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APPLICATION NUMBER:

213793Orig1s000

OTHER REVIEW(S)

Product Quality Assessment – CDER Immunogenicity Consult

Application Number:	NDA 213793
Consult Request Date:	April 13, 2020
Consult Due Date:	September 11, 2020
Consult Requester Office:	FDA/CDER/OCHEN/DDLO
Sponsor	Rhythm Pharmaceuticals
Product:	Setmelanotide (RM-493)
Indication:	Obesity with POMC- and LEPR-deficiency
Drug classification:	Melanocortin 4 receptor (MC4R) agonist peptide
Reason for Consult:	Review of immunogenicity assays for a new molecular entity (NME) original NDA submission (priority review)
Primary Reviewer:	Ian McWilliams, CDER/OPQ/OBP/DBRR-II
Secondary Reviewer:	William Hallett, CDER/OPQ/OBP/DBRR-II

RECOMMENDATION:

OBP Recommends Approval of this NDA from an Immunogenicity Assay perspective.

OBP was consulted to assess the immunogenicity assays in NDA 213793. In response to the immunogenicity consultation, we have the following recommendations regarding the adequacy of the submitted anti-RM-493 anti-drug antibody (ADA) assay, anti-alpha-MSH antibody assay, anti-RM-493 neutralizing antibody (NAb) assay, and anti-mPEG-DSPE antibody assay.

1. The anti-RM-493 ADA assay is not suitable for its intended use. There is substantial intra-assay variability of the confirmatory assay and the results are uninterpretable. The Sponsor will need to address the confirmatory assay methods in order to establish reproducibility and interpretability of the resulting ADA data. A PMC to improve setmelanotide confirmatory assay reliability and reproducibility has been agreed to by the Sponsor.

   PMC: Improve the performance and repeatability of the setmelanotide confirmatory ADA assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples.

   Study Completion: May-July 2021
   Final Report Submission: July-September 2021

2. The anti-alpha-MSH antibody assay is suitable for its intended use.
3. The anti-RM-493 NAb assay is suitable for its intended use for adult samples with less than 10 ng/mL of serum RM-493. The assay was not validated with pediatric serum and results of the NAb assay for pediatric samples will need to be assessed on a case-by-case basis to confirm adequate cut-point establishment.
4. The Sponsor has been unable to develop an anti-mPEG-DSPE antibody assay and will no longer pursue its development. Because mPEG-DSPE is an excipient, the development of antibodies to PEG will not impact product potency and is low risk.

OBP has provided draft PMC language and section 6.2 Immunogenicity label language for the Setmelanotide (RM-493) NDA program.

ASSESSMENT:

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Background

Rhythm Pharmaceutical's RM-493 (setmelanotide, formerly BIM-22493) is a synthetic cyclic octapeptide melanocortin type 4 receptor (MC4R) agonist for the treatment of obesity with underlying pro-opiomelanocortin (POMC) or leptin receptor (LEPR)-deficiencies, (b) (4) . Leptin produced from adipocytes signal through LEPR to promote the production of POMC. POMC is the precursor protein for adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (MSH), β-MSH, and γ-MSH, which act upon melanocortin receptors (MCRs) to decrease food intake and increase energy expenditure. Replacement therapy with RM-493 aims at restoring MC4R signaling in BBS and AS patients to decrease appetite and weight.

For the pivotal study RM-493-012, RM-493 was administered once daily subcutaneously with adult doses of 1.0 mg (week 1-2), 1.5 mg (week 3-4), 2.0 mg (week 5-6), 2.5 (week 7-8), and 3 mg (week 9-10), and pediatric/adolescent doses of 0.5 mg (week 1-2), 1.0 mg (week 3-4), 1.5 mg (week 5-6), 2.0 (week 7-8), 2.5 mg (week 9-10), and 3.0 mg (week 11-12). Patients returned to the clinic every 2 weeks to assess efficacy and determine if an individual patient's dose was to be increased according to the dose titration schedule. Once the patient's therapeutic dose was determined, the same dose/volume was administered throughout the remainder of the study. Pivotal study RM-493-015 followed a similar dose titration plan with an additional 8 week withdrawal period if 5 kg of 5% weight loss (if < 100 kg) was achieved.

RM-493 is formulated in a slow absorption injection formulation: RM-493 (10 mg/mL), mPEG2000-DSPE (100 mg/mL), carboxymethylcellulose (8 mg/mL), and mannitol (b) (4) mg/mL). For pivotal studies RM-493-012 and RM-493-015, ADA sampling takes place prior to drug administration at the screening visit (V1; -4 to 0 weeks), 1 week (V2), 5 weeks (V4), 13 weeks (V6), 27 weeks (V9), 39 weeks (V11), 53 weeks (V13), and at the final visit; ADA sampling will take place upon early termination of the study.

Immunogenicity Assay Regulatory History

Rhythm contracted the development of an ADA assay to RM-493 (validation report AR149-C1103-17-0086) and an assay to detect antibody to endogenous α-MSH (validation report AR149-C1103-18-0004). The amino acid sequence of RM-493 is RCAHFRWC, which has the same HFRW amino acid motif as α-MSH (SYSMEHFRWGKPV), β-MSH (AEKKDEGPYRMEHFRWGSPPKD), and γ-MSH (YVMGHFRWDRFG). The inclusion of the endogenous α-MSH will help determine whether pre-existing antibodies are present or whether there is de-novo generation of antibodies to endogenous proteins with similar motifs to RM-493.

There have been several communications with the Sponsor regarding their immunogenicity assay development that are summarized in the table below for IND 112595 Setmelanotide and NDA 213793 Setmelanotide (RM-493).

IND 112595			
Date	Correspondence Type	IND Sequence #	COMMENTS
28 Oct 2016	Rhythm submission of Anti-RM-493 ADA method validation report	0058	Anti-RM-493 ALTA REPORT: AR4070
17 Mar 2017	FDA Advice/ Information Request	–	3Mar2017 DARRTs submission
13 Sep 2017	Rhythm response to FDA Advice/ Information Request	0093	Rhythm response to 17Mar2017 FDA comments
31 Oct 2017	FDA Advice/ Information Request	–	23Oct2017 DARRTs submission
14 Dec 2017	Rhythm response to FDA Advice/ Information Request	0100	Rhythm response to 31Oct2017 FDA comments
02 Mar 2018	FDA Advice/ Information Request	–	15Feb2018 DARRTs submission
08 Jun 2018	Rhythm response to FDA Advice/ Information Request	0117	Rhythm response to 02Mar2018 FDA comments
07 Sep 2018	FDA Advice/ Information Request	–	FDA comments on 08Jun2018 Rhythm response
11 Oct 2018	Rhythm response to FDA Advice/ Information Request	0129	Rhythm response to 07Sep2018 FDA comments
29 Oct 2018	Rhythm submission of draft C1103-17-0086 method validation report	0132	Addendum to Rhythm response to 07Sep2018 FDA comments, includes draft validation report for Anti-RM-493-antibody assay from (b) (4)
10 Jan 2019	FDA Advice/ Information Request	–	14Dec2018 DARRTs submission
21 Feb 2019	Rhythm response to FDA Advice/ Information Request and final method validation report	0140	Rhythm response to 10Jan2019 FDA comments, includes final validation report for Anti-RM-493-antibody assay from (b) (4) (C1103-17-0086)
27 Mar 2019	Addendum to final validation report for Anti-RM-493- antibody assay from (b) (4) (C1103-17-0086)	0144	Note to File as Addendum to Seq 0140; final validation report for Anti-RM-493-antibody assay from (b) (4) (C1103-17-0086)
16 Apr 2019	FDA Advice/ Information Request	–	5Apr2019 DARRTs submission
03 Jul 2019	Rhythm response to FDA Advice/ Information Request	0156	Rhythm response to 16Apr2019 FDA comments

