

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210557Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 064119

MEETING MINUTES

AMAG Pharmaceuticals, Inc
Attention: Helen Milton, Ph.D.
Vice President, Regulatory Affairs
1100 Winter Street
Waltham, MA 02451

Dear Dr. Milton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bremelanotide (BMT) subcutaneous injection.

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2017. The purpose of the meeting was to discuss your proposed plan for your NDA submission.

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

If you have any questions, call Jeannie Roule, Regulatory Project Manager at (301) 796-3993.

Sincerely,
{See appended electronic signature page}

Christina Chang, M.D., M.P.H.
Clinical 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: Pre-NDA
Meeting Date and Time: September 18, 2017 @ 11:00AM- 12:30 PM
Meeting Location: White oak, Building # 22, Room 1311
Application Number: IND 064119
Product Name: Bremelanotide (BMT) subcutaneous injection
Indication: Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)
Sponsor Name: Palatin Technologies, Inc.
Meeting Chair: Christina Chang, M.D., M.P.H.
Meeting Recorder: Jeannie Roule

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Christine Nguyen, M.D. – Acting Director
Audrey Gassman, M.D. – Deputy Director
Christina Chang, M.D., M.P.H. – Clinical Team Leader
Marcea Whitaker, M.D. – Medical Officer
Jennifer Lawrence, M.D. – Medical Officer
Nneka McNeal-Jackson, M.D. – Medical Officer
Leslie McKinney, Ph. D. – Pharmacology/Toxicology Reviewer
Mukesh Summan, Ph.D. – Supervisor, Pharmacology/Toxicology
Joseph Tinning, M.D., M.P.H. – Associate Director of Biomedical Informatics
Jennifer Mercier – Chief, Project Management Staff
Jeannie Roule – Regulatory Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCPIII)

Doanh Tran, Ph.D. – Clinical Pharmacology Team Leader

Division of Biometrics III (DBIII)

Mahboob Sobhan, Ph.D. – Statistical Team Leader
Jia Guo, Ph. D. – Statistical Reviewer

Clinical Outcome Assessments (COA) Staff:

Selena Daniels, Pharm D. M.S. – COA Team Leader
Wen-Hung Chen, Ph. D. – COA Reviewer

Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA), Office of Pharmaceutical Sciences (OPS)

Mark Seggel, Ph.D. – CMC Lead

Center for Devices and Radiological Health (CDRH)

Carolyn Dorgan, M.S. – Team Lead

Office of New Drug API, Branch II

Lawrence Perez, Ph.D. – Reviewer

Controlled Substance Staff

Katherine Bonson, PhD, Pharmacologist/Reviewer

Divison of Cardiology and Renal Products (DCRP)

Preston Dunnmon, M.D. – Reviewer

Office of Scientific Investigation (OSI)

Roy Blay, Ph.D., Reviewer

Division of Risk Management

Jacqueline Sheppard, PharmD, – Risk Management Analyst

Office of Surveillance and Epidemiolgy (OSE)

Sarah Harris, PharmD, – Safety Regulatory Project Manager

Wei Liu, PhD, Epidemiologist

SPONSOR ATTENDEES

Carl Spana, Ph.D., President & Chief Executive Officer, Palatin

Robert Jordan, Vice President, Clinical Operations and Program Management, Palatin

Stephen T. Wills, Chief Operating Officer, Palatin

Johna Lucas, M.D., Chief Medical Officer, Palatin

Shailesh Vengurlekar, Ph.D., MBA, Vice President, Pharmaceutical Development, Palatin

Julie Krop, M.D., Chief Medical Officer, AMAG Pharmaceuticals

Helen Milton, Ph.D., Vice President Regulatory Affairs, AMAG Pharmaceutical

Qansy Salako Ph.D., RAC, Director Regulatory CMC, AMAG Pharmaceutical

Laura Williams, M.D., M.P.H., SVP Clinical Development, AMAG Pharmaceutical

(b) (4)

BACKGROUND

Palatin Technologies, Inc. (the Sponsor) is developing subcutaneous bremelanotide (BMT) injection for the as-needed treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Bremelanotide, a melanocortin ^(b)₍₄₎receptor agonist, is a synthetic peptide analog of alpha-melanocyte-stimulating hormone.

