

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213793Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 112595

MEETING MINUTES

Rhythm Pharmaceuticals, Inc.
Attention: Joanne Totosy de Zepetnek, PhD
VP Regulatory Affairs
222 Berkeley Street; Suite 1200
Boston, MA 02116-3748

Dear Dr. Totosy de Zepetnek:

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

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2019. The purpose of the meeting was to reach agreement on submission of a new drug application (NDA) for setmelanotide.

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

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

John M. Sharretts, MD
Deputy Director (Acting)
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 27, 2019; 11:00 AM - 12:30 PM
Meeting Location: White Oak; Bldg 21 - Room 1537

Application Number: IND 112595
Product Name: setmelanotide (RM-493) injection

Indication: treatment of obesity [REDACTED] (b) (4) associated with pro-opiomelanocortin (POMC) deficiency obesity or leptin receptor (LEPR) deficiency obesity in individuals 6 years of age and above

Sponsor Name: Rhythm Pharmaceuticals, Inc.

Meeting Chair: John M. Sharretts, MD
Meeting Recorder: Patricia Madara, MS

FDA Attendees

Office of New Drugs (OND): Program for Rare Diseases

Melanie Blank, MD Medical Officer

OND: Clinical Outcomes Assessment (COA) Team

Elektra Papadopoulos, MD, MPH Associate Director
Ebony Dashiell-Aje, PhD Team Leader (Acting)
Yujin Chung, PharmD COA Reviewer

OND: Office of Drug Evaluation II

Mary Thanh Hai, MD Director (Acting)

OND: ODE II: Division of Metabolism and Endocrinology Products

Lisa Yanoff, MD Director (Acting)
John Sharretts, MD Deputy Director (Acting)
Ovidiu Galescu, MD Medical Officer
Fred Alavi, PhD Pharmacology/Toxicology Reviewer
Patricia Madara, MS Regulatory Project Manage

Office of Translational Sciences (OTS): Office of Biostatistics: Division of Biometrics II

Feng Li, PhD	Team Leader
Roberto Crackel, PhD	Statistical Reviewer

OTS: Office of Clinical Pharmacology (OC): Division of Clinical Pharmacology II

Jaya Vaidyanathan, PhD	Clinical Pharmacology Team Leader
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OTS; OC; Genomics and Targeted Therapy Group

Katarzyna Drozda, PharmD, MS	Reviewer
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Office of Pharmaceutical Quality(OPQ):Office of New Drug Products API:Branch II

Joe Leginus, PhD	CMC Reviewer
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Office of Pharmaceutical Quality (OPQ); Office of New Drug Products II; Branch VI

Muthukumar Ramaswamy, PhD	Quality Assessment Lead
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OPQ: Office of Biotechnology Products (OBP): Division of Biotechnology Review and Research II (DBRR II):

Harold Dickensheets, PhD	Team Leader
Sarah Johnson, PhD	Biologist

Center for Device Evaluation and Radiological Health: Office of In Vitro Diagnostics and Radiological Health: Division of Chemistry and Toxicology Devices: Cardio-Renal Diagnostics Branch

Brittany Schuck, PhD	Senior Staff Fellow
Paula Caposino, PhD	Cardio-renal Diagnostic Branch Chief

OSE: OMEPRM: Division of Risk Management (DRISK)

Till Olickal	General Health Scientist
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Office of Compliance: Office of Scientific Investigations: Division of Clinical Compliance Evaluation: Good Clinical Practice Assessment Branch

Min Lu, MD, MPH	Team Leader
Cynthia Kleppinger, MD	Senior Medical Officer

Sponsor Attendees

Joanne Totosy de Zepetnek, PhD
Murray Stewart, MD
Elizabeth Stoner, MD
Hillori Connors, MD
Scott Segal, MD

(b) (4)

Iliial Cetovkin
Jaya Gautam

(b) (4)

Keith Gottesdiener, MD

(b) (4)

Vice-President, Regulatory Affairs
Chief Medical Officer
Senior Medical Advisor
Vice-President, Clinical Operations
Clinical Development

(b) (4)

Rhythm Pharmaceuticals
Rhythm Pharmaceuticals

(b) (4)

Chief Executive Officer

(b) (4)

1.0 Background

Setmelanotide (RM-493) is a melanocortin 4 receptor (MC4R) agonist being developed as a treatment for severe, early-onset obesity and hyperphagia associated with rare, genetically defined syndromes impacting the hypothalamic leptin-melanocortin-MC4R pathway. The sponsor (Rhythm Pharmaceuticals, Inc.) has proposed that by directly stimulating the MC4R, setmelanotide will be an effective treatment for syndromes resulting from defects upstream of the MC4R.

On May 1, 2017, FDA granted Breakthrough Therapy Designation (BTD) for setmelanotide for the indication described above. Phase 3 studies of setmelanotide as a treatment for proopiomelanocortin (POMC) deficiency and leptin receptor (LEPR) deficiency are currently ongoing.

On July 3, 2019, the sponsor requested a preNDA meeting with FDA and the meeting was granted on July 17, 2019. In addition, on July 26, 2019, Rhythm submitted a request for rolling submission of portions of the new marketing application. This request was granted on August 7, 2019, and a portion of the first module was submitted on August 23, 2019.

The purpose of this preNDA meeting was to obtain guidance and reach agreement on the organization and presentation of data in the application. Since setmelanotide is a new molecular entity (NME), it will be reviewed under "the Program." Therefore, it will be important to reach agreement on a complete application, and any minor components to be submitted within 30 days. Discussions and agreements will be summarized at the end of the meeting and in these minutes.

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2.0 Discussion

FDA provided preliminary comments on September 25, 2019, and the sponsor sent premeeting responses / questions on September 26, 2019. There was no review of the sponsor responses prior to the meeting.

FDA premeeting comments are in regular font, Rhythm's premeeting responses follow in italics. The meeting discussion is in bold font.

Prior to discussion of the questions, the sponsor provided a brief update on the status of setmelanotide development.

2.1. Clinical

Question 1: Efficacy

Does FDA agree that the top line efficacy data from the Phase 3 trials demonstrate a clinically meaningful effect of setmelanotide on weight loss (b) (4) in POMC and LEPR patients?

FDA Pre-meeting Comment

1. The reported results of the Phase 3 studies appear to demonstrate a clinically meaningful effect on weight in both populations. The final determination of effectiveness on the weight loss endpoints will depend on our review of the data.
2. We acknowledge that your trials are complete and that you have provided preliminary results on the Daily Hunger Questionnaire (b) (4), the open-label design of the treatment phases in Study RM-493- 012 and Study RM-493-015 pose a limitation to patient-reported outcome (PRO) data interpretation. Patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect. Lack of blinding will need to be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial. PRO results can also be further supported by findings from other endpoints and by sensitivity or subgroup analyses comparing the findings relative to other data collected in the trial. For instance, reduction in hunger measured by a PRO assessment could be further supported by weight loss or reduction in waist circumference.
3. Insufficient evidence was provided for us to assess whether the Daily Hunger Questionnaire is fit-for-purpose. You need to provide the following for review under the NDA:
 - a. Evidence to support the content validity
 - b. Results from the evaluation of the psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change)
 - c. User manuals or patient/investigator training materials, including instructions for

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administration, for all clinical outcomes assessments (COAs) that were administered in the study

- d. Scoring algorithm(s) with rationale for any weighting of items or response options and corresponding information on how the instrument's scores will be analyzed as part of an endpoint
- e. A priori improvement threshold (or range of thresholds) representing clinically meaningful within-patient change in the instrument's scores using anchor-based methods (along with eCDF curves).

A small study sample will make interpretation of clinically meaningful within-patient change results challenging, therefore, we recommend that you also submit individual patient profiles to characterize observed improvements experienced by patients throughout the duration of the study. This data will help to provide an accumulation of evidence that will aide in interpretation of what would constitute a clinically meaningful improvement in PRO scores. Please provide the following for Agency review in your NDA.

Protocol RM-493-012**A. GROUP SUMMARY TABLES**

- a. Provide a summary of clinical and demographic characteristics for each of the patients (≥ 12 years of age) enrolled in the RM-493-012 Study.

	Patient 001	Patient 002	...	Patient XXX
Age [years]	--	--		--
Gender (Male, Female)	--	--		--
Race/Ethnicity	--	--		--
Treatment Regimen	--	--		--
Baseline Symptom Severity	--	--		--

B. INDIVIDUAL PATIENT PROFILES (ORGANIZED BY EACH PATIENT; ALL INFORMATION BELOW PRESENTED PER PATIENT)

- a. Provide individual patient profiles, in tabular format for each of the patients (≥ 12 years of age) enrolled in Study RM-493-012.

Example: Patient 001

	PRO: Hunger Score (Average)	PRO: Hunger Score (Most hungry)	PRO: Hunger Score (Least hungry)	PRO: Hunger Score (This morning)	PRO: Global Hunger Item 1	PRO: Global Hunger Item 2	Weight	BMI	BP/HR	HbA1C	Lipid Profile	Waist circumference	Height
Baseline	--	--	--	--	--	--	--	--	--	--	--	--	--
Week 3	--	--	--	--			--					--	
Week 5	--	--	--	--			--					--	
Week 9	--	--	--	--			--					--	
Week 13	--	--	--	--	--	--	--	--	--	--	--	--	--
Week 17	--	--	--	--	--	--	--					--	

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Protocol RM-493-015

C. GROUP SUMMARY TABLES

a. Provide a summary of clinical and demographic characteristics for each of the patients (≥ 12 years of age) enrolled in the RM-493-015 Study.

