

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219469Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 129492

MEETING MINUTES

Bayer HealthCare Pharmaceuticals Inc.
Attention: Harpreet Sandhu, PhD, MBA
Director, Regulatory Affairs
100 Bayer Blvd., P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Sandhu:

Refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for elinzanetant (BAY 3427080).

We also refer to the teleconference between representatives of your firm and the FDA on February 1, 2024. The purpose of the meeting was to discuss your planned New Drug Application (NDA) submission.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Medical Officer Team Leader
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, and
Reproductive Medicine
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 1, 2024, 11:00 AM to 12:00 PM
Meeting Location: Teleconference

Application Number: IND 129492
Product Name: elinzanetant (BAY 3427080)

Proposed Indication: Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause

Sponsor Name: Bayer HealthCare Pharmaceuticals Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

CDER Participants:

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPUM)

Janet Maynard, MD, MHS, Director

Division of Urology, Obstetrics, and Gynecology (DUOG)

Christina Chang, MD, MPH, Director

Shelley R. Slaughter, MD, PhD, Clinical Team Leader

Sergio Oehninger, MD, Medical Officer

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Margaret Kober, RPh, MPA, Chief, Project Management Staff

Samantha Bell, Regulatory Health Project Manager

Division of Hepatology and Nutrition

Paul "Skip" Hayashi, MD, MPH, FAASLD, Physician Lead, Drug-Induced Liver Injury (DILI) Team

Office of Clinical Pharmacology

Yanhui Lu, PhD, Clinical Pharmacology Team Leader

Yoo Jin Moon, PhD, Clinical Pharmacology Reviewer

Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Leslie McKinney, PhD, Pharmacology and Toxicology Reviewer

Kimberly Hatfield, PhD, Pharmacology and Toxicology Supervisor

Office of Biostatistics

Solomon Chefo, PhD, Team Leader

Yung Tang, PhD, Reviewer

Office of Pharmaceutical Quality (OPQ), Office of New Drug Products

Hamid Shafiei, PhD, Senior Pharmaceutical Quality Assessor

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis (DMEPA)

Stephanie DeGraw, PharmD, Team Leader

Justine Kalonia, PharmD, Safety Evaluator

OSE, Division of Risk Management (DRM)

Yasmeen Abou-Sayed, PharmD, Team Leader

Courtney Cunningham, PharmD, Pharmacist

OSE, Office of Pharmacovigilance & Epidemiology (OPE), Division of Epidemiology (DEPI)

Adebola Ajao, PhD, Team Leader

Keewan Kim, PhD, Epidemiologist

OSE, Division of Pharmacovigilance (DPV)

Miriam Chehab, PharmD, BCPPS, Safety Evaluator

Office of Scientific Investigations

Michelle Fedowitz, MD, Good Clinical Practice (GCP) Assessment Branch, Team Leader

SPONSOR ATTENDEES

Lineke Zuurman, MD, Global Clinical Leader

Pablo Arriagada, MD, Clinical Development Head of Women's Healthcare

Maja Francuski, MD, Global Safety Leader

U.S. Food and Drug Administration

Silver Spring, MD 20993

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Judith Schwarz, MD, Pharmacovigilance
Uwe Mellinger, MS in Mathematics, Principal Statistician
Nazanin Haseli Mashhadi, MSc in Statistics, Lead Statistician
Claudia Haberland, PhD, Patient Reported Outcomes
Tobias Mundry, PhD, Drug Product Development, CMC
Alla Rosenberg, Global Regulatory Affairs, CMC
Wendy Sikorski, US Regulatory Affairs, CMC
Marcus-Hillert Schultze-Mosgau, PhD, Clinical Pharmacology
Klaus Francke, MD, PhD, Director, Early Clinical Development
Lisa Halvorson, MD, US Medical Affairs
Cecilia Caetano, MD, Global Medical Affairs
Gabriele Braeunlich, PhD, Head of Regulatory Affairs Strategy and Labeling
Alison Maloney, PhD, MFS, MBA, Head of Regulatory Affairs, America
Sven Nisius, MDRA, Global Regulatory Strategist
Harpreet Sandhu, PhD, MBA, Global Regulatory Strategist
Naimesh Solanki, PhD, RAC, Global Regulatory Strategist
Georgios Foteinos, Development Team Leader
Katie Bang, MHA, Global Integrated Product Team Leader

1.0 BACKGROUND

Bayer HealthCare Pharmaceuticals Inc. (Bayer) is developing elinzanetant, an oral, once daily, selective neurokinin 1, 3 receptor antagonist (NK 1,3), for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. An End-of-Phase 2 (EoP2) meeting was held on November 17, 2020. Bayer intends to submit, by the end of the second quarter of 2024, an NDA based on the results of three phase 3 studies (OASIS 1, OASIS 2, and OASIS 3). Bayer has requested this meeting to discuss their planned NDA submission.

FDA sent Preliminary Comments to Bayer on January 30, 2024. In an email communication dated January 31, 2024, Bayer requested clarification on FDA's responses to the questions 1, 3b, 5 and 7b.

2.0 DISCUSSION

2.1. Quality

Question 1: Drug Substance and Drug Product manufacturing, as well as primary packaging is being transferred and scaled up at commercial manufacturing sites for market supply. Bayer intends to provide primary stability data on three batches manufactured at the clinical manufacturing

sites, along with supportive stability data on batches manufactured at the commercial manufacturing site. A stability commitment will be provided for the first three validation batches manufactured at commercial scale, at the commercial manufacturing site as per proposed stability protocol. Does the Agency consider this stability data package to be adequate for NDA filing?

FDA Response:

Your proposed comparability determination, using a pilot batch of drug product manufactured at the commercial drug product manufacturing site and using a drug substance batch manufactured at the commercial drug substance manufacturing site, appears reasonable. Submit three months of long-term and accelerated stability data from three batches of drug product manufactured at the commercial manufacturing site using the same process and equipment at minimum scale of 1:10 (pilot scale) of intended commercial scale packaged in the to-be-marketed container closure at the time of submission of your NDA. The adequacy of data to support an NDA filing and approval will be a review issue.