The Sponsor's stated objectives for this Pre-NDA meeting are to:

- Discuss overall content of the New Drug Application (NDA) (CMC, clinical and non-clinical studies).
- Reach agreement on the proposed analysis strategies for both the integrated summary of safety (ISS) and integrated summary of efficacy (ISE).
- Discuss and/or obtain feedback on the DRAFT proposed bremelanotide subcutaneous injection package insert (label).
- Discuss timing of the clinical pharmacology studies, including human abuse liability in conjunction with the FDA Controlled Substances Staff.
- Discuss data elements and statistical plans.

The Sponsor informed the FDA that a partnership agreement with AMAG Pharmaceuticals (AMAG) would be formalized shortly. AMAG intends to file a NDA for BMT in the first quarter of 2018.

DISCUSSION AND QUESTIONS

Preliminary responses were provided to the Sponsor on September 14, 2017, in response to the questions posed in the Sponsor's meeting package provided to the Division on August 17, 2017. The Sponsor's questions are presented below in **bolded** text, followed by the Division's responses in regular text.

In addition, on September 18, 2017, the Sponsor submitted (via email) a slide presentation that included additional questions and clarification of the Division's responses to Questions 4, 5, 7 and 13. Additional meeting discussion regarding these four questions is shown in *italicized* text. No meeting discussion occurred for the remainder of the questions posed by the Sponsor and no discussion took place concerning the Division's additional clinical comments. The slides are attached in their entirety at the end of this document.

CLINICAL

Adequacy of Data to Support Proposed Indication

Question 1

Palatin believes that the clinical data package is adequate for submission of the NDA to support bremelanotide for the indication of HSDD in premenopausal women.

Does the Agency concur?

FDA Response:

Based on the information presented in the briefing package, you have conducted two randomized, placebo-controlled Phase 3 trials and other supportive studies.

Whether the body of clinical data will be acceptable for submission will be determined following our filing review.

Integrated Summary of Efficacy (ISE) Strategy

Question 2

Palatin proposes to provide both individual primary pivotal study efficacy results and to present integrated efficacy data from the two Phase 3 pivotal studies (core studies) BMT-301 and BMT-302 (b) (4)

Is this acceptable to the Agency?

FDA Response:

No. (b) (4)

(b) (4)

Under 21 CFR 314.50(d)(5)(v), the ISE must include:

- An integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication;
- Evidence that supports the dosage and administration section of the labeling, including support for the recommended dosage and dose interval;
- Effectiveness data analyzed by sex, age, and racial subgroups, identifying any modifications of dosing for specific subgroups;
- Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease.

We recommend that you refer to the 2015 Guidance for Industry: Integrated Summary of Effectiveness (at <https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf>) for the format and content of the ISE.

Integrated Summary of Safety (ISS) Strategy

Question 3a

Does the Agency agree with the pooling strategy for the ISS?

FDA Response:

No. In general, pooling of studies may obscure meaningful differences and it is important that you explore the range of incidences across studies/clinical trials being pooled.



Question 3b

Does the Agency agree with the proposed approach regarding  **(b) (4)**

FDA Response:



Question 3c

Does the Agency agree that our proposal for presentation of CRFs and patient narratives is adequate?

FDA Response:

The proposal appears adequate. We request that you also provide patient narratives for those with liver injury as well as outlier blood pressure data [systolic blood pressure (SBP) >160 mmHg or change >20 mmHg, diastolic blood pressure (DBP) >100 mmHg or change >20 mmHg] or heart rate values (HR >100 beats per minute or change >20 beats per minute).

Question 3d

Does the Agency agree with the planned presentation of the ISE, ISS, SCE and SCS, as described in the Briefing Document?

FDA Response:

No. See responses to Questions 2, 3a above.