21 Aug 2019	FDA Advice/Information request	-	20Aug2019 DARRTs submission
23 Aug 2019	Pre-NDA Meeting Package	0161	Package to prepare for 25 Sept. 2019 pre-NDA meeting with Agency
20 Sept 2019	Rhythm response to FDA Advice/ Information Request which included Addendum to anti-RM-493 antibody assay validation report	0162	Rhythm response to 21Aug2019 FDA comments
05 Mar 2020	Rhythm response to FDA Advice/ Information Request	0176	Rhythm response to 20Nov2019 FDA comments
05 Mar 2020	Rhythm response to FDA Advice/ Information Request	0177	Rhythm response to 20Dec2019 FDA comments
12 Mar 2020	Rhythm response to FDA Advice/ Information Request	0178	Rhythm corrections to SN 0177
17 Apr 2020	Advice/Information Request	-	08Apr2020 DARRTs submission
NDA 213793			
Date	Correspondence Type	NDA Sequence #	COMMENTS
06 Jun 2020	Rhythm response to FDA Advice/ Information Request	0015	In response to 06Jun2020 DARRTs IR submission
06 Aug 2020	Rhythm response to FDA Advice/ Information Request	0019	In response to 17Jul2020 DARRTs IR request submission
16 Oct 2020	Rhythm Quality Information	0028	In response to 8 Oct 2020 PMC/PMR list communication

Assessor comment: In the pre-NDA meeting minutes, provided to the Sponsor October 25th, 2019 for IND 112595, the following agreement was made:

> *FDA also stated that they concurred with the Sponsor proposal to provide* [redacted] (b) (4) *as a post-approval submission, due to delays in assay development.*

An IR was sent to the Sponsor July 17th, 2020 (during the NDA review cycle) that asked for clarification of the timeline for completion of the anti-mPEG2000 assay that stated:

> *Section 5.3.5.3 ISI subsection 2.5 Assay Description for the Detection of Antibodies to mPEG states that the development and validation of an assay to detect anti-mPEG-DSPE antibodies is ongoing. Further, you state that "the method validation report and sample analysis results will be submitted to the Agency when available as previously agreed with the FDA (20 Aug 2019 Advice/Information Request Letter)". You have not provided a timeline for the completion of this commitment. Provide an estimated timeline for the completion of assay development and validation, testing of clinical samples, and reporting the rates.*

In response (08/06/2020; eCTD 0019/SDN-19) the Sponsor stated that the development of an anti-mPEG-DSPE antibody assay has been unsuccessful and that they will no longer pursue development of this assay. This is not what was agreed to prior to the NDA submission. A PMC was drafted and sent to the Sponsor for comment with the PMR/PMC list on October 8th, 2020. In the Sponsor's response (10/16/2020; eCTD 0028/SDN-28), they reiterated that they have been unable to develop a successful anti-mPEG-DSPE assay.

After additional internal discussion, we have decided the elimination of this assay from the immunogenicity program is acceptable. Pre-existing antibodies to PEG in the general population are common and considered low risk for immunogenic responses. As mPEG-DSPE is an excipient, we do not anticipate that anti-mPEG-DSPE antibodies will influence the potency of the drug product itself. Therefore, the elimination of the mPEG-DSPE assay is low risk.

Validation of Anti-Drug Antibody (ADA) Assays

The validated anti-RM-493 ADA assay, AR149-CC1103-17-0086, and anti-α-MSH antibody assay, Ar149-c1103-18-0004, are direct ELISAs. RM-493 or α-MSH is immobilized to an ELISA plate and incubated with patient serum. The plates are washed and a secondary goat anti-Human IgG/A/M-HRP antibody is added to bind to anti-RM-493 or anti-α-MSH bound antibodies. TMB substrate is then added to react with HRP to visualize the level of bound antibody. Samples are considered negative if the mean OD is less than or equal to the cut-point. For the anti-RM-493 assay, samples are screened positive if post-dose samples with anti-RM-493 ADA signals below the CP but above their pre-dose sample ADA signal by at least 2-fold will be considered positive or all samples with signals above CP will be considered positive. Samples that screen positive are tested in the confirmatory assay; samples that are confirmed positive are further tested in the titer assay with a 2-fold dilution series starting at 1:1 to 1:128. The highest diluted sample above the titer cut point is reported as the clinical sample titer and samples with positive signal above the maximum dilution (1:128) are reported as > 128. The ADA method validation results are summarized in the table below.

Validation Parameter	Anti-RM-493	anti-α-MSH
Contract research organization	(b) (4)	(b) (4)
	Assessor comment: *There are no concerns with the CRO.*	
Report number	AR149-CC1103-17-0086 (Re-development)	Ar149-c1103-18-0004
Clinical trial	RM-493-011 RM-493-012 (Pivotal) RM-493-014 RM-493-015 (Pivotal) RM-493-022 RM-493-026	RM-493-011 RM-493-012 (Pivotal) RM-493-014 RM-493-015 (Pivotal) RM-493-022 RM-493-026
Assay principle	direct ELISA	direct ELISA
	Assessor comment: *The direct ELISA is a common ADA assay format. There are no objections to the selection of this method format.*	
Sample pre-treatment	No sample pre-treatment	No sample pre-treatment
	Assessor comment: *There has been discussion about including an acid-dissociation step in the anti-RM-493 assay if a sample tests positive in the alpha MSH assay. The Sponsors stated that this work is ongoing and will be submitted when finished (IND 112595 SDN-179 March 10, 2020). Validation of an acid dissociation step has not been included in the validation report and is not used in the assessment of clinical samples. The acid disassociation step would improve the assay's drug tolerance.*	
Positive control (PC)	Affinity purified Rabbit anti-RM-493 (Rabbit 3704 Production Bleed antibody) (Rhythm, Lot. # 1011053.AP1) ***Assessor comment:*** *The antibody used is a polyclonal anti-RM-493 antibody. The PC demonstrates a low and high signal for the LPC and HPC, respectively, and is acceptable for use.*	Affinity Purified Rabbit pAb anti-α-MSH, Abcam (Abcam Catalog # ab123811, Lot GR79104-14) ***Assessor comment:*** *The antibody used is a polyclonal anti-α-MSH antibody. The PC demonstrates a low and high signal for the LPC and HPC, respectively, and is acceptable for use.*
PC Dose Curve and Hook Effect	No dose curve is provided	PC antibody concentrations from 200,000 ng/mL to 25 ng/mL

