

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210557Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 17, 2019

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for VYLEESI (bremelanotide injection), for subcutaneous use

NDA: 210557

In response to DBRUP's consult request dated April 6, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for VYLEESI (bremelanotide injection), for subcutaneous use.

PI and PPI/IFU: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DBRUP on June 6, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI/IFU will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 15, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 17, 2019

To: Hylton Joffe, MD
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): VYLEESI (bremelanotide injection)

Dosage Form and Route: for subcutaneous use

Application Type/Number: NDA 210557

Applicant: AMAG Pharmaceuticals Inc.

1 INTRODUCTION

On March 23, 2018, AMAG Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application (NDA) for VYLEESI (bremelanotide injection), for subcutaneous use. The proposed indication for VYLEESI (bremelanotide injection), for subcutaneous use is for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to 1) a co-existing medical or psychiatric condition, 2) problems with the relationship, or 3) the effects of a medication or drug substance. VYLEESI (bremelanotide injection), for subcutaneous use is not indicated for the treatment of HSDD in postmenopausal women, men, or to enhance sexual performance.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on April 13, 2018 and April 6, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for VYLEESI (bremelanotide injection), for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft VYLEESI (bremelanotide injection), for subcutaneous use PPI and IFU received on March 23, 2018 and received by DMPP on June 6, 2019.
- Draft VYLEESI (bremelanotide injection), for subcutaneous use PPI and IFU received on March 23, 2018, and received by OPDP on June 13, 2019.
- Draft VYLEESI (bremelanotide injection), for subcutaneous use Prescribing Information (PI) received on March 23, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on June 6, 2019.
- Draft VYLEESI (bremelanotide injection), for subcutaneous use Prescribing Information (PI) received on March 23, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on June 6, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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06/17/2019 10:00:04 AM

LASHAWN M GRIFFITHS
06/17/2019 10:05:02 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 30, 2019

Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

Application Type and Number: NDA 210557

Product Name and Strength: Vyleesi (bremelanotide) injection, 1.75 mg/0.3 mL

Applicant/Sponsor Name: AMAG Pharmaceuticals, Inc.

FDA Received Date: April 15, 2019

OSE RCM #: 2018-634-2

DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS

DMEPA Team Leader: Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised Instructions for Use (IFU), container label, and carton labeling for Vyleesi(bremelanotide) injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^{ab}

2 CONCLUSION

As currently presented, the format for the expiration date on the revised container label and carton labeling for Vyleesi(bremelanotide) injection is not defined. See Section 3 for our recommendations.

^a Whaley, E. Review of Revised Label and Labeling Memorandum for Vyleesi (NDA 210557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 04. RCM No.: 2018-634-1.

^b Whaley, E. Human Factors Study Report and Labels and Labeling Review for Vyleesi (NDA 210557), Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 30. RCM No.: 2018-634 and 2018-912.

3 RECOMMENDATIONS FOR AMAG PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of NDA 210557:

- A. As currently presented, the format for the expiration date on the revised container label and carton labeling for your proposed bremelanotide injection is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 15, 2019

Instructions for Use (not pictured) Available in EDR via:

\\cdsesub1\evsprod\nda210557\0052\m1\us\114-label\1141-draft-label\draft-carton-container-labels-patient-brochure.pdf

Container labels

(b) (4)



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04/30/2019 03:30:04 PM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 22, 2019

To: Hylton Joffe, M.D., M.M.Sc., Director
Division of Bone, Reproductive and Urologic Products

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Bremelanotide (Vyleesi)
NDA 210557 (IND 64119)
Indication: treatment of hypoactive sexual desire disorder (HSDD)
Dosage: 1.75 mg, s.c., once within a 24-hour period
Sponsor: Palatin Technologies, Inc.
PDUFA Goal Date: June 23, 2019

Materials reviewed: NDA 210,557

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1. BACKGROUND

This memorandum responds to a CSS consult request from the Division of Bone, Reproductive and Urologic Products to evaluate abuse-related preclinical and clinical data submitted by Palatin Technologies, Inc., for bremelanotide (Vyleesi) under NDA 210557.

Bremelanotide (previously known as PT-141) is a new molecular entity peptide analog of α -melanocyte-stimulating hormone (α -MSH) that acts as a non-selective agonist of melanocortin receptors, including MC1, MC3, MC4, and MC5 subtypes.

The neuropeptide hormone, α MSH, is expressed in the hypothalamic loci with projections to various brain sites. The melanocortin system plays a role in sexual function, the regulation of feeding and obesity, and regulation of immune response.

The Sponsor proposes subcutaneous administration of bremelanotide at 1.75 mg (once within a 24-hour period) as a treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women. The Sponsor states that bremelanotide should not be scheduled under the Controlled Substances Act, based on a lack of abuse-related signals in preclinical and clinical studies with bremelanotide.

2. CONCLUSIONS

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 210557 for bremelanotide and concludes that the drug has negligible abuse potential. This conclusion is based on the data described below:

- In receptor binding studies, bremelanotide did not have affinity to any receptor sites currently associated with abuse potential.
- In tests of general behavior, bremelanotide produced some signs of CNS activity, but these behavioral changes were transient and not inherently indicative of abuse potential.
- In a drug discrimination studies in rats, intravenous administration of bremelanotide did not produce full generalization to the amphetamine interoceptive cue. This shows bremelanotide does not produce sensations similar to a stimulant.
- In a self-administration study in rats, the single doses of bremelanotide to which animals had access for self-administration were too high because a single self-administration would produce suprathreshold plasma levels. Under these conditions, it is not possible to determine if the lack of animal self-administration is because the drug does not have rewarding properties or instead is because the animals are satiated by rewarding effects from a single drug self-administration. The Sponsor had been informed by CSS prior to study initiation that they should

utilize doses for self-administration that produced subtherapeutic plasma levels. If a drug has rewarding properties, continued self-administration will produce dose accumulation to therapeutic or suprathreshold plasma levels. Thus, this study is not valid for evaluating whether bremelanotide produces rewarding effects that are reinforcing.

- In a physical dependence study in rats, 14 days of continuous intravenous administration of bremelanotide did not produce any withdrawal signs during drug discontinuation. This suggests that bremelanotide does not produce physical dependence.
- In a human abuse potential study, subcutaneous administration of bremelanotide at therapeutic (1.75 mg) and suprathreshold (3.5 and 5.25 mg) doses to stimulant abusers produced responses on positive subjective responses such as Drug Liking, Overall Drug Liking, Take Drug Again, Good Effects that were statistically indistinguishable from responses produced by placebo. Bremelanotide was also not identified as being similar to known drugs of abuse and did not produce abuse-related adverse events. In contrast, oral phentermine (45 and 90 mg) produced statistically significant increases in these positive subjective measures compared to placebo and was identified as being similar to known stimulants. These data demonstrate that bremelanotide does not produce subjective responses that are predictive of abuse potential.
- No abuse-related adverse events (including euphoria-related ones) were reported in Phase 1 or Phase 2/3 clinical safety studies. This demonstrates that bremelanotide does not produce abuse-related signs.

3. RECOMMENDATIONS

Based on the CSS determination that bremelanotide has negligible abuse potential, that it will have currently accepted medical use upon NDA approval, and that it does not appear to produce physical dependence:

- a) CSS concludes that bremelanotide should not be recommended for control under the Controlled Substances Act.
- b) CSS recommends Section 9 (Drug Abuse and Dependence) not be included in the drug label.

4. DISCUSSION

A. Chemistry of Bremelanotide

Bremelanotide is a peptide analog of α -melanocyte-stimulating hormone (α -MSH) with the following structural formula: Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys-OH)(Ac-Nle₄, Asp₅, D-Phe₇, Lys₁₀)-cyclo-a-MSH (4-10). The IUPAC condensed name is: Ac-Nle-Asp(1)-His-D-Phe-Arg-Trp-Lys(1)-OH.

Bremelanotide (USAN name) is a new molecular entity identified by CAS registry number: 189691-06-3. It is a white powder has a molecular formula of C₅₀H₆₈N₁₄O₁₀ and a molecular weight of 1025.182.

B. Preclinical Abuse-Related Studies with Bremelanotide

1. Receptor Binding Studies with Bremelanotide (Study #5040a)

In receptor binding studies with bremelanotide, Bremelanotide has high affinity for the melanocortin receptors subtypes MC1R and MC4R. However, there was no significant affinity of bremelanotide for sites associated with abuse potential, including opioid, GABA, dopamine, serotonin, or NMDA receptors, and the dopamine transporter.

2. Animal Behavioral Studies

a. General Behavioral Observations (Study #1486/PAL)

Male rats (n = 5/treatment) were evaluated in the Irwin test following acute administration of bremelanotide (10, 75 and 300 μ g/kg, i.v.) or vehicle. Detailed observations were performed at 0.5, 1, 4 and 24-hours post-dose.

All three tested doses tested produced mild hyperactivity, piloerection, fear, loss of muscle tone, reactivity to touch, stereotypies, ptosis, and grooming, with peak behavioral responses at 30 and 60 minutes after bremelanotide administration. The observation of hyperactivity suggests that bremelanotide might have slight stimulant effects and that a stimulant could be an appropriate positive control for the abuse-related animal studies.

b. Abuse-Related Behavioral Studies

i. Drug Discrimination Study (Study #8360928)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals

serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq 75\%$ on the bar associated with the training drug.

On September 13, 2017, CSS informed the Sponsor that:

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

However, the Sponsor proceeded with the drug discrimination study and submitted the study report in the NDA. In this study male and female rats (8-10/sex) were trained to discriminate amphetamine (0.3 mg/kg, s.c.) from placebo using an FR10 schedule of reinforcement. Rats were then challenged with amphetamine (0.1, 0.3, and 1.0 mg/kg, s.c.), bremelanotide (0.5, 2.0, and 3.5 mg/kg), and placebo.

The highest dose of bremelanotide produces 3 to 5 times the plasma level of the target clinical efficacious dose, while the lowest dose of 0.5 mg/kg produces plasma exposure equivalent to the maximum plasma level observed for the target clinical efficacious dose. The pretreatment times for the training sessions with amphetamine were 15 minutes while the pretreatment times for the test sessions was 5 minutes.

The outcome data showed that amphetamine produced a dose-dependent generalization to the amphetamine cue, with full generalization ($>75\%$) at the two highest doses of 0.3 and 1.0 mg/kg. Each dose of bremelanotide tested produced generalization to amphetamine of $<20\%$, indicating that bremelanotide produced effects most similar to placebo.

Thus, bremelanotide does not produce effects similar to that of amphetamine.

(b) (4)



c. Physical Dependence Study in Rats (Study # 996-057)

Male and female rats (n = 8/sex/treatment) received continuous 24-hour intravenous infusions of the study treatments for 14 days. The treatments included: bremelanotide (20 and 200 µg/kg/hour), amphetamine (6 mg/kg/day), and placebo (0 µg/kg/hour). The Sponsor provided the following justification dose levels: “The bremelanotide dose levels selected for this study were based on achieving therapeutic plasma levels in the rat at the low infusion rate, and a higher infusion rate that was both a multiple of the low dose and also would result in a steady-state bremelanotide plasma concentration equal to or greater than that observed for the C_{max} values in human studies after a single subcutaneous administration of the efficacious dose of 1.75 mg.”

Evaluations were conducted at baseline and on Day 16, 17, 18, 19, and 20 following drug discontinuation on Day 15. Body weight was evaluated in addition to the following:

Functional Observational Battery

- Thermal Response
- Mean Forelimb Grip Strength
- Mean Hindlimb Grip Strength
- Body Weight
- Body Temperature
- Rearing
- Defecation
- Urination
- Mean Hindlimb Splay
- Posture Scores Test
- Ease of Removal
- Handling Reactivity
- Lacrimation

Palpebral Closure
Piloerection
Exophthalmus
Salivation
Clonic Movements
Tonic Movements
Gait
Mobility
Arousal
Vocalizations
Respiration
Stereotypy
Bizarre Behavior
Approach Response
Touch Response
Click Response
Tail Pinch Response
Pupil Response
Righting Reflex

Locomotor Activity

Basic Movements
Fine Movements
Rearing
Total Distance

Amphetamine produced only a mild hypoactivity in the first 12 hours following drug discontinuation. This is characterized by the Sponsor as a mild withdrawal syndrome, demonstrating study validity.

In contrast, bremelanotide did not produce any signs of behavioral changes from baseline during drug discontinuation. This suggests that continuous infusion of bremelanotide for two weeks does not produce physical dependence.

C. Human Pharmacokinetic Studies with Bremelanotide (Study #PT-141-56 and PT-141-54)

Following subcutaneous administration, bremelanotide produced peak plasma concentrations (T_{max}) at 60 minutes, with a mean C_{max} value of 77.1 ng/ml following the therapeutic dose of 1.75 mg (s.c.). Plasma concentrations increased in a dose-proportional manner, with a plateau in plasma levels at a dose of 7.5 mg (s.c.). The half-life of bremelanotide is ~2-3 hours, with pharmacodynamic effects lasting up to 16 hours (5 half-lives of the drug). The drug has low binding to human plasma protein.

As a peptide, the metabolism of bremelanotide involves hydrolysis of amide bonds to release the drug's constitutive amino acids. The free amino acids are primarily cleared through the urine (65%) with no parent drug detected. An additional 23% of the drug is cleared through the liver.

D. Human Abuse Potential Study with Bremelanotide (Study #BMT-117)

“A double-blind, double-dummy, randomized, crossover study to assess the abuse potential of subcutaneous bremelanotide compared to phentermine and placebo in recreational stimulant users”

This was an in-patient, randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover study that evaluated the abuse potential, safety, tolerability, and pharmacokinetics of bremelanotide (1.75, 3.5, and 5.25 mg, s.c.), phentermine (45 and 90 mg, p.o.) and placebo (s.c. and p.o.) in healthy nondependent recreational polydrug users (n = 36 completers).