Per the 2015 Guidance for Industry: Integrated Summary of Effectiveness (link provided above), the summary of clinical efficacy (SCE) and Integrated Summaries (ISE/ISS) may contain the same information only in usual cases, such as having only a single trial, or a number of small studies, to serve as primary support for efficacy and safety. Such is not the case in your planned NDA.

The ISS should also include other studies (e.g., nonclinical studies, clinical pharmacology studies, human factor studies, etc.) that are relevant to safety.

Analysis of Clinical Benefit for BMT-301 and BMT-302

Question 4

Palatin believes that the establishment of the Independent Anchor Assessment Committee, and their review and recommendations addresses the Agency's request for anchoring of efficacy data in order to determine clinical benefit.

Does the Agency agree?

FDA Response:

No. Additional information is needed for us to determine whether the Independent Anchor Assessment Committee (IAAC) review and recommendations have addressed our concerns regarding how the thresholds for meaningful change were established.



Additional Discussion:

Palatin believes that the establishment of the Independent Anchor Assessment Committee (IAAC), and their review and recommendations addresses the Agency's request for anchoring of efficacy data in order to determine clinical benefit. The IAAC carried out the following:

1. *Identified relevant anchors from patient-reported outcome (PRO) measures included in Studies 301 and 302:*
 - *Relevant concept measured (i.e., sexual desire, distress, sexual satisfaction, etc.)*
 - *Relationship with targeted PRO endpoints (i.e., FSFI-D, FSDS-Q13)*
 - *Selected 3 static anchors and GAQ3 (treatment benefit; questions and cutoffs for "responder" (i.e. $GAQ3 \geq 5$))*
 - *EDQ-Q9: Satisfaction with level of desire and interest*
 - *FSDS-DAO item 1: Distressed about sex life*
 - *FSFI-Q16: Satisfied with overall sex life*
2. *Conducted analyses comparing baseline to End of Study (EOS) changes in FSFI-D and FSDS-Q13 scores by 4 selected anchors:*
 - *ANOVAs with various anchor thresholds*
 - *Cumulative distribution functions*

3. *Determined clinically meaningful thresholds for changes in FSFI-D and FSDS-Q13 scores based on the totality of evidence from anchors-based analyses:*
 - *Reviewed summaries of anchor-based analysis results*
 - *Normative evaluation of effect sizes (i.e., distribution-based methods)*
 - *Considered clinical perspective in understanding treatment benefits*

4. *Conducted further evaluation of anchors and anchor-based thresholds based on post-study exit survey data to obtain:*
 - *Further supportive evidence for identified thresholds for selected anchors*
 - *Further supportive psychometric evidence for clinically meaningful thresholds for changes in FSFI-D and FSDS-Q13 scores*

The FDA stated that, based on information provided in the meeting package, it was unclear how the IAAC and the Sponsor came to their conclusions. To assist the FDA with their review, the Sponsor should provide additional details to describe the IAAC's decision-making process and clarify the rationale supporting the IAAC's conclusions. Further, since patients' perspective can inform the determination of threshold(s) for meaningful change in assessments, the Sponsor should submit the final report from the patient exit interview study.

The Sponsor informed FDA that they plan to submit to the IND additional psychometric information, including:

- *Amended Anchor Assessment report*
 - *Expanded methods section*
 - *Additional Exit Survey questions/anchors analyses, using the post-study exit survey data to more completely define the responses for the other anchors [FSFI Question 16, Female Sexual Distress Scale-Desire, Arousal, Orgasm, (FSDS-DAO) Question 1, Elements of Desire Questionnaire (EDQ) Question 9], similar to what was performed for General Assessment Questionnaire (GAQ) Question 3*
- *EDQ Supplemental Analysis report*

CLINICAL PHARMACOLOGY

Blood Pressure Effects

Question 5

Palatin believes that the comments and recommendations noted in the March 3rd, 2017 Advice/Information Request letter from FDA have been adequately addressed. It is Palatin's position that



Does the Agency agree?