		Assessor comment: The concentration's used for the LPC and HPC show low and high signals, respectively. The HPC of 4800 ng/mL is not expected to elicit a hook effect and the selection of LPC and HPC are appropriate.	*Assessor comment: No hook effect is noted. The selection of the LPC and HPC give a low and high signal, respectively. The selection of the PC antibody and PC concentrations are acceptable.*
LPC		LPC1 (600 ng/mL) LPC2 (300 ng/mL) LPC3 (150 ng/mL) LPC4 (75 ng/mL)	LPC 1: 150 ng/mL LPC 2: 100 ng/mL LPC 3: 70 ng/mL
HPC		4,800 ng/mL	5000 ng/mL
Matrix and negative controls		Matrix: Pooled Normal Human Serum (PNHS), Obese Adult Serum (OAS), Obese Pediatric Serum (OPS) Negative controls: Rabbit NC (detected with anti-rabbit HRP), Human NC (detected with anti-human HRP), IC (Isotype control, unlabeled human IgG)	Matrix: Pooled Normal Human Serum (PNHS), Obese Adult Serum (OAS), Obese Pediatric Serum (OPS). Negative controls: Pooled normal human serum (PNHS). Used as negative control (NC) for both anti-human and anti-rabbit antibodies used
		Assessor comment: The Sponsor was asked to provide justification for the selection of OAS and OPS as representative of the patient population. The Sponsor provided a response (eCTD 0025/SDN-25; June 30th, 2020) that surrogate populations based on age and BMI (pediatrics and adults) were used to generate the validation cut-points. The established cut-points using the surrogate sera appear are discussed in detail in Assessment of the anti-RM-493 Assay Performance in Clinical Studies and Assessment of the Anti-Alpha-MSH Assay Performance in Clinical Studies.	
MRD		1:10; no pre-treatment steps *Assessor comment: MRD of 1:10 is consistent with the 2019 immunogenicity guidance document.*	1:10; no pre-treatment steps *Assessor comment: MRD of 1:10 is consistent with the 2019 immunogenicity guidance document.*
System suitability range	NC	Isotype Control must be within the validated range and have a %CV between replicates ≤ 20%.	Isotype Control must be within the validated range and have a %CV between replicates ≤ 20%.
	LPC/HPC	Four out of six Positive Controls, with at least one PC at each level, must be within the validated range and have a %CV between replicates ≤ 20%. HPC signal > LPC signal > SCP; LPC > NC	Four out of six Positive Controls, with at least one PC at each level, must be within the validated range and have a %CV between replicates ≤ 20%. HPC signal > LPC signal > SCP; LPC > NC PC %Inhibition ≥ CCP
	Assessor comment	*The values set for system suitability per run are appropriate. The LPC must be above the plate cut-point and above the negative control in order for the assay to proceed.*	
Screening cut-point	FPR	5% FPR; floating cut-point (S/N log transformed 95% percentile)	5% FPR; floating cut-point
	PNHS	1.08 – serum from 27 males/27 females – parametric	1.27
	OAS	1.60 – serum from 27 males/27 females – parametric	1.35
	OPS	1.91 – serum from 16 males/16 females – non-parametric	1.27

	Assessor comments	*The cut-points were established using an acceptable number of serum samples with 3 analysts over 12 runs. The OPS cut-point study resulted in a bi-modal distribution of cut-points and a cut-point of 3.85. Subsequently, the Sponsors removed bi-modal samples from analysis and re-established the cut-point at 1.91. This is acceptable as it will allow for more samples to test positive and be added to confirmatory testing where they will be confirmed ADA+ or ADA-. Confirmation of in-study cut-point is discussed under Assessment of the anti-RM-493 Assay Performance in Clinical Studies.*	*The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods. Confirmation of in-study cut-point is discussed under Assessment of the Anti-Alpha-MSH Assay Performance in Clinical Studies.*
Confirmatory cut-point	FPR	1% FPR; fixed cut-point (99th percentile, parametric)	1% FPR; %INH = 100 × [1 - (OD inhibited / OD uninhibited)]; fixed cut-point
	Spiked	500 ng/mL RM-493	10 ng/mL α-MSH; lowest concentration that showed inhibition of the anti-α-MSH antibody PC without signal reduction in the NC samples.
	PNHS	13.2% – serum from 27 males/27 females – parametric	20.2%– serum from 27 males/27 females – parametric
	OAS	11.4% – serum from 27 males/27 females – parametric	14.6% – serum from 27 males/27 females – parametric
	OPS	9.2% – serum from 16 males/16 females – parametric	18.7%– serum from 16 males/16 females – parametric
	Assessor comments	*The confirmatory assay is performed in triplicate and 2/3 must be greater than the confirmatory cut-point in order for the sample to be considered confirmed ADA+. 500 ng/mL causes ~ 50-60% inhibition at LPC3 and 30-50% inhibition at LPC1. Additional discussion of the confirmatory cut-point is provided under Assessment of the anti-RM-493 Assay Performance in Clinical Studies. The performance of the confirmatory assay for the clinical samples is inadequate as there is too much variation in the triplicate inhibitory ratios. Subsequently, the anti-RM-493 assay is not adequate for use in assessing clinical samples.*	*The generation of this cut-point was performed appropriately with sufficient samples, runs, analysts, and statistical methods. Discussion of the confirmatory cut-point is provided under Assessment of the Anti-Alpha-MSH Assay Performance in Clinical Studies.*
Titer Cut Point (TCP)	FPR	1% FPR; floating cut-point	1% FPR; floating cut-point
	PNHS	1.46; 27 males/27 females sera	1.51; 27 males/27 females sera
	OAS	2.52; 27 males/27 females sera	1.68; 27 males/27 females sera
	OPS	1.51; 16 males/16 females sera	1.58; 16 males/16 females sera
	Assessor comments	*The titer assay cut-point was established using an adequate number of samples, runs, analysts, and statistical methods.*	*The titer assay cut-point was established using an adequate number of samples, runs, analysts, and statistical methods.*
Interference	α-MSH	See Table A of AR149-C1103-17-0086 RM-493 ADA MVR ADDENDUM 2	PC samples prepared at 25, 50, 100, 200, and 2000 ng/mL, and then spiked with 0, 6, 60, and 600 pg/mL purified αMSH.