The study consisted of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit (up to 2 weeks after last treatment). In the Treatment Phase, subjects were confined to the unit the day prior to the first study drug administration (at check-in).

Subjects

Number of Subjects

During the Qualification Study, 197 subjects participated. During the Main Study, 56 adult subjects (age 18-55 years; 38 men and 18 women) who passed the Qualification Phase were randomized from the Qualification Phase into the Treatment Phase. There were 36 study completers. Subjects had a body mass index of 19.8 to 30.0 kg/m².

Inclusion Criteria, for participation in either study phase, are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject had at least 10 lifetime non-therapeutic experiences (i.e., for psychoactive effects) with stimulants (e.g., amphetamine, cocaine, methamphetamine, methylphenidate, MDMA, or phentermine, but not including nicotine or caffeine).
- Had at least 1 non-therapeutic experience with stimulants in the past year

Exclusion Criteria are standard but include the following criteria that are relevant for a human abuse potential study:

- Alcohol or substance dependence within the 12 months prior to Screening (except nicotine) including cannabis, as defined by the Diagnostic and Statistical

Manual of Mental Disorders, fourth edition, text revision, or any self-reported dependence or “addiction” within the subject’s lifetime (except nicotine).

- Subjects who had ever been in treatment for substance use disorder(s) (except smoking cessation) or who were currently seeking treatment for substance use disorder(s).
- Had a positive urine drug screen (UDS) and alcohol breath test result at the Qualification Visit and treatment visits.
- History or presence of any clinically significant psychiatric or neurologic major disease or illness.

Main Study:

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

1. Ability to distinguish phentermine from placebo on Drug Liking visual analog scale (VAS), with a 15-point peak increase (of at least 65 points) for Drug Liking relative to placebo;
2. Acceptable placebo response on Drug Liking VAS between 40 to 60, inclusive;
3. Ability to tolerate study treatments and ability to produce acceptable responses; and
4. General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

On the bipolar Drug Liking VAS Emax, placebo responses were appropriate (mean = 50 ± 0.2), as were responses to phentermine 60 mg (mean = 86 ± 10).

Oral Drug Doses

Main Study

Qualification Phase (single blinded)

Subjects were required to fast at least 8 hours prior to and at least 4 hours after study drug administration in the Qualification Phase.

The following treatments were administered orally:

- Phentermine 60 mg
- Placebo

The Sponsor provided the following justification for selecting phentermine for the positive control:

“At the time of the design of this study, there were no available controlled substances with a similar pharmacology to BMT, a selective MCR agonist, that aimed to increase desire, therefore, a positive control with stimulant properties (as opposed to sedative properties) was selected. Phentermine, a sympathomimetic amine, is considered a mild stimulant drug in Schedule IV of the Controlled Substance Act, and was determined as the positive control for the study.”

There was a washout period of at least 92 hours between the last drug dose in the Qualification Phase and the start of the Treatment Phase.

Treatment Phase (double-blind)

Subjects were required to fast at least 8 hours prior to and at least 4 hours after study drug administration in the Treatment Phase.

Subjects were randomized to 1 of 6 treatment sequences, according to a 6×6 Williams squares. During each treatment session, subjects received 3 injections administered using 3 separate auto-injectors and 3 capsules for oral ingestions. The 6 treatments were administered subcutaneously (using autoinjectors handled by nursing staff) and by oral administration (PO) following an overnight fast:

- BMT 1.75 mg (1 active SC injection + 2 placebo SC injections + 3 placebo PO capsules)
- BMT 3.5 mg (2 active SC injections + 1 placebo SC injection + 3 placebo PO capsules)
- BMT 5.25 mg (3 active SC injections + 3 placebo PO capsules)
- Phentermine 45 mg (3 placebo SC injections + 3 \times 15 mg phentermine PO capsules)
- Phentermine 90 mg (3 placebo SC injections + 3 \times 30 mg phentermine PO capsules)
- Placebo (3 placebo SC injections + 3 placebo PO capsules)

There was a washout period of at least 5 days inbetween treatments, which was calculated on the basis an elimination period of 5 half-lives for the 2 study treatments:

- bremelanotide (2 hours \times 5 half lives = 10 hours = <0.5 days)
- phentermine (up to 25 hours \times 5 half lives = 125 hours = 5 days)

Pharmacodynamic Variables

All subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 24 hours after drug administration, except for VAS for Overall Drug Liking and Take Drug Again, which was assessed at 12 and 24 hours. Drug Identification was assessed at 12 hours.

Primary Measure:

Drug Liking VAS (Emax)

Secondary Measures:

Balance of effects:

- Drug Liking VAS
- Overall Drug Liking VAS
- Take Drug Again VAS

Positive effects:

- Good Effects VAS

Negative effects:

- Bad Effects VAS

Other drug effects:

- Any Effects VAS
- Alertness/Drowsiness VAS
- Agitated/Relaxed VAS

Drug Identification

Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG
- Physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medication

Pharmacokinetic Evaluation:

Venous blood samples (6 ml) were collected at baseline, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours after drug administration.

Results

Subjective Responses

Table 1 below depicts the effects of study treatments on the subjective measures used in this study for all study completers (n =36). The data are compiled from two analyses. The FDA statistical evaluation (see next section below) provided an analysis of mean and standard deviation responses to drug treatments only for the VAS for Drug Liking, Overall Drug Liking, Take Drug Again, and Good Drug Effects. The Sponsor provided mean responses (but not standard deviation data) to drug treatments to Bad Drug Effects, Alert/Drowsy, Agitated/Relaxed and Any Drug Effects in the study report (Study #BMT-117).

Table 1: Effects of Placebo (p.o. and s.c.), Phentermine (45 and 90 mg, p.o.), and Bremelanotide (1.75, 3.5, 5.25 mg, s.c.) on Subjective Measures (VAS) – Emax Scores (n = 36)

Measure	Placebo	PHT 45	PHT 90	BMT 1.75	BMT 3.5	BMT 5.25
Drug Liking VAS* bipolar	54 ± 9	71 ± 14	74 ± 16	54 ± 6	56 ± 8	55 ± 8
Overall Drug Liking VAS* bipolar	51 ± 4	68 ± 18	62 ± 26	44 ± 22	42 ± 22	36 ± 21
Take Drug Again VAS* bipolar	51 ± 4	67 ± 20	64 ± 31	42 ± 22	37 ± 23	31 ± 22
Good Drug Effects VAS* unipolar	7 ± 17	44 ± 30	50 ± 33	12 ± 17	19 ± 25	21 ± 25
Bad Drug Effects VAS** unipolar	4	8	20	19	33	36
Alert/Drowsy VAS** bipolar	55	69	78	55	57	58
Agitated/Relaxed VAS** bipolar	51	55	64	57	61	62
Any Drug Effect VAS** bipolar	8	46	58	24	39	40

mean ± s.d., * data provided by FDA Office of Biostatistics, mean only, ** data provided by Sponsor without standard deviation

Statistical Analysis of Subjective Measures

The following is the **verbatim** analysis from Dr. Anna Sun, Statistician in the Office of Biostatistics (DARRTS, August 27, 2018):

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Good Effects, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The mean difference was statistically significant for the comparisons between Phentermine 90 mg and placebo (P-value=0.0227). For the Phentermine 45 mg compared with placebo, the mean difference in Emax was not statistically significant (P-value=0.1556), however, the study was designed and conducted based on the recommendations in the draft guidance on the Assessment of Abuse Potential of Drugs (Jan 2010), thus, the study was not powered with an adequate sample size to perform this post-hoc analysis, which should be considered in the interpretation of this result.
- For the relative abuse potential tests:
 - All 3 BMT doses were associated with significantly lower effects than the positive controls on the primary endpoint and secondary endpoints of Good Effects, Take Drug Again and Overall Drug Liking (P value <0.01), indicating that subjects liked the positive controls significantly more than BMT.
- For the absolute abuse potential test:
 - For the primary PD endpoint Drug Liking, all 3 BMT doses versus placebo were statistically significant (P value <0.01), the results showed that all 3 BMT doses were similar to placebo.
 - For the secondary endpoints, except for Good Effect VAS, all 3 BMT doses versus placebo were statistically significant (P value <0.01), showing that all 3 BMT doses were similar to placebo.
- Overall, BMT produced abuse-related responses that were not significantly different than placebo.

Drug Identification

The Drug Identification question asks subjects to report if that day's drug treatment produced effects that were similar to any of the following drugs: THC, caffeine, cocaine, amphetamine, nicotine, morphine, "ecstasy" (MDMA), LSD or benzodiazepine. The Sponsor provided the following summaries of the Drug Identification data:

- Phentermine (45 and 90 mg) was identified as similar to numerous drugs with stimulant properties, such as: caffeine (19% and 30%, respectively), cocaine

- (22% and 34%, respectively), amphetamine (33% and 59%, respectively), and “ecstasy” (MDMA) (31% and 45%, respectively).
- Bremelanotide did not produce drug similarity scores of greater than 10 out of 100 for any of the drug classes listed.

Adverse Events in Human Abuse Potential Study

The Sponsor provided an analysis of adverse events in the human abuse potential study. Bremelanotide produced a remarkably negligible degree of AEs overall as well as no significant psychiatric or neurological AEs indicative of abuse potential. **Table 2** (below) shows psychiatric or neurological AEs with an incidence >2% that were reported for any subject who received placebo, phentermine, or bremelanotide (n = 42-47):

Table 2: Psychiatric or Neurological Adverse Events Following Administration of Placebo, Phentermine (45 and 90 mg), and Bremelanotide (1.75, 3.5, 5.25 mg) (n = 42-47) (Excerpted from Sponsor’s Study Report BMT-117)

	Placebo n = 45	PHT 45 mg n = 44	PHT 90 mg n = 47	BMT 1.75 mg n = 45	BMT 3.5 mg n = 43	BMT 5.25 mg n = 42
Psychiatric						
Euphoric mood	3 (7%)	11 (25%)	12 (26%)	2 (4%)	1 (2%)	1 (2%)
Nervous system						
Headache	3 (7%)	4 (9%)	10 (21%)	5 (11%)	4 (9%)	8 (19%)
Gastrointestinal						
Nausea	1 (2%)	2 (5%)	9 (19%)	9 (20%)	12 (28%)	14 (33%)

PHT = phentermine, BMT = bremelanotide

For the AE of “euphoric mood”, the response to BMT at any dose tested was less than that produced by placebo (2-4%, n = 1-2 vs. 7%, n = 3) and effectively equivalent. The other AEs of note were not ones associated with abuse potential (headache and nausea).

Thus, there were no abuse-related signals in the human abuse potential study from the bremelanotide AE data analysis.

Overall Conclusions

In this HAP study, bremelanotide at the therapeutic dose (1.75 s.c.) and supra-therapeutic doses (3.5 and 5.25 mg, s.c.) did not mediate effects predictive of abuse potential. In a drug identification test, bremelanotide was not identified at any dose as producing effects similar to any drug class associated with abuse potential.

The incidence of euphoria produced by bremelanotide did not differ from that of placebo.

E. Abuse-Related Adverse Events in Clinical Studies

The Sponsor conducted 23 clinical studies with bremelanotide during drug development:

- Eighteen controlled and uncontrolled single- and multiple- dose Phase 1/2 studies in non-HSDD subjects. Of the 18 studies, 17 studies were Phase 1 studies and 1 study was designated a Phase 2 safety study in subjects with controlled hypertension.
- Three randomized, double-blind, placebo-controlled, Phase 2 studies in premenopausal women with HSDD.
- Two multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies in premenopausal women with HSDD. Both studies had an open-label extension (OLE) period.

The Integrated Summary of Safety submitted in the NDA shows that in Phase 1 studies with bremelanotide (excluding the human abuse potential study reported above), euphoric mood was reported in 7 of 740 subjects who participated in pharmacokinetic studies, with an incidence of 0.9%. In Phase 2/3 studies with bremelanotide, there was a single incidence of euphoric mood (1 of 297 subjects, <0.01%). There were also no reports of other abuse-related adverse events with an incidence of 2% or greater.

The Sponsor additionally states that subjects were offered the option to request additional bremelanotide doses during the 52-week open-label extension period of the Phase 3 studies. However, there was a negligible increase in bremelanotide use during the OLE period, which is consistent with a drug that has no meaningful abuse potential.

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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: 3/1/2019

Reviewer(s): Adebola Ajao, PhD, Epidemiology Reviewer
Division of Epidemiology II

Team Leader: Jie (Jenni) Li, PhD, Epidemiology Team Leader
Division of Epidemiology II

Division Director: CAPT David Moeny, MPH, RPh, USPHS
Division of Epidemiology II

Subject: ARIA Insufficiency Memo for Pregnancy Safety Concerns

Drug Name(s): Bremelanotide Subcutaneous Injection

Application Type/Number: NDA 210557

Applicant/sponsor: AMAG Pharmaceuticals, Inc

OSE RCM #: 2018-753



A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Bremelanotide (NDA 210557) is a synthetic heptapeptide and a high affinity ligand and agonist for melanocortin receptors (MCRS). Bremelanotide is indicated for treatment of premenopausal women with acquired and generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes distress or interpersonal difficulty. Currently, the product is being reviewed by the FDA under section 505 (b) (1) with a PDUFA goal date of March 23, 2019. Bremelanotide is pre-packed as a (b) (4) disposable, prefilled autoinjector pen. The recommended dosage for bremelanotide is 1.75 mg in 0.3 mL volume administered subcutaneously into the abdomen or thigh as desired at least 45 minutes before anticipated sexual activity. Efficacy of bremelanotide was evaluated through two pivotal, randomized, double blind, placebo controlled, parallel groups phase 3 trials. In the efficacy trials, 1.7mg of bremelanotide showed a significant treatment benefit compared to placebo in both primary endpoints (desire and distress). The target population for bremelanotide is premenopausal women 18 years and over and this population is also of child bearing age.