FDA Response:

We continue to recommend that you perform the ambulatory blood pressure monitoring (ABPM) trial as discussed in the Advice letter dated March 3rd, 2017. However, (b) (4)



Additional Discussion:

The Sponsor referenced (b) (4) clinical studies (outlined below) to support their position that the comments and recommendations noted in the March 3rd, 2017 Advice/Information Request letter from FDA have been adequately addressed:

- Study 54 – Phase 2B
 - Three 24-hour ABPM periods after single dose
 - Placebo (V2)

- *Randomized study drug (V5)*
- *Randomized study drug (V7)*
- *3-month Randomized Treatment period post 2nd Randomized ABPM period*
 - *At-home, as needed dosing*

(b) (4)

- *BMT-301 & BMT-302 – Phase 3 trials*
 - *Sparse BP post in-clinic doses (placebo & randomized)*
 - *Monthly BPs obtained during in-clinic visits*

(b) (4)

Time to Onset and Duration of Action

Question 6

Section 2.1, Full Prescribing Information, Recommended Dosage

Does the Agency agree that the rationale for proposed dosing instructions provided in the draft label included in this Briefing Document is adequate?

FDA Response:

No. The time to onset in labeling should be based on the dosing instruction used in the pivotal Phase 3 studies, i.e., “at least 45 minutes before anticipated sexual activity.” The current

New Clinical Pharmacology Studies

Question 7

Does the Agency agree that the completed and to-be-completed clinical pharmacology studies are sufficient for NDA filing?

FDA Response:

Whether these clinical pharmacology studies will be adequate to support an NDA submission will be determined following our filing review. We have the following recommendations for your submission:

- Clarify if there were formulation changes to the formulation intended for subcutaneous injection during drug development.
- Provide information on the induction effect of BMT on CYP enzymes.
- Clarify whether immunogenicity assessment has been conducted for BMT.

We also have the following recommendations related to your drug-drug interaction (DDI) studies:

- As noted in our March 3, 2017 advice letter, DDI studies in your clinical program would be helpful if there are concerns for pharmacokinetic or pharmacodynamic interactions with specific drugs that are commonly used in the population likely to use your product, if it is approved. On their own, these single-dose or short-term DDI studies are unlikely to adequately address concerns relating to long-term cardiovascular safety. Specifically, these studies are unlikely to mitigate concerns stemming from concomitant use of BMT in women with underlying medical conditions and require chronic medical therapies such as antihypertensive, lipid-lowering, anti-diabetic agents, etc.
- Regarding Study BMT-118 (metformin/hypoglycemic study): As the purpose of the study is to determine whether there is an interaction between BMT and hypoglycemic medication, the patient population should be Type 2 diabetics and not normal subjects. The anti-diabetic agent used should be a sulfonylurea or other drug with a propensity for hypoglycemia. Metformin is not an acceptable choice for this study because it is not known for causing hypoglycemia in either patients with type 2 diabetes or in normal subjects.
- Regarding Studies BMT-101 and BMT-103:
 - Labeling will likely reflect a limitation of use excluding patients with hypertension or elevated blood pressures as your studies did not include evaluation of these patients
 - Flag outliers in Studies BMT-101 and BMT-103 as follows: SBP >180, SBP >160, SBP >140, change in SBP >30, change in SBP >20, change in SBP >10, DBP > 120, DBP > 100, DBP >90, change in DBP >20, change in DBP >10, HR >120, HR >100, change in HR >30, and change in HR >20.
 - Provide a table describing the blood pressure shifts during treatment and include a baseline column indicating absolute change from baseline.
- Update all Informed Consent Forms (ICF) for ongoing or to-be-conducted studies to clarify that the liver injury case could “possibly be related” to BMT.

We also recommend that you update the status (e.g., ongoing, completed) of your other Phase 1 studies.

Additional Discussion:

The Sponsor clarified that no formulation changes for the subcutaneous injection drug product have been made.

The FDA requested information concerning immunogenicity studies; the Sponsor stated that they will provide that information.

The Sponsor provided a status update on their ongoing Phase 1 PK studies per Division request (below) and inquired if the Agency agreed that the completed and ongoing clinical pharmacology studies are sufficient for NDA filing.