		Result: 60 pg/mL alpha-MSH at 150 ng/mL anti-α-RM-493 PC *Assessor comment: Serum alpha-MSH concentrations in healthy individuals is estimated to be 60 pg/mL. The assay is able to detect positives at concentrations at LPC3 (150 ng/mL), which demonstrates that interference from alpha-MSH is unlikely to occur.*	Result: 25 ng/mL anti-alpha-MSH PC is positive in the presence of 60 pg/mL alpha-MSH *Assessor comment: Serum alpha-MSH concentrations in healthy individuals is estimated to be 60 pg/mL. The assay is able to detect positives at concentrations below LPC3, which demonstrates that interference is unlikely to occur.*
	RM-493	5 ng/mL RM-493 at all α-MSH and mPEG-DSPE concentrations Updated to 30 ng/mL on 10/13/2020 (in response to PMC/PMR list, provided to the Agency on 10/16/2020 in eCTD 0028/SDN-28). *Assessor comment: On page 120 of the combined validation document under "Drug tolerance to RM-493 and mPEG-DSPE", the Sponsor states that the assay can tolerate 10 ng/mL RM-493 alone, but that "In 2 out of 4 tests the presence of 10 ng/mL RM-493 and 500 or 1,000 ng/mL mPEG-DSPE showed a reduction of signal at the LPC level of approx. 30% and 20%, respectively." This data is not provided.* *It was previously communicated to the Sponsor during the IND development that additional studies needed to be performed as part of interference studies. The last IND 112595 communication (SN 0176; March 5th 2020) stated that interference studies are ongoing and will be reported to the Agency when completed. The Sponsors submitted the NDA without completion of these interference studies.* *There is concern that serum concentrations above 5 ng/mL will interfere in the assay. See further discussion under Assessment of the anti-RM-493 Assay Performance in Clinical Studies. There are many pivotal samples that test negative with serum RM-493 concentrations above 5 ng/mL. These samples are considered inconclusive as there is no way of determining whether the assay is performing appropriately under those conditions. Subsequently, the anti-RM-493 assay is not adequate for use in assessing clinical samples.*	Anti-α-MSH PC samples prepared at 25, 50, 100, 200, and 2000 ng/mL, and then spiked with 0, 0.6, 6.0, and 60 ng/mL RM-493 Result: 60 ng/mL of RM-493 *Assessor comment: Serum concentrations are lower than 60 ng/mL and this is acceptable for anti-alpha-MSH testing.*

		Update 10/13/2020: The Sponsor provided additional drug tolerance data using LPC (150 ng/mL) and up to 30 ng/mL of RM-493. This is discussed further under Assessment of the anti-RM-493 Assay Performance in Clinical Studies.	
	mPEG-DSPE	> 1000 ng/mL	Not determined *Assessor comment: The Sponsor stated in IND 112595 communication (SN 0176; March 5th 2020) that interference assessment is ongoing and will be reported to the Agency when completed. This data was not provided with the NDA submission. The Sponsor demonstrates that high levels of mPEG-DSPE do not interfere with the anti-RM-493 assay and it is likely that the anti-alpha-MSH based on similar principles will behave similarly.*
Sensitivity (includes MRD)	PNHS	103 ng/mL	52.7 ng/mL
	OAS	184 ng/mL	58.2 ng/mL
	OPS	240 ng/mL	52.7 ng/mL
	Assessor comments	*Sensitivity calculations account for MRD. The sensitivities reported are above the recommendation in the 2019 Immunogenicity guidance, however, these ranges are only ~2 fold higher and should be able to capture the formation of ADA.*	*Sensitivity calculations account for MRD and are consistent with the 2019 immunogenicity guidance.*
Repeatability/Intra-assay variability		3.3 % at HPC 3.3 % at LPC1 2.7 % at LPC2 3.2 % at LPC3 7.9 % at LPC4 *Assessor comment: CV < 20% is acceptable.*	LPC2 (100 ng/mL) Screening: 7.0% CV Confirmatory: 10.3% CV HPC (2000 ng/mL) Screening: 3.3% CV Confirmatory: 2.2% CV *Assessor comment: CV < 20% is acceptable.*
Intermediate Precision (IP)/inter-assay variability		14.75% at HPC 7.6 % at LPC1 7.2 % at LPC2 14.5 % at LPC3 15.1 % at LPC4 *Assessor comment: CV < 20% is acceptable.*	LPC1 (150 ng/mL) Screening: 12.1% CV Confirmatory: 11.2% CV LPC2 (100 ng/mL) Screening: 10.7% CV Confirmatory: 17.5% CV LPC3 (70 ng/mL) Screening: 8.8% CV Confirmatory: 16.6% CV HPC (2000 ng/mL) Screening: 10.5% CV Confirmatory: 9% CV *Assessor comment: CV < 20% is acceptable.*
Selectivity		10/10 PNHS confirmed at LPC3 (100 ng/mL) 9/10 OPS confirmed at LPC2 (300 ng/mL)	10/10 PNHS confirmed at LPC2 (100 ng/mL) 10/10 OPS confirmed at LPC2 (100 ng/mL)

	10/10 OAS confirmed at LPC2 (300 ng/mL) *Assessor comment: The Sponsor set the acceptance criteria of >80%*	8/8 OAS confirmed at LPC2 (100 ng/mL) *Assessor comment: The Sponsors set the acceptance criteria of >80%*
Stability	The PC is stable for 5 freeze/thaw, 24 hours at RT, and -70°C for 24 months according to IC-P-1040-08.A2 assay worksheet. *Assessor comment: The data for stability testing is not provided. The assay worksheet for the updated ADA assay states that the PC is stable under the conditions listed. This is acceptable for PC stability.*	HPC and LPC2 in PNHS samples frozen at -70 ± 10°C for at least 12 hours, thawed and left at room temperature (RT) for 24 hours or subjected to 8 freeze/thaw cycles. To pass, CV ≤ 25.0% *Assessor comment: The Sponsors demonstrate adequate PC stability.*
Lipemia	No interference noted.	No interference noted.
Hemolysis	No interference noted.	No interference noted.
ADA Assay Assessment	Not suitable	Suitable

Validation of Neutralizing Anti-Drug Antibody Assay

The Nab assay uses the DiscoverX Path Hunter ® U2OS cell-based assay that monitors G Protein-Coupled Receptor (GPCR) functional activation using Enzyme Fragment Complementation (EFC) technology. Briefly, a β-galactosidase (β-gal) enzyme divided into two complementary inactive portions:

1. The β-gal enzyme donor (ED) fused to the Melanocortin 4 (MC4R) GPCR
2. The β-gal enzyme acceptor (EA) fused to β-arrestin.