1.2. Describe the Safety Concern

Bremelanotide is indicated in premenopausal women age 18 years and over, therefore, there is a high likelihood of use in women of child bearing age. However, pre-approval safety database lacked safety data on pregnancy outcomes in women exposed to bremelanotide in pregnancy. Since inadvertent exposure during pregnancy is anticipated if bremelanotide is approved in the intended population, there is need for additional data on pregnancy outcomes. FDA is requesting that the sponsor conduct both a prospective pregnancy registry and retrospective claims study to identify any safety issues such as major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes associated with bremelanotide use in pregnant women.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	<input type="checkbox"/>
Assess signals of serious risk	<input type="checkbox"/>
Identify unexpected serious risk when available data indicate potential for serious risk	<input checked="" type="checkbox"/>

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy

is recognized

- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.[†]
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).[†]

[†] **If checked, please complete General ARIA Sufficiency Template.**

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Exposures

There is potential for exposure misclassification when measuring exposure to “as needed” (PRN) drugs such as bremelanotide using claims data. There are ways to assess the extent of misclassification to bremelanotide exposure in claims data. One way is to survey pregnant women with prescription for bremelanotide in pregnancy to assess use and extent of use and correlate self-reported Bremelanotide use to prescription claims data. FDA will issue instructions to the sponsor about including a survey in their study protocol to assess the extent of exposure misclassification to Bremelanotide. Another way is to conduct a sensitivity analysis and define exposed patients as women with at least one refill of bremelanotide during pregnancy i.e. 2 or more prescriptions filled during pregnancy, although such a sensitivity



analysis may likely be underpowered. Finally, the sponsor could utilize patient survey or exposure data collection using a mobile device application.

Analytical tool

ARIA is sufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are currently linked in Sentinel. Although the exposure corresponding to the mother and potential outcomes corresponding to the infant can possibly be assessed, ARIA continues to be insufficient for broad-based signal detection. ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The pre-approval safety database lacked sufficient clinical data on pregnancy outcomes in women exposed to bremelanotide in pregnancy. Therefore, the division requires additional data on pregnancy outcomes. FDA has determined that the sponsor is required to conduct the following post-marketing studies:

1. A prospective, registry-based, observational cohort study that compares maternal, fetal, and infant outcomes in women exposed to (b) (4) during pregnancy to an internal, unexposed (b) (4) cohort of pregnant women. The registry will identify major and minor congenital malformations, spontaneous abortions, elective terminations, small for gestational age, pre-term births, and any other adverse pregnancy outcomes. These outcomes will be adjudicated with medical chart review. Infant outcomes including effect on post-natal growth and development will be assessed through at least the first year of life.
2. A retrospective cohort study using electronic claims data that compares maternal, fetal, and infant outcomes in women exposed to bremelanotide during pregnancy to an internal, unexposed (b) (4) cohort of pregnant women. Maternal, fetal, and infant outcomes, (b) (4)
(b) (4) Pregnant women exposed and unexposed to (b) (4) be matched by age at pregnancy and gestational age at cohort entry. This study will complement the post marketing pregnancy registry study. To assess the extent of misclassification for (b) (4) exposure in claims data, conduct an evaluation of the validity of claims exposure data, compared to patient self-reported data. (b) (4)
(b) (4)

FDA will review sponsor's submission of the full study protocols to determine the appropriateness of the data source and study design.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 4, 2019
Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number: NDA 210557
Product Name and Strength: Vyleesi (bremelanotide) injection, 1.75 mg/0.3 mL
Applicant/Sponsor Name: Amag Pharmaceuticals Inc.
FDA Received Date: February 1, 2019
OSE RCM #: 2018-634-1
DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Lolita White, PharmD
DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised Instructions for Use (IFU), container label, and carton labeling for Vyleesi (Appendix A) to determine if they are acceptable from a medication error perspective. DMEPA previously completed a review of the IFU, container labeling and carton labeling, and provided several recommendations to minimize the potential of medication errors.^a

2 CONCLUSION

^a Whaley E. Human Factors Validation Study Results and Label and Labeling Review for Vyleesi (NDA 210557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 30. RCM No.: 2018-634; 2018-912.

The revised IFU, container label, and carton labeling are unacceptable from a medication error perspective. The IFU labeling was revised (e.g. (b) (4)) without justification and/or additional human factors data to support that no new risks will be introduced by the revisions. In addition, the strength statement on the container label and carton labeling is not in accordance with 21 CFR 201.15(a)(6), the NDC numbers on the carton labeling and container label (b) (4) which is not recommended, and the container label does not include a linear barcode as required per 21 CFR 201.25(c)(2).

3 RECOMMENDATIONS FOR AMAG PHARMACEUTICALS INC.

We provide recommendations in Table 1 below. We recommend the following be implemented prior to approval of this NDA 210557:

Table 1: Identified Issues and Recommendations for Amag Pharmaceuticals (entire table to be conveyed to Applicant)

	Identified Issue	Rationale	Recommendation
Instructions for Use (IFU)			
1.	IFU Step 3 (b) (4) was revised from the validated version of the IFU that was tested in your HF validation study. (b) (4)	IFU Step 3 is associated with a critical task (Hold device pressed against skin for 5 seconds after second click). It is unclear why this revision was made. In addition, because this change impact critical task, we do not have any data demonstrating that this revision does not introduce new use-related risks.	Revise the IFU to include the (b) (4)
Container Label			
1.	The strength statement lacks sufficient prominence.	Lack of prominence might lead to confusion regarding the product strength.	Increase the size of the strength statement to be in accordance with 21 CFR 201.15(a)(6).
2.	The carton containing (b) (4)	We acknowledge your	As previously noted, the (b) (4)

		(b) (4)	
3.	Your container label does not include a linear barcode as required per 21 CFR 201.25(c)(2).	As previously noted, the drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety feature that should be part of the label whenever possible.	Revise the container label to include a linear barcode as required per 21 CFR 201.25(c)(2).
Carton Labeling			
1.	See container label recommendations #1 and #2 above and revise accordingly.		

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Clinical Inspection Summary

Date	January 17, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Christina Chang, M.D., Clinical Team Leader Marcea Whitaker, M.D., Reviewer Jeannie Roule, Regulatory Project Manager Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA#	210557
Applicant	AMAG Pharmaceuticals, Inc.
Drug	VYLEESI® (bremelanotide)
NME	Yes
Review Priority	Standard
Proposed Indication	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty
Consultation Request Date	June 5, 2018
Summary Goal Date	January 23, 2019
Action Goal Date	March 23, 2019
PDUFA Date	March 23, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Twede, Dunn, Jacobs, and Johnson were inspected in support of this NDA. As this application was for a New Molecular Entity (NME), an inspection of the sponsor, AMAG Pharmaceuticals, Inc., was also conducted. Based on the results of these inspections, the studies (Protocols BMT-301 and BMT-302) appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication. The final classification of the inspections of Drs. Twede, Dunn, Jacobs, and Johnson, and the sponsor, AMAG, was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of VYLEESI® (bremelanotide) for the treatment of premenopausal women with, acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty.

Clinical inspections were requested for the following identical protocols in support of this application:

Protocols BMT-301 and BMT-302, “A Phase III Study Evaluating the Efficacy and Safety of Bremelanotide (BMT-302) in Premenopausal Women with Hypoactive Sexual Desire Disorder (HSDD) (with or without Decreased Arousal)”

Protocol BMT-301 randomized 653 subjects into the double-blind portion of the study at 91 sites in the United States and Canada. Protocol BMT-302 randomized 614 subjects at 88 sites in the United States and Canada.

The primary objective of these studies was to evaluate the efficacy of bremelanotide (BMT) 1.75 mg, administered subcutaneously (SC), compared to placebo (PBO) on an as-desired basis for the treatment of HSDD (with or without decreased arousal) in premenopausal females.

The two *co-primary efficacy endpoints* were the change from Baseline to EOS (last 28 days of the individual subject's participation in the Core Study) in level of desire as measured by the FSFI Q1 and Q2 (desire domain) AND the frequency of being bothered by low sexual desire as measured by the FSDD-DAO Q13

Rationale for Site Selection

The clinical sites of Drs. Twede, Dunn, Jacobs, and Johnson were selected for inspection for the following reasons:

At Dr. Johnson's site, the index potential drug-induced liver injury (DILI) case (Subject (b) (6)) was, per the review division (DBRUP), “not identified as being a clinically significant event by the investigator. Because of the investigator’s assessment, the sponsor delayed reporting of this case until 4 months after its occurrence, acting on the request of an independent data safety monitoring board (DSMB).” Data analysis using the clinical investigator site selection tool indicated that the site also had the highest enrollment among all the sites and a high site-specific enrollment weighted efficacy.

Dr. Dunn’s site demonstrated a high level of efficacy and was one of the higher enrollers overall.

Dr. Twede’s site was a high enroller with moderate efficacy and a high site-specific weighted efficacy.

Dr. Jacob’s site was the highest enroller for Study 302 and had an overall high risk and moderate efficacy.

III. RESULTS (by site):

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #168 Dunn, Michael M.D. 10040 Regency Circle, Suite 375 Omaha, NE 68114	BMT-301 Subjects: 18	24-28 Sep 2018	NAI
Site #208 Jacobs, Mark, M.D. 7580 Fannin Street, Suite 220 Houston, TX 77054	BMT-302 Subjects: 24	20-24 Aug 2018	NAI
Site # 116 Johnson, Kimball, M.D. 125 Clairemont Avenue, Suite 470 Decatur, GA 30030	BMT-301 Subjects: 37	5-12 Sep 2018	NAI
Site #269 Twede, Michael, M.D. 11724 South State Street, Suites 200 & 201 Draper, UT 84020	BMT-302 Subjects: 23	10-13 Sep 2018	NAI
Sponsor AMAG Pharmaceuticals, Inc. 1100 Winter Street Waltham, MA 02451	BMT-301 BMT-302	15-22 Oct 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Dunn, Michael M.D.

At this site for Protocol BMT-301, 33 subjects were screened, 18 subjects were randomized to the test article, and 14 subjects completed the core study. Informed consent was obtained appropriately from all subjects prior to any study-related activities.

Of those randomized, Subjects [REDACTED]^{(b) (6)} withdrew prior to treatment for unclear reasons, Subject [REDACTED]^{(b) (6)} was discontinued prior to treatment for failure to meet an inclusion criterion (recognized belatedly), and Subject [REDACTED]^{(b) (6)} withdrew soon after receiving the active test article due to adverse events of elevated blood pressure, facial flushing, nausea, and vomiting (per the line listings).

Other records reviewed included, but were not limited to, IRB/sponsor/monitor correspondence, financial disclosure, delegation of duties, inclusion/exclusion criteria, enrollment log, protocol deviations, adverse events, concomitant medications, and test article accountability and storage.

There was no evidence of under-reporting of adverse events. The co-primary efficacy endpoint data were compared against the data listings provided by the sponsor for 14 randomized subjects. No discrepancies were noted.

2. Jacobs, Mark, M.D.

At this site for Protocol BMT-302, 43 subjects were screened, 15 subjects were screen failures, 28 subjects were enrolled/randomized, 14 subjects were discontinued/withdrawn, and 14 subjects completed the core study. Informed consent was obtained appropriately from all 43 screened subjects prior to any study-related activities.

Per the line listings, of the 14 enrolled/randomized subjects who were discontinued/withdrawn, four subjects who were never treated either withdrew or were lost to follow up (Subjects [REDACTED]^{(b) (6)} [REDACTED]). The remaining ten discontinued subjects were treated with the test article. Table 1 below indicates treatment group and reason for discontinuation

Table 1 Treated Subjects Who were Discontinued at Site #208

Subject ID	Treatment Group	Reason for Discontinuation	AE (preferred term)
(b) (6)	BMT	Adverse event	Pain in extremities*
(b) (6)	PBO	Withdrawal by subject	
(b) (6)	BMT	Adverse event	Muscle fatigue*
(b) (6)	BMT	Lost to follow up	
(b) (6)	BMT	Adverse event	Nausea*
(b) (6)	BMT	Change of partner	
(b) (6)	PBO	Withdrawal by subject	
(b) (6)	BMT	Lost to follow up	
(b) (6)	PBO	Adverse event	Depressed mood*
(b) (6)	BMT	Lost to follow up	

*Reported in the line listings

Review of the records of 22 subjects included, but was not limited to, IRB/sponsor/monitor correspondence, training verification, financial disclosure forms, delegation logs, source documents, ePRO questionnaires, and test article accountability and storage.

There was no evidence of under-reporting of adverse events. The co-primary efficacy endpoint data were compared against the data listings provided by the sponsor for all randomized subjects. No discrepancies were noted.

3. Johnson, Kimball, M.D.

At this site for Protocol BMT-301, per the Screening and Enrollment Log, 48 subjects were screened (an additional subject was transferred to the study per communication from the ORA investigator), and nine subjects (including the transferred subject) completed the study. Informed consent was obtained appropriately from all 48 screened subjects prior to any study-related activities.

Per the CSR, Table 16.2.1.2, seven subjects randomized to treatment were discontinued. The Table 2 below indicates subject number, treatment, and reason for discontinuation.