BMT-101	Anti-HTN DDI	Ongoing
<i>BMT-103</i>	<i>SSRI/SNRI/Contrave DDI</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-104</i>	<i>OC DDI</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-105</i>	<i>DDI w/ meds that increase BP</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-107</i>	<i>ADME</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-115</i>	<i>Renal Impairment</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-116</i>	<i>Hepatic impairment</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-117</i>	<i>Human Abuse Liability</i>	<i>Fully Enrolled; Report Pending</i>
<i>BMT-118</i>	<i>Hypoglycemic (Metformin) DDI</i>	<i>Fully Enrolled; Report Pending</i>

The Sponsor presented available data in Type 2 diabetics taking bremelanotide and inquired about FDA's rationale in a study in Type 2 diabetics taking sulfonylurea. The Sponsor stated that there were a total of 30 female subjects with diabetes enrolled in their Phase 3 program for HSDD. However, (b) (4)

BMT was well-tolerated with one case of hypoglycemia reported in a patient receiving placebo.

(b) (4)

The Sponsor questioned the feasibility of giving placebo to women whose diabetes is controlled and inquired as to whether a study in healthy individuals would be preferred. The Sponsor inquired if the FDA is interested in the change in the glucose level and not the actual hypoglycemic episode; they also sought clarification as to what specific PK data will be necessary and whether BMT's effect on PK of all sulfonylureas should be evaluated.

The FDA responded that safety data will need to be collected for both laboratory and clinical evidence of change in blood glucose/hypoglycemia. The FDA further clarified that it is interested in the pharmacodynamic (PD) interactions, rather than the PK interactions. As information on the effect of BMT in patients with diabetes is preferred, the FDA continues to recommend that the Sponsor enroll patients with diabetes instead of healthy subjects in such a trial, if one is still planned.

Post-meeting comments:

Regarding DDI with oral hypoglycemic therapy:

- *A single dose exposure of BMT with a concomitant hypoglycemic agent in a DDI study may be of limited value. We request clarification on the following:*

(b) (4)

2) your position on whether a new DDI study using a different hypoglycemic agent (i.e., sulfonylurea) is or is not necessary, and a justification for the population to be enrolled (type 2 diabetics or non-diabetics) if a study is planned, and 3) if such a study is conducted, describe the plan for evaluation of absolute change in blood glucose and symptomatic hypoglycemic events.

-

(b) (4)

Regarding immunogenicity:

- *In your NDA submission, provide a risk assessment of the immunogenicity of BMT because even peptides as short as 7 – 8 amino acids can be immunogenic. BMT shares sequence homology with the endogenous human peptide hormone alpha-melanocyte-stimulating hormone (α -MSH). Therefore, there is a risk that anti-BMT antibodies could cross-react with and inhibit the function of α -MSH. In your NDA submission provide an assessment of the risk that anti-BMT antibodies will form in treated subjects and the potential impacts of anti-BMT antibodies on product safety and efficacy. Support your risk assessment with in silico and, if indicated by the in silico results, in vitro data.*

PHARMACOLOGY/TOXICOLOGY

Question 8

Does the Agency agree that the completed and ongoing nonclinical studies are sufficient for NDA filing?

FDA Response:

Yes. However, adequate bridging from the drug substance used in the pivotal studies to the current drug substance will be a review issue. The following should be included in the NDA submission:

- Provide a table that lists the lot numbers of the drug product used in the pivotal nonclinical studies. Include impurity profiles on the lots used and state clearly whether impurities have been qualified.
- Include studies that established the analytical methods for measuring drug substance in the plasma from nonclinical species in your NDA submission.
- Include a nonclinical summary should state clearly whether a nonclinical study supporting this NDA replaces one that was conducted at an earlier date under other INDs for this drug.

If possible, submit electronic study reports to the IND prior to NDA submission.

QUALITY (CMC)

Key Raw Materials

Question 9

Palatin believes that adequate controls are in place for all starting materials used in the manufacture of bremelanotide drug substance.