Addition of 5 ng/mL setmelanotide (RM-493) and binding of the MC4R receptor causes a conformational change in the MC4R GPCR allowing complementation of the two β-gal enzyme pieces and enzyme activation. Activation then hydrolyzes the β-gal substrate and generates a chemiluminescent signal. The presence of neutralizing antibodies will bind to and inhibit RM-493 causing a reduction in signal. 20 µL of prepared test sample is added directly to a 96-well assay plate containing cells in 80 µL of cell culture media. To achieve the final MRD 1:10, all samples prepared for the testing should contain 50% serum with 5× concentrations of the assay test reagents (setmelanotide, spiked PC, etc.). The NAb method validation results are summarized in the table below.

Validation Parameter	RM-493	*Assessor Comments*
Contract Research Org	(b) (4)	*There are no concerns with the CRO.*
Report number	AR6666	*No comment on the report number.*
Clinical trial	No samples confirmed positive from the anti-RM-493 assay	*No samples were confirmed positive during the clinical study samples. Subsequently, the NAb assay was not performed.*
Assay principle	Cell-based NAb assay using the DiscoverX PathHunter® MC4R β-Arrestin GPCR Kit with the Thaw-and-Use PathHunter® U2OS MC4R Bioassay Cells.	*A cell-based NAb assay is consistent with methods listed in the 2019 immunogenicity guidance and it acceptable for use in this study.*
Sample Pretreatment	No pre-treatment	*No pre-treatment is performed and the MRD is not affected.*
Positive control (PC)	Affinity purified positive control (AP-PC) Rabbit anti-RM-493 (Rabbit 3704 Production Bleed antibody) (Rhythm, Lot. # 1011053.AP1)	*The Sponsor lists two positive controls. The Sponsor states that the RB-PC was used in the assay after neutralizing activity was assessed relative to the AP-PC. This means that the amounts used for AP-PC and RB-PC are normalized for*

		Non-affinity purified rabbit 3705 setmelanotide production bleed positive control (RB-PC) was assessed relative to AP-PC	*their inhibition. The Sponsor provides an estimated equivalent amount for RB-PC and AP-PC. The positive control antibodies are demonstrated to be specific for RM-493 and not for alpha-MSH. This approach is reasonable.*
PC Dose Curve and Hook Effect		AP-PC concentrations: 10, 3.33, 1.11, 0.37, and 0.123 µg/mL RB-PC 1:1000, 1:2000, 1:4000, 1:8000, 1:16000, 1:32000	*The LPC and HPC are appropriately designated for amounts that have a high signal (LPC) and low signal (HPC). No hook effect is noted.*
LPC		1:7000 dilution of RB-PC (estimated around 0.65 µg/mL of AP-PC equivalent)	
HPC		1:1000 dilution of RB-PC (estimated around 4.7 µg/mL of AP-PC equivalent)	
Matrix and negative controls		Negative: Pooled obese human serum (POHS) Drug Control (DC): 5 ng/mL of setmelanotide in 10% POHS	*The Sponsors use POHS to validate the assay. The drug control demonstrates what a positive signal (RLU) in the assay prior to the addition of patient samples. These controls are acceptable.*
MRD		1:10	*The MRD aligns with the 2019 immunogenicity guidance.*
NC system suitability range		Replicate CV < 25% DC > NC	*Ideally, the PC suitability should be "HCP < LPC < SCP". The way the suitability is phrased leaves room for the LPC to not be below the SCP. However, the assay is validated appropriately and these criteria should allow sufficient control over each run.*
LPC system suitability range		Replicate CV < 25% HPC < SCP HCP < LPC	
HPC system suitability range			
Screening cut-point (Mean Normalized Signal (NS) - 1.645*(SD))	FPR	5% FPR; floating cut-point; parametric	*2 analysts tested 30 serum samples (14 male/16 female) over 6 runs to establish cut-points (180 observations). The sample are drug naïve individuals whose ages ranged from 20 to 64 years and Body Mass Index (BMI) ranged from 30 to 50. These samples are representative of the adult population but not of the pediatric population in the RM-493 studies. The anti-RM-493 ADA assay has separate cut-points for adult and pediatric populations. There is a concern that these cut-points will not be acceptable for testing pediatric patient samples. No samples were confirmed positive in the anti-RM-493 ADA assay and the NAb assay was not used to assess samples. It is not possible to confirm with in-study samples whether the cut-point is appropriately set for the pediatric population.*
	POHS	0.79	
Confirmatory cut-point (Mean NS - 2.326*(SD))	FPR	1% FPR; floating cut-point; parametric Normalized ration (NR) = normalized signal (NS)/normalized baseline signal (NSo)	
	POHS	0.84	
αMSH interference		Not tested	*The Sponsor states that 5 ng/mL of setmelanotide had similar affects as 200 ng/mL of alpha-MSH. Since the*

			estimated serum concentration of alpha-MSH is 60 pg/mL, the assay will be able to tolerate the addition of a significant amount of alpha-MSH before affect would been seen. This is acceptable for the validation of this assay.
RM-493 drug interference		10 ng/mL in LPC	*Increasing RM-493 concentration led to false-negatives in the study. This demonstrates that serum samples collected that have serum concentrations greater than 10 ng/mL may appear negative even when positive. Thus, this assay is not adequate for use for samples with serum concentration over 10 ng/mL.*
mPEG-DSPE interference		Not tested	*The Sponsor did not test whether mPEG-DSPE interference will occur in the NAb assay. PEG moieties are not anticipated to interfere with setmelanotide binding or β-gal activation. Th*
Sensitivity	POHS	NS (screening): 0.57 ± 0.04 µg/mL in 10% serum NR (confirmatory): 0.51 ± 0.06 µg/mL in 10% POHS serum	*Sensitivity assessment for the NAb assay is performed correctly and is acceptable.*
Repeatability/Intra-assay variability		<u>Using AB-PC</u> LPC = 8.5% HPC = 8.1%	*CV < 20% is acceptable.*
Intermediate Precision (IP)/inter-assay variability		<u>Using AB-PC</u> LPC = 5.8% HPC = 6.4%	*CV < 20% is acceptable.*
Selectivity		NS: 9/10 positive in LPC NR: 10/10 positive in LPC	*> 80% positive is acceptable.*
Stability		Benchtop stability: 24 hours at Room Temperature Freeze/thaw stability: 5 cycles between room temperature and -70 ±10 °C	*The Sponsors demonstrate adequate PC stability and sample stability.*
Hemolysis		No interference noted at LPC	*No issue noted.*
ADA Assay Assessment		Suitable for samples with < 10 ng/mL RM-493 Cut-point is not validated with pediatric serum and will need to be confirmed with in-study samples in the event that testing occurs. This is not an approvability issue.	