	Patient 001	Patient 002	...	Patient XXX
Age [years]	--	--		--
Gender (Male, Female)	--	--		--
Race/Ethnicity	--	--		--
Treatment Regimen	--	--		--
Baseline Symptom Severity	--	--		--

D. INDIVIDUAL PATIENT PROFILES (ORGANIZED BY EACH PATIENT; ALL INFORMATION BELOW PRESENTED PER PATIENT)

a. Provide individual patient profiles, in tabular format for each of the patients (≥ 12 years of age) enrolled in Study RM-493-015.

Example: Patient 001

	PRO: Hunger Score (Average)	PRO: Hunger Score (Most hungry)	PRO: Hunger Score (Least hungry)	PRO: Hunger Score (This morning)	PRO: Global Hunger Item 1	PRO: Global Hunger Item 2	Weight	BMI	BP/HR	HbA1C	Lipid Profile	Waist circumference	Height
Baseline	--	--	--	--	--	--	--	--	--	--	--	--	--
Week 3	--	--	--	--			--					--	
Week 5	--	--	--	--			--					--	
Week 9	--	--	--	--			--					--	
Week 13	--	--	--	--	--	--	--	--	--	--	--	--	--
Week 17	--	--	--	--	--	--	--					--	

Sponsor Pre-Meeting Response

1. *Rhythm appreciates the Agency's concurrence that the top line efficacy data appear to demonstrate a clinically meaningful effect of setmelanotide on weight in both populations and acknowledges that the final determination will depend on the review. No discussion required.*
2. *Due to the rarity of POMC and LEPR deficiency, it was only possible to conduct a single-arm study. An 8-week double-blind placebo-controlled period was included in the study design, during which patients received active treatment for 4 weeks and placebo for 4 weeks; the patients were unaware of the treatment being administered. In POMC and LEPR patients, during the active treatment period, the hunger scores decreased, and during the placebo period there was an increase in hunger scores. The trends for each of the hunger items (morning, worst and average hunger) were similar. In addition to the changes in hunger, there was a statistically significant increase in weight during the placebo withdrawal period, which resulted in an approximately 5 and 5.5 kg weight gain for LEPR and POMC respectively. As part of the psychometric evaluation Rhythm will be further evaluating the relationship between changes in hunger and weight.*

Does the Agency agree that this is sufficient?

3. *Thank you very much for your ongoing guidance regarding the hunger assessments. Prior to implementing the hunger items in the clinical trials, we conducted a literature review and qualitative interviews with POMC and LEPR patients and/or caregivers. More recently, we have initiated a psychometric evaluation of the hunger items in both populations, including the evaluation of reliability, validity, responsiveness, and meaningful change. We are also preparing to conduct additional qualitative interviews in patients who completed the pivotal clinical trials in Germany to gather more detailed information about patients' experiences and perceptions of hunger. At the time of the NDA, we will be providing all of the available evidence to the Agency in addition to all instructions and training materials. With respect to the scoring algorithm, please note that consistent with prior discussions, we do not anticipate creation of a hunger composite score but rather focus on the item addressing maximum hunger ('most hungry') (b) (4). Unless the Agency has specific concerns, no discussion regarding the extent to which the hunger items are fit for purpose is needed.*

We understand and appreciate the request for patient-level data. As previously agreed with the Division, the CSRs will contain a series of individual patient case narratives that will include specific data for weight loss, hunger and all other safety and efficacy parameters, including those outlined in Tables B and D. Although the content is similar, the requested format is very different from what was previously discussed and agreed.

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Rhythm would appreciate if the Division could share the importance and rationale for requesting the data in this format, including the specific variables listed. If the patient case narratives are not sufficient to address the need for patient-level data, we propose to provide the data referenced in Tables B and D on a per visit basis rather than by week in order to align with the presentation of other efficacy and safety parameters in the NDA. Given the specific weeks selected for the example tables, this proposal appears to align with the Agency's request; however, we would appreciate confirmation that this approach would be acceptable. Finally, as a reminder, the Agency requested removal of the item addressing minimum hunger ('least hungry'); therefore, data pertaining to this item cannot be included in the tables.

Meeting Discussion

Regarding the patient reported outcomes (PRO) instrument, FDA stated they were not concerned about the validity of the data, but rather, the interpretability of the PRO data, since the sponsor intends to use all of the data from the trial in their analyses (i.e., including data generated during the open-label treatment period). The sponsor acknowledged this potential limitation on data interpretation. The sponsor indicated that

(b) (4)
[Redacted text block]

FDA asked the sponsor whether they intend to include all data from both younger and older patients in the endpoint analysis. The sponsor confirmed that they intend to use data from all patients in their analyses. FDA noted that the sponsor administered two separate questionnaires (a PRO for older patients ages 12 and above; a ClinRO for younger patients ages 6-11); therefore, further discussion would need to occur regarding their proposed analysis plan. FDA requested that these details also be submitted for review.

The sponsor asked for clarification on why FDA requested that the sponsor submit individual patient profile data in the format provided in Tables B and D of the preliminary comments document. FDA explained that the purpose of the tables was to facilitate the review of data, and that the format presented in the preliminary comments was just an example to consider and not intended to be prescriptive.

The sponsor indicated that they intend to submit very detailed patient narratives in the NDA submission and asked whether the Agency could look at that template to determine whether the original format and data elements would meet

regulatory needs. FDA agreed to this plan.

The sponsor explained that they are looking at the correlation between weight loss and hunger. However, both adults and children may see benefits in their quality of life as a response to changes in hunger, without seeing much change in weight. FDA acknowledged this and noted that children, especially those in a regimented environment, may not experience weight reduction, but nonetheless might demonstrate a clinical response manifested as weight stabilization or decreased rate of weight increase over time.

FDA stated that intends to incorporate these considerations when it analyzes the data. The sponsor suggested exploring the relationship with other variables, such as waist circumference. FDA cautioned the sponsor about the limitations of supportive variables other than weight or BMI, such as the potential for measurement error or poor reproducibility. Nonetheless, it will be important to see how the data from the PRO instruments complement the weight loss data.

Question 2: Safety

- a. Does FDA agree that the top line safety data from the pivotal studies demonstrate no significant safety concerns that would warrant special safety considerations?
- b. Does FDA agree that patient safety can be monitored through standard clinical and post marketing safety surveillance (i.e., no REMS)?
- c. Does FDA agree that it is acceptable to submit eCRFs for SAEs, deaths, and discontinuations due to AEs/SAEs from the POMC and LEPR trials only (011, 012, 015, 022)?

FDA Pre-meeting Comment

- a. From the data submitted to the IND to this date, there do not appear to be any significant safety concerns; however, the division will reserve comments regarding the safety profile pending review of the data.
- b. It is premature to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.
- c. No, we do not agree. You should submit relevant safety data, including case narratives, from all studies, not just the pivotal trials in POMC and LEPR. The Division reserves the right to request additional narratives for cases of interest as well as adjudication packages for specific events.

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Sponsor Pre-Meeting Response:

- a. *Rhythm appreciates the Agency's concurrence that there do not appear to be any significant safety concerns and acknowledges that the final determination is pending review of the data.*
- b. *We understand this will be a review issue and have no comments at this time.*
- c. *Rhythm agrees that safety data for all completed and ongoing studies will be provided in CSRs with the NDA. For the ongoing studies, the eCRFs will be provided up to the date of the data cut. As agreed previously with the Agency, we will also provide any SAES that occur after the date of study cut-off and the NDA filing.*

Meeting Discussion

FDA reiterated that it was premature to determine the requirement for a REMS.

Question 3: Immunogenicity

- a. Does the Agency agree or have additional guidance regarding the anti-drug antibody methodologies and description of clinical anti-drug antibody testing?
- b. Does FDA agree that the immunogenicity data package is sufficient for the NDA submission?

FDA Pre-meeting Comment

- a. As stated in the Agency comments provided on August 21, 2019, final assessment of the anti-drug antibody methodologies cannot be made until updated, final immunogenicity assay validation reports for all assays, including updated validation data are provided to the Agency for evaluation. These should include:
 1. All updates to the RM-493 neutralizing antibody detection assay validation information including those provided in response to the September 7, 2018 Agency comments.
 2. Final validation reports with validation parameters updated throughout the RM-493 ADA assay development. Supportive assay developmental data including the minimum required dilution(s), sera sample stability necessary for evaluation of assay validation should also be provided. Provide a tabulation of validation report and addendum report numbers with corresponding updates to validation parameters to allow for comprehensive review. Ensure the appropriate final validation reports also include data assessing the interference of the mPEG-DSPE excipient or potential anti- α -MSH antibodies in the RM-493 ADA assays.

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3. Final validation report for the anti- α -MSH antibody detection assay as outlined in your July 7, 2019 response.