Table 2 Treated Subjects Who were Discontinued at Site #116

Subject ID	Treatment Group	Reason for Discontinuation	AE (preferred term)
(b) (6)	BMT	Adverse event	Nausea*
	BMT	Lost to follow-up	
	BMT	Withdrawal by subject	
	BMT	Prohibited medication (sertraline)*	
	BMT	Lost to follow-up	
	BMT	Adverse event	Skin hyperpigmentation*
	BMT	Withdrawal by subject	

*Reported in the line listings

The records for 18 subjects were reviewed. Records reviewed included, but were not limited to, IRB/sponsor/monitor correspondence, financial disclosure, training verification, monitoring visit logs, inclusion/exclusion criteria, protocol deviations, clinical laboratory results, diary printouts, and test article accountability and storage.

There was no evidence of under-reporting of adverse events. The co-primary efficacy endpoint data were compared against the data listings provided by the sponsor for nine subjects. No discrepancies were noted.

Of note, DBRUP questioned the circumstances regarding the finding of acute hepatitis for Subject (b) (6) and asked the field investigator to collect more information during the inspection, as they had concerns regarding how this adverse event was classified (i.e., non-SAE) and handled.

- Specifically, a Medwatch Report dated 01/18/2017 reported this as a (1) Adverse Event and (2) Other Serious (Important Medical Events). The MedWatch Report described the subject as being diagnosed with acute hepatitis on (b) (6), after self-administration of 11 doses of bremelanotide. Subject provided multiple blood samples throughout (b) (6), demonstrating abnormally high liver enzyme and bilirubin levels that decreased at each subsequent sampling time (b) (6). A further sample on (b) (6) continued to demonstrate decreases in ALT and bilirubin. Follow up discussion with the hepatologist indicated that since relevant laboratory tests and viral titers were negative and liver function tests continued to improve, the attribution of acute hepatitis to treatment with the test article could not be ruled out. By mid-(b) (6) the subject had resumed normal activities. Lab tests performed on (b) (6) indicated liver enzyme and bilirubin levels at or approaching normal limits.
- EIR exhibits collected during the inspection of Dr. Johnson included copies of communications of the CI with the consulting hepatologist, the medical monitor, and the CRO as well as progress notes and laboratory results. The information/data in these exhibits appear to support the clinical course of events summarized in the MedWatch Report.

Reviewer's Comment: This adverse event was discussed at length with the reviewing medical officer in DBRUP in light of the additional information obtained during the inspection. The incident does not meet the usual definition of a serious adverse event (SAE) in clinical trials. A very conservative assessment of this adverse event based on the protocol-specified criteria for a SAE might have warranted reporting this as a SAE, but in the end, this appears to have been a judgement call that was made in good faith by the CI. In conclusion, there does not appear to be any clear mishandling of the case or evidence of any problematic assessment of safety information in general by the clinical investigator. The reviewing medical officer in DBRUP appeared to be satisfied with this conclusion.

4. Twede, Michael, M.D.

At this site for Protocol BMT-302, 38 subjects were screened, 15 subjects failed screening criteria or withdrew consent, 23 subjects were enrolled in the study, five subjects discontinued from treatment, and 18 subjects completed the core study. Informed consent was obtained appropriately from all screened subjects prior to any study-related activities. Table 3 below indicates subject number, treatment, and reason for discontinuation.

Table 3 Treated Subjects Who Were Discontinued at Site #269

Subject ID	Treatment Group	Reason for Discontinuation	AE (preferred term)
(b) (6)	BMT	Prohibited medication (HCTZ)*	
	BMT	Non-compliance with study drug	
	BMT	Non-compliance with study drug	
	BMT	Adverse event	Vomiting*
	PBO	Lost to follow up	

*Reported in the line listings

Source records for the 23 enrolled subjects were reviewed. Records reviewed included, but were not limited to, IRB/sponsor/monitor correspondence, financial disclosures, site training, delegation logs, laboratory results, inclusion/exclusion criteria, randomization, protocol deviations, and test article accountability and storage.

There was no evidence of under-reporting of adverse events. The co-primary efficacy endpoint data were compared against the data listings provided by the sponsor for the 23 randomized subjects. No discrepancies were noted.

5. AMAG Pharmaceuticals, Inc.

The inspection of AMAG Pharmaceuticals, Inc. focused on the control, oversight, and management of Protocols BMT-301 and BMT-302. Records reviewed included, but were not limited to, organizational charts, vendor recruitment, standard operating procedures, clinical investigator selection, monitor recruitment and training, quality assurance practices, record retention practices, electronic records and audit trails, transfer of obligations, financial disclosure forms, adverse event reporting, and drug accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. However, discussion with management included differences in practices regarding the qualification of study personnel to conduct HSDD assessments in that the medical monitor required that diagnosticians have a clinical degree (in line with protocol requirements) while the clinical trial manager (CTM) confirmed with the sponsor that noted site staff (psychometricians) without clinical degrees were qualified to complete HSDD assessments. In either case, the CI reviewed all HSDD assessments made by the psychometricians and approved the final diagnosis

Reviewer Comment: The fact that site staff without clinical degrees were approved by the CRA to conduct HSDD assessments is indicative of a protocol violation, but this is a violation on the part of the CI, not the sponsor. The CI is ultimately responsible to ensure that the protocol is followed at the site as well as that all site staff are adequately trained on the protocol and qualified by background/training to performed delegated tasks. In terms of data reliability, it is reassuring that the CI reviewed all HSDD assessments made by the psychometricians and approved the final diagnosis.

{See appended electronic signature page}

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CONCURRENCE:

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/s/

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M E M O R A N D U M

Date: January 4, 2019

From: Melissa Reyes, MD, Clinical Reviewer, DDDP

Through: Kendall Marcus, MD, Division Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP

To: Marcea Whitaker, MD, Clinical Reviewer, DBRUP
Christina Chang, MD, Clinical Team Leader, DBRUP
Jeannie Roule, RPM, DBRUP
Barbara Gould, CPMS, DDDP

Re: DDDP Consult #1954 – DBRUP consult for **bremelanotide for hypoactive sexual desire disorder**.

DDDP has been consulted by DBRUP to provide input on the following questions:

1. Potential risk of skin cancer following long term exposure to MC1R activation. Are there any intermediate outcome measures or biomarkers (e.g., onset of freckles) that would suggest increased risk for developing malignancy?
2. Whether hyperpigmentation could mask a true malignancy and delay diagnosis.
3. Comment on the increased incidence of hyperpigmentation in Black subjects with incomplete resolution in 4 of 8 subjects. Is there any precedence for labeling this effect under special populations?
4. Whether additional nonclinical studies or clinical studies would be needed to discern the concerns outlined above.

Material Reviewed:

- NDA 210557

Background:

Bremelanotide(BMT) is a synthetic cyclic heptapeptide, high-affinity ligand, and agonist for melanocortin receptors (MCRs), superficially MC1R, MC3R, and MC4R. The sponsor is developing BMT for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD).

The melanocortin (MC) receptor family includes 4 members (MC1R, MC2R, MC3R, MC4R, and MC5R) with variable tissue expression. MC3R and MC4R are located primarily in the CNS and regulate food intake and sexual function.

The applicant has submitted information from 5 studies to support the NDA for BMT in the treatment of HSDD

- Core studies (BMT-301 and -302): Two multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies in premenopausal women with HSDD (with or without decreased arousal) with open-label extension (OLE) period.
- Three randomized, double-blind, placebo-controlled, Phase 2 studies:
 - One large Phase 2 dose-finding study in women with a primary diagnosis of HSDD (PT-141-54)
 - Two Phase 2 studies conducted in women with female sexual arousal disorder (FSAD) (PT-141-2004-52FB and PT-141-2005-53FB)

Review of NDA 210557:

Two Phase 3 trials had identical design (BMT-301 and BMT-302). These were multicenter, randomized, placebo-controlled, parallel-group trials designed to evaluate the efficacy and safety of a fixed dose (1.75 mg) of BMT versus placebo administered subcutaneously on an as desired basis in premenopausal females with HSDD (with or without decreased arousal). These trials consisted of 2 parts: a Core Study and an Open-label Extension (OLE) Study. The Core Study consisted of a 4-week no-drug Screening period, followed by a 4-week single-blind placebo period, with the first dose administered in-clinic. Following the end of the single-blind period, which served as the Baseline, eligible subjects were then randomized to a 24-week double-blind outpatient treatment period, with the first dose administered in-clinic. The OLE Study consisted of approximately a 52-week open-label treatment period during which all subjects received BMT 1.75 mg SC.

PT-141-54 was a Phase 2b, randomized, double-blind, placebo-controlled, dose-finding study in premenopausal women with female sexual arousal disorder (FSAD), HSDD, or mixed FSAD/HSDD and evaluated BMT 0.75, 1.25, and 1.75 mg SC doses. After screening, subjects entered a 4-week no-drug period followed by a single, in-clinic dose of single-blind placebo with 24-hour ambulatory blood pressure monitoring. After 24-hours, qualified subjects received a 4-week supply of single-blinded placebo for outpatient use. After 28 days, qualified subjects then received 2 in-clinic doses of randomized, double-blind study drug treatment one-week apart, followed by 12 weeks of double-blind study drug for outpatient use.

During the NDA review, on November 1, 2018, the Agency requested the following information from the applicant:

2. Provide the following regarding hyperpigmentation and hyperpigmentation/dyscoloration-related events:
 - a. MedDRA terms (verbatim to preferred term) used to code the hyperpigmentation/dyscoloration events
 - b. Narratives and case report forms for subjects with any pigment-related adverse events (AE), not just subjects who discontinued due to pigmentation disorders.

This should include, but is not limited to, lip discoloration, gingival discoloration, skin hyperpigmentation, skin discoloration, and pigmentation disorder.

- c. Photographs of pigmentation related AEs
- d. An analysis of pigmentation disorder AEs by race and duration of treatment.

The applicant submitted a response on November 20, 2018. Of note, no photographs were taken as part of the development program, and thus there are no photographs of the hyperpigmented AEs. The following analysis was submitted by the sponsor (pages 7-8) evaluating hyperpigmentation and discoloration AEs by race and relation to BMT exposure.

Table 2 Treatment-emergent Adverse Events of Hyperpigmentation/Discoloration (Pigmentation Disorders) by Race and Duration (Months) of BMT Exposure (BMT Phase 3 Core and Extension Studies- Safety Population)

Preferred term	Subject Groups with Duration of BMT 1.75 mg SC Exposure											
	>0 - 3 Months (N=223) n (%)			>3 - 6 Months (N=199) n (%)			>6 - 9 Months (N=206) n (%)			>9 - 12 Months (N=63) n (%)		
	White N=202 n (%)	Black N=15 n (%)	Other N=6 n (%)	White N=167 n (%)	Black N=25 n (%)	Other N=7 n (%)	White N=181 n (%)	Black N=21 n (%)	Other N=4 n (%)	White N=48 n (%)	Black N=12 n (%)	Other N=3 n (%)
Any AE of pigmentation disorder	1 (0.5)	2 (1.3)	0	2 (1.2)	3 (12.0)	0	2 (1.1)	0	0	0	1 (8.3)	0
Skin hyperpigmentation	0	1 (6.7)	0	1 (0.6)	3 (12.0)	0	1 (0.6)	0	0	0	0	0
Skin discoloration	0	0	0	1 (0.6)	0	0	0	0	0	0	1 (8.3)	0
Gingival hyperpigmentation	0	0	0	0	1 (4.0)	0	0	0	0	0	0	0
Lip discoloration	0	1 (6.7)	0	0	0	0	0	0	0	0	1 (8.3)	0
Melanocytic naevus	0	0	0	0	0	0	0	0	0	0	0	0
Pigmentation disorder	1 (0.5)	0	0	0	0	0	1 (0.6)	0	0	0	0	0
Scleral pigmentation	0	0	0	0	0	0	0	0	0	0	0	0
Seborrhoeic keratosis	0	0	0	0	0	0	0	0	0	0	0	0
Skin lesion	0	0	0	0	0	0	0	0	0	0	0	0

Preferred term	Subject Groups with Duration of BMT 1.75 mg SC Exposure							Total			
	>12 - 15 Months (N=222) n (%)			>15 Months (N=144) n (%)			Any BMT Exposure (N=1057) n (%)				
	White N=190 n (%)	Black N=24 n (%)	Other N=8 n (%)	White N=123 n (%)	Black N=20 n (%)	Other N=1 n (%)	White N=911 n (%)	Black N=117 n (%)	Other N=29 n (%)	Total N=1057 n (%)	
Any AE of pigmentation disorder	2 (1.1)	2 (8.3)	0	3 (2.4)	2 (10.0)	0	10 (1.1)	10 (8.5)	0	20 (1.9)	
Skin hyperpigmentation	0	1 (4.2)	0	0	1 (5.0)	0	2 (0.2)	6 (5.1)	0	8 (0.8)	
Skin discoloration	0	1 (4.2)	0	2 (1.6)	1 (5.0)	0	3 (0.3)	3 (2.6)	0	6 (0.6)	
Gingival hyperpigmentation	0	0	0	0	1 (5.0)	0	0	2 (1.7)	0	2 (0.2)	
Lip discoloration	0	0	0	0	0	0	0	2 (1.7)	0	2 (0.2)	
Melanocytic naevus	2 (1.1)	0	0	0	0	0	2 (0.2)	0	0	2 (0.2)	
Pigmentation disorder	0	0	0	0	0	0	2 (0.2)	0	0	2 (0.2)	
Scleral pigmentation	0	0	0	0	1 (5.0)	0	0	1 (0.9)	0	1 (<0.1)	
Seborrhoeic keratosis	1 (0.5)	0	0	0	0	0	1 (0.1)	0	0	1 (<0.1)	
Skin lesion	0	0	0	1 (0.8)	0	0	1 (0.1)	0	0	1 (<0.1)	

BMT=bremelanotide; SC=subcutaneous; PT=preferred term; TEAE=treatment emergent adverse events.
 Note: BMT Phase 3 Core and Extension Studies: Studies BMT-301 (core and extension study) and BMT-302 (core and extension study).
 Adverse events are coded using MedDRA Version 18.1. Only TEAE of Hyperpigmentation/Discoloration (Pigmentation disorders) are summarized. For each PT, subjects are counted once in 1 of the applicable exposure duration subgroup columns, and once in the overall Total (Any BMT Exposure) column, even if they experienced multiple events in that PT. For calculating exposure duration, 1 month is defined as 28 days.
 Dataset: [ADSL, ADAE]. Program: ah_t_ae_pigment_race_bmtdur.sas, Output: ah-t-ae-pigment-race-bmtdur.rtf, Generated on: 08NOV2018 12:35

For the purposes of this review, the primary safety population includes subjects that took part in placebo-controlled period of two identical Phase 3 trials (BMT-301 and -302) and one Phase 2b dose finding trial (PT-141-54) because the study population, dosing, and dosing regimen were similar for these 3 studies. To ascertain whether the duration of dosing had effect on incidence of AEs, we also evaluated open-label portion of the identical Phase 3 trials. The Phase 2b dose ranging study did not include an open-label period.

