similar efficacy for the 50 mg and 100 mg doses. However, it appears that some endpoints demonstrated better efficacy at the 100 mg dose compared to the 50 mg dose.

We also note: 1) adverse event reports of orthostatic hypotension in Phase 1 studies, especially at doses of 150 mg or higher, 2) three adverse events of orthostatic hypotension in the 100 mg group in Part 1 of Protocol 008, and 3) dizziness and headache were reported at slightly higher incidences in the 100 mg group compared to placebo in Part 1 of Protocol 008. The current dose selection assumes some risk if there is a lack of incremental clinical benefit and also safety concerns for the 100 mg dose. These findings could adversely affect the final risk/benefit analysis for the 100 mg dose.

If you wished to reduce this risk, you might consider a maximum dose of 50 mg and/or addition of a lower dose (e.g., 25 mg) in your Phase III studies.

Question 14: (b) (4)

FDA Response to Question 14: (b) (4)

Discussion: (b) (4)

Statistical Plan

Question 15a: Does the Agency agree that the approach for the statistical analysis and type I error control for the primary and secondary hypotheses included in the Phase III efficacy trials is acceptable to support registration?

FDA Response to Question 15a: Yes. However, we note that the multiplicity adjustment in Part 2 of Protocol 019 was not specified. We remind you that additional discussion is needed to

clarify [redacted] (b) (4) in the protocol.

Question 15b: Does the Agency agree that the proposed unblinding procedures for Phase III studies (Protocol 019, Protocol 020 and Protocol 021) are acceptable to support the registration of the MK-4618?

FDA Response to Question 15b: Yes, however we have concerns in regard to the unblinding of PK data from the phase III studies prior to the database lock (see response to Question 6). We also remind you that additional discussion is needed to clarify a path forward towards a combination claim.

Additional Statistical Comments:

- Randomization should be described separately for the two parts in each of the three studies.
- The evaluation of the primary and key secondary endpoints must be clearly specified in the final protocol, including the timeframe and method of handling missing data.
- We recommend that the response vector in your cLDA model excludes the baseline values.

  Discussion: ***The Sponsor explained that they intend to continue to use cLDA because it enhances observation and is instrumental if there is missing data. cLDA assumes that baseline may not be the same for all strata. The Division expressed concern that inclusion of baseline values in the response vector would result in a smaller estimate of treatment difference. The Sponsor was encouraged to submit a statistical analysis plan (SAP) and to include a rationale including baseline values in the response vector.***
- We recommend that all your statistical models include a fixed effect of region, such as U.S. vs. non-U.S. Region should be pre-specified in your final protocol.
- Sensitivity analysis should also be specified to address the impact of missing values using last observation carried forward.
- The final Phase III protocols should be submitted for more detailed review.

Cardiovascular Monitoring

Question 16a: Does the Agency agree that the planned ECG monitoring in Phase III is adequate?

FDA Response to Question 16a: Yes. ECG at baseline and at week 12 is acceptable.

Question 16b(i): Blood Pressure Monitoring - Does the Agency agree that the planned assessment of blood pressure in Phase III is adequate?

FDA Response to Question 16b(i): Yes. Standardized measurement of blood pressure and heart rate at weeks 0, 4, 8, 12, 18, 26, 39 and 52 is acceptable.

Question 16b(ii): Blood Pressure Monitoring - Does the Agency agree that the planned assessment of blood pressure in Phase III in conjunction with the ABPM study described in Section 3.2.2.6, is adequate to characterize overall effect, or lack of effect, of MK-4618 on blood pressure? Assuming the blood pressure data are supportive, does the Agency agree (b) (4)

FDA Response to Question 16b(ii): We agree that the results of blood pressure assessments in Phase 1 and Phase 2, and the proposed plans for blood pressure assessments in Phase 3, when taken in conjunction with the ABPM study, are adequate to characterize the effect of MK-4618 on blood pressure. We do not agree, however, that (b) (4) will need further evaluation.

In addition, we request that increased blood pressure/hypertension be added as a Tier 1 adverse event of interest in Phase 3 studies.

Discussion: ***The Sponsor stated that because of the known small increase in blood pressure for mirabegron, they plan a dedicated ambulatory blood pressure monitoring (ABPM) study to further clarify the effects of MK-4618 on blood pressure.*** (b) (4)

(b) (4)

Nonetheless, the Division recommended that the Sponsor submit the draft protocol, along with questions, which the Division would consult to the Division of Cardiovascular and Renal Products.