We also communicated in the August 21, 2019 Agency comments a recommended strategy for identification of positive samples using the anti-drug antibody screening assay. We continue to recommend classification of a sera sample as screened positive if a reading above pre-dose levels is obtained in post-dose samples, **OR** a sample reading is above cut point, rather than the proposed strategy (Figure 9 of your briefing package). Your proposed strategy may under-report true ADA-positive samples. Note also that clinical effects of ADA are not limited to treatment-emergent antibodies. Pre-existing drug-binding antibodies may also impact drug half-life and should be characterized. The 2019 Agency guidance for industry "[Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection](#)" discusses strategies regarding pre-existing antibodies, including assessing changes in antibody titers as an evaluation of treatment-boosted ADAs.

- b. Based on the limited immunogenicity data and ADA assay information provided in the meeting briefing document, this question will be a review issue. The quality of the immunogenicity data package will be assessed during evaluation of your submission.

In addition to the integrated summary of immunogenicity (ISI) recommendations sent on September 7, 2018 and May 16, 2019, we also recommend that you provide a tabular summary of the specific validated assays used for each clinical study. For each assay this should include their relevant validation report number, cut point (the validated CP and/or any in-study CP), assay sensitivity, and drug interference level as used to assess ADAs in each RM-493 clinical study.

Sponsor Pre-Meeting Response:

a.1. Rhythm would like to note that the August 21, 2019 FDA Advice/ Information Request regarding immunogenicity was received after the pre-NDA Briefing Book for setmelanotide was finalized for submission to the Agency. Thus, some of the questions noted by the Agency in the pre-NDA Preliminary Meeting Comments were addressed in Rhythm's response to the August letter, submitted on September 20th, 2019 to the Agency. In the responses below, Rhythm will delineate information that was provided in the letter to the Agency on September 20th.

In response to Question 1 of the Agency, Rhythm would like to ask for clarification as to the request regarding providing updates to the NAb assay validation. In particular, the NAb assay was validated and the validation package submitted to the Agency on June 7, 2018 as Method Validation Report AR6666. The NAb assay described in the validation report has not been utilized for clinical study sample analysis to date, as no ADA positive for anti-RM-493 antibodies have been identified in the Screening or

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Confirmatory Assays.

In reference to the FDA's September 7, 2018 response to the Request for Information/Advice, Rhythm provided the following information in the October 11th, 2018 response:

- i. Details describing the validation of the minimum required dilution (MRD) of 1:10 for patient serum used in the assay validation;*
- ii. Details describing the expected levels of the study drug in patient sera samples and the acceptability of a 10 ng/mL drug tolerance;*
- iii. A discussion of the need to include the bench-top and freeze/thaw stability of all controls used in the assay;*
- iv. Data from additional PC Ab titrations at lower RM-493 concentrations within the linear portion of the dose response curve to demonstrate that the 5 ng/mL RM-493 dose selected provides a response level that is appropriate; and*
- v. Information and justification on the positive control used in the assay.*

The results reported in Rhythm's October 11th 2018 response are the final determination and no additional data have been generated since this date. Could the FDA please clarify what additional information is being requested?

a.2. Rhythm will provide a complete package of assay development for the anti-RM-493 ADA assay in the NDA, including supportive assay method development data regarding the minimum required dilution(s), a tabulation of validation report and addendum report numbers with corresponding updates to validation parameters, and ensure the appropriate final validation reports also include data assessing the interference of the mPEG-DSPE excipient in the RM- 493 ADA assays.

However, Rhythm requests additional clarification as to the request for serum sample stability. Rhythm has not observed a positive ADA to RM-493 to date, and therefore, does not have a representative sample to monitor for stability. Assessment of long-term stability of the positive control (PC) may not be representative of a patient ADA response. Thus, to ensure patient sample stability, samples are stored under the same conditions as the PC. The PC is then monitored over time based on assay performance characteristics relative to the validation parameters, as recommended in "The 2019 Agency Guidance for Industry, "Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection" (page 14). This methodology of monitoring the PC over time is also utilized to extend the expiry date of the PC.

Rhythm asks the Agency to please clarify what additional stability information is being requested.

Rhythm also requests clarification regarding ensuring the appropriate final validation reports also include data assessing the interference of the mPEG- DSPE excipient or potential anti- α -MSH antibodies in the RM-493 ADA assays. Rhythm provided an

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addendum to the Method Validation Report for antibodies to RM-493 in the September 20th 2019 response letter to the FDA. This addendum to the validation assessed the potential for interference of mPEG-DSPE and α - MSH in the anti-RM-493 antibody assay, as requested in the Agency response of April 16, 2019:

“Provide a timeline for updated validation for the screening/confirmatory/titer assay(s) to detect anti-RM-493 antibodies in patient sera. These validation updates should include:

Assessment of cross-reactivity potential of patient anti-RM-493 antibodies to α -MSH as proposed in your 13 September 2017 and 8 June 2018 response to Agency comments.”

This was also stated in earlier communication from the Agency on March 5, 2018:

“To clarify, we also advise you to assess the cross-reactivity potential of patient antibodies to endogenous α -MSH, as communicated previously in the 18 April 2016 meeting, in patients from indications where α -MSH may be expressed, including the POMC/PCSK1-deficient patient population where non-functional α -MSH may be expressed.”

However, the request from the Agency in the preliminary comments to the pre- NDA briefing document is to provide information as to whether anti- α -MSH antibodies interfere in the anti-RM-493 assay, not α -MSH.

Please clarify if the Agency is now requesting information on both α - MSH and antibodies to α -MSH interferences in the assay.

In lieu of testing the interference of anti- α -MSH antibodies in the anti-RM-493 assay, Rhythm proposes the following. As communicated to the Agency in the September 20th 2019 letter, Rhythm is in the process of finalizing the validation report for antibodies to α -MSH. Once the validation of the anti- α -MSH antibody assay has been completed, and input from the Agency has been received, the clinical samples will be assayed for anti- α -MSH antibodies. Should Rhythm determine a sample positive for anti- α -MSH antibodies, the sample will be tested in the anti-RM-493 ADA assay with and without acid dissociation, to determine if anti- α -MSH antibodies are interfering in the assay.

a.3. Rhythm requests further clarification of the Agency’s recommendation to classify a serum sample as screened positive if a reading above pre-dose levels is obtained in post-dose samples, OR a sample reading is above cut point, rather than the proposed strategy. In the Agency’s response letter of August 21st, 2019, the Agency requested the following:

“Note that the proposed cut-point strategy thus far may omit post-dose samples from the study subjects that test below the RM-493 ADA assay CP yet are above test results for their pre-dose samples. We recommend that you consider a serum sample to be positive in the screening ADA assay if either:

i. A reading above pre-dose levels is obtained in post-dose samples, or

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ii. Sample reading is > cutpoint.”

Post-dose samples >pre-dose but below the cutpoint

To date, Rhythm has utilized the decision tree provided in prior communications with the Agency and in the original validation in 2011, wherein a post-dose sample must be greater than the pre-dose sample and above the cutpoint to be considered positive in the Screening assay. As recommended by the Agency in the August 21st letter, Rhythm has incorporated the following into the assay decision tree: post-dose samples that are below the cutpoint but above the pre-dose by at least 2-fold shall be considered positive in the Screening assay. (See response to the Agency letter of September 20th, 2019). Utilizing these criteria, no post-dose samples below the cutpoint but above pre-dose have been found to meet the criteria of a Screening positive.

Post-dose samples >pre-dose but above the cutpoint

In sample analysis for the pivotal and supporting studies to be submitted to the NDA, Rhythm has NOT considered a post-dose sample as a Screening positive if the post-dose OD value was below the pre-treatment value and above the cutpoint. These samples have been considered Screening negative. As an example, below are the ADA sample analysis results for a subject in Study RM-493-015 that had a high (> than the cutpoint for that population) treatment naïve pre-dose sample, and a subsequent high post-dose sample.

Visit	OD 1	OD 2	Mean	%	Patient	Pediatric	Screen	Confirmator
V1/pre-dose/	0.399	0.383	0.391	2.9	Pediatric	0.297	Positive	Negative
V2a / post-	0.36	0.359	0.359	0.2	Pediatric	0.297	Negative	NA
V2b / post-	0.335	0.335	0.335	0	Pediatric	0.297	Negative	NA
V2c / post-	0.313	0.313	0.313	0	Pediatric	0.297	Negative	NA
V4 / post-	0.311	0.314	0.312	0.7	Pediatric	0.297	Negative	NA
V6 / post-	0.324	0.328	0.326	0.9	Pediatric	0.297	Negative	NA
V11 / post-	0.689	0.685	0.687	0.4	Pediatric	0.297	Positive	Negative

One sample had an OD above the pre-dose sample. The high post-dose sample was found to be negative for ADA to RM-493 in the Confirmatory assay. Thus, it is unlikely that other post-dose samples that are higher than the cutpoint but below the pre-dose value will confirm positive.

Any change to the decision tree will require significant effort beyond sample analysis (eg updating TLFs/database). Rhythm would like the Agency to be aware that Rhythm may be unable to complete the assessment prior to the NDA filing.