Does the Agency agree that the currently identified key raw materials are adequately controlled?

FDA Response:

The listed specifications for the (b) (4) amino acids and other key raw materials are reasonable for an NDA submission.

Drug Product Process Validation Batches

Question 10

Palatin utilized three separate lots of Drug Substance to manufacture three separate Drug Product Registration batches to support our NDA for bremelanotide. Palatin believes that a strategy of using a single well-characterized batch of recently synthesized bremelanotide Drug Substance to manufacture the three bremelanotide Drug Product Process Validation batches is appropriate.

Does the Agency agree that a single lot of Drug Substance is acceptable to manufacture 3 process validation lots of separate drug product lots during process validation to support the NDA for bremelanotide?

FDA Response:

We cannot comment on your query without the evaluation on the registration batch development information including the control of active pharmaceutical ingredient (API), in-process testing data, batch release and stability results. In principle, one API lot for three drug product batches at process validation stage may be sufficient provided that the adequacy of process development and API control is demonstrated.

Drug Product Stability

Question 11

Palatin believes that the data from the registration batches is adequate for approval and establishment of the shelf-life for the final product. Does the Agency agree?

FDA Response:

Stability data obtained on the registration batches described in the meeting package appears suitable for use in the establishment of an initial commercial shelf-life of the final product. However, confirm that the to-be-marketed final product is identical to the registration product (i.e., there are no significant changes in manufacturing process, manufacturing site, container closure system, etc.).

Drug Product Batch Size and Validation

Question 12

Palatin believes that the proposed process validation and stability strategy is adequate to support commercial production.

Does the Agency agree?

FDA Response:

The adequacy of the proposed strategy is a review issue. We can only make decision based on the knowledge and experience gained throughout the drug product development (formulation and process). Please note that the process validation plan should be finalized post approval and should be in compliance with the approved process and control strategy.

For additional guidance refer to following:

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, September 2004, at

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf> and

Process Validation: General Principles and Practices, January 2011, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

Autoinjector Pen

Question 13

Palatin believes that the eCTD approach described for the Autoinjector Pen is adequate to support approval. Does the Agency agree?

FDA Response:

You have proposed to include the container closure information for the prefilled syringe (PFS) and autoinjector (final product) in module 3.2.P.7. You have further stated that the device component, manufacturing, and controls will be presented within module 3.2.R. Your proposal seems a reasonable location for the device information.

We recommend that you include the following in your future marketing application:

- For the specific delivery device(s) you intend to market, your marketing submission should include the following design documentation for each device:
 - The design input and design output documentation, including requirements specifications, drawings, etc.
 - Design verification and validation data confirming that the finished product meets the design output specifications.
 - Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.
- We recommend that you address the recommendations contained in the relevant FDA guidance documents for the devices, such as Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products;
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

In addition, please ensure to include the essential performance specifications for the device in Section 3.2.P.5.1 Specifications and include the essential performance specifications within the stability testing in Section 3.2.P.8. Finally, please ensure that both biocompatibility and shipping studies are included within the submission.

Additional comments regarding the Human Factor study and Instruction for Use (IFU) may be provided in the final Meeting Minutes as a Post-Meeting Addendum.

Additional Discussion:

Palatin believes that the eCTD approach described for the Autoinjector Pen is adequate to support approval.

The Sponsor further clarified that (b) (4) Device and (b) (4) syringe are platform devices and are being used for BMT injection. For the delivery device the Sponsor intends to market, the (b) (4) syringe is housed inside the (b) (4) autoinjector. As the pre-filled syringe was part of the design verification/validation for the device, the Sponsor proposed to include Design History File for the delivery device (inclusive of design input, design output, design verification, validation, manufacture, risk analysis, etc.) in appropriate sections of the NDA.

The Sponsor inquired if the proposed additional specifications/tests along with the current specifications/tests would be adequate for NDA filing.

The FDA remarked that the Sponsor's plan appears appropriate and noted that all testing should have been done on the to-be-marketed device.

The Sponsor also noted that the drug is predominantly (b) (4) and they plan to include more specs for any future batches.