Discussion:

Bayer asked for clarity on the amount of stability data requested by the FDA in the NDA. Bayer proposed to submit the following at the time of NDA submission and asked for FDA concurrence:

- a. Three drug product batches produced at the clinical manufacturing site, (b) (4) in the commercial packaging:
 - two batches with 24 months long-term and 6 months accelerated data
 - one batch with 12 months long-term and 6 months accelerated data.
- b. Two batches produced at the commercial manufacturing site, (b) (4) in the commercial packaging:
 - one pilot batch (at 1/5 of commercial scale) with 12 months long-term and 6 months accelerated stability data
 - one commercial scale batch with 1 month long-term and 1 month accelerated stability data.

FDA explained that the Agency had previously requested 12 months of long term stability data and 6 months of accelerated stability data from the commercial manufacturing site. However, the Agency may instead accept three months of long-term and accelerated stability data from three batches of drug product manufactured at the commercial manufacturing site at a scale of 1:10 of the commercial scale. FDA emphasized that clinical batches do not represent commercial batches and referred to the Scale-Up and Post-Approval Changes – Immediate Release

(SUPAC-IR) guidance document regarding post-approval CMC changes. FDA reiterated that nothing less than three months of long-term and accelerated stability data from three batches of drug product manufactured at the commercial manufacturing site is acceptable for submission in the NDA. However, FDA did agree that this data could be submitted within 30 calendar days after the submission of the original application.

2.2. Non-clinical development

Question 2: Bayer has conducted a comprehensive non-clinical study program to support the development of elinzanetant. Does the Agency agree that the completed non-clinical program is adequate to support an NDA filing and approval?

FDA Response:

The nonclinical program, including the ongoing pre-/post-natal development, carcinogenicity, and abuse potential studies, intended to support NDA submission appears complete. The in vitro studies pertaining to drug metabolism and drug-drug interaction also seem reasonable. The adequacy of data to support an NDA filing and approval will be a review issue.

Discussion:

There was no further discussion at the meeting.

2.3. Clinical development

Question 3a: Bayer has performed a comprehensive clinical pharmacology and biopharmaceutics characterization of elinzanetant to support the NDA. Does the Agency agree that the overall clinical pharmacology program is adequate to allow review of the NDA to support filing and approval of elinzanetant for the proposed indication?

FDA Response:

Based on the information provided, your clinical pharmacology program appears reasonable. The adequacy of data from your clinical pharmacology program to support filing and approval will be determined upon review of your NDA submission.

Discussion:

There was no further discussion at the meeting.

Question 3b: Does the Agency agree with the proposed submission plan for the driving ability study i.e. to submit the topline data in the initial NDA and the final study report during the 120-Day Safety Update?

FDA Response:

No. We have following comments:

- a) All final trial reports of trials to be reviewed in the NDA should be included at the time of the initial NDA submission.
- b) Should your NDA ultimately receive approval, the decision to include any results from your planned driving ability study in labeling will be a review issue to be considered during the NDA review cycle.
- c) Should you have questions regarding the Agency's recommendations for the design and conduct of a driving ability study, refer to FDA Guidance for Industry, entitled Evaluating Drug Effects on the Ability to Operate a Motor Vehicle, at: <https://www.fda.gov/media/90670/download>.
- d) Ensure that the elinzanetant dosing used in the driving ability study is sufficient to reach steady state.

Discussion:

Bayer proposed to provide the final data of the driving ability study with the initial NDA submission and the final clinical trial report within 60 days of the NDA submission. FDA reiterated that the complete and final trial report is to be submitted at the time of NDA submission. FDA explained that this clinical trial report is considered a major component of the NDA and that Bayer should wait to submit the NDA until all final clinical trial reports can be submitted for review. Bayer stated they will consider the FDA's comments and how to move forward. FDA emphasized that the advice regarding submission of the clinical trial report at the time of the NDA submission is not merely a recommendation. Failure to include the final clinical trial report will likely constitute a refuse-to-file issue.

Question 4: Demonstration of clinical efficacy of elinzanetant for the treatment of VMS associated with menopause will be based on two pivotal Phase 3 studies, OASIS 1 and OASIS 2. In the NDA, efficacy results from these two studies will be presented by individual study. An additional pooled efficacy analysis across these two studies will be presented and is considered supportive.

Does the Agency concur with the proposed strategy for presentation of the efficacy data?

FDA Response:

Yes. Our efficacy determination will be made based on corroborating positive results from each of phase 3 Trials OASIS 1 and OASIS 2, intended to provide substantial

evidence of effectiveness. Pooled efficacy data from the two trials will be considered supportive.

In addition, as previously communicated, assess the four primary efficacy endpoints (i.e., frequency and severity at Weeks 4 and 12) as co-primary efficacy endpoints where each endpoint should be tested for superiority at a two-sided significance level of 5% to claim trial success.

Discussion:

There was no further discussion at the meeting.

Question 5: Demonstration of clinical safety of elinzanetant will be based on a pooled analysis across the pivotal efficacy studies (OASIS 1 and 2), the long-term safety & efficacy study (OASIS 3) and the Phase 2 study (SWITCH-1, 120 mg arm)).

Does the Agency concur with the proposed pooling strategy and the presentation of the clinical safety data in the NDA?

FDA Response:

Base the primary assessment of long-term safety solely on randomized, placebo-controlled, 52-week Trial OASIS 3. Pooled safety data of OASIS 1 and Oasis 2 will serve as supportive for long-term safety up to 26 weeks. To account for pooled data that includes variable duration of exposures to placebo, use the exposure adjusted incidence rate (EAIR) of adverse events for statistical analysis of adverse events. Pooled safety data of OASIS 1 and Oasis 2 and Switch-1 (120 mg arm only) will serve as supportive information for safety at 12 weeks.

If we determine that your NDA submission is acceptable for filing, we intend to consult CDER's Drug-Induced Liver Injury (DILI) team on all cases of elevated hepatic enzymes with or without elevated bilirubin or symptoms to assess for possible cases of DILI. To facilitate the Agency's review, follow the recommendations in the two documents attached to these preliminary responses.