With regard to PK, an assessment of PK for those that confirmed positive for ADA will be provided in the NDA. As mentioned above, no samples have been found to be positive for ADA to RM-493 to date.

b. Rhythm will provide the indicated information in the NDA, subject to further understanding of FDA's requests and the impact on timing. Depending on the review time for the anti- α -MSH Validation Report, which will be submitted in October, the sample results for subjects in the pivotal and supporting studies may not be available prior to the NDA submission.

As communicated previously, due to difficulties in assay development of an anti-mPEG-DSPE assay, the validation and sample analysis for antibodies to mPEG-DSPE will not be included in the NDA, although Rhythm continues to work on assay

Meeting Discussion

3.a.1. NAb assay

FDA clarified that the NAb assay data referred to in the Sponsor October 11, 2018 response and described on pages 10-11 of the Sponsor response (9/26/2019) should be included in the final validation reports or addendums submitted to the NDA. In general, any method development data should be included to aid the Agency's evaluation of the immunogenicity assays validation exercises. One of the purposes of the integrated summary of immunogenicity (ISI) requested by the Agency is to provide all assay validation amendments and updates from various communication dates in one place, to see the totality of the assay(s) validations.

3.a.2. Final validation reports submissions

a). FDA provided clarification to the sponsor query regarding serum stability studies. FDA informed the sponsor that serum stability of samples relates to both clinical samples and the assay positive control (PC) serum samples. However, in the context of the current discussion serum stability refers to the in-use stability of the patient samples and PC during assay use, and not long-term stability of clinical samples during storage.

b). FDA provided clarification that yes, both cross-reactivity of alpha-MSH in the RM-493 ADA assay and potential cross-reactivity of antibodies to alpha-MSH with RM-493 drug are expected to be addressed in the NDA. Furthermore, FDA informed the sponsor that while the strategy proposed in their meeting response document to assess α -MSH antibodies may be acceptable, this will be a review matter. FDA indicated that a response would be included in a post-meeting document.

- The sponsor asked whether the α -MSH assay validation data should be included in the NDA submission. FDA replied that this would require internal discussion and that they would be informed later.**

- The sponsor confirmed that the validation for the assay to detect antibodies to α -MSH will be submitted sometime in October and they will await testing of samples until assessment is completed by the Agency.
- FDA also stated that they concurred with the sponsor proposal to provide (b) (4) as a post-approval submission, due to delays in assay development.

3.a.3. FDA provided clarification to the sponsor query regarding the cut point (CP) strategy proposed by FDA in the meeting response and the 21 August 2019 Agency comments. FDA stated this was due to the high background level of noise seen in pivotal study samples in the RM-493 ADA screening assay. FDA also noted that not all ADAs are treatment emergent. Further, FDA stated that care was being taken with the assay validation in part due to the potential use of the assays for patients with other disease indications.

- The sponsor stated that no samples had been confirmed positive for anti-RM-483 antibodies and referred to the table in the meeting briefing document response discussing one patient's serial samples that screened positive but were not confirmed positive and further demonstrated no adverse events or clinical outcomes.
- FDA stated that they were familiar with the data, but it represented only a single patient and did not include all phase 3 patients.

During the end of meeting wrap-up, the sponsor indicated their willingness to have a telephone conference in order to discuss additional immunogenicity issues as necessary prior to NDA application. FDA acknowledged the comment.

FDA Post-Meeting Comment: The OBP immunogenicity review team will provide additional advice after review of your September 20, 2019, submission.

Question 4: Dosing

Does FDA agree with Rhythm's approach to the setmelanotide dosing recommendations?

FDA Pre-meeting Comment

The accelerated titration scheme seems reasonable. You should present data to support the proposed approach with the NDA. Although data suggesting tolerability in other populations is supportive, you will need to bridge tolerability for this schedule to the intended population.

Sponsor Pre-Meeting Response:

Thank you for your feedback supporting our approach to an accelerated titration scheme. We have data from the pivotal studies demonstrating that patients can resume

treatment at a therapeutic dose after a placebo washout period with good tolerability. In addition, we can provide data from other study populations where we have implemented a simplified titration schedule. We will present data to support the approach and to bridge tolerability to the intended population in the NDA as recommended by the Agency.

Meeting Discussion

FDA agreed that the proposed dosing regimen sounds acceptable provided that the data are supportive upon review.

Question 5: Indication

- a. Does FDA agree that (b) (4) treatment of obesity (b) (4) (b) (4) to include in the indication statement?
- b. Does FDA agree with the recommended age for the indication?

FDA Pre-meeting Comment

- a. Final labeling will depend upon review of the data. Please see the response to Clinical Question 1 regarding specific review concerns.
- b. Given the rarity of these conditions, extrapolation to lower age groups may be appropriate if adequate scientific justification is provided. Whether the data supports an indication in the lower age groups will be a review issue.

Sponsor Pre-Meeting Response:

- a. (b) (4)
Patients and their families continue to emphasize to us how disruptive extreme hunger is to their quality of life. We designed our trials where the key endpoints relate to weight and hunger and have shown very large effects on both.
(b) (4)
- b. *The Sponsor proposes that based upon the data obtained to date, the lower age limit be 6 years of age. In the NDA, we will provide the justification.*

Meeting Discussion

The sponsor noted that they have treated one eleven-year-old child and two ten-year-old children, but there were no younger patients currently enrolled in the development program. The sponsor indicated that the request for approval to treat 6-year-old children and older was somewhat arbitrary. FDA suggested it may be possible to extrapolate results to younger populations (below 6 years)

depending on review of both the efficacy and safety data, and noted that the review team intends to discuss this issue with the Division of Pediatric and Maternal Health during the review cycle.

Question 6: Genetic Testing

- a. Does FDA agree with Rhythm's understanding of the approach to genetic testing in POMC- and LEPR-deficiency obesity patients?
- b. Does FDA agree that the genetic testing information Rhythm proposes to provide in the NDA is sufficient for setmelanotide approval?

FDA Pre-meeting Comment

- a. As discussed previously, since subjects enrolled into the pivotal clinical trials to determine safety and effectiveness of setmelanotide include only subjects with genotype results and, if successful, setmelanotide will be indicated for the genetic subset of patients that are identified by a genetic test, an FDA-cleared or approved companion diagnostic will be needed. As indicated in our face-to-face meeting on August 27, 2019, it is FDA's policy that the companion diagnostic is reviewed by FDA to ensure there is a safe and effective in vitro diagnostic (IVD) device available.

Since you are not proposing that an FDA cleared or approved companion diagnostic will be made available for setmelanotide, if approved, we do not agree with your understanding of the approach to genetic testing for POMC- and LEPR- deficiency obesity to identify which patients would be eligible for setmelanotide.

As discussed during our face-to-face meeting on August 27, 2019, CDRH is able to provide feedback on co-development of an IVD sequencing assay to the IVD sponsor and continues to strongly recommend the IVD sponsor submit a pre-submission to CDRH to discuss a least burdensome approach for the co-development of the IVD sequencing device. CDRH is committed to working with the IVD sponsor to identify a least burdensome pathway for analytical validation and quality system requirements for a companion diagnostic for setmelanotide. CDRH recommends that the IVD sponsor include in their pre-submission a detailed description of the test and the analytical validation studies that have been completed for the test. Please refer to our written feedback on August 24, 2018 regarding considerations for a least burdensome pathway for analytical validation.

Since you have indicated that Rhythm has identified (b) (4) as the Rhythm-preferred CLIA-LDT genetic testing post-NDA, CDRH is able to work with (b) (4) using CDRH's pre-submission process. It is our understanding that (b) (4) holds a license in New York and therefore would have submitted their test for approval to New York State

Department of Health (NYSCDOH). If Rhythm and (b) (4) determine that (b) (4) would be the IVD sponsor for the companion diagnostic, CDRH would be able to review in a pre-submission the information (b) (4) submitted to NYSDOH to provide feedback on the information that could be leveraged from the NYSDOH package in support of a future IVD companion diagnostic premarket submission.

- b. Please refer to our feedback to Question 6.a. above regarding our feedback on the co-development of a companion diagnostic. The type of information you describe that will be provided in the NDA is consistent with the type of information we would expect to see in any future marketing authorization submission for a companion diagnostic to support that the sequencing assay is accurate and reliable for its intended use.

Sponsor Pre-Meeting Response:

Rhythm appreciates the feedback on our approach to genetic testing. We apologize that we have been delayed in obtaining direct feedback from CDRH on the co-development of a diagnostic for the sub-set of genetically confirmed patients with obesity. We have been working diligently with (b) (4) on the development of a clinical trial assay and validating it to CLIA/CAP/NYDOH standards for the POMC/LEPR indication. We may have mis-interpreted your feedback at last year's meeting, but FDA's advice is now clear that we should work with (b) (4) to work towards a Class II IVD clearance.

Rhythm welcomes the advice to schedule a pre-submission. We will promptly request a meeting with CDRH to enable a rapid path towards a de novo application. We remain grateful for FDA's willingness to help with a least burdensome path for these ultra-rare genetic disorders, with only a handful of known patients worldwide. As such, we are mindful that patient samples are almost impossible to obtain, so we look forward to a discussion of what is a reasonable data set to support analytical validity. As advised, we

will review with (b) (4) their NYDOH package, and we believe that (b) (4) has the capabilities and willingness to support (b) (4)

Rhythm would like to assure the FDA that (b) (4) will be expeditiously pursued.