The Division reiterated that the current data from controlled clinical trials appear to demonstrate a small effect of MK-4618 on blood pressure and reminded the Sponsor that the totality of the available vital signs data would be evaluated as part of the NDA review.

Question 16c: Does the Agency agree that the planned assessment of heart rate in Phase III is adequate to characterize overall effect, or lack of effect, of MK-4618 on heart rate?

FDA Response to Question 16c: We agree that the results of heart rate assessments in Phase 1 and Phase 2, and the proposed plans for heart rate assessments in Phase 3, are adequate to characterize the effect of MK-4618 on heart rate. We note that a small mean increase in heart rate appears to already have been demonstrated for MK-4618.

Question 17: Does the Agency concur that the total overall clinical exposure planned for the application, including the projected long term safety exposure to MK-4618 in the clinical program, is adequate to support registration of MK-4618?

FDA Response to Question 17: Yes. However, additional discussion is needed in regard to the timing of the NDA submission relative to the collection of additional safety information and your plans for the contents of the 120-Day Safety Update.

You propose to submit the NDA with 213 subjects exposed to MK-4618 for at least 1 year and 577 subjects exposed to MK-4618 for at least 6 months. Your plan appears to meet the minimum ICH exposure requirements for a new molecular entity (NME): 1500 patients exposed with 300-600 for 6 months and at least 100 patients for 1 year.

However, you expect that 819 subjects and 484 subjects will be exposed to MK-4618 for at least 6 months and at least 1 year, respectively, at 8 months after submission. The large amount of additional safety information that will become available just months after NDA submission would be important for NDA review. Further discussion regarding the timing of the NDA submission and the contents of the 120-Safety Update is appropriate.

In addition, the total number of subjects and duration of exposure required for a combination indication with antimuscarinics requires further discussion.

***Discussion:* The Sponsor provided a revised copy of Table 94, as attached, which shows the estimation of patient exposure at the time of the 120-day safety data. For monotherapy, a total of 375 and 819 subjects would have been exposed to MK-4618 for at least 1 year and 6 months, respectively.**

With this in mind, the Division recommended that filing of the NDA be delayed by 4 months.

In addition, the Division reiterated a concern (b) (4) ***According to the current plan, 179 subjects would have at least 1 year of combination exposure at the time of the 120-safety update. If the NDA submission were delayed for 4 months, this more robust experience would be available in the original NDA submission.***

Pediatric Plan

Question 18a: Does the Agency agree that a partial waiver can be granted for children (b) (4) *years of age and younger, and that pediatric studies in children older than* (b) (4) *years can be deferred until the safety and efficacy and the benefit to risk have been established in adults?*

FDA Response to Question 18a: On its face, this plan appears reasonable. However, your pediatric plan, including any requests for waiver and/or deferrals, will need to undergo review by the Pediatric Review Committee (PeRC).

Question 18b: Is it acceptable to the Agency for the submission of the Pediatric Plan for MK-4618 to occur by July 18, 2013?

FDA Response to Question 18b: No. You must submit a Pediatric Study Plan (PSP) within 60 days of your End-of-Phase 2 meeting. 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

ATTACHMENTS AND HANDOUTS

- Table 94 *Summary of Anticipated Exposures to MK-4618 from Phase IIB/III by Dose and Duration*, - provided by Sponsor at the time of the meeting.

Table 1 (Updated 1/18/2012)

Summary of Anticipated Exposures to MK-4618 from Phase IIB/III by Dose and Duration

MK-4618 Dose	**< 6 months**	**6 months < 1 year**		**≥1 year**		
		At Time of Filing	End of Phase III	At time of Filing	At 120 day safety update	End of Phase III
100 mg	1614	577	819	213	375	484
50 mg	1645	572	814	227	395	498
100 mg + tolterodine/ background antimuscarinic therapy	1074	343	619	62	179	338
50 mg + tolterodine/ background antimuscarinic therapy	1098	281	557	19	136	295
	Some patients will be exposed to more than one treatment and are included in more than one dose category but are only counted once while receiving a specific treatment. Assumption: Patient drop-out rate is estimated to be 15% every 3 months.					

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

/s/

NENITA I CRISOSTOMO
02/25/2013

MARK S HIRSCH
02/26/2013