Review of the ADAE dataset and submitted verbatim term to MedDRA preferred term revealed that hyperpigmented-related AEs (hrAE) were reported under three different MedDRA terms (“AEDECOD” = skin discoloration, pigmentation disorders, and hyperpigmentation). For the purposes of our analysis, we included only those subjects with verbatim terms that clearly described increased pigmentation (i.e., “darkening,” “darkened”) and excluded subjects with verbatim terms that did not clearly describe increased pigmentation (i.e., “discoloration”).

No hrAEs reported terms were identified in the Phase 2 study initially included due to similar dosing and study population as the Phase 3 trials BMT-301 and -302. Thus, this study is not included in the analysis presented below.

Revision of the hrAEs reported terms (“AETERM”) identified an additional 7 subjects reporting at least one hrAE. The table below summarizes the number of subjects reporting at least one hrAE by the study period the first hrAE occurs. During the placebo-controlled period of two Phase 3 trials, no subjects on placebo experienced an hrAE while 6 (1%) subjects on BMT experienced 8 hrAEs. Of 8 reported hyperpigmentation AEs, 4 have resolved.

Subjects completing the placebo-controlled period from Phase 3 trials could continue to the open-label extension period. Three of six subjects who experienced hrAE during the placebo-controlled period continued into the open-label extension period.

During the open-label period, an additional 7 (1%) subjects experienced hrAE. Of these subjects, 6 subjects were from placebo arm of placebo-controlled period and 1 subject was from BMT arm.

Table 1. Subjects Experiencing Hyperpigmentation During Trials BMT-301 and BMT-302

	Randomization at Baseline	
	Placebo	BMT
Double-Blind Treatment ¹	0/620	6/627
Open-Label Extension ²	6/684	1/684

¹: Double-Blind Treatment period was 24 weeks in the Phase 3 trials and 12 weeks in the Phase 2b study.

²: Open-Label Extension (up to 52 weeks long) and includes only subjects from Phase 3 trials BMT-301 and -302.

The table below summarizes the occurrence of hrAE by race and study period. A higher proportion of African American subjects compared to Caucasian subjects experienced hrAEs for both the placebo-controlled and open-label extension periods.

Table 3: Subjects Reporting their First Hyperpigmentation-related AE¹ by Race

	Placebo-Controlled Period		Open-Label Period ²
	# Subjects w AE/# Subjects (%)		# Subjects w AE/# Subjects (%)
	BMT (N = 627)	Placebo (N = 620)	N = 680
African American	3/73 (4.11)	0/71 (0.00)	4/70 (5.71)
Caucasian	3/536 (0.56)	0/531 (0.00)	3/590 (0.51)
Other	0/18 (0.00)	0/18 (0.00)	0/20 (0.00)

¹: Hyperpigmentation-related AE terms included: skin spot discoloration right cheek; darkened pigmented spot on face; dark spots on face and ear; darkened areolas, bilateral breasts; facial skin darkening; skin darkening; darkening of facial skin; darkening of skin; hyperpigmentation (6); hyperpigmented areas of face; increased pigmentation; and darkening of hyperpigmented areas of skin on face.

²: Open-Label Extension includes only subjects from Phase 3 trials BMT-301 and -302

Reports of melanocytic nevi and cutaneous malignancy

During the development of BMT, the reports on melanocytic nevi and cutaneous malignancy were as follow:

- No subject experienced a cutaneous malignancy
- One subject (b) (6) experienced “changing mole with pigment changed” that was mild, not related to study drug, recovered/resolved, and did not lead to dose change.
- One subject (b) (6) experienced “melanocytic nevus, compound with moderate atypia” that was mild, possibly related to study drug, recovered/resolved, and did not lead to dose change.

Conclusion

During the development program for bremelanotide, approximately 1% of subjects reported AEs of hyperpigmentation. All subjects who reported these AEs were treated with BMT. Therefore, it is reasonable to conclude that AE of hyperpigmentation is due to the study drug. Of subjects who experienced hyperpigmentation during the placebo-controlled period, half (4 subjects) reported resolution of this AE. Additionally, of subjects who experienced hyperpigmentation, a higher proportion was African American. Most subjects developed hyperpigmentation during first 6 months of exposure to BMT. The most frequently reported anatomical locations of pigmentary changes were on the face, breasts, and gingiva. No malignant melanomas or other cutaneous malignancies were reported during the development of BMT.

Recommendation

We recommend that adverse reaction of hyperpigmentation be included in **Warning and Precautions** section of labeling. We propose the following wording:

Hyperpigmentation

In controlled clinical trials hyperpigmentation, including face, gingiva, and breasts, were reported in subjects who received bremelanotide. Patients with dark skin were more

likely to develop hyperpigmentation. Complete resolution of hyperpigmentation did not occur in some subjects.

Responses to Consult Questions:

Question 1:

Potential risk of skin cancer following long term exposure to MC1R activation. Are there any intermediate outcome measures or biomarkers (e.g., onset of freckles) that would suggest increased risk for developing malignancy?

DDDP Response to Question 1:

In general, pigmented lesions (melanocytic nevi, ephelides, lentiginos) observed on the skin may be due to increased numbers of melanocytes or increased pigment production from a normal number of melanocytes. We are not aware of any biomarkers capable of detecting early malignancy of pigmented lesions, and therefore, besides more frequent skin examinations of patients with such skin findings, we have no additional recommendations for early detection of skin malignancies.

Question 2:

Whether hyperpigmentation could mask a true malignancy and delay diagnosis.

DDDP Response to Question 2:

We could not find information on whether diffuse or localized hyperpigmentation of the skin could mask a cutaneous malignancy and delay diagnosis. The review of the literature suggests that in individuals with darker skin or in patients with pro-melanogenic state, cutaneous lesions suspicious for malignancy have similar clinical features to suspicious cutaneous lesions in individuals with light skin and normal melanogenic state. Thus, routine skin examination may be adequate for monitoring cutaneous malignancies in a pro-melanogenic state.

We reviewed literature that discusses increased skin pigmentation during pregnancy (generalized mild hyperpigmentation, darkening of hyperpigmented area such as the genitals, perineum, neck, axillae, inner thighs, periumbilical skin, and areolae). Increased skin pigmentation during pregnancy may be due to increased melanogenesis secondary to increased circulating β and α melanocyte-stimulating hormone (MSH), estrogen, progesterone, and β -endorphin. α -MSH is a major agonist for MC1R. A review article on melanocytic nevi in pregnancy argues that a changing melanocytic nevus in pregnancy (e.g., darkening in color, growth, atypical appearance) should be treated in a same manner as that in a non-pregnant woman.

Question 3:

Comment on the increased incidence of hyperpigmentation in Black subjects with incomplete resolution in 4 of 8 subjects. Is there any precedence for labeling this effect under special populations?

DDDP Response to Question 3:

Based on a search of FDA Label, it does not appear there is precedence for inclusion of the terms “hyperpigmentation,” “dyspigmentation,” or “pigmentation disorder” in Section 8 Use in Specific Populations.

Given the greater proportion of African American subjects experiencing a hrAE compared to Caucasian subjects (4.1% versus 0.6% in the placebo-controlled period and 5.1% versus 0.5% in the open-label period), we recommend inclusion of adverse reaction of hyperpigmentation in in the Section 5 **Warnings and Precautions** as pigmentary changes reported were in aesthetically important anatomical locations (face, gingiva).

Question 4:

Whether additional nonclinical studies or clinical studies would be needed to discern the concerns outlined above.

DDDP Response to Question 4:

We are not aware of additional nonclinical or clinical studies that would be useful in addressing the concerns presented in Questions 1 – 3.

In our opinion, routine post-marketing pharmacovigilance will be adequate to assess for potential of skin malignancy.

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/s/

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Maternal Health Team Review

Date: December 11, 2018 **Date consulted:** September 13, 2018

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

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

Drug: Bremelanotide

NDA: 210557

Applicant: AMAG Pharmaceuticals

Subject: Post-Marketing Requirement (PMR) to assess safety in pregnancy

Proposed Indication:

For the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical condition, problems with the relationship, or the effects of a medication or drug substance.

Materials Reviewed:

- Applicant's submission, dated March 23, 2018
 - Module 2.5, Clinical Overview
 - Module 2.7.4, Clinical Summary of Safety
 - Module 5.3.5, Integrated Summary of Safety, Section 3.4.3
 - Draft labeling

- Prior Division of Pediatric and Maternal Health Review NDA 022526, by L. Sahin, July 24, 2018 (DARRTS Ref ID 3796904)

Consult Question: Provide input on postmarketing studies to assess the potential risk of adverse outcomes with use of the drug during pregnancy

INTRODUCTION

On March 23, 2018, the applicant, AMAG Pharmaceuticals, submitted an original NDA for bremelanotide (BMT) for the treatment of premenopausal women with, acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty is not due to a co-existing medical condition, problems with the relationship, or the effects of a medication or drug substance. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested input from Division of Pediatric and Maternal Health (DPMH) on the approach to monitor/mitigate the risk of adverse pregnancy outcomes in the target population if the drug product should be approved.

BACKGROUND

Drug Characteristics

- BMT is a first-in-class, melanocortin (b) (4) receptor (b) (4) agonist
- Mechanism of action: (b) (4)
- Dosing regimen: 1.75 mg administered subcutaneously one time in 24 hours, as desired; packaged as a pre-filled syringe contained in a single use autoinjector
- MW: 1025.16 Daltons
- Plasma binding: low
- Half-life: mean 2.7 hours (range: 1.91 - 3.98 hours)
- Pharmacodynamic effect last up to 24 hours
- Important safety concerns (per communication with DBRUP Medical Officer): elevated blood pressure, hyperpigmentation, and intentional misuse.

Other HSDD Treatment

There is one FDA-approved treatment for HSDD, Addyi (flibanserin), a 5-HT agonist/5-HT2A antagonist. Addyi is administered orally one time a day, and may be discontinued after 8 weeks of no improvement. Addyi is available only through a Risk Evaluation and Mitigation Strategy (REMS) program that includes a restricted distribution program due to the risks of hypotension and syncope caused by an interaction between Addyi and alcohol. Prior DPMH consult for Addyi at the time of approval recommended PMR pregnancy studies.¹

REVIEW

Nonclinical Experience

DBRUP Nonclinical review is ongoing.

¹ DPMH Review NDA 022526, by L. Sahin, July 24, 2018 (DARRTS Ref ID 3796904)

Per the applicant’s proposed labeling, there were no adverse developmental effects when BMT was administered subcutaneously to mice at doses up to approximately 760 times the recommended human dose, or to dogs at dose exposures approximately 220 times the exposure at the recommended human dose. However, in a multigenerational study in mice, developmental delays were observed in the offspring of pregnant mice dosed at exposures approximately 125 times or greater the exposure at the recommended human dose.

Clinical Experience

There were 13 pregnancies that occurred during Phase 2/3 clinical trials; 7 with BMT-exposure. Four of these seven reported use of a contraceptive method (i.e., oral contraceptive, implant, IUD). The other three used no contraception. Pregnant patients were discontinued from the clinical trials and followed for outcome. Outcomes of the 7 BMT-exposed pregnancies were 4 full-term live births, 1 premature infant, 1 spontaneous abortion, and 1 outcome unknown. No congenital malformations were reported. Details from the BMT-exposed pregnancies are summarized in Table 1 below.

Reviewer Comment

The BMT-exposed pregnant patient (b) (6) with the unknown outcome was noted to have positive serum and urine pregnancy tests on the day she completed the study, (b) (6). Follow-up one month later noted the pregnancy was ongoing, with an estimated due date of (b) (6). Additional follow up by the investigator in (b) (6) noted that the patient was continuing the pregnancy, however, the patient declined to provide any further information and wished not to be contacted in the future.

Table 1: Summarized Outcomes of Bremelanotide-Exposed Pregnancies Reported in Phase 2/3 Clinical Trials (Courtesy: M. Whitaker, DBRUP Medical Officer)

USUBJID	Age/race	Exposure period	Outcome
(b) (6)	27 BF	(b) (6) 2 days after last dose (7 total doses)	Last information pregnancy ongoing. Subject declined further follow-up.
	37 WF	(b) (6) 42 days after last dose (6 total doses)	Spontaneous abortion 56 days after last dose (b) (6) SAE
	27 WF	(b) (6) 51 days after last dose (11 total doses)	Premature male infant at 37 weeks (b) (4)
	29WF	(b) (6) 43 days after last dose (10 total doses)	Full term live birth
	34 BF	(b) (6) 25 days after last dose (6 total doses)	Full term live birth
	40 BF	(b) (6) days after last dose (6 total doses)	Full term live birth
	35 BF	(b) (6) 2 days after last dose (61 total doses)	Full term live birth

*Based on Module 5.3.5, Integrated Summary of Safety, section 3.4.3, pp. 82-83.