Can the Agency confirm that the clearance of the IVD will not delay approval of the POMC/LEPR indication?

Meeting Discussion

Rhythm apologized for not contacting CDRH sooner. They have been working through the development process with (b) (4) sponsor of the In Vitro diagnostic (IVD). Rhythm asked if clearance of the IVD could delay approval. FDA explained that if an IVD was deemed necessary for safe and effective use of the drug, generally contemporaneous authorization of the companion IVD would be required for approval of the drug. However, there are

certain scenarios where concurrent approval of the IVD may not be required, as described in FDA's guidance on companion diagnostics. FDA clarified that whether contemporaneous approval of the IVD companion diagnostic is required will be determined during review of the NDA.

FDA clarified that based on FDA's current understanding of the risk profile of setmelanotide, it appears that a (b) (4) request would be the appropriate regulatory pathway for an IVD companion diagnostic for setmelanotide. FDA further clarified that an official classification determination will be made during premarket review of the IVD.

Rhythm explained that it was unlikely that the data required for submission of the IVD would be ready when the NDA is submitted. The sponsor noted that (b) (4) has validated their tests but, depending on the feedback received by CDRH in the pre-submission they intend to submit, further IVD development process may take a significant amount of time. CDRH acknowledged Rhythm's concern and stated that they couldn't comment on whether the validation data performed by the IVD sponsor thus far would be sufficient to support a premarket submission, since CDRH doesn't have detailed information on the proposed IVD.

CDRH stated that CDRH is willing to review information and data that are available from the IVD sponsor in a pre-submission to further discuss what information and data can be leveraged in support of the future premarket submission, and what additional information, if any, would be needed. In addition, FDA noted that if setmelanotide was moving toward approval, and approval of setmelanotide represented a scenario in which contemporaneous approval of the IVD was not needed per FDA's companion diagnostic policy, FDA would consider development and authorization of an in vitro companion diagnostic as a postmarketing commitment. FDA stated that it is not expected that authorization of an IVD companion diagnostic would delay the NDA approval.

Rhythm noted that the variants that would be tested by an IVD companion diagnostic are rare and described concerns with the level of validation FDA may expect for such a test. FDA acknowledged that the variants for POMC- and LEPR-deficiency obesity are rare and referred to FDA's prior feedback which suggested that FDA will work with the IVD sponsor on a least burdensome pathway for analytical validation for the IVD. CDRH stated that they strongly encourage the IVD sponsor to submit a pre-submission to CDRH.

Rhythm stated that they would be submitting a pre-submission, along with the IVD sponsor, the week after the meeting. CDRH reiterated their commitment to work with the IVD sponsor on a least burdensome approach to analytical validation for the IVD companion diagnostic.

Question 7: Clinical Pharmacology / Pharmacokinetics

- a. Does FDA agree these data are adequate to support the NDA?
- b. Is it acceptable to include the population PK report early during the NDA review process?

FDA Pre-meeting Comment

- We recommend providing clinical pharmacology data following administration of the to-be-marketed product (formulation and device), and adequate bridging information if there were changes in the presentation (formulation or device) during clinical development.
- We recommend providing comprehensive clinical pharmacology data related to factors potentially affecting setmelanotide exposure (e.g., intrinsic factors such as age, body weight or organ impairment, and extrinsic factors such as drug interaction(s)) and proposed labeling to manage any clinically significant changes.
- All pivotal data should be complete and included in the NDA at the time of submission. If population PK report is considered as supplemental information

without impact on labeling, it is acceptable to be submitted not later than 30 days after the submission of the original application.

Sponsor Pre-Meeting Response:

- a. *Thank you for the comments. Rhythm has no further comments on this question and assumes that the following approach to PK will be adequate and comprehensive.*

The formulation assessment will be provided for each study, for pooled data (studies -012, -014 and -015) and in the population PK report. Because the PK data are relatively sparse (mostly 8 hr profiles and trough values), the PK assessments for individual studies and the pooled data will utilize inter-subject comparisons. The population PK report will include formulation as a covariate. All available covariates will be included in the model. Rhythm will evaluate intrinsic factors as feasible.

- b. *Rhythm intends to include the population PK report in the NDA at the time of final submission.*

Meeting Discussion

The sponsor stated they will provide the population PK data as a part of the original NDA submission.

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2.2. Regulatory

Question 8: Rolling CMC submissions

Does FDA agree with the proposed filing strategy to submit CMC Filing 1 in August 2019, CMC Filing 2 in November 2019 with the final NDA, and during review in January 2020 submit the two revised DP stability documents?

FDA Pre-meeting Comment

We do not agree with your Option 1 plan. We agree with the approach for submittal of CMC information as detailed in Option 2 of your meeting package. We remind you that the manufacturing sites for both the Drug Substance and Drug Product should be ready for inspection at the time of NDA submission.

Sponsor Pre-Meeting Response:

Thank you for your response. We will proceed with Option 2.

We confirm that drug substance and drug product sites will be ready for inspection at the time of final NDA submission.

Meeting Discussion

The sponsor agreed to submit CMC information using "option 2" and noted that all manufacturing sites would be ready for inspection.

Question 9: Advisory Committee

Does FDA agree that the setmelanotide NDA does not need to be referred to an Advisory Committee?

FDA Pre-meeting Response

This question is premature. The need for an Advisory Committee meeting is determined during the review cycle.

Sponsor Pre-Meeting Response:

Thank you, we have no further comments.

Meeting Discussion

No discussion.

2.3. Additional FDA Comments

Additional COA Pre-Meeting comment:

1. [REDACTED] (b) (4)

Sponsor Pre-Meeting Response:

1. [REDACTED] (b) (4)

Meeting Discussion

Additional Statistics Pre-Meeting comments:

1. For all studies included in the submission, you must submit either ADaM or analysis datasets, and either SDTM or CRF tabulation datasets. You must also submit reviewer's guides for all submitted datasets.
2. Each analysis dataset should include baseline assessments and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.
3. Include sufficient detail, such as definitions or descriptions of each variable in the datasets, algorithms for derived variables (including source variable[s] used) in the analysis dataset documentation (Define.pdf).
4. Include the software programs that are used to create the derived datasets for the efficacy endpoints and the software programs that are used for efficacy data analysis.

Sponsor Pre-Meeting Response:

1. *Thank you for your response. Rhythm plans to submit the following datasets:*
 - *For studies (legacy studies and ongoing studies) that started after December 17th, 2016, Rhythm plans to provide datasets in CDISC compliant format in .xpt, accompanied by relevant data definition files (Define.xml) and reviewers' guides.*
 - *For two Phase I legacy studies (specifically, RM-493-001, and RM-493-002) that were completed before December 17, 2016, Rhythm intends to provide datasets in non-CDISC standard datasets, as agreed with the agency in the meeting held in August 27th, 2018. Raw datasets will be provided in .xpt format and accompanied by annotated CRFs, and the derived datasets will be accompanied by define-like documents.*
2. *We agree with the suggestion and will include variables that were used to identify the efficacy records from imputation.*

3. *Thank you for the recommendation. Rhythm plans to include these details in define.xml and reviewers' guide document.*
4. *We appreciate the recommendation. Rhythm intends to submit the SAS programs that were used to derive and analyze the primary and key secondary efficacy endpoints.*

3.0 Additional Important Information

MEETING DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- **The content of a complete application was discussed. Specific topics included:**
 - a. **Immunogenicity testing and assay validation:** The sponsor will work with the OBP immunogenicity review team to resolve remaining issues and submit all the data requested with the original application.
 - b. **The sponsor agreed to submit individual patient profile data to help characterize the sample and aid in the interpretation of changes in Hunger Questionnaire scores. The Agency agreed to review the sponsor's proposed patient profile template to determine if the format and data elements are sufficient for review.**
 - c. **A detailed analysis plan specifying the sponsor's proposed approach to evaluating the hunger endpoint(s) using two separate questionnaires (a PRO for older patients ages 12 and above; a ClinRO for younger patients ages 6-11), will need to be submitted for Agency review and comment.**
 - d. **The sponsor confirmed that all CMC information requested by OPQ (option 2) will be submitted with the NDA.**
- **All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.**
- **A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication.**
- **Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The sponsor stated that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.**

No agreements were reached regarding submission of minor components

In addition, we note that chemistry pre-submission written responses were issued on April 26, 2019, and a follow-up CMC only teleconference was held on May 22, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

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Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

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

Office of Scientific Investigations (OSI) Request

The Office of Scientific Investigations (OSI) requests that the items described in the draft “Guidance for Industry: Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions” (February 2018; available at the following link <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>) and the associated document “Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications” (available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can describe the location or provide a link to the requested information.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- a. Immunogenicity testing and assay validation will require additional discussion between the sponsor and the OBP immunogenicity review team.
- b. The Agency indicated that further discussion will need to take place regarding the sponsor's proposed analysis plan since all Hunger Questionnaire data (for patients ages 6 and above) will be included.