Discussion:

Bayer agreed that the primary assessment of long-term safety will be based on the randomized, placebo controlled, 52-week study OASIS 3, but proposed a different strategy for pooled safety data. Bayer proposed pooling OASIS 1, 2, 3 and SWITCH-1 (120 mg arm) with summary of safety data for Weeks 1 through 12 and Weeks 1 through 52 where Week 1 through 52 data includes the 26-week data of OASIS 1 and 2. FDA was in agreement regarding the summary for Weeks 1 through 12 and Weeks 1 through 52, but instructed that an additional assessment for Weeks 1 through 26 of the proposed pooled data be included for additional perspective on the

timing of occurrence for adverse safety outcomes. Bayer stated they would take FDA's request into consideration.

Post-Meeting Comment:

Also provide the exposure adjusted incidence rate (EAIR) of adverse events in your primary safety analysis based on data from trial OASIS 3 alone.

Question 6: Does the Agency agree with adequacy of the proposed content for the 120-Day safety update report?

FDA Response:

Your proposal for the content of the 120-Day Safety Update appears reasonable with the exception of the proposed inclusion of the final study report for driving ability Study 22653, which should be submitted instead at the time of the initial NDA submission. See also our response to Question 3b.

Discussion:

See discussion under Question 3b.

2.4. Multidisciplinary

Question 7: Does the Agency agree that the proposed content and organization of the planned NDA are acceptable and that there are no barriers to submission and filing?

FDA Response:

The proposed content and organization of the proposed future NDA submission appear reasonable. Fileability will be determined following your NDA submission.

Also, submit the following items at the time of NDA submission:

- a) To support that the clinical outcome assessment (COA) (i.e., Hot Flash Daily Diary) is fit-for-purpose for use as the primary endpoints, compile all qualitative and quantitative evidence into a final evidence dossier. We will review the completed qualitative and quantitative data to evaluate the content validity, other measurement properties, and interpretability (i.e., clinical meaningfulness) of the Hot Flash Daily Diary at the time of NDA submission.
- b) Submit all analysis datasets and SAS programs used to generate the reports requested in (a), along with the dataset reviewer's guide and define.pdf.

Create a folder named “datasets” in Module 5. Regarding the “datasets” folder structure, consult Section 7 (Figure 1 and Table 2) of the Agency’s ‘Study Data Technical Conformance Guide’ document, at <https://www.fda.gov/media/119807/download>.

Discussion:

Bayer requested FDA’s response as to whether the acceptable format is define.xml or define.pdf. The FDA agreed that either format is acceptable.

Question 8: The eCTD NDA submission will contain electronic datasets from individual studies and the integrated analyses database as described in this pre-NDA briefing package. Does the Agency agree with the proposal regarding the scope, format, and documentation of the electronic datasets to be submitted?

FDA Response:

From the technical perspective, the proposal regarding the scope, format, and documentation of the electronic datasets to be submitted, is acceptable.

Refer also to our response to Question 7.

Discussion:

See discussion under Question 7.

Question 9: Does the Agency agree with the Sponsor’s proposal regarding the information required by the Office of Scientific Investigation (OSI) to facilitate the issuance of inspection assignments as well as financial disclosure information?

FDA Response:

We agree with your proposal to submit Bioresearch Monitoring (BIMO) data for the phase 3 trials (OASIS 1, OASIS 2, and OASIS 3).

Because you propose to pool data from Switch-1 with OASIS 1 and OASIS 2 to support the safety of the 120 mg dose at 12 weeks, also provide financial disclosure information for this trial.

Discussion:

There was no further discussion at the meeting.

ADDITIONAL DISCUSSION:

FDA inquired about when Bayer intends to submit the NDA, and Bayer stated the end of June 2024. FDA noted that the timeline for Bayer's submission of the NDA application should take into consideration the FDA's requirements discussed at this meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See discussion under Questions 1 and 3b.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: stability data package as discussed under Question 1. Identify this submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - QUALITY

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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ 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.²

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 Information³ and Pregnancy and Lactation Labeling Final Rule⁴ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

¹ <https://www.fda.gov/media/86340/download>

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁴ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

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*, and the associated conformance guide, *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*.⁵

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
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⁵ <https://www.fda.gov/media/85061/download>

Meeting Minutes	FDA	March 2, 2024
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6.0 ATTACHMENTS AND HANDOUTS

pre-NDA meeting - Bayer's follow-up to Preliminary Responses.pdf

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/

SHELLEY R SLAUGHTER
02/26/2024 03:57:56 PM



IND 129492

MEETING MINUTES

Bayer HealthCare Pharmaceuticals Inc.
Attention: Shefali Goyal, M.Sc., M.S.
Executive Director, Regulatory Affairs Strategy
Women's Health Care
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915

Dear Ms. Goyal:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAY 3427080 (NT-814).

We also refer to the teleconference between representatives of your firm and the FDA on November 17, 2020. The purpose of the meeting was to discuss your phase 3 development program.

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, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine
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: November 17, 2020
09:00 a.m. – 10:00 a.m. EST

Meeting Location: Teleconference

Application Number: IND 129492
Product Name: BAY 3427080 (NT-814)

Proposed Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause

Sponsor Name: Bayer HealthCare Pharmaceuticals Inc. (Bayer)
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Kim Shiley, R.N., B.S.N.

FDA ATTENDEES

Division of Urology, Obstetrics, and Gynecology (DUOG)
Audrey Gassman, M.D., Deputy Director
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader
Theresa van der Vlugt, M.D., Clinical Reviewer
Leah Berhane, M.D., Clinical Reviewer
Kimberly Hatfield, Ph.D., Pharmacology and Toxicology Team Leader
Frederic Moulin, D.V.M., Ph.D., DABT, Pharmacologist

Office of Regulatory Operations
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Kim Shiley, R.N., B.S.N., Regulatory Health Project Manager

Office of Biostatistics
Jia Guo, Ph.D., Biostatistics Reviewer
Yun Tang, Ph.D., Biostatistics Reviewer

Office of Clinical Pharmacology
Yanhui Lu, Clinical Pharmacology Team Leader
Peng Zou., Clinical Pharmacology Reviewer
Mohamad Kronfol, Clinical Pharmacology Reviewer

Division of Cardiometabolic and Endocrine Pharmacology

Office of Clinical Pharmacology

Girish Bende, Ph.D.