The applicant states that there is no clinical data on BMT in pregnancy and lactation, and “[w]hile there is no perceived safety risk, . . . intends to conduct a (b) (4)

There is no information on use of BMT during lactation or the amount of BMT in human milk.

DISCUSSION

BMT is a new molecular entity (NME). There are no adverse developmental effects demonstrated in animal studies at doses and exposures clinically relevant to that of the recommended human dose. The limited human data (7 reported BMT-exposed pregnancies) are insufficient to identify a potential risk of major birth defects, miscarriage, or adverse maternal or infant outcomes. Pregnant women were excluded during the clinical development program, however, if approved, BMT is anticipated to have a larger number of exposures in the postmarketing setting, especially as the approved drug for HSDD (Addyi) has a restricted distribution program.

BMT’s indicated population is females of reproductive potential. The CDC reports that 10% of females of reproductive potential become pregnant each year and half of all pregnancies are unintended. Therefore, it is likely that exposures during pregnancy will occur. Postmarketing studies to assess outcomes following exposure in pregnancy are important to help characterize BMT’s safety in pregnancy.

A pregnancy exposure registry is the Agency’s preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.² In addition, pregnancy registries allow collection of patient level detailed data on potential confounders. However, pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design.³ Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a case control study or a retrospective cohort study using claims or electronic medical record data.

In addition, because there is anticipated high use in females of reproductive potential, it is important to collect information about potential for BMT exposure via breastmilk. A milk-only lactation study is recommended to determine drug concentration in breastmilk during a period of maximal use.

RECOMMENDATIONS

DPMH recommends postmarketing studies to evaluate the safety of BMT use during pregnancy and lactation: 1) a pregnancy registry study, 2) an additional observational study of a different design, and 3) a clinical lactation study.

² FDA Guidance for Industry Establishing Pregnancy Exposure Registries

³ FDA webpage Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>

DPMH recommends the following PMR language:

FDA has determined that you are required to conduct the following post-approval safety studies in pregnant women:

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to (b) (4). The registry will (b) (4) major and minor congenital malformations, spontaneous abortions, (b) (4) elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be (b) (4). Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

And

An additional study that uses a different study design from the Pregnancy Registry (for (b) (4)). (b) (4) Collect information to include, but not limited to, the following data elements (to the extent possible):

- *Age, demographics, body mass index*
- *Exposure to smoking, alcohol, drugs*
- *Medical history, concomitant medications, prenatal vitamins, obstetrical history*
- *Current pregnancy: date of last menstrual period/gestational dating, prenatal tests and ultrasound results; pregnancy status*
- *Bremelanotide exposure data (timing of exposure in pregnancy, dose, duration)*

And

Perform a lactation study (b) (4)

For guidance on how to establish a pregnancy exposure registry, the applicant should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626f1l.htm>. For information on complementary study methods, the applicant should review the FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>.

For information on clinical lactation studies, the applicant should review the Guidance for Industry: Clinical Lactation Studies Study- Design, Data Analysis, and Recommendations for Labeling available at <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf>. Draft study protocols should be submitted three months after product approval.

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/

TAMARA N JOHNSON
12/11/2018

LYNNE P YAO
12/12/2018

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 30, 2018

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Application Type and Number: NDA 210557

Product Type: Combination product

Drug Constituent Name and Strength Vyleesi (bremelanotide) injection, 1.75 mg/0.3 mL

Device Constituent: Autoinjector

Rx or OTC: Rx

Applicant/Sponsor Name: Amag Pharmaceuticals Inc

Submission Date: March 23, 2018; June 1, 2018

OSE RCM #: 2018-634; 2018-912

DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS

DMEPA Team Leader: Lolita White, PharmD

Associate Director for Human Factors: QuynhNhu Nguyen, MS

DMEPA Deputy Director: Danielle Harris, PharmD, BCPS

1. REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested a consultative review of a human factors (HF) validation study report and labels and labeling submitted under NDA 210557 for Vyleesi (bremelanotide) injection. This is a combination product with a proposed autoinjector device constituent part.

1.1 PRODUCT DESCRIPTION

The sponsor proposes an autoinjector (AI) presentation for Vyleesi (bremelanotide injection), which is intended for subcutaneous administration by patients at least 45 minutes before anticipated sexual activity. The proposed product is intended to treat premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty. Per the proposed Prescribing Information, patients should not administer more than one dose within 24 hours (see Appendix A).

1.2 REGULATORY HISTORY

On June 20, 2017, the sponsor submitted a use related risk analysis and human factors (HF) validation study protocol for Agency review.

On October 18, 2017, we provided recommendations for the HF validation study protocol and requested that the sponsor address the identified areas of concern prior to commencing the HF validation study.^a

On March 23, 2018, the sponsor submitted the HF validation study results and labels and labeling as part of this NDA submission.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering	C

^a Baugh, D. Human Factors Study Protocol Review for Bremelanotide injection IND 64119. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No.: 2017-1152.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
(HFE) Process	
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the HF study design, errors/close calls/use difficulties observed with critical tasks (Table 2), and our analysis to determine if the HF study results support the safe and effective use of the proposed product. We also provide our independent assessment of the labels and labeling and device (e.g. autoinjector).

3.1 SUMMARY OF STUDY DESIGN

We previously reviewed the HF validation study protocol and note that our recommendations were implemented.^b We find the study methodology acceptable.

The HF validation study included 32 female patient participants (16 with experience injecting an autoinjector and 16 without experience injecting an autoinjector). All participants were untrained and use of the IFU was optional and self-directed by the participants.

Each study participant attempted 2 injections: (1) a first-time use scenario, followed by (2) a second-time use scenario (study participants were instructed to imagine several days had passed and they were ready to use the product again).

We note that the HF validation study included a knowledge task question regarding the frequency of administration (e.g. “How often can you use this product?”) as previously recommended by the Agency in the HF protocol review. At the time of our HF protocol review, the proposed frequency of administration was one dose of Vyleesi per day and 8 doses per 4-week period. However, since the HF validation study, the sponsor revised the frequency of administration instructions to be less restrictive (e.g. no limit on doses within a 4-week period). We defer to the clinical review team regarding the acceptability of the revised frequency of administration instructions (see Appendix E).

^b Baugh, D. Human Factors Study Protocol Review for Bremelanotide injection IND 64119. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No.: 2017-1152.

3.2 RESULTS AND ANALYSES

Table 2 describes the errors/close calls/use difficulties observed with critical tasks in the HF study, the Applicant's analyses and proposed mitigation strategies, and DMEPA's analyses and recommendations.

APPEARS THIS WAY ON ORIGINAL

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

*Injection naïve patient = IN

Injection experienced patient = EX

Critical Tasks	Number and Details of Use Errors, Close Calls & Use Difficulties*	Applicant’s Root Cause Analysis	Applicant’s Mitigation Strategies	DMEPA’s Analysis and Recommendations
<p>Keep device pressed against skin until injection is complete (second click)</p>	<p>Session 1 2 participants did not keep the device pressed down until the second click</p> <ul style="list-style-type: none"> - 1 participant (EX16) did not keep the AI pressed down until the second click. The participant stated that they did not know to listen for a second click because their Humira device only has one click and she thought that the two devices would work similarly. - 1 participant (EX21) did not keep the AI pressed down until the second click. The participant said that their child’s EpiPen only has one click and assumed that the first click on this device meant that the injection was complete 	<ul style="list-style-type: none"> - Negative transfer (previous experience with Humira and EpiPen) 	<p>The sponsor noted that the IFU instructs users to listen for two clicks approximately two seconds apart and then wait for about additional 5 seconds and that both participants were able to locate and understand the IFU instructions. The sponsor determined that no further mitigation is required.</p>	<p>The potential harm associated with removing device prior to second click is underdose and drug leakage from injection site. In discussion with the clinical reviewer, we note that the risk of underdose does not have major clinical significance for this product. We also note that the sponsor indicated that a complete dose of the product is delivered within 1.6 seconds from the start of the injection (first click).</p> <p>Our review of the study results determined that the failures occurred in Session 1 only, which demonstrates to us that users may improve their performance with repeated use and potentially when pulling out the AI early, they would notice a “wet injection”.</p> <p>Additionally, our review of the study results did not identify subjective feedback indicating that the IFU could be improved to mitigate the risk of failures with this task.</p> <p>Our review of the labels and labeling finds the IFU instructions are acceptable. In particular, we find the IFU instructions</p>

Critical Tasks	Number and Details of Use Errors, Close Calls & Use Difficulties*	Applicant's Root Cause Analysis	Applicant's Mitigation Strategies	DMEPA's Analysis and Recommendations
				<p>are prominent and provide clear instruction to, "Press down and hold the autoinjector pen firmly against your skin...In about two seconds, you will hear a second click". There is also an accompanying graphic which further emphasizes to users to "Listen for SECOND CLICK about two seconds after injection".</p> <p>Therefore, we agree that no additional mitigation is required to address risk of the failure to properly remove device from injection site.</p>
<p>Hold device pressed against skin for 5 seconds after second click</p>	<p>Session 1 4 participants held the AI against the injection pad for less than 5 seconds after the second click</p> <ul style="list-style-type: none"> - 1 participant (IN01) quickly counted to 5 after the second click. The participant held the device against the pad for approximately 1 second after the second click. - 1 injection experienced participant (EX20) counted to five in their head. The participant held the device against the pad for approximately 2 seconds after the second click. - 1 participant (EX19) thought that the appearance of purple in the viewing window was indicated that it was okay to lift the AI. The participant indicated that they are used to watching the viewing window for Humira and Enbrel and thought this AI would work similarly. The participant held the device against the pad for approximately 2 seconds after the second click. - 1 participant (IN11) thought the IFU indicated to the lift the AI after the second click because she did not read 	<ul style="list-style-type: none"> - Counted the 5 seconds too quickly - Estimated the 5 seconds without counting - Did not count - Believed the appearance of purple in the viewing window was sufficient - Negative transfer (previous experience with Humira) - IFU confusion (did not read last bullet of Step 3) 	<p>The sponsor noted that a complete dose is delivered within 1.6 seconds from the start of the injection (first click) and the 5 second wait time is a greater duration than what is required. The sponsor stated that the majority of the participants that committed failure with this task held the AI against the skin for at least 2 seconds after the first click. The sponsor determined that no further mitigation is required.</p>	<p>The potential harm associated with not holding the device pressed against skin for 5 seconds after the second click is underdose and drug leakage from injection site. As previously noted, the risk of underdose does not have major clinical significance for this product. Additionally, our review of the study results indicates that 7 of the participants who committed failures held the device down for at least 2 seconds after the second click, which indicates a complete dose was administered. According to the sponsor, the actual injection delivery time is 1.6 seconds.</p> <p>Our review of the instructions for holding down the device and participant subjective feedback finds the instructions</p>

Critical Tasks	Number and Details of Use Errors, Close Calls & Use Difficulties*	Applicant's Root Cause Analysis	Applicant's Mitigation Strategies	DMEPA's Analysis and Recommendations
	<p>the last bullet of Step 3 and picture C's text sounded like you were done after the second click because picture D's text not close enough to picture C. The participant held the device against the pad for approximately 2 seconds after the second click.</p> <ul style="list-style-type: none"> - Note: For Session 1, only 30/32 participants were assessed because the 2 participants who could not be assessed because they lifted the AI before the second click (see previous task failures). <p>Session 2: 9 participants held the AI against the injection pad for less than 5 seconds</p> <ul style="list-style-type: none"> - 2 participants (b) (6) repeated the same failures in Session 2. - 1 participant (b) (6) quickly counted to 5 after the second click. The participant indicated that they would call the "800 number" in the IFU to describe what happened and ask for advice. - 1 participant (b) (6) counted to five in their head. The participant held the device against the pad for approximately 4 seconds after the second click. - 1 participant (b) (6) counted too quickly. The participant held the device against the pad for approximately 3 seconds after the second click. - 1 participant (b) (6) did not count out the 5 seconds because they were focused on monitoring the clicks and viewing window. The participant held the device against the pad for approximately 2 seconds after the second click. - 1 participant (b) (6) estimated the timeframe without counting. The participant held the device against the pad for approximately 2 seconds after the second click. 			<p>are acceptable. In particular, we find the IFU instructions are prominent and provide clear instruction to, "Continue to press and hold the autoinjector pen firmly against your skin for about 5 seconds after the second click to be sure your injection is complete.". There is also an accompanying graphic which further emphasizes to users to "Wait 5 seconds" after the second click.</p> <p>We agree that no additional mitigation is required to address risk of the failure to properly remove device from injection site.</p>

Critical Tasks	Number and Details of Use Errors, Close Calls & Use Difficulties*	Applicant's Root Cause Analysis	Applicant's Mitigation Strategies	DMEPA's Analysis and Recommendations
	<ul style="list-style-type: none"> - 1 participant (b) (6) misread the IFU and though the instruction said 3 seconds instead of 5 seconds. The participant said that they saw the viewing window was purple and knew the injection was complete. The participant held the device against the pad for less than 5 seconds after the second click. - 1 participant (b) (6) stated that they did not know to hold the AI for 5 seconds after the second click because they do not have to wait long after one click with Humira and thought the devices would work similarly. The participant held the device against the pad for less than 2 seconds after the second click. 			
<p>Remove device from injection site</p>	<p>Session 1: 2 participants did not remove the device from the injection site correctly</p> <ul style="list-style-type: none"> - 1 participant (b) (6) tilted the AI before removing it from the injection site. The participant was trying to visualize the viewing window to confirm completion and the IFU detail did not stand out to the participant. - 1 participant (b) (6) was also trying to visualize the viewing window to confirm completion and they knew from the IFU to insert needle with viewing window visible, but forgot during point of use. 	<ul style="list-style-type: none"> - Attempting to visualize the viewing window - IFU detail did not stand out to participant - Forgot IFU step at point of use 	<p>The sponsor noted that after prompting, both participants were able to locate and understand the IFU language regarding removal of the device. As such, the sponsor determined that the IFU is clear. The sponsor stated that once the AI has been activated and the injection cycle is completed, the needle mechanism is retracted and locked in place. The sponsor determined that no further mitigation is required.</p>	<p>The potential harm associated with not properly removing the AI from the injection site (e.g. AI moved/ tilted) is risk of detachment or breakage of cannula. Our review of the study results determined that the failures occurred in Session 1 only, which demonstrates to us that users may improve their performance with repeated use.</p> <p>Our review of the instructions for removal of the AI finds the instructions are acceptable. In particular, the IFU instructs users in bold font to, "Remove the autoinjector pen from your skin by lifting it straight out.". Therefore, we agree that no additional mitigation is required to address risk of the failure to properly remove device from injection site.</p>

3.3 ANALYSIS OF ESSENTIAL /NON-CRITICAL TASKS

We acknowledge that there were use-related issues (e.g. use errors, close calls, and use difficulties) on non-critical tasks. However, our review of the subjective feedback and root cause analyses did not generate any concerns from a medication error perspective. In addition, we disagree with the sponsor's categorization of the following tasks as critical tasks as they are not unique to the use of the proposed product: clean injection site, remove cap and do not replace, failure to check expiration date, and failure to check drug and device appearance/integrity. We reviewed the failures of the other essential tasks and find the risks are mitigated to an acceptable level.