5.0 ACTION ITEM

Action Item/Description	Owner	Due Date
Determination if the α-MSH assay validation data should be included in the NDA submission	FDA	TBD - internal discussion required
Submit the proposed patient profile template Submit the proposed analysis plan.	Sponsor	

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/

JOHN M SHARRETTS
10/25/2019 05:05:12 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 112595
Request Receipt Date	March 7, 2017
Product	setmelanotide (RM-493)
Indication	treatment of leptin receptor deficiency obesity
Drug Class/Mechanism of Action	melanocortin 4 receptor (MC4R) agonist peptide
Sponsor	Rhythm Pharmaceuticals, Inc.
ODE/Division	ODE II / DMEP
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	May 7, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

Setmelanotide is indicated for the treatment of obesity [REDACTED] (b) (4) associated with leptin receptor (LEPR) deficiency obesity.

However, the sponsor has proposed for FDA consideration an alternative indication described as [REDACTED] (b) (4) associated with melanocortin 4 (MC4) pathway deficiency obesity.

The Division is first reviewing and seeking agreement from the MPC regarding the appropriateness of a breakthrough designation for the LEPR deficiency obesity indication. However, we also seek input from the MPC regarding the sponsor's proposal to broaden the treatment indication.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

YES NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

YES NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - Undetermined
 - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
 - i. Only animal/nonclinical data submitted as evidence
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
 - v. No or minimal clinically meaningful improvement as compared to available therapy^{2/} historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Setmelanotide (formerly known as RM-493) is an 8-amino-acid peptide agonist of the melanocortin 4 receptor (MC4R) administered subcutaneously once a day. The IND was initially opened in June 2011 for [REDACTED] (b) (4) and in May 2013, a face-to-face type C meeting was held to discuss a variety of development

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

approaches for various niche indications related to severe obesity. The sponsor is now pursuing development of setmelanotide for the treatment of obesity (b) (4) associated with (b) (4) specific genetic obesity disorders impacting the **hypothalamic leptin receptor– POMC – melanocortin 4 pathway** (referred to by sponsor as the MC4 pathway), which is an integrated neuroendocrine regulatory network controlling appetite, energy expenditure, and ultimately body weight. One of the first disorders studied by the sponsor was POMC deficiency obesity, a rare monogenic obesity disorder with hyperphagia and severe early onset of obesity.

Setmelanotide was granted BTD for POMC deficiency obesity in December 2015 based primarily on preliminary clinical evidence of substantial weight loss in 1 patient with this rare genetic disorder. **The subject of the current BTD request is leptin receptor deficiency obesity, which shares many of the same clinical characteristics of POMC deficiency obesity and is also a monogenic obesity disorder within this hypothalamic pathway.**

In the hypothalamus, leptin, a fat-derived hormone, signals satiety through the leptin receptor, which activates the transcription and post-translational processing of the POMC protein yielding the native ligands of the melanocortin 4 receptor. Subsequent stimulation of the melanocortin 4 receptor (MC4R) decreases food intake and increases energy utilization (Figure 1).

In patients with POMC deficiency obesity, the native MC4R agonist is absent as a result of defects in either the *POMC* gene or as a result of defective processing of the POMC protein.

Similarly, in patients with LEPR deficiency obesity, the native MC4R agonist is also absent, but it differs from POMC deficiency in the *location* of the signal disruption. In these patients, the leptin receptors found on hypothalamic POMC neurons fail to transmit the signals responsible for the synthesis and processing of POMC.

The sponsor’s hypothesis for both of these syndromes (b) (4) is that the resulting defects in the hypothalamic leptin receptor-POMC-MC4R signaling pathway can be bypassed by direct stimulation of the MC4R by setmelanotide, thereby restoring appetite regulation and energy homeostasis.

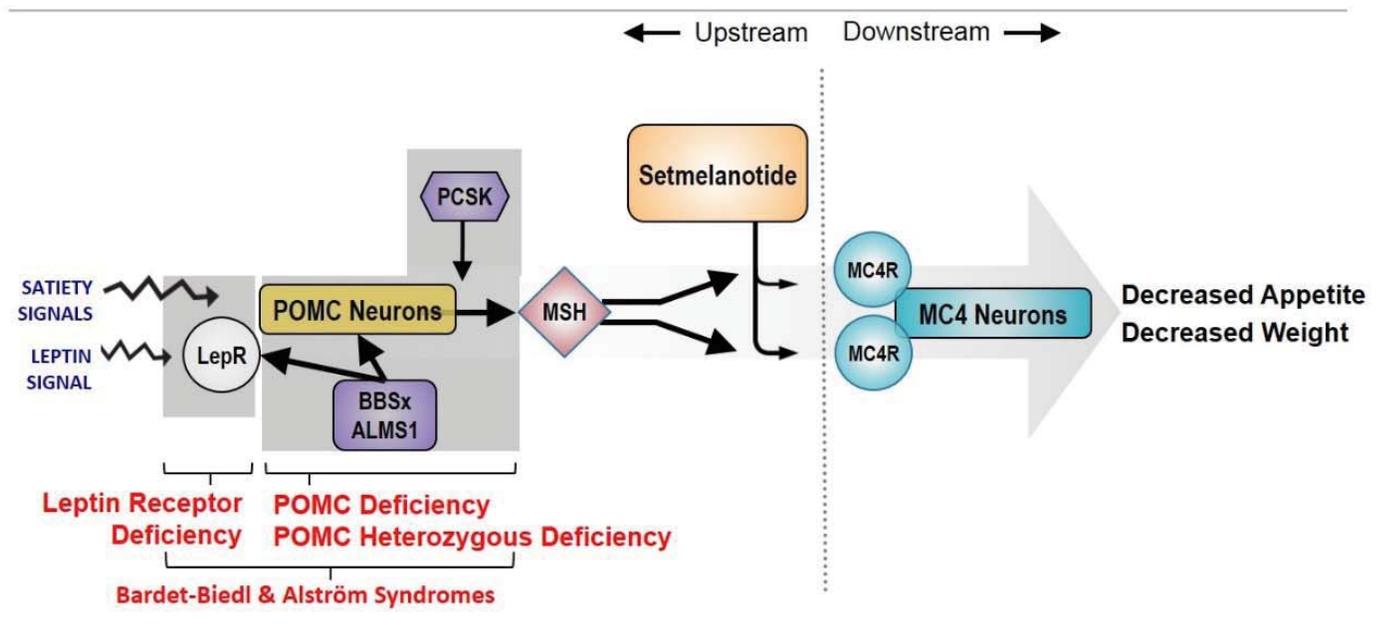


Figure 1. Hypothalamic LEPR-POMC-MC4R Pathway.

Source: Sponsor’s Breakthrough Therapy Designation Request Figure 1

Leptin receptor deficiency

Leptin receptor mutations were first reported in 1998 in three adult siblings from a consanguineous family. Since, it is been estimated that 1 to 3% of selected patients with hyperphagia and severe, early-onset obesity³ have loss-of-function leptin receptor mutations (Clement 1998, Farooqi 2007, Huvenne 2015). Patients with complete loss of function of the leptin receptor present with severe obesity, often in infancy as shown in the growth charts of three

³ Defined as severe obesity (BMI standard deviation score >3) occurring before the age of 10.

siblings with leptin receptor deficiency (Figure 2). Extreme hyperphagia and food-seeking behaviors, which generally begin in infancy, apparently drive this massive and early-onset weight gain. In a case series of 10 patients carrying biallelic LEPR gene defects published by Farooqi et al, the mean BMI standard-deviation Z score for LEPR deficiency patients was 5.1 ± 1.6 with mean percent body fat equal to $52.8 \pm 3.2\%$ (Farooqi 2007). Linear growth during childhood is generally normal; however, final height is generally reduced due to lack of pubertal growth spurt as a function of variable degrees of hypothalamic hypogonadism. Affected patients also exhibit alterations in immune function, and LEPR deficiency may be associated with more frequent childhood infections (Farooqi 2007). Few adults have been described in the literature, and it is unknown whether this is a result of underdiagnosis or early mortality (e.g., 2 out of 10 patients in the Farooqi case series died after an acute infection in first decade of life). The sponsor provides a worldwide prevalence estimate for LEPR deficiency patients of around 1000 patients based on estimates from small case series from specialized academic centers.