Co-Lead, IRT for Cardiac Safety Studies

SPONSOR ATTENDEES

BHC, US

Shefali Goyal, M.Sc., M.S., U.S. Head – Women's Health Care Group 2, Regulatory Affairs Strategy, Women's Health Care

Todd Paporello, Pharm.D., M.B.A., V.P. and Head, North American Regulatory Affairs, Pharmaceuticals Research and Development Site Head

Jeffrey Goldstein, D.O., NAMS Certified Menopause Provider, Senior Medical Director, US Medical Affairs Women's Healthcare

Bayer AG, Germany

Christian Seitz, M.D., Director, Clinical Development Gynecologic Therapies, Therapeutic Area (TA) Women's Healthcare

Matthias Schaefer, M.D., Vice President, Clinical Development Gynecologic Therapies, TA Women's Healthcare

Cecilia Caetano, M.D., Director, Medical Affairs, TA Women's Healthcare

Marcus-Hillert Schultze-Mosgau, Ph.D., Director, Clinical Pharmacology - Gynecological Therapy / Specialized Therapeutics

Esther Groettrup-Wolfers, M.D., Pharmacovigilance/Benefit Risk Management, Head TA Group Women's Healthcare

Christoph Gerlinger, Ph.D., Senior Director, Statistics and Data Insights, Expert statistician Women's Healthcare

Rudolf Knauth, Ph.D., Global Program Head, Clinical Development - TA Women's Healthcare

Ulrike Bodesheim, Ph.D., MDRA, Head, Regulatory Affairs Strategy, Women's Health

NeRRe Therapeutics, UK

Stephen Pawsey M.B. B.S. FFPM, Chief Medical Officer

Consultant, US

(b) (4)

BACKGROUND

Bayer acquired NT-814 from NeRRe Therapeutics Ltd. (NeRRe) on September 8, 2020. NeRRe acquired NT-814 from GlaxoSmithKline (GSK) in 2012. In April 2016, PIND Written Responses Only meeting minutes were provided to NeRRe. In June 2016, the IND was opened with a phase 1b/2a trial (known as RELENT-1) which evaluated the pharmacokinetics, safety and preliminary efficacy of NT-814 in postmenopausal women with moderate to severe vasomotor symptoms.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

The purpose of this meeting is to discuss the findings of the phase 2b dose-finding trial known as SWITCH-1 and the elements of Bayer's phase 3 clinical program, to include the general plan, size of clinical safety database, clinical pharmacology elements, and preclinical program sufficiency.

FDA sent Preliminary Comments to Bayer on November 10, 2020. Bayer acknowledged the Division's comments and stated they did not require further discussion of Questions 1, 2, 3, 6, 8, 10, 11, and 12.

DISCUSSION

Nonclinical

Question 1: *A comprehensive summary of completed, ongoing and planned preclinical studies with NT-814 and, where necessary, its major metabolites is provided. Does the Division consider that the completed studies as well as the currently ongoing or planned studies to characterize the relevant metabolites of NK-814 are sufficient to support Phase 3 studies? And upon completion of the additionally proposed non-clinical studies, the preclinical program will be sufficient to support an NDA?*

FDA Response:

The nonclinical program described in your briefing document, including the proposed investigation of the major human metabolites, appears adequate to support phase 3 studies and an eventual NDA submission. Final determination of the adequacy of the nonclinical development program, however, will depend on review of the final nonclinical study reports submitted. Additional nonclinical studies may be warranted in certain circumstances such as significant changes in pharmacokinetic (PK) profile, unexpected toxicity, formulation changes, or emerging clinical safety concerns.

Clinical Pharmacology

Question 2: *Does the Division agree that the proposed clinical pharmacology program including the planned pharmacometric analyses is appropriate to support Phase 3 studies and the submission and approval of an NDA for NT-814 for the proposed indication?*

FDA Response:

No, we do not agree. We have following comments:

1. Your study MNK111587 showed that repeat dosing of NT-814 oral suspension 200 mg for 28 days increased the AUC of co-administered midazolam by 1.9 fold. If the exposure to NT-814 at the intended to-be-marketed (TBM) dose(s) is higher than that of NT-814 oral suspension 200 mg, the results from Study MNK111587 will be inadequate to support labeling for NT-814. Conduct either a clinical study or mechanistic modeling to assess the inhibition and induction of CYP3A4 at the to-be-marketed highest dose.

2. Investigate the CYP2B6 induction potential of NT-814 using mechanistic models or by conducting a clinical drug interaction study with a sensitive index substrate (see the FDA guidance *"In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions"* for more information).
3. We disagree with your statement that the effect of co-administered acid-reducing agents (ARAs) on the absorption of NT-814 was addressed with the data from food effect studies. The magnitude of the effect of food on the absorption of NT-814 may differ from that of ARAs. The fat in a meal and increased intestinal bile acids following a meal may affect the solubility and increase oral absorption of NT-814. Also, a meal can reduce drug transit in the gastrointestinal tract, which may improve oral absorption of NT-814. In contrast, ARAs have no such effects. Therefore, the 30-40% decrease in the AUC of NT-814 observed in food effect studies may not represent the effect of ARAs on the oral absorption of NT-814. The results from food effect studies cannot be used to support labeling language regarding concomitant use of ARAs.
4. If your TBM formulation is different from the soft gel capsule formulation to be used in your phase 3 trials, an additional bioequivalence study(ies) may be needed for bridging.
5. A new food effect study should be conducted with your TBM formulation if the TBM formulation is different from the NT-814 formulation used in study 814-1-02 where you evaluated food effect on the PK of NT-814.

Meeting Discussion:

Bayer agreed to investigate the effect of NT-814 at the exposure of the TBM dose on induction of CYP2B6 using mechanistic modeling. Based on the outcome of the modeling, Bayer will decide about confirming the modeling results in a clinical drug-drug interaction study. FDA opined that the proposal appears reasonable.

Bayer agreed to conduct a dedicated clinical drug-drug interaction study with acid-reducing agents (ARAs).