The FDA remarked that the information appears to be adequate for filing and recommended that the Sponsor ensure dose accuracy is clearly defined in the submission. Pending filing review, the FDA may have additional questions or comments.

Post-meeting comments:

Additional comments regarding the Human Factor study and Instruction for Use (IFU) will be provided in a separate advice letter.

POTENTIAL ABUSE LIABILITY PROGRAM

Question 14

The proposed Abuse Liability program described in the May 25, 2017 submission (Serial No. 115) is intended to supply adequate information for NDA filing. Palatin believes that the proposed abuse liability program should supply adequate data for NDA filing.

Does the Agency agree?

FDA Response:

It appears from your submission that a human abuse potential study (BMT-117, based on revisions we proposed in the May 3, 2017 advice letter) is currently being conducted. Data from that study, in conjunction with data from studies evaluating receptor binding, general behavior, self-administration, conditioned place preference, physical dependence, and abuse-related adverse events in clinical studies, will be sufficient for an abuse assessment of bremelanotide.

We also provide responses to questions you posed in the May 25, 2017 submission regarding the proposed abuse liability program below.

Question 14 a

Does the Agency agree with the design of the Rat Drug Discrimination Study as set forth in the study synopsis provided in this Briefing Document, including [questions regarding use of FR10, 15 minute pretreatment time, and dose range of test drug]?

FDA Response:

Yes, we agree that the study is generally well designed with regard to the schedule of reinforcement (Question #1b in your meeting package), the pretreatment time (Question #1c) and the dose range of bremelanotide (Question #2). However, drug discrimination is highly reliant on a drug's mechanism of action in order for there to be generalization between the training drug and the test drug. Given that bremelanotide is a melanocortin receptor agonist, and that there are no drugs with this mechanism that are scheduled under the Controlled Substances Act, there is no clear training drug for a drug discrimination study with bremelanotide (including your proposed training drug, amphetamine, in Question #1a).

Thus, it will not be necessary to conduct a drug discrimination study with bremelanotide.

Question 14 c (Question 3 in your meeting package)

Does the Agency agree with the design of the Rat Self-Administration Study as set forth in the study synopsis provided with the May 25, 2017 submission, including the following specific questions? Does the Agency agree to the use of cocaine as a training drug and amphetamine as a reference drug in the self-administration study?

FDA Response:

Yes, we agree that cocaine may serve as the training drug and that amphetamine can serve as the positive control drug.

Question 14 d (Question 3 a in your meeting package)

Does the Agency agree that the bremelanotide dose levels are acceptable?

FDA Response:

No. (b) (4)

[Redacted]

Question 14 e (Question 3 b in your meeting package)

(b) (4) **Does the Agency agree that this is sufficient, given that bremelanotide is a relatively short acting compound?**

FDA Response:

(b) (4)

Question 14 f (Question 3 c in your meeting package)

Is the group design of 7 male and 7 female rats per dose level of bremelanotide trained to self-administer, sufficient for testing the potential self-administration of bremelanotide?

FDA Response:

Yes, that number is high enough to determine sex differences between the two subgroups, and also large enough when the two groups are combined for an overall assessment.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

Question 15

Does the Agency agree that the bremelanotide NDA will qualify for a waiver of the pediatric study requirement as supported in our Agreed Initial Pediatric Study Plan submitted December 13, 2016 (Serial No. 094)?

FDA Response:

Your request for a full pediatric waiver has been reviewed by the Pediatric Review Committee (PeRC), which preliminarily concurred with your request. A final PeRC determination will be made during the NDA review.

ADVISORY COMMITTEE MEETING

Question 16

The NDA for BMT provides safety and efficacy data from two large, well-controlled pivotal Phase 3 studies (BMT-301 and BMT-302) of subcutaneous bremelanotide versus placebo in premenopausal women with HSDD.

Does FDA anticipate convening an advisory committee meeting for discussion of the bremelanotide NDA for the HSDD indication?

FDA Response:

Yes. At this time, we anticipate convening an advisory committee meeting to discuss this application for the HSDD indication.