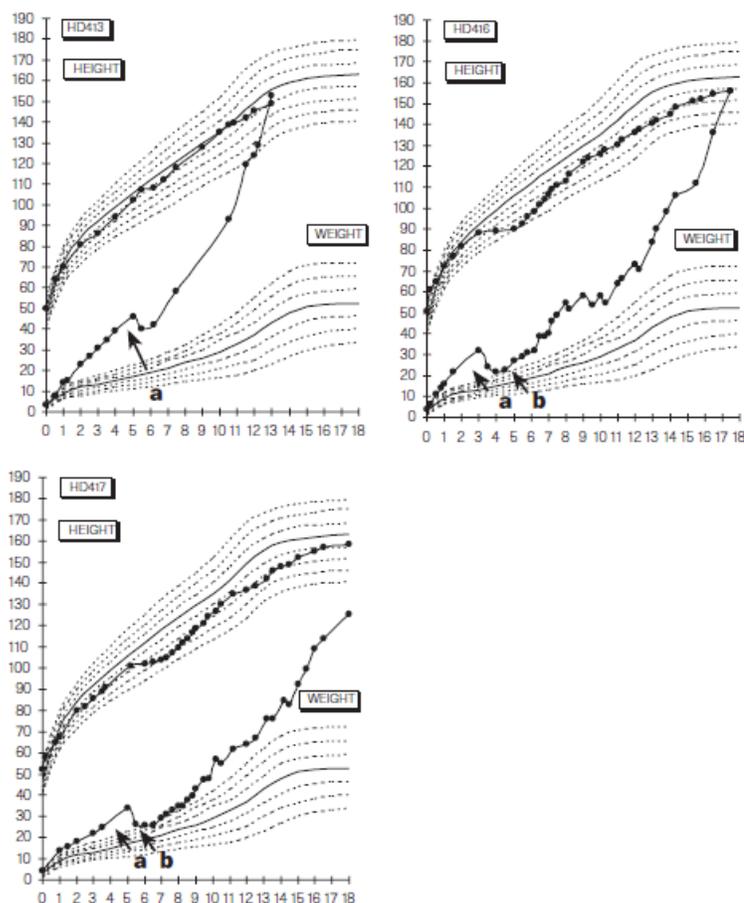


Figure 2. Growth curves of 3 siblings with homozygous mutation in leptin receptor

The letter a indicates a period of food-intake restriction to 500 kcal/day resulted in transient weight loss and decrease in growth velocity; b indicates the introduction of thyroid hormone and growth hormone

x-axis age in years; y-axis height in cm, weight in kg

Source: Clement et al. Nature 1998; Sponsor BTDR submission

7. Information related to endpoints used in the available clinical data:

As described below, the clinical data provided in support of this BTDR are the results from treating a single patient with leptin receptor deficiency with setmelanotide. Two additional patients, treated for 17 and 13 weeks to date, provide supportive data. In each case, the primary efficacy endpoint is percent weight loss from baseline with a key secondary endpoint being change in an investigator-created hunger score (Likert-type scale with 0 = no hunger, and 10 = extreme hunger). Other endpoints include change in body composition, insulin and glucose parameters, and energy expenditure. Given the massive and early-onset weight gain among these patients, a substantial reduction in weight would be considered a clinically meaningful outcome. Conceptually, a demonstrated reduction in hyperphagia would also be considered clinically meaningful.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Currently available therapies are not specifically indicated for obesity and hyperphagia associated with LEPR deficiency obesity.

The following drugs are FDA-approved for chronic weight management in adults with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with a weight related comorbidity. There are no data available to evaluate the effectiveness of these therapies in the target population. Anecdotal reports suggest extremely limited efficacy with lifestyle interventions in these patients.

Table 1. FDA-approved drugs for chronic weight management in general obese or overweight with comorbidities population

	SAXENDA Liraglutide 3 mg QD	CONTRAVE Naltrexone 32 mg/ Bupropion 360 mg QD	QSYMIA Phentermine 3.25-15 mg/ Topiramate 23-92 mg QD	BELVIQ Lorcaserin 10 mg BID	XENICAL Orlistat 60 or 120 mg TID
1-year mean placebo-subtracted weight loss	4.5%	4.1%	8.6% (high dose)	3.3%	3%
% achieved $\geq 5\%$ weight loss at 1 yr	62.3% vs 34.4% (Pbo)	42% vs 17% (Pbo)	70% (high dose) vs 21% (Pbo)	47.1% vs. 22.6% (Pbo)	57% (120 mg TID) vs. 31% (Pbo)
Year approved	2014	2014	2012	2012	1999

There are case reports of bariatric surgery outcomes in patients with leptin receptor deficiency obesity with variable success (Huvenne 2015, Le Beyec J 2013). The index patient in this BTDR underwent gastric banding with initial weight loss that could not be maintained due to excessive hunger and food intake.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation⁴.

There are no drugs in development for LEPR deficiency obesity. As mentioned previously, the current drug received BTDR for POMC deficiency obesity in December 2015.

10. Information related to the preliminary clinical evidence:

Evidence supporting this request is largely based on results from the first patient with leptin receptor deficiency enrolled in Study RM-493-011, which was initiated in Germany in January 2015 and originally enrolled patients with POMC deficiency obesity. This protocol was subsequently amended to allow enrollment of other monogenic obesity disorders involving the leptin/POMC/melanocortin pathway. This non-IND study is a 13-week, open-label, single-arm, pilot study of setmelanotide, followed by an extension period. Setmelanotide treatment starts at 0.5 mg daily and is escalated every two weeks based on weight loss and hunger reduction. Two additional patients with LEPR deficiency have preliminary results following 17 and 4 weeks of treatment.

Efficacy

The index patient is a 22-year-old man, with a homozygous *LEPR* gene mutation. He had significant weight gain beginning in infancy and weighed 150 kg at age 15. At age 18, he was offered the option of bariatric surgery if he could maintain his weight in order to undergo general anesthesia. His weight plateaued during late adolescence because of intensive efforts by the patient (and family) to qualify as a bariatric surgical candidate. Following bariatric surgery (gastric banding), his weight fell from 144 kg to 108 kg (25% weight loss) within a few months. However,

⁴ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

sustained weight loss was unsuccessful due to extreme hyperphagia and food intake. His weight trajectory sharply increased 1 year following surgery with weight gain of 22 kg over 1 to 2 years (Figure 3).

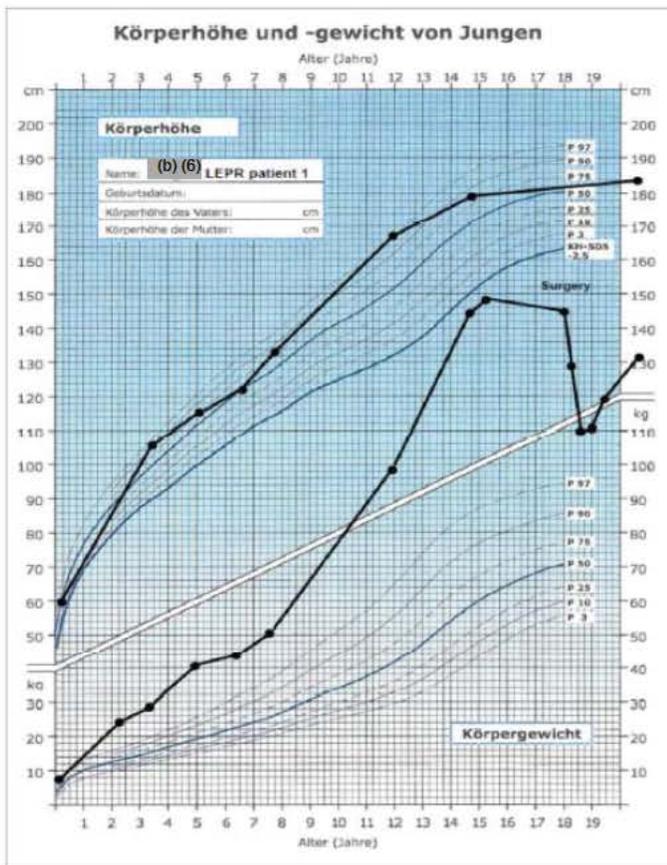


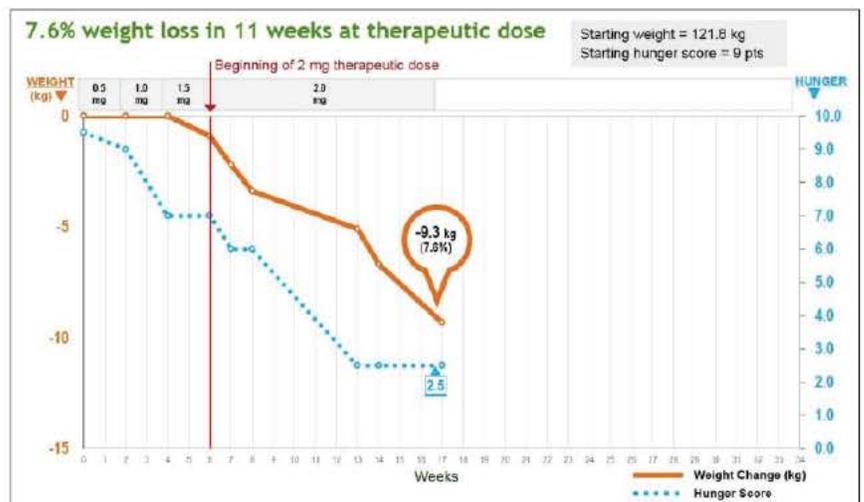
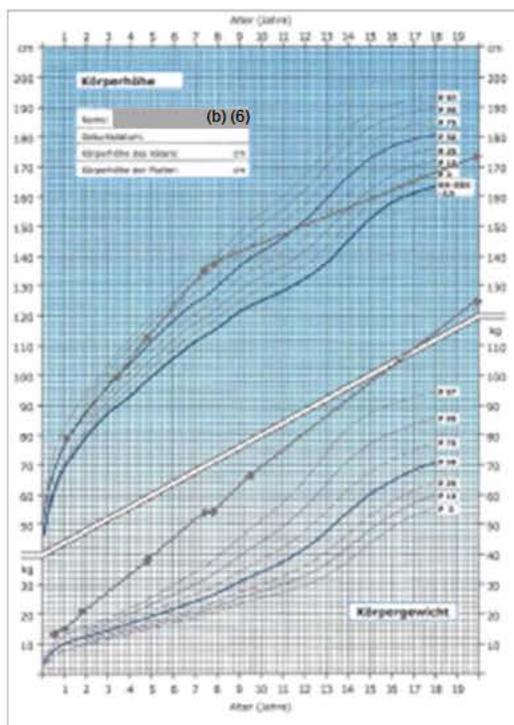
Figure 3. Patient 1 Growth Chart