Bayer confirmed that the soft gel formulation used in study 814-1-02 is identical in composition to the TBM formulation, with the exception that the dosage strength used in study 814-1-02 was 40 mg whereas the intended TBM product is a 60 mg dosage strength capsule. The size of the capsules is slightly different (b) (4) Bayer is planning to conduct a clinical pharmacokinetic study to bridge the two formulations. Also, in Bayer's response to Question 8, Bayer mentioned that they are planning a pharmacokinetic study to further investigate the effect of food on the systemic exposure of NT-814 and the results will be

used to inform the final exposure-response analyses. FDA opined that the proposal appears reasonable.

QT (TQT) study

Question 3: *Based on the absence of any signal in the available preclinical and clinical data, supported by an exposure-response model on QT prolongation, it is Bayer's assessment that a TQT study can be waived. Investigation of potential QT prolongation is proposed via a safety study at supratherapeutic dose exposure in parallel to Phase 3 and submitted as part of the NDA. Does the Division agree with the proposal to waive a TQT study, to be replaced with a high dose safety study conducted in parallel to Phase 3?*

FDA Response:

No, we cannot agree at this time that a thorough QT/QT_c (TQT) study can be waived. For the high dose safety study to be used as a substitute for a thorough QT study, design it according to the revised ICH E14 Q&A 5.1. Submit your protocol for the high dose safety study for our review and comment. Include the following along with your protocol:

- a. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (<https://www.fda.gov/media/129685/download>)
- b. Statistical analysis plan
- c. Investigator's Brochure

Your proposed high dose safety study can be conducted in parallel with your phase 3 trial.

Clinical

Question 4: *Based on data from the SWITCH-1 dose range finding and other studies, it is Bayer's assessment that a 120 mg once daily dose as soft gel capsule formulation is the appropriate dose to be evaluated in pivotal registration studies. Does the Division agree with the proposed dose?*

FDA Response:

No, we do not agree. In your completed phase 2b Trial 814-PM-02 (SWITCH-1), the 120 mg dosage strength did not meet all of the four co-primary vasomotor symptoms endpoints of mean change in moderate to severe frequency and severity of hot flashes at Weeks 4 and 12. Reported results for SWITCH-1 show that the daily 120 mg dose of NT-814 demonstrated a statistically significant reduction in moderate to severe hot flash frequency compare to placebo at Weeks 4 and 12 (MMRM p-values of 0.0002 and 0.0116, respectively). However, a statistically significant reduction in the severity of hot flashes at Week 4 (MMRM p-value of 0.0896) and Week 12 (MMRM p-value of 0.2606) was not demonstrated for the daily 120 mg NT-814 dose. Based on these reported results, you may be at risk of not identifying an effective

dose of NT-814 for a treatment of moderate to severe vasomotor symptoms indication in your proposed phase 3 development program.

As conveyed to NeRRe Therapeutics Ltd (former sponsor of IND 129492) on April 4, 2016, to support an indication for the treatment of moderate to severe vasomotor symptoms due to menopause, the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (hereafter referred as the Agency's 2003 draft Hormone Therapy Guidance), recommends the following four co-primary endpoints:

1. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4
2. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12
3. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 4
4. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 12

For products intended to treat moderate to severe vasomotor symptoms, the primary efficacy analysis should show both a clinically meaningful and statistically significant reduction in the frequency and statistically significant reduction in the severity of hot flashes in the treated group(s) compared with placebo. This reduction should occur within 4 weeks of initiation of treatment and be maintained through 12 weeks of treatment. A clinically meaningful reduction in frequency is identified as a reduction of at least two moderate to severe hot flashes above that demonstrated with placebo per day (14 per week) at Week 4 and maintained through Week 12.

To fully demonstrate a reduction in severity of hot flashes at Week 4 maintained through Week 12, we recommend that mild, moderate, and severe hot flashes be captured at these time points. Primary efficacy endpoints are assessed at Week 4 and Week 12. Calculate severity at Week 4 and Week 12 as follows:

$$[(1 \times \text{the number of mild hot flashes/day}) + (2 \times \text{number of moderate hot flashes/day}) + (3 \times \text{number of severe hot flashes/day})] / \text{total number of mild, moderate, and severe hot flashes.}$$

Additionally, at or before phase 3, identify the lowest effective dose of your product for the treatment of moderate to severe vasomotor symptoms due to menopause. Labeling for such products generally recommends that healthcare providers prescribe the lowest effective dose for the shortest duration consistent with treatment goals. Conduct one or more dose ranging phase 3 trial(s) including a clearly ineffective dosage strength and one or more higher dosage strengths which are anticipated to be effective.

Meeting Discussion:**Bayer:**

1. Bayer expects that the planned sample size in the phase 3 trials will be adequate to demonstrate statistically significant differences in the planned endpoints for the 120 mg NT-814 dosage group versus the placebo group. Based on the results of the SWITCH-1 dose-finding study, Bayer considers the 120 mg NT-814 dose the lowest effective dose (b) (4)
2. The phase 2b dose-ranging trial, SWITCH-1, showed that daily doses below 120 mg (namely 40mg or 80 mg per day) will not result in an improvement that meets FDA's definition of clinical meaningfulness (at least two moderate to severe hot flashes per day less than demonstrated with placebo). The Agency's recommendation to also include an ineffective dose in phase 3 trial(s) appears to reflect the specific and complex situation of estrogen/progestin combinations for which the respective guidance was originally developed, particularly the recommendation to demonstrate an ineffective progestin dose on the endometrium. Bayer asked the FDA to clarify what scientific and/or clinical benefit would be expected from inclusion of a clearly ineffective dose in the phase 3 trial(s) considering the different mode of action of NT-814.
3. Bayer advised that they will consider conducting the phase 3 trials (b) (4) and confirmed that the 80 mg dose used in SWITCH-1 is not available for phase 3 trials.

FDA:

1. FDA reaffirmed its preliminary responses to Question 4 regarding the proposed single 120 mg NT-814 dose in planned phase 3 clinical trials. FDA agreed with Bayer that proposed 120 mg single dose is the sponsor's decision, however, results of SWITCH-1 do not clearly demonstrated either an effective dose or ineffective dose of NT-814 compared to placebo.
2. FDA continued to recommend a dose ranging trial in phase 3 to demonstrate both effective and ineffective doses of NT-814.