3.4 LABELS AND LABELING

We identified concerns with the label and labeling from a medication error perspective. Table 3 for the division and Table 4 for sponsor include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

3.5 ASSESSMENT OF DEVICE

We received samples of the proposed device (e.g. autoinjector) for evaluation. We did not identify any additional areas of concern.

Table 3: Identified Issues and Recommendations for Division of Bone, Reproductive, and Urologic Products			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	(b) (4)		

Table 4: Identified Issues and Recommendations for Amag Pharmaceuticals (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The IFU (Word version only) has formatting issues.	Formatting issues might contribute to confusion regarding administration.	<p>We note you submitted IFUs in PDF and Word format. However, conversion of the IFU from PDF to Word appears to have led to formatting issues on the Word version. For example:</p> <ul style="list-style-type: none"> - The color of the purple tip of the autoinjector appears gray instead of purple - The “Wait 5 seconds” graphic in Step 3 appears distorted - The graphics in Step 4 appear distorted <p>Please confirm whether your intend-to-market product will use the IFU in PDF format only or both PDF and Word format. If you intend to use the IFU in Word format as part of the intend-to-market labeling, address the formatting issues above.</p>
Container Labels			
1.	(b) (4)		

2.	The container label does not have a barcode.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Revise the container label to include a linear barcode as required per 21 CFR 201.25(c)(2).
3.	The expiration date is not defined.	As currently presented, the format for the expiration date is not defined.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY- MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY- MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4.	The Rx Only statement has equal prominence to other important information on the principal display panel (PDP).	The “Rx only” statement should appear less prominent than other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP.	Decrease the prominence of the statement “Rx Only” as this information appears to equal prominence with the established name on the PDP. ^c
5.	The container label does not indicate the frequency of administration.	The clinical review team identified the potential for intentional misuse. The presence of a usual dose statement on the container label might help mitigate risk of intentional misuse.	If space permits, include the statement “No more than 1 dose in 24 hours” on the container label.
Carton Labeling			
1.	The Rx Only statement is not on the PDP.	The Rx only statement should appear on the PDP.	Relocate the “Rx Only” statement to the principal display panel (PDP) and ensure that it appears less prominent than other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP. ^d

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

2.	The expiration date format is prone to confusion.	As currently presented, the format for the expiration date might be confused and deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, revise the current expiration date (e.g. 100917). FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	The carton labeling does not indicate the frequency of administration.	The clinical review team identified potential for intentional misuse. As such, we find the usual dose statement on the carton labeling can be revised to indicate the frequency of administration.	Consider revising the statement [REDACTED] (b) (4) to include “No more than 1 dose in 24 hours”.

4. CONCLUSION AND RECOMMENDATIONS

We acknowledge that use errors occurred in the HF validation study. However, based on our assessment of the subjective feedback and user interface, for reasons listed in Table 2, we find the residual risks are acceptable. However, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the applicant/sponsor so that recommendations are implemented prior to approval of this NDA 210557.

4.1 RECOMMENDATIONS FOR THE AMAG PHARMACEUTICALS

Based on our evaluation of the HF validation study results and our evaluation of proposed packaging, label and labeling, we identified areas of vulnerability that may lead to medication errors. We have provided recommendations in the “Identified Issues and Recommendations” table below and we recommend that you implement these recommendations and submit the revisions to your NDA 210557.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for bremelanotide injection that Amag Pharmaceuticals submitted on June 1, 2018.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	NME; melanocortin ^(b) ₍₄₎ receptor agonist
Active Ingredient (Drug or Biologic)	bremelanotide
Indication	<p>treatment of premenopausal women with, acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:</p> <ul style="list-style-type: none"> • A co-existing medical or psychiatric condition, • Problems with the relationship, or • The effects of a medication or drug substance. <p>Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation or partner.</p>
Route of Administration	subcutaneous
Dosage Form	injection solution
Strength	1.75 mg/0.3 mL
Dose and Frequency	<p>1.75 mg administered subcutaneously as desired at least 45 minutes before anticipated sexual activity. ^(b)₍₄₎</p> <p>Administered by subcutaneous injection via a prefilled autoinjector pen into the abdomen or thigh, based on patient preference. Patients should not administer more than one dose within 24 hours.</p>
How Supplied	Available as 1.75 mg in 0.3 mL solution in a single use, disposable prefilled autoinjector; available as a 4-pack (NDC 64011-701-04).
Storage	Store at or below 25°C (77°F). Do not freeze. Protect from light.

Container Closure/Device Constituent	(b) (4)
Intended Users	Patients
Intended Use Environment	Home

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On June 18, 2018, we searched the L:drive and AIMS using the term, bremelanotide, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews^{e,f}, and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

^e Baugh, D. Human Factors Study Protocol Review for Bremelanotide injection IND 64119. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No.: 2017-1152.

^f Fava, W. Human Factors Review for Bremelanotide injection IND 64119. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 6. RCM No.: 2016-639.

<\\cdsesub1\evsprod\nda210557\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hsdd-in-pre-menopausal-women\5354-other-stud-rep\pala0311\pala0311.pdf>

APPENDIX D HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\cdsesub1\evsprod\nda210557\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hsdd-in-pre-menopausal-women\5354-other-stud-rep\pala0311\pala0311.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

In a June 1, 2018 Information Request, we requested that the sponsor clarify the intend-to-market IFU labeling due to a difference in the IFU used in the HF validation study as compared to the intend-to-market IFU. In their response, the sponsor stated that noted that they do not intend to reference “no more than 8 doses in a 4-week period” in the commercial IFU because they find that bremelanotide has been dosed more than 8 times in a 4-week period without any safety concerns. The sponsor also submitted supporting clinical data. We defer to the Clinical review team regarding the acceptability of this supporting information.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Bremelanotide injection labels and labeling submitted by Amag Pharmaceuticals Inc.

- Container label received on June 1, 2018
- Carton labeling received on June 1, 2018
- Instructions for Use (Image not shown) received on June 1, 2018
- Prescribing Information (Image not shown) received on June 1, 2018

F.2 Label and Labeling Images

Container label



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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/

EBONY A WHALEY
11/30/2018

LOLITA G WHITE
11/30/2018

QUYNHNHU T NGUYEN
12/03/2018

DANIELLE M HARRIS
12/04/2018



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Pharmaceutical Quality
Office of Biotechnology Products/Division III
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum of Immunogenicity Review

NDA: 210557

Subject: To evaluate whether the Sponsor adequately addressed the immunogenicity of the drug, Bremelanotide

Primary Reviewer: Davinna L. Ligons, Ph.D.
Secondary Reviewer: Susan Kirshner, Ph.D.

Product: Bremelanotide

Sponsor: AMAG Pharmaceuticals, Inc.
Indication: Hypoactive sexual desire disorder (HSDD)

Route of Administration: Subcutaneous injection
Dose Regimen: 1.75 mg as desired

RPM: Jeannie Roule

Clinical Division: Division of Bone, Reproductive, and Urologic Products

Received Date: 5/10/2018
Action Due Date: 10/30/2018

Recommendation:

From an immunogenicity assay perspective, this NDA is recommended for approval. A competitive binding assay demonstrates that bremalanotide most likely does not bind HLA class II alleles which is required to drive an anti-drug antibody response. Consistent with these findings, pharmacokinetic and clinical efficacy responses do not appear to be impacted by anti-drug antibody responses.

Review:

Background

Bremalanotide (BMT) is a synthetic cyclic heptapeptide and has high affinity for melanocortin receptors, MC1R, MC3R, and MC4R. BMT is an analog of alfa-melanocyte-stimulating hormone (α -MSH). BMT and α -MSH share 4 amino acids in their sequence.

Bremalanotide: Ac-Nle-cyclo (Asp-His-D-Phe-Arg-Trp-Lys-OH)

α -MSH: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH₂

Immunogenicity assessment of BMT was not performed; however, as requested by the Agency, a risk assessment was provided to address potential cross-reactivity to α -MSH. Based on the risk assessment, the following reasons were proposed to support the lack of anti-BMT responses and the possible cross-reactivity to α -MSH.

1. Contains a non-natural amino acid, a D- amino acid, and cyclic structure which are expected to reduce immunogenicity
2. Minimal sequence and structural homolog with α -MSH
3. Low probability of binding to HLA class II molecules and thus, low probability of inducing anti-drug responses
4. Failure to bind to tested HLA class II molecules
5. No systemic adverse immune drug responses reported following subcutaneous administration of the drug
6. No rapid diminishing response to the drug suggesting no anti-drug responses or neutralizing antibodies are formed
7. Consistent drug exposure levels for up to 18 months of subcutaneous administration on an as needed basis

The below comment was communicated to the Sponsor at the pre-IND meeting by the Agency:

“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 alfa-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.”

Review of Risk Assessment

1. Bremelanotide (BMT): Potential for Immunogenicity

The Sponsor was not successful in generating anti-BMT antibodies. Antibodies were only generated to BMT when BMT was conjugated to keyhole limpet hemocyanin (KLH) protein, which suggests that BMT on its own is not sufficient to generate an immune response. The Sponsor proposes that the short peptide sequence of 7 amino acids, the cyclic structure, presence of a D-amino acid, and the non-natural amino acid norleucine decreases its ability to bind to HLA class II molecules and generate an anti-BMT antibody response. α -MSH has 10 amino acids and is linear. The Sponsor suspects that even if an immune response to BMT were to be induced, it is unlikely that there would be cross-reactivity to α -MSH because of the differences in structure and amino acid composition.

In silico technology could not be used to determine the binding affinity to HLA class II because the in silico programs are not designed to examine D-amino acids, cyclic structures, and peptides with fewer than 10 amino acids. Thus, the Sponsor examined the binding of BMT to HLA class II molecules in vitro. A competitive binding assay addressed the ability of BMT to compete with medium and high affinity control peptides to the following HLA class II molecules: DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*0801, DRB1*1101, DRB1*1301, DRB1*1501. The control tracer peptide is fluorescently labeled and fluorescent counts of the control tracer peptide are maintained even when increasing amounts of unlabeled BMT are added to the assay as indicated by the red line in Figure 1 below. These data indicate that BMT does not compete for binding the HLA molecule which suggests that BMT may have low or no affinity for HLA II molecules.