<u>Assessment of the Anti-RM-493 Assay Performance in Clinical Studies</u>

Anti-RM-493 Assay Drug Tolerance

Assessor comment: The assessor comment at the end of this section was updated with the new drug tolerance limit of 30 ng/mL of RM-493 (10/16/2020; eCTD 0028/SDN-28). The original review is left in place to capture the data and assessment of the information that was originally submitted.

The validated anti-RM-493 method has a drug tolerance of 5 ng/mL of RM-493. The serum concentrations of RM-493 in pivotal studies are higher than 5 ng/mL at later testing time-points. Additional ADA data was provided for later time-points with the 120-day submission. An IR was sent to the Sponsor to get more information about anti-RM-493 and anti-alpha-MSH antibody results compared to serum concentrations of RM-493. This IR stated that:

1. Section 5.3.5.3 Integrated Immunogenicity Summary (ISI) provides anti-drug antibody (ADA) assay validation information for the re-developed anti-RM-493 antibody assay (AR149-C1103-17-0086) and anti-alpha-MSH antibody assay. The RM-493 drug tolerance of the anti-RM-493 antibody assay is 5 ng/mL and RM-493 drug tolerance of the anti-alpha-MSH antibody assay is 60.0 ng/mL. In order to assess the ability of the assays to detect the development of ADA in clinical samples, provide an Excel table that lists every patient, the clinical study number, the ADA raw data, the cut point used, the ADA positivity status, and the RM-493 serum concentration (if available) for every ADA timepoint. Separate tables should be provided for healthy, adult POMC/LepR-deficient and pediatric POMC/LepR-deficient patient populations.
2. Your ADA testing plan, provided in section 5.3.5.3 ISI subsection 3 Clinical Study Designs and Sampling Strategies, states that pivotal clinical samples from RM-493-012 and RM-493-015 will be tested in both anti-RM-493 and anti-alpha-MSH assays. The data provided in the IR response received June 10th, 2020, and the 120-day safety update provided July 15th, 2020, do not include patient data using both assays. For example, patient (b) (6) has anti-RM-493 ADA data reported, but no data is provided from anti-alpha-MSH testing. Provide anti-RM-493 and anti-alpha-MSH data for all ADA samples collected for RM-493-012 and RM-493-015 to the Excel table that will be provided with IR item #1. Justification will need to be provided if data is not available from both assays.

The Sponsor responded (08/06/2020; eCTD 0019/SDN-19) by providing side-by-side ADA testing results with RM-493 serum concentrations for the pivotal studies RM-493-12 and RM-493-15, Phase 2 studies RM-493-11 and RM-493-14, and RM-493-22 extended study. The table below summarizes the results of the submitted data.

Clinical Study	ADA samples	Screened negative samples			Screened positive samples		
	Total	Total	Serum RM-493 > 5 ng/mL	No PK reported	Total	Serum RM-493 > 5 ng/mL	No PK reported
RM-493-11 (Phase 2)	63	53	3	41	10	1	7
RM-493-12 (pivotal)	130	85	6	16	45	7	10
RM-493-14 (Phase 2)	324	189	26	84	135	15	86
RM-493-15 (pivotal)	112	57	11	0	55	18	2
RM-493-22 (extended)	133	79	36	21	54	29	12
Total	762	463/762 (~60.7% of total ADA samples)	82/463 (~17.7% of total screened negative samples)	162/463 (~35.0% of total screened negative samples)	299/762 (~39.2% of total ADA samples)	70/299 (~23.4% of total screened positive samples)	117/299 (~39.1% of total screened positive samples)

Assessor comment: The data provided from the Sponsor indicate that for anti-RM-493 testing that ~ 56.6% ((82+162+70+117)/762) of anti-RM-493 ADA samples are inconclusive because of RM-493 serum concentrations of greater than 5 ng/mL and where PK data is not reported. After discussions with the review team, (b) (4) the proportion of negative screened ((82+162)/463 = ~53%) and positive screened ((70+117)/299 = ~62.5%) samples that were determined to be inconclusive.

It was previously communicated to the Sponsor that additional interference testing is warranted for their immunogenicity assay program. In the most recent IR response to the IND 112595 (SN 0176; March 5th 2020), the Sponsor stated that additional studies for drug tolerance are ongoing and would be reported to the Agency when completed. The Sponsor did not provide the results of these validation attempts with the submission of the NDA package and have not provided these results with IR responses for the NDA. Subsequently, the RM-493 immunogenicity assay is not valid for assessing over a 1/10th of the pivotal ADA samples and should be further validated for the purposes of reporting immunogenicity ADA results for labeling.

Update 10/13/2020
A PMC for drug tolerance was drafted and sent to the Sponsor for comment with the PMR/PMC list on October 8th, 2020. In response, the Sponsor provided (10/16/2020; eCTD 0028/SDN-28) additional validation data supporting a higher drug tolerance limit of 30 ng/mL for the anti-setmelanotide ADA assay. Drug tolerance was assessed using rabbit anti-RM-493 HPC, LPC, and no PC with RM-493 concentrations of 0, 10, 20, and 30 ng/mL spiked into samples. A summary of the LPC data is provided in the table below.

RM-493 (ng/mL)		Run# 100a		Run# 100b		Run# 103	
		Mean RLU	%Inh	Mean RLU	%Inh	Mean RLU	%Inh
30		0.160	33.5	0.138	34.1	0.203	45.0
20		0.153	36.4	0.146	30.2	0.218	40.9
10		0.169	29.7	0.153	26.9	0.251	32.1
0		0.241	n/a	0.209	n/a	0.369	n/a
Rabbit NC SCP	Normal	0.051		0.051		0.052	
	Pediatric	0.090		0.090		0.092	
	Adult	0.075		0.075		0.077	

The added drug demonstrated an approximately 33-45% inhibition at 30 ng/mL; however, the mean RLU at the 150 ng/mL LPC remained above the normal, pediatric, and adult cutpoints that were set off of the rabbit NC. This demonstrates that the assay is able to maintain a positive signal at 150 ng/mL in the presence of up to 30 ng/mL. The sensitivity of the assay for 184 ng/mL for OAS and 240 ng/mL for OPS. The LPC drug tolerance demonstrates that drug tolerance is acceptable at the lower limit of sensitivity for both adult and pediatric populations. Further, clinical ADA serum concentrations are largely below the 30 ng/mL drug tolerance limit, meaning that screening results from this assay are reliable at these drug concentrations. Subsequently, the Sponsor has demonstrated that the anti-RM-493 ADA assay drug tolerance is adequate.