Figure 4 demonstrates this patient’s change in body weight and hunger score with setmelanotide treatment. At baseline, his weight was 130.6 kg, BMI was 39.9 kg/m², and hunger score was 9 out of 10. His dose was escalated to 1.5 mg over 4 weeks. At the end of the 13-week treatment period, the patient reported reduced hunger scores (1-2 out of 10) and had lost 17.5 kg (13.4% of initial body weight). After 26 weeks of treatment, the patient has lost 28.2 kg (21.6% of initial body weight). Although this is a single patient on open-label treatment using a historical control (i.e., the patient’s previous weight trajectory over his lifetime), the weight loss following setmelanotide treatment is substantial. The amount of weight lost over 26 weeks of setmelanotide treatment is roughly similar to the weight loss initially observed following gastric banding. Furthermore, in contrast to setmelanotide treatment, gastric banding did not appear to affect the patient’s hunger drive. At this time, it is unknown if the reduced feelings of hunger will sustain longer-term weight loss.



Figure 4. Index patient's weight loss (left scale; green line) and hunger score (Likert scale 0=no hunger; right scale; blue line) over 26 weeks

Two additional patients with leptin receptor deficiency have been treated with setmelanotide. The second patient is a 22-year-old man with leptin receptor deficiency with intractable weight gain from infancy (Figure 5). His starting weight at the beginning of setmelanotide treatment was 121.8 kg. After 17 weeks (11 weeks on a dose of 2 mg/day) he has lost 9.3 kg (-7.6% of initial body weight) and his hunger score has dropped to 2.5 out of 10 points. Escalation to 2.5 mg setmelanotide is planned due to weight loss less than 2 kg/week and hunger score >2.



Body weight change (kg; left scale and orange lines) and hunger scores (0-10 points, from no hunger to extreme hunger; right scale and dotted blue lines) during treatment. Doses are indicated at the top, time is indicated by weeks since study start.

(A)

(B)

Figure 5. Patient #2 with leptin receptor deficiency obesity Growth chart (A); Weight loss and hunger score on setmelanotide (B)

The third patient with leptin receptor deficiency is a 14-year-old girl and the first adolescent treated with setmelanotide. When she was 10-years-old she weighed approximately 80 kg (176 pounds). Over the next 4 years, she gained approximately 9 kg (20 pounds) per year. At 14-years-old when she started setmelanotide, her weight was 120.4 kg (~265 pounds; BMI 44.2 kg/m²). She demonstrated weight loss at the 0.5 mg and 1 mg dose titration steps losing 7 kg (-6.9% body weight) in the first 4 weeks. She was advanced to 1.5 mg/once daily, and very preliminary data show that her weight

loss slowed [at 13 weeks her weight was 111.1 kg (BMI 40.5 kg/m²)] with a weight loss of 9.3 kg overall – about 7.7% of initial body weight.

In comparison to patients with POMC deficiency obesity, higher doses of setmelanotide may be required in LEPR deficiency patients to attain desired weight loss of 2 kg/week (minimum effective dose in POMC deficiency – 1.5 mg). However, it is unclear if this variability is due to the small number of patients treated or a differential treatment response depending on a patient’s underlying genetic condition. Regardless, it is compelling that in the context of a well documented history of unrelenting weight gain in which medical management is extremely challenging there appears to be hunger reduction and ~1 kg/week weight loss with setmelanotide treatment in patients with leptin receptor deficiency.

As mentioned previously, setmelanotide was initially developed to target (b) (4). Average weight loss in short-term (2 to 4 weeks) Phase I studies of these patients has been approximately 1 kg/week. In a 12-week study in healthy general obese patients (n=32) treated with 1.5 mg/day setmelanotide, the placebo-subtracted weight loss was approximately 2.5%.

Safety

In clinical studies with other MC4R agonists, dermatological (skin pigmentation and atypical nevi, hypersensitivity reactions at injection sites), spontaneous erections, and cardiovascular adverse events (elevated blood pressure and heart rate) have been observed, suggesting off-target effects at other melanocortin receptors. Results from genetic and pharmacologic studies suggest a role for melanocortinergic signaling in control of human blood pressure.

In contrast to other MC4R agonists, no consistent pattern of heart rate or blood pressure elevation has been noted thus far with setmelanotide; however, the duration and number of patients with exposure to setmelanotide in the general healthy obese population is small; therefore, conclusions regarding the cardiovascular safety of setmelanotide are quite limited. In the patients with POMC deficiency (1 patient treated out to 86 weeks) and leptin receptor deficiency, there have been no increases in blood pressure after the first dose or with dose escalations.

Consistent with this class, dermatological changes (skin tanning, new skin lesions) suggesting off-target effects at MC1R and spontaneous erections and genital discomfort/sexual arousal in women have been observed in setmelanotide-treated patients with general obesity. The first two patients with leptin receptor deficiency have reported skin darkening. The most common adverse events are injection site reactions, headache, and dry mouth.

11. Division’s recommendation and rationale (pre-MPC review):

GRANT :

Provide brief summary of rationale for granting:

The sponsor has identified another rare cause of early-onset severe obesity, which they refer to as “leptin receptor deficiency obesity,” comprising loss of function mutations in the leptin receptor. The estimated prevalence of patients with leptin receptor deficiency is approximately 1000 worldwide. Key features of this condition include hyperphagia beginning in infancy and subsequent refractory severe, early-onset, obesity. Extreme weight gain throughout childhood into adulthood contributes substantial morbidity to these patients’ lives.

There are currently no medications specifically indicated for leptin receptor deficiency obesity, and lifestyle and other weight loss interventions have been largely ineffective. Given the mechanisms underlying the clinical phenotype of leptin receptor deficiency, it is reasonable to hypothesize that bypassing the disrupted pathway and directly stimulating the MC4 receptor could be particularly effective in these patients. The preliminary clinical evidence of a setmelanotide-treated patient with leptin receptor deficiency experiencing reduced hunger and weight loss over a short period of time is compelling, especially given the reported natural history of hyperphagia and severe, early, unrelenting weight gain in children with this condition. The preliminary results from the 2 additional patients provide favorable support, although limited by the short treatment duration, for granting the request for breakthrough designation for setmelanotide.

DENY:

Provide brief summary of rationale for denial: Not applicable

12. Division’s next steps and sponsor’s plan for future development:

The Division has had several interactions with the sponsor since the granting breakthrough designation for setmelanotide and POMC deficiency obesity. Many of the issues already in discussion with the sponsor will also apply to the LEPR deficiency obesity development program, including the development of an appropriate patient and/or observer-reported outcome assessment to assess hyperphagia coordinated with input from the clinical outcome assessment team. The sponsor has submitted instruments to the COA staff to review and comment on for use in pivotal studies. Discussions are underway with the clinical pharmacogenomics group and others regarding whether a companion diagnostic would be required vs. relying on commercially available genetic testing to determine the appropriate identification of obese patients for setmelanotide treatment.

The sponsor is now focusing development on patients with several genetic forms of early-onset extreme obesity and associated co-morbidities that are caused by mutations or other genetic defects in the critical LEPR-POMC-MC4R hypothalamic pathway (referred to by the sponsor as the “MC4 pathway”). POMC deficiency obesity and LEPR deficiency obesity represent two specific monogenic disorders caused by mutations in genes within this pathway;

[Redacted text block]

[Redacted text block]

13. List references, if any:

Clement K et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature*. 1998;392:398-401.

Farooqi I et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *NEJM*. 2007;356:237-47.

Huvenne H et al. Seven novel deleterious LEPR mutations found in early-onset obesity: a ΔExon6-8 shared by subjects from Reunion Island, France, suggests a founder effect. *JCEM*. 2015;100:E757-66.

Le Beyec J et al. Homozygous leptin receptor mutation due to uniparental disomy of chromosome 1: response to bariatric surgery. *JCEM*. 2013;98:E397-402.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

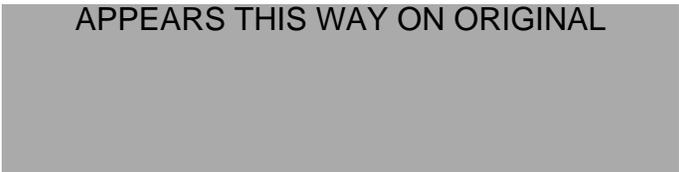
15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

APPEARS THIS WAY ON ORIGINAL



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

/s/

MARY D ROBERTS
05/03/2017

JAMES P SMITH
05/05/2017