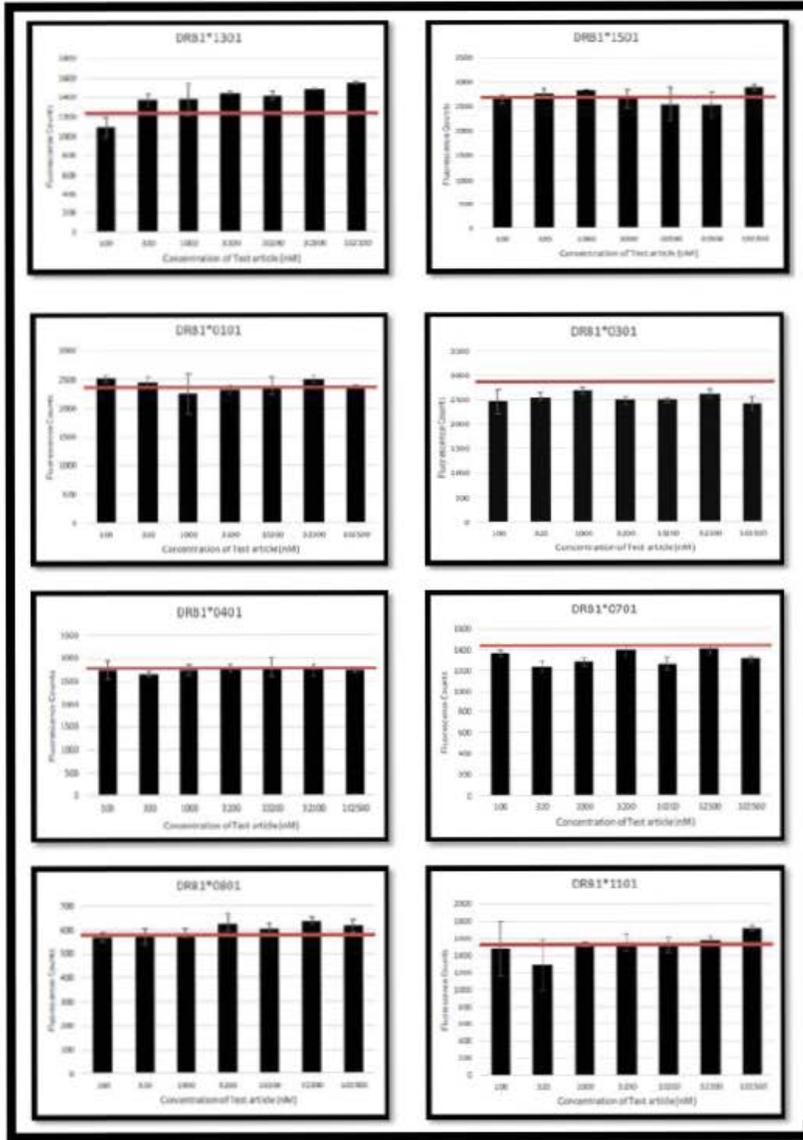
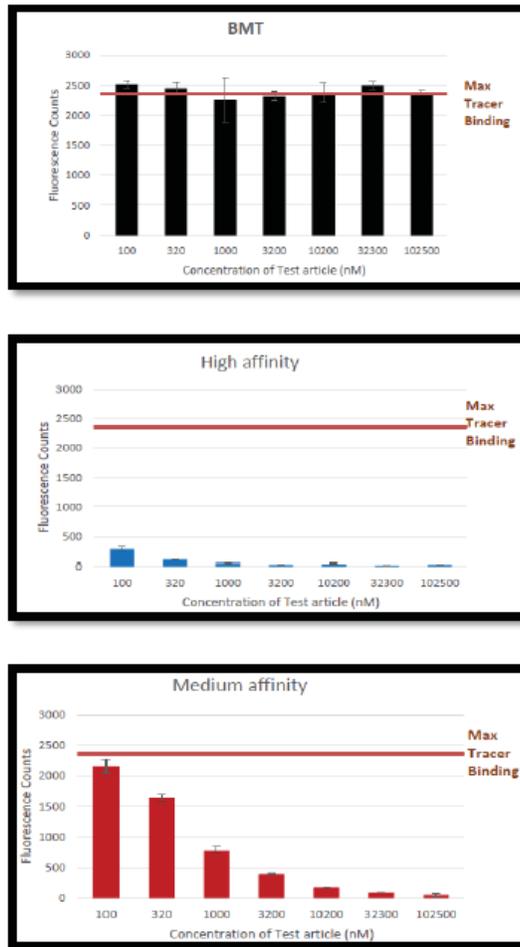


FIGURE 1: BMT (test article) Class II HLA binding results for the eight alleles. Raw fluorescence counts are shown in relation to the fluorescence recorded in absence of competitor peptide (Red Line).

When other unlabeled peptides with known affinity to HLA class II molecules were added in the binding assay, they were competitive and reduced the fluorescent signal as shown for DRB1*0101 in the figure below.

DRB1*0101



Representative result from the class II HLA binding assays (shown are data from DRB1*0101 allele). **Top Panel:** BMT fails to inhibit binding of biotinylated competitor peptide. Shown are raw fluorescence counts in relation to the fluorescence recorded in the absence of competitor peptide (i.e., **Max Tracer Binding**). **Middle Panel:** High affinity control peptide (test article) inhibits binding of biotinylated competitor peptide. **Bottom Panel:** Medium affinity control peptide (test article) inhibits binding of biotinylated competitor peptide in a dose-dependent manner.

In the information request (IR) response dated September 14, 2018 (sequence #0028), the Sponsor provided additional data to show that the binding pattern of BMT resembles a “non-binder” pattern, as shown in Figure 2 below. The Sponsor tested over 1,000 peptides –allele pairs and the profiles in Figure 2 were observed. Depending on the dose response curves and the IC_{50} , the peptides could be determined to have high, medium, or low affinity or a non-binder.

Figure 2: Figure 2. Class II HLA binding results for High/Medium/Low/Negligible Affinity and Non-binder peptides



Raw fluorescence counts are shown in relation to the fluorescence recorded in absence of competitor peptide (Dark Orange Line). Dose response curves are seen for all of the peptides (see decrease in raw fluorescence counts as concentration of test article increases) with important exceptions: For low and negligible affinity peptides, dose response is only seen at the highest concentrations. When the test article does not interact with the HLA binding groove (non-binder), no decrease in fluorescence is seen.

Figure 3 shows the binding results for BMT across the eight alleles that were tested in the assay. The results for BMT are most consistent with the “non-binder” profile shown in Figure 2; BMT does not exhibit any discernible dose response even at the highest concentration tested (100,000nM) for any of the alleles.

Reviewer comments:

Based on the data provided in the immunogenicity risk assessment, we suspected that using a low affinity peptide in the binding assay may reveal that BMT is a competitive binder to class II molecules and that BMT does bind HLA class II alleles. In response to an IR, the Sponsor stated that low affinity peptides are not suitable for the following reasons: 1) high disassociation rate leading to reduced binding, 2) higher concentrations required, and 3) increased non-specific binding. The Sponsor proposes that using a low affinity peptide will shift the dose response curve relative to the control; however, the profile of the dose response curve should not change. The Sponsor expects that if a low affinity peptide was used in the competitive assay with BMT, a “non-binder” profile would still emerge. If this is the case, this would be consistent with the data observed when using medium and high peptides. Furthermore, depending on the dose dependent profile, the competitive binding assay is capable of distinguishing low, and negligible affinity peptides from non-binders. Specifically, the non-binders do not show a dose response at the high concentrations of the competitor which contrast with low and negligible affinity peptides.

In addition, the Sponsor proposes that the competitive binding assay is more informative than a direct binding assay, in this case, because peptides can bind outside the HLA peptide groove which cannot be distinguished in a direct binding assay. The competitive assay allows for the detection of the binding of competitor peptide to the HLA groove, because of competition with a tracer peptide that binds the HLA groove.

The Sponsor provided data indicating that distribution of the selected HLA alleles used in the competitive assay and their representative family members covers about 95% of the global population.

Overall, the competitive binding assay is acceptable to demonstrate that BMT most likely has no affinity to HLA class II alleles.

Clinical Data Are Consistent with Lack of BMT Immunogenicity

Approximately 3500 patients have been treated with Bremelanotide in 43 clinical studies involving indications of erectile dysfunction, (b) (4) and HSDD. Specifically regarding HSDD, more than 1500 women received at least 1 subcutaneous dose of BMT, 430 received intranasal BMT, and 10 received intravenous BMT with dosing up to 20 mg. Based on clinical experience, no adverse events that could be associated with an immune response to BMT were found and no rapid loss in drug response has been observed. Specifically, for patients in the HSDD phase III clinical trials, 28 patients had local skin reactions at the injection site and 4 patients developed mild to moderate hypersensitivity at the inject site which 2 of these patients withdrew from the trial. None of the patients exhibited systemic manifestations suggestive of a hypersensitivity reaction.

Efficacy and treatment response to BMT was maintained throughout both phase III clinical trials (301 and 302) as shown in figure 2 below for the clinical endpoint of desire. The clinical endpoint of distress declines overtime in the BMT treated group.

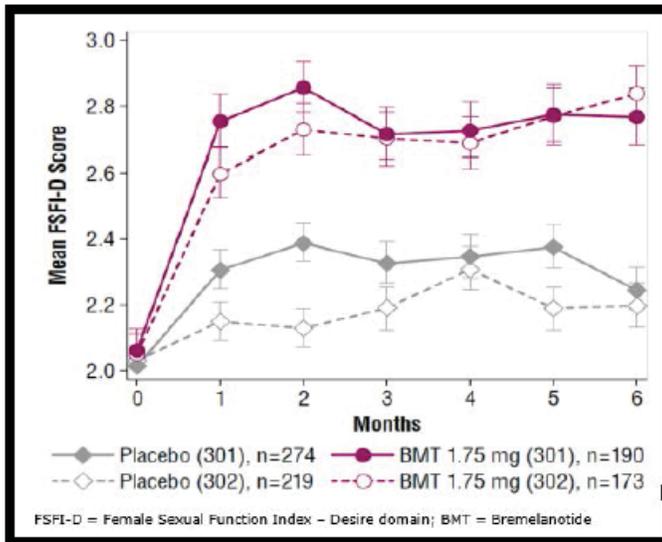


FIGURE 2: Mean FSFI Desire Domain Scores for Placebo and BMT over the Core (Double-Blind) Phase 3 Studies (BMT-301 (closed purple circles) and BMT-302 (open purple circles))

Drug levels in the blood were evaluated on days 2, 8 and 15 with 3 doses of BMT administered per day. The drug levels were consistent as indicated by the ratio being near 1 when comparing day 8 to day 2, day 15 to day 8, and day 15 to day 2 as shown in the table below.

TABLE 1: Summary of Accumulation Ratios for Day 8 to Day 2, Day 15 to Day 8, and Day 15 to Day 2.

COMPARISON	STATISTIC	RATIO
DAY 8/DAY 2	N	26
	MEAN	0.9558
	95% CI FOR MEAN	0.8643-1.047
DAY 15/DAY 8	N	26
	MEAN	1.120
	95% CI FOR MEAN	1.046-1.194
DAY 15/DAY 2	N	27
	MEAN	1.046
	95% CI FOR MEAN	0.9583-1.134

CSR PT-141-2008-38 Table 11.2.2

Note(s): Accumulation ratio was calculated as the mean concentration at 1 hour following the first dose on the later day divided by the mean of the earlier day. SD = standard deviation; %CV = coefficient of variation; CI = confidence interval.

Reviewer comments:

Regarding pharmacokinetic (PK) analysis, 15 days is likely not enough time to observe a robust immune response that would affect drug levels. The clinical pharmacology reviewer confirms that for BMT administered via subcutaneous injection there are no PK data available beyond 15 days. Pharmacodynamic (PD) effects of the drug are not strongly demonstrated when compared to the placebo group. Thus, it is difficult to assess anti-drug antibody responses from an efficacy point of view. The clinical reviewer confirms that the clinical endpoint of desire was constant overtime while distress steadily declined overtime. The PK data and reported efficacy are the expected results if there was no effect of anti-drug antibodies. In addition, the absence of a hypersensitivity response is not indicative of the absence of anti-drug antibody responses or the lack of cross-reactivity to related endogenous antigens. However, while anti-drug antibodies do not always have an effect on PK, and PD or induce hypersensitivity, these clinical data in combination with the in vitro binding assay data which suggest that BMT does not bind HLA class II supports that there is likely not an immune response to BMT.

As a reference, the clinical design for phase II and phase III studies are provided in the table below.

Study	Study Treatments	Randomized Subjects	Route of Admin.	Subject Population	Treatment Duration
PHASE 3 CLINICAL STUDIES					
BMT-301 (Core) and BMT-301 (OLE) Efficacy and safety of SC administered BMT in premenopausal women with HSDD with or without decreased arousal	PBO: 0.3 mL in autoinjector Study drug: 1.75 mg BMT (0.3 mL in autoinjector)	<u>Single-blind period:</u> 723 subjects (PBO) <u>Double-blind period:</u> (randomized): 643 subjects (safety population: 324 BMT; 319 PBO)	SC	Subjects with HSDD (with or without decreased arousal)	<u>Core Study Phase:</u> <u>Single-blind:</u> 4 weeks (PBO) <u>Double-blind:</u> 24 weeks (subjects randomized 1:1 to PBO or BMT) <u>OLE Study Phase:</u> 52 weeks
BMT-302 (Core) and BMT-302 (OLE) Efficacy and safety of SC administered BMT in premenopausal women with HSDD with or without decreased arousal	PBO: 0.3 mL in autoinjector Study drug: 1.75 mg BMT (0.3mL in autoinjector)	<u>Single-blind period:</u> 703 subjects (PBO) <u>Double-blind period</u> (randomized) 604 subjects (safety population: 303 BMT; 301 PBO)	SC	Subjects with HSDD (with or without decreased arousal)	<u>Core Study Phase:</u> <u>Single-blind:</u> 4 weeks (PBO) <u>Double-blind:</u> 24 weeks (subjects randomized 1:1 to PBO or BMT) <u>OLE Study Phase:</u> 52 weeks
PHASE 2 CLINICAL STUDIES					
PT-141-54 Dose-finding study, evaluation of safety and efficacy of SC administered BMT	PBO Study drug: 0.75/1.25/1.75 mg BMT	397 subjects total BMT: 149 subjects PBO: 248 subjects	SC	FSAD and/or HSDD	<u>Core:</u> <u>Single-blind:</u> 4 weeks (PBO) <u>Double-blind:</u> 14 weeks (subjects randomized 1:1:1:1 to PBO or BMT)
PT-141-2004-52FB Effect of SD (IN) BMT in premenopausal and postmenopausal women with FSAD	PBO Study drug: 20 mg BMT (SD crossover)	45 subjects total Premenopausal: 18 subjects Postmenopausal: 27 subjects	IN	FSAD with/without decreased desire	2 to 10 mg BMT doses/day on 2 days (2 to 7 days apart)
Study					
PT-141-2005-53FB Exploratory study to evaluate safety and efficacy of IN administered BMT	PBO Study drug: 10 mg BMT	163 subjects total Premenopausal: 76 subjects Postmenopausal: 87 subjects	IN	FSAD with/without decreased desire	8 weeks (10 doses of study drug provided to subjects for self-administration randomized 1:1)

Abbreviations: BMT=bremelanotide; FSAD=female sexual arousal disorder; HSDD=hypoactive sexual desire disorder; IN=intranasal; OLE=open-label extension; PBO=placebo; SC=subcutaneous; SD=single dose.

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/s/

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