(b) (4)

3. FDA recommended including the rationale [REDACTED] (b) (4) in the protocol.

Question 5: *Bayer plans to conduct two confirmatory Phase 3 studies with largely identical design to evaluate efficacy and safety of NT-814 for treatment of VMS in menopausal women. The main elements of the study design are described in the company position below and further details are provided in the attached Study Concept (see Appendix A: Phase 3 Study Concept). Does the Division agree that the proposed Phase 3 studies are adequate to characterize the efficacy and safety profile of NT-814 for NDA?*

FDA Response:

Your proposal to conduct two confirmatory, “largely identical,” 52-week phase 3 clinical trials is acceptable and is consistent with the recommendations of the Agency’s 2003 draft Hormone Therapy Guidance. Your proposed stratification of symptomatic (at least 7 moderate to severe hot flashes per day) women meeting criteria for postmenopausal status to your proposed placebo-controlled efficacy subgroup (first 12 weeks placebo-controlled with randomization to either 120 mg of NT-814 or placebo, then a 40 week open-label extension period with all women using your proposed 120 mg NT-814 dose) is acceptable. Likewise, your proposed stratification of postmenopausal women, meeting criteria for postmenopausal status but not meeting at least 7 moderate to severe hot flashes per day, to your proposed placebo-controlled safety-only subgroup (using either proposed 120 mg of NT-814 or placebo for a total of 52-weeks) is also acceptable. Refer to our response to Question 4 for our recommendation for dosage strengths to be evaluated in phase 3.

We have the following additional comments:

- Our definition of postmenopausal status does not include a serum estradiol concentration of < 30 pg/mL as proposed in your meeting briefing package as inclusion criterion Number 3b and criterion Number 3c. You may retain a serum estradiol concentration inclusion criterion if you intend it to meet recommendations of another regulatory agency (such as the EU Committee for Medicinal Products for Human Use).

Meeting Discussion:

Bayer will determine whether to retain or remove the serum estradiol concentration inclusion criterion after interaction with other regulatory agencies.

- We do not agree with the following enrollment criterion, as stated under “Patient Population” on page 28 of 128 in your meeting briefing package,

[REDACTED] (b) (4)

(b) (4) This criterion appears to allow for enrollment of women who may be perimenopausal (not postmenopausal) and is therefore not acceptable. Include in your trials only postmenopausal women who are in the age range you identify, 40 to 65 years. We define postmenopausal as:

- at least 12 months of spontaneous amenorrhea, or
- at least 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL, or
- at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy

Meeting Discussion:

1. Bayer clarified that the purpose of the criterion, (b) (4) is to allow recruitment of hysterectomized women who have not had a bilateral oophorectomy at an earlier age, and who would otherwise not clearly meet one of the standard criteria.
 2. FDA reaffirmed the definition of postmenopausal as conveyed to Bayer in the preliminary comments. FDA recommended that for hysterectomized women with intact ovaries who are at the younger end of the age spectrum, repeat serum FSH evaluation be performed to verify FSH concentrations consistent with postmenopausal status and thus avoid the inclusion of perimenopausal woman.
- Proposed Inclusion criterion number 8 states “Subject has recorded an average of at least 7 moderate or severe hot flashes per day (including night-time) over the last 7 days that the Hot Flash Daily Diary (HFDD) was completed (assessed at the Baseline Visit).” Clarify if the “last 7 days” are consecutive days prior to randomization to trial medication.

Meeting Discussion:

Bayer proposed to modify Inclusion Criterion #8 as follows: “Participant has recorded at least 50 moderate to severe hot flashes over the last 7 consecutive days that the HFDD was completed (assessed at the Baseline Visit).”

- Proposed exclusion criterion number 2 states, (b) (4)

(b) (4)

(b) (4)

- Modify proposed exclusion criterion number 5 to include heart block and QT prolongation, in addition to clinically significant prior or ongoing history of arrhythmias (as proposed).

Meeting Discussion:

Bayer acknowledged the Agency's response and will amend the criterion as recommended.

- Modify proposed exclusion criterion number 8 "Uncontrolled hypertension" . We define hypertension as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure as ≥ 80 over three readings on at least two different occasions. Medically clear any postmenopausal woman with a medical history of hypertension to participate in your phase 3 trials.

Meeting Discussion:

1. Bayer noted that, based on the mode of action of NT-814, an increased risk of cardiovascular events is not foreseen and no effects on blood pressure have been observed in the clinical program with NT-814 to date. (b) (4)

2. FDA noted that women with hypertension should be medically cleared to participate in the phase 3 trials.

- We agree with your proposal to obtain (b) (4) endometrial biopsy specimen for diagnosis during screening in any participant with a uterus. In order to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer, repeat any screening endometrial biopsy reported as insufficient tissue. Do not enroll into

your phase 3 clinical trials any woman with a uterus with a screening endometrial biopsy diagnosis of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer.

Meeting Discussion:

Bayer acknowledged the Agency's response.

- We do not agree [REDACTED] (b) (4) as proposed in the Schedule of Activities on page 12 in Appendix A: Phase 3 Study Concept. Perform an endometrial biopsy in any participating woman with a uterus who completes the 52-week, phase 3 trial.

For histological assessment of the endometrium, follow the Agency's draft 2003 Hormone Therapy Guidance for Industry recommendation that endometrial biopsy samples be evaluated by three blinded pathologists with independent institutional affiliation and financial responsibilities. The concurrence of two of the three pathologists is to be accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis is to be used as the final diagnosis.

Have the three independent expert pathologists 1) use the same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer and 2) fully characterize endometrial polyps as to glandular proliferation and atypia. You can view the standardized criteria for histologic evaluation in the Agency's draft 2003 Hormone Therapy Guidance at www.FDA.gov.

Meeting Discussion:

Refer to discussion under Question 9.

- Evaluate all enrolled non-hysterectomized women receiving treatment in the phase 3 trials with endometrial biopsy at Week 12 if they decline participation in the 40-week open-label extension, at early termination (after 10 weeks of trial drug exposure), or for assessment of uterine bleeding (as proposed). Follow up any woman with a diagnosis of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer through treatment and/or resolution as appropriate.

Meeting Discussion:

Refer to discussion under Question 9.