Additional Clinical Comment:



(b) (4)

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 14, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

- The content of a complete application was discussed. A complete application should be submitted for filing review. Late submission of application components will not be accepted without prior agreement with the Division.
- 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.
- A preliminary discussion on the need for a REMS was not discussed during the meeting.

Post Meeting comment:

Whether there is a need for a risk evaluation and mitigation strategy (REMS) will be determined during the review of your application. We would consult the Office of Surveillance and Epidemiology (OSE) if we determine that a REMS will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be.

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>

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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>.

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.				

Office of Scientific Investigations (OSI) Requests

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

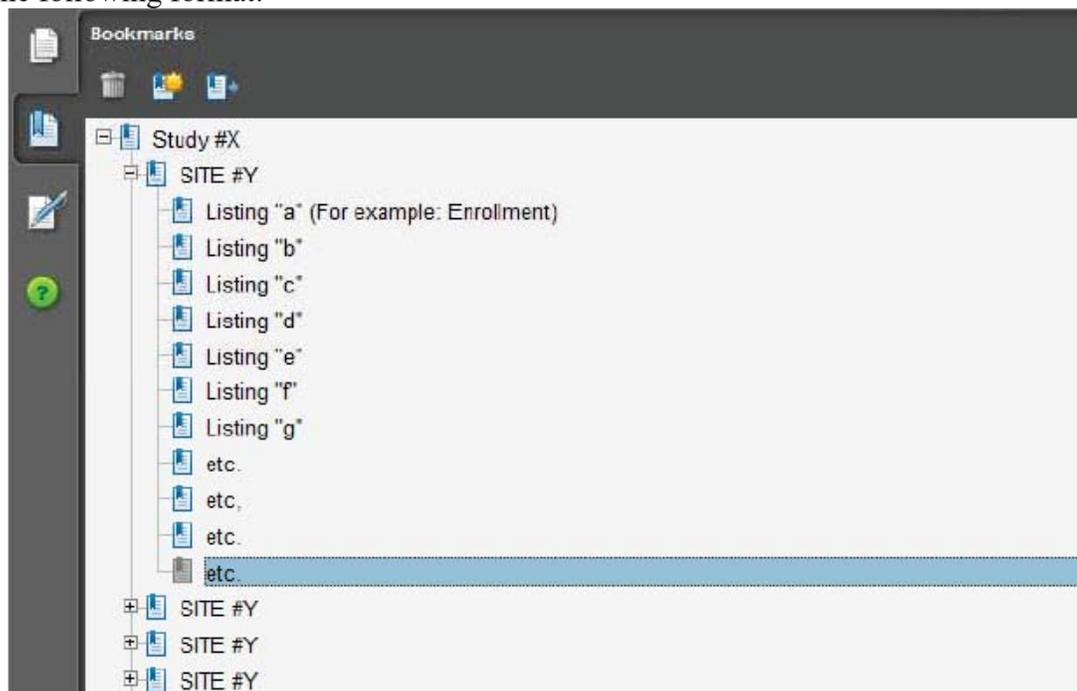
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number

- b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

APPEARS THIS WAY ON ORIGINAL

Attachment 1

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

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

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The meeting minutes will be sent to the Sponsor within 30 days of the Industry meeting.

ATTACHMENTS AND HANDOUTS

See attached.

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immediately following this page

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

/s/

CHRISTINA Y CHANG
10/17/2017



IND 064119

MEETING MINUTES

Palatin Technologies, Inc.
Attention: Jeff Edelson, M.D.
Chief Medical Officer
4-B Cedar Brook Drive
Cranbury, NJ 08512

Dear Dr. Edelson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Bremelanotide (BMT) Subcutaneous Injection.

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2013. The purpose of the meeting was to discuss your End of Phase 2 development plan.

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

If you have any questions, call Charlene Williamson, Regulatory Project Manager at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Christina Chang, M.D., M.P.H.
Acting Clinical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

11 Pages have been Withheld in Full as b4 (CCI/TS)
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA Y CHANG
04/30/2013