Anti-RM-493 Cut-Point Establishment

The RM-493 cut-points were established using surrogate serum for adult and pediatric populations. It was noted in the establishment of the screening cut-points for the RM-493 assay that there was a bimodal distribution of results and that, after eliminating the higher bimodal curve, the cut-point was established on the lower values. The Sponsors state that the bimodal distribution is likely due to the presence of pre-existing antibodies to alpha-MSH. Subsequently, the screening cut-points are established low which will lead to larger amount of potential false negatives being screened positive. In order to confirm the establishment of the screening cut-point with in-study samples, the number of samples that are screened positive at the screening

visit (pre-treatment) are summarized in the table below (from data submitted on 08/06/2020; eCTD 0019/SDN-19).

Pre-treatment POMC- and LEPR-deficient	Pre-treatment samples	Pre-treatment samples screening ADA+	%Pre-treatment screening ADA+	Confirmed ADA+
Pivotal study RM-493-12				
Adult ADA cut-point	8	4	50%	0
Pediatric ADA cut-point	12	5	41.7%	0
Pivotal study RM-493-15				
Adult ADA cut-point	13	8	61.5%	0
Pediatric ADA cut-point	12	5	41.6%	0

Assessor comment: *Assessment of the pre-treatment samples demonstrate that the cut-points are set so that approximately 50% of sample will be found positive, which is higher than what is statistically projected for a 5% FPR. This is acceptable as the pediatric cut-point establishment demonstrated a bimodal distribution that necessitated a lower cut-point. The adult cut-point has also set low so that more samples will be considered positive and be tested in the confirmatory assay. This approach is appropriate to ensure that true-positives will be included in the confirmatory assay.*

Anti-RM-493 Confirmatory Assay Variability

The confirmatory cut-point for the anti-RM-493 assay was established by performing the assay with adult obese and adult pediatric serum samples with a 1% FPR rate. The confirmatory cut-point establishment was performed by testing individual samples across 4 plates with 3 different operators and an example of the adult obese results are provided below from Table 10 of AR149-C1103-17-0086 RM-493 ADA MVR ADDENDUM 1 Attachment 4:

Group	Subject	Set 1	Set 2	Set 3	Set 4
A	(b) (6)	-6.3	-3.0	1.6	31.2(c)
A		-4.2	-11.3	-8.5	-1.0
A		-2.3	-5.7	-4.6	3.7
A		5.6	-8.7	1.0	-8.8
B		-1.1	9.7	3.7	7.5
B		0.4	-7.7	-2.1	-3.2
B		-14.0	-6.6	-3.6	-4.9
B		0.0	-17.9(c)	-7.6	-2.0
B		-4.0	-10.8	-4.3	-5.7
C		-9.3	4.4	-3.1	-3.2
C		-7.1	-2.1	-2.4	-4.9
C		-14.6	1.1	-3.7	-2.0
C		0.0	-5.3	1.7	-5.7

Assessor comment: *Although the Sponsor provides a histogram of the results for adult and pediatric confirmatory cut-points that demonstrates a parametric curve, there is a critical issue with the variation between set 1 through 4 results. For example, Group A Subject* (b) (6) *(second on the list) has results of -4.2%, -11.3%, -8.5%, and -1.0%. The coefficient of variation (standard deviation/mean*100) of these results is ~73%. The Sponsor demonstrated during validation that the HPC and LPC inter- and intra-plate precision is acceptable, so although the set 1 through set 4 display large variation, there is potential for limited variation when all samples are run on one plate. With the clinical data that the Sponsor provided on August 6th, 2020*

(eCTD 0019/SDN-19) the intra-plate variation between confirmatory triplicate is much greater than 25% CV. An example of the patient data from pivotal study RM-493-12 is adapted in the table below.

Subject ID/Sample Description	Triplicate number	Spiked (500 ng/mL) or unspiked	OD1	OD2	Mean RLU	%CV of OD1 and OD2	% Inhibition	Result	Final result
(b) (6) (pediatric) / V11 / Day 267 DF = 1	1	Unspiked	0.627	0.612	0.6195	1.712	11.703	Positive	Negative Immuno-depletion
		Spiked	0.557	0.537	0.547	2.585			
	2	Unspiked	0.673	0.625	0.649	5.230	0.385	Negative	
		Spiked	0.668	0.625	0.6465	4.703			
	3	Unspiked	0.59	0.601	0.5955	1.306	1.847	Negative	
		Spiked	0.588	0.581	0.5845	0.847			

*As is seen in the example above, the Sponsor is calculating the %CV between OD1 and OD2, but not between the triplicate values of 11.70, 0.39, and 1.85. The %CV between these values is 134.7% (standard deviation/mean*100). Even though one of these samples is identified as positive in the example above, it does not reach the 2 of 3 samples needed to be considered positive and the final result is negative immunodepletion. Subsequently, there is too much variability with the confirmatory assay to be able to determine if a sample is confirmed positive.*

The Sponsor provided the following rationale in section 'Low Confirmatory Cutpoint and Potential Impact on Sample Analysis' for the inclusion of the 2 of 3 criteria for positive confirmatory assay.

> *It is known that the relatively low confirmatory cutpoints determined for this assay (pending comparison to study data from drug-naïve samples for appropriateness) present a risk of false positive results as the inhibition required is within the acceptable intra-assay variability for a ligand-binding immunoassay. To mitigate this risk, confirmatory results of study samples will be based on 3 independent analyses of each sample.*

The 1% FPR calculation is what determines the false positive rate. The inclusion of the 2 of 3 criteria for confirmatory assay positive confirmation is not supported by this rationale. Further, the 2 of 3 criteria does not resolve the variance that is seen in the confirmatory assay results and the results of the confirmatory assay are not reliable for ADA determination. The Sponsor needs to improve the reproducibility of the confirmatory assay method in order to provide assurance that the assay will perform as intended.

A PMC to improve the performance and repeatability of the setmelanotide confirmatory ADA assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples will be provided to the Sponsor.

Assessment of the **Anti-α-MSH** Antibody Assay Performance in Clinical Studies

Pivotal study data using the anti-α-MSH ADA assay was provided for RM-493-12 and RM-493-15 in an IR response, provided 08/06/2020 (eCTD 0019/SDN-19). The table below summarizes the number of pre-treatment positive samples, to assess cut-point establishment, and all samples to examine the suitability of the anti-α-MSH Antibody Assay.