- Because women in your proposed 52-week phase 3 trials are ≥ 40 years of age, document a negative mammogram within 12 months prior to enrollment in these trials. Alternatively, perform a mammogram at screening. Also perform a mammogram at the completion of your proposed 52-week clinical trials for all participating postmenopausal women; this is consistent with the United States Preventative Services Taskforce (USPSTF) recommendation that women greater than 40 years of age have an annual screening mammogram performed. See also the Agency's A/IR letter to NeRRe Therapeutics, dated October 4, 2016.

Meeting Discussion:

Bayer acknowledged the Agency's response and will implement the USPSTF recommendation for all trial sites in the US. In other trial countries, Bayer will follow the locally applicable recommendations for screening mammography. If annual screening is required in a given country, like in the United States, a mammogram will also be planned at the time of completion of the 52-week clinical trials.

- Exclude from trial participation any postmenopausal woman with abnormal cervical lesions and/or pathology. Obtain written documentation of a normal (negative) Pap smear within the past 2 years; in compliance with the USPSTF recommendation that a postmenopausal woman with a cervix have a Pap smear evaluated every 3 years. Alternatively, obtain a Pap smear at the screening visit.

Meeting Discussion:

Bayer acknowledged the Agency's response.

- Postmenopausal women constitute the appropriate exposure population for a treatment of moderate to severe vasomotor symptoms indication. We generally follow the ICH E1 guidelines for patient exposure for drug products intended for chronic use. The ICH E1 guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range anticipated to be efficacious. Note that larger numbers of exposed patients may be recommended prior to approval to further characterize safety signals that emerge during drug development.

Meeting Discussion:

Bayer acknowledged the Agency's response.

- Complete drug interaction studies and renal/hepatic impairment studies prior to initiating the phase 3 trials.

Meeting Discussion:

1. Bayer proposed to initiate phase 3 trials before the pharmacokinetic (PK) data from renal/hepatic impairment studies and some drug interaction studies are available. To mitigate the safety risk to patients with hepatic impairment, Bayer proposed to exclude women with any degree of hepatic impairment in the phase 3 trials.
 2. FDA agreed with Bayer's proposal but commented that the drug product may be prohibited for use in women with any degree of hepatic impairment in future drug labeling if these women are excluded from phase 3 trials and a significant increase in the exposure of NT-814 is observed in the hepatic impairment study.
 3. Bayer proposed to prohibit concomitant use of strong CYP3A4 inhibitors and inducers in the proposed phase 3 trials. Because of the significant overlapping between CYP3A4 inhibitors and P-gp inhibitors, Bayer believed that the exclusion of strong CYP3A4 inhibitors would also avoid concomitant use of P-gp inhibitors.
 4. FDA commented that strong CYP3A4 inhibitors and P-gp inhibitors may not be 100% overlapping and recommended that Bayer consider prohibiting concomitant use of clinical P-gp inhibitors listed in the FDA drug interaction website (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).
- You propose to administer NT-814 capsules with or without food in the phase 3 trials. Study 814-1-02 showed that a meal decreased the C_{max} and AUC of NT-814 from soft gel capsules 120 mg by 70% and 42%, respectively. Conduct exposure-response analyses and evaluate the food effect on the efficacy endpoints to support your plan of administering your drug product with or without food in your phase 3 trials.

Meeting Discussion:

Bayer noted that, in the phase 2b trial, effective systemic exposure has been demonstrated with the proposed therapeutic dose of 120 mg. In that trial, an evening dosing was applied and no restrictions on intake of food were implemented showing that although no food restrictions were implemented, effective systemic exposures were achieved.

Bayer noted that given the timing of PK samples obtained in SWITCH-1 (the day after the evening dose), the response model was linked to trough

plasma concentrations, in full agreement with the receptor occupancy studies demonstrating that full central receptor occupancy is achieved throughout the dose interval with the concentrations associated with a 120 mg dose. Based on data from Study 814-1-02, trough plasma concentration after 24 h were not reduced after food intake. Bayer is planning a PK study to further investigate the effect of food on the systemic exposure and will use the results to inform the final exposure-response analyses.

Question 6: *The planned primary efficacy endpoints to assess the efficacy of NT-814 for the treatment of VMS are described in the company position below and in more detail in the attached Study Concept (Appendix A: Phase 3 Study Concept). Does the Division agree with the proposed primary efficacy endpoints, and with the approach towards data collection and assessment?*

FDA Response:

We agree that your proposed four co-primary efficacy endpoints comply with the Agency's 2003 draft Hormone Therapy Guidance as follows:

1. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4
2. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12
3. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 4
4. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 12

We recommend electronic data capture using a device with a reminder or alarm function, when appropriate and feasible, because this tends to facilitate subject operation, minimize the extent of missing data, and allows for the collection of other important information (e.g., timestamps for data input). Refer to the 2013 FDA Electronic Source Data in Clinical Investigations Guidance at www.FDA.gov.

We do not distinguish between hot flashes experienced by women during the nighttime hours (commonly referred to as night sweats) and those experienced during the daytime hours. Count and classify the severity (mild, moderate, severe) of all hot flashes experienced by each participating woman during a 24-hour period consistently using the same definitions regardless of whether hot flashes are experienced during the day or in the evening/nighttime hours. Refer you to the Agency's 2003 draft Hormone Therapy Guidance for these definitions.

Provide each final phase 3 protocol and Statistical Analysis Plan for our review and comments.

Question 7: *Bayer also plans to define some key secondary endpoints to fully evaluate the benefit of NT-814 in the postmenopausal VMS patient population. The endpoints are described in the company position and in more detail in the attached Study Concepts. Does the Division have any comments on the selection of these key secondary endpoints* (b) (4) ?

FDA Response:

Results of the proposed *secondary and exploratory objectives/endpoints analyses* (for example, PROMIS SD SF 8b, MENQOL, BDI-II, ISI PGI-C, EQ-5D-5L) will not be considered for purposes of determination of effectiveness of daily oral NT-814 in reducing the frequency and severity of moderate to severe hot flashes for an indication of treatment of moderate to severe vasomotor symptoms due to menopause, (b) (4). See also the Agency's A/IR letter to NeRRe Therapeutics, dated April 4, 2019.

Meeting Discussion:

Bayer:

1. Bayer acknowledged the advice from the Agency (b) (4)

(b) (4)

2. Bayer inquired whether it was the Agency' position that NT-814 should receive as part of 'Class Labeling', the Boxed Warning.

FDA:

1. FDA stated that 'Class Labeling' for an approved vasomotor symptoms indication will include efficacy findings for the four primary vasomotor symptom endpoints and the clinically meaningful reduction in hot flash frequency, and safety findings as

appropriate. Outcomes of secondary endpoints [REDACTED] (b) (4) [REDACTED] are not used to determine the effectiveness of the drug product for a vasomotor symptom indication and are not included in labeling. NT-814 will receive labeling consistent with other drugs approved for the same vasomotor symptom indication.

2. FDA indicated [REDACTED] (b) (4) [REDACTED]
3. FDA indicated that it is premature to discuss the details of potential NT-814 labeling. The Agency will review the data to determine whether all, any, or no elements of the Boxed Warning should be included in labeling of NT-814, should it eventually receive approval.

Statistical

Question 8: *In order to adjust for multiplicity, Bayer plans to test the primary and key secondary endpoints with a sequential testing strategy as outlined in the company position. Does the Division have any comments on this statistical approach?*

FDA Response:

As indicated in our response to Questions 4, your product should achieve statistical significance in all 4 co-primary endpoints.

In addition, as indicated in our response to Question 7, your proposed 3 key secondary endpoints will not be considered for inclusion in product labeling. Therefore, the multiplicity adjustment strategy you propose for “7 hypotheses related to 4 co-primary and 3 key secondary endpoints”, as proposed under “Statistical methods and determination of sample size” in Appendix A: Phase 3 Study Concept, is not applicable.

Planned Safety Assessments

Question 9: *The safety assessments proposed for the planned Phase 3 efficacy and safety studies are outlined in the company position below and described in more detail in the attached Study Concept. These assessments have been selected based on the mechanism of action of NT-814, the findings in pre-clinical safety studies, and the safety findings in the completed clinical studies. Does the Agency have any comments on the proposed selection and/or planned analysis of safety parameters?*

FDA Response:

We do not agree [REDACTED] (b) (4) [REDACTED] as proposed in the Schedule of Activities on page 12 in Appendix A: Phase 3 Study Concept. Perform an endometrial biopsy on any participating non-hysterectomized postmenopausal

woman at Week 52 or Week 12 if she declines participation in the 40-week open-label extension, at early termination (after 10 weeks of trial drug exposure), or for assessment of uterine bleeding in your proposed phase 3 clinical trials. See also our response to Question 5.

Refer any participating non-hysterectomized postmenopausal woman with an endometrial biopsy diagnosis of disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer for standard of care therapy and appropriately follow up the woman to resolution of these histologic findings.

Meeting Discussion:

1. Bayer indicated that the request (b) (4)

[REDACTED]

[REDACTED] Bayer requested that, considering the mechanism of action of NT-814, FDA clarify the expected scientific and/or clinical value, and the benefit:risk justification, of repeating this obtrusive and relatively invasive procedure at end of treatment (or even earlier) in participants without clinical suspicion.

2. FDA clarified that although NT-814 is not an estrogen or an estrogen containing product, neurokinin 3 receptors are found in peripheral tissues, including female reproductive tissues (uterus and endometrium) and bone. The assessment of the effects of NT-814 on endometrial histology is important to the characterization and understanding of the safety of NT-814. Additionally, the SWITCH-1 trial reported two cases of postmenopausal vaginal bleeding. In one case, the endometrial biopsy showed “non-significant hyperplasia”, presumed to be simple hyperplasia without atypia. No endometrial biopsy was performed in the second case of abnormal vaginal bleeding. FDA cannot assume no effect of NT-814 on endometrium without supportive data.

Proposed Safety Database

Question 10: *Bayer plans to conduct a Phase 3 clinical program that includes two (replicate) 1-year randomized, double-blind, placebo-controlled studies that will evaluate the efficacy and safety of extended treatment with NT-814. Together with the existing clinical safety experience in >400 subjects, this program will provide a safety database that meets the requirements of the ICH E1 Guidance.*

Does the Division agree that, in principle, this program would be sufficient to characterize the safety profile of NT-814 as a treatment for moderate to severe vasomotor symptoms associated with the menopause in support of a New Drug

Application?

FDA Response:

No, we do not agree. Postmenopausal women constitute the appropriate exposure population for an indication of treatment of moderate to severe vasomotor symptoms due to menopause. (b) (4)

See also our response to Question 5. We generally follow the ICH E1 guidelines for patient exposure for drug products intended for chronic use. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range anticipated to be efficacious. Note that larger numbers of exposed patients may be recommended prior to approval to further characterize safety signals that emerge during drug development.

Your proposed (b) (4) in your phase 3 trials appears to be low.

Regulatory

Question 11: *Proposed label concepts for the endpoints are presented. Does the Division agree that if the Phase 3 data is supportive,* (b) (4)

FDA Response:

No, we do not agree. (b) (4)

Pediatric Assessment

Question 12: *Based on the indication for postmenopausal VMS, does the Division agree with a request of full waiver for pediatric studies?*

FDA Response:

We cannot agree at this time. See PREA REQUIREMENTS below. Separately submit your initial Pediatric Study Plan (iPSP) to the Agency within 60 days of this teleconference.

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

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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.

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*.¹ 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.²

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.³

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards.

¹ 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>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁴ 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.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 Resources⁶ and the CDER/CBER Position on Use of SI Units for Lab Tests website.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*.⁸

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*, and the associated conformance guide, *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

⁵ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁷ <https://www.fda.gov/media/109533/download>

⁸ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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*.⁹

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

⁹ <https://www.fda.gov/media/85061/download>

endpoint measures, dose, and/or population)

- Other significant changes
- Proposed implementation date

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	December 17, 2020

ATTACHMENTS AND HANDOUTS

See attached Bayer provided handout "BAY 3427080 (NT-814); 17 November 2020, End of Phase 2 – Type B Meeting Response to FDA."

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/

SHELLEY R SLAUGHTER
12/17/2020 03:29:34 PM