Pre-treatment screening results

Pivotal study	Cut-point	Number of samples	Number screened ADA+	%ADA+	Confirmed ADA+	Titer
RM-493-12	Adult	6	0	0%	0	n/a
	Pediatric	7	0	0%	0	n/a
RM-493-15	Adult	3	1	33.3%	0/1	n/a
	Pediatric	4	1	25.0%	1/1	4
Total	Adult	9	1	11.1%	0/1	n/a
	Pediatric	11	1	9.1%	1/1	4
All ADA results						
Pivotal study	Cut-point	Number of samples	Number screened ADA+	% Screened ADA+	Confirmed ADA+	Titer
RM-493-11 (Phase 2)	Adult	59	9	15.3%	0/9	n/a
	Pediatric	3	1	33.3%	0/1	n/a
RM-493-12 (pivotal)	Adult	41	6	14.6%	0/6	n/a
	Pediatric	71	7	9.9%	0/7	n/a
RM-493-14 (Phase 2)	Adult	77	31	40.2%	2/31	1, 1
	Pediatric	63	17	27.0%	1/17	8
RM-493-15 (pivotal)	Adult	20	7	35.0%	1/7	1
	Pediatric	37	19	51.4%	2/19	1, 4 (at screening)
RM-493-22 (extended)	Adult	2	0	0%	0/0	n/a
	Pediatric	3	1	33.3%	0/1	n/a
Total	Adult	199	53	26.6%	3/53	1, 1, 1
	Pediatric	177	45	25.4%	3/45	1, 4 (at screening), 8

Assessor comment: *The anti-α-MSH antibody assay has demonstrated the ability to screen, confirm, and titer pediatric and adult patient serum. The cut-points established for the anti-α-MSH are reasonable to identify anti-α-MSH antibody positive individuals. This assay is suitable for its intended purpose.*

Of note, the Sponsor had indicated that all samples tested with the anti-setmelanotide ADA assay would also be tested with the anti-alpha-MSH assay. With the data provided 08/06/2020 (eCTD 0019/SDN-19), it became clear that not all samples were tested with both assays and this was communicated to the clinical pharmacology review team for their assessment. This is not a review concern for the validation of ADA assays,

EXECUTIVE SUMMARY

1. Anti-RM-493 ADA assay: Not suitable for its intended use.
    a. The confirmatory assay has substantial intra-assay variation and the results are uninterpretable. The Sponsor will need to address the confirmatory assay methods in order to establish reproducibility and interpretability of the resulting data.

2. Anti-alpha-MSH antibody assay: Suitable for its intended use
3. Anti-RM-493 NAb assay: Suitable for its intended use for adult samples with less than 10 ng/mL of serum RM-493
    a. The assay was validated using serum from adult populations and not with serum from pediatric populations. The cut-point may work with both adult and pediatric populations, but the assay was not used on any clinical samples because no samples were confirmed positive for anti-RM-493 ADA. In-study data may demonstrate that the assay is suitable for both populations and should be assessed if the information becomes available.
4. Anti-mPEG-DSPE antibody assay: No longer needed for the setmelanotide ADA immunogenicity program.

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

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

Memorandum

Date: October 21, 2020

To: Patricia Madara, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Monika Houstoun, Associate Director for Labeling, DDLO

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for IMCIVREE (setmelanotide) injection, for subcutaneous use

NDA: 213793

In response to DDLO's consult request dated May 1, 2020, 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 Imcivree.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail (SharePoint Link) from DDLO on October 6, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on October 19, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 7, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani (240) 402-1348 or Meena.Savani@fda.hhs.gov.

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MEENA R SAVANI
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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 Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 19, 2020
To:	Patricia Madara Regulatory Health Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, 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):	IMCIVREE (setmelanotide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 213793
Applicant:	Rhythm Pharmaceuticals, Inc.

1 INTRODUCTION

On March 27, 2020 Rhythm Pharmaceuticals, Inc. submitted for the Agency's review the Final Rolling Submission-Clinical and Chemistry, Manufacturing, and Controls (CMC) Filing 2 to the original New Drug Application (NDA) 213793 for IMCIVREE (setmelanotide) injection, for subcutaneous use. The first (CMC Filing 1) and second (Nonclinical) parts of the rolling submission were filed on August 23, 2019 and October 31, 2019, respectively.

The proposed indication for IMCIVREE (setmelanotide) injection, for subcutaneous use is for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older.

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 Diabetes, Lipid Disorders, and Obesity (DDLO) on May 1, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for IMCIVREE (setmelanotide) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 10, 2020.

2 MATERIAL REVIEWED

- Draft IMCIVREE (setmelanotide) injection, for subcutaneous use PPI and IFU received on March 27, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on October 6, 2020.
- Draft IMCIVREE (setmelanotide) injection, for subcutaneous use PPI and IFU received on March 27, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on October 6, 2020.
- Draft IMCIVREE (setmelanotide) injection, for subcutaneous use Prescribing Information (PI) received on March 27, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on October 6, 2020.
- Draft IMCIVREE (setmelanotide) injection, for subcutaneous use Prescribing Information (PI) received on March 27, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on October 6, 2020.

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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

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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MARCIA B WILLIAMS
10/19/2020 11:49:25 AM

LASHAWN M GRIFFITHS
10/19/2020 11:50:23 AM

Clinical Inspection Summary

Date	10/08/2020; updated 10/22/2020
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ovidiu A. Galescu, M.D., Clinical Reviewer John Sharretts, M.D., Clinical Team Leader Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Patricia Madara, Regulatory Health Project Manager Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
NDA	213793
Applicant	Rhythm Pharmaceuticals, Inc.
Drug	setmelanotide
NME	Yes (Priority review breakthrough therapy)
Therapeutic Classification	Melanocortin 4 receptor agonist
Proposed Indication	Treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC) deficiency obesity or leptin receptor (LEPR) deficiency obesity
Consultation Request Date	4/6/2020
Summary Goal Date	10/9/2020
Action Goal Date	11/23/2020
PDUFA Date	11/23/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic sites in addition to the sponsor.

An inspection assignment was issued on 4/10/2020 and the plans to conduct good clinical practice (GCP) inspections of five clinical investigator sites and the sponsor, covering Studies RM-493-012, RM-493-015, (b) (4), were scheduled by the Office of Regulatory Affairs (ORA). Of note, for Study RM-493-015, only foreign sites are involved.

The ongoing COVID-19 global pandemic has significantly limited ORA's ability to conduct onsite foreign GCP inspections. As a result, inspections of Dr. Allison Bahm/Canada (Site 004, Study RM-493-012), Dr. Karine Clement/France (Site 002, Study RM-493-015) and Dr. Peter Kuehnen/Germany (Site 001, Study RM-493-012) were not conducted. Remote data investigation of source records by ORA was not feasible due to local restriction to obtain remote access of

subject source records.

In general, based on the inspections of the two domestic clinical sites and the sponsor, covering Studies RM-493-012, RM-493-015, [redacted] (b) (4), the inspectional findings support validity of data as reported by the sponsor under this NDA.

II. BACKGROUND

Rhythm Pharmaceuticals, Inc. (Rhythm) submitted a rolling submission of a new drug application (NDA) for setmelanotide, a Breakthrough Therapy designated for the treatment of obesity associated with rare genetic disorders of obesity (RGDO) due to specific genetic defects that impact the functioning of the melanocortin 4 receptor (MC4R) pathway, a highly conserved hypothalamic pathway critical for regulation of appetite, energy expenditure, and body weight. The proposed indication is for the treatment of obesity [redacted] (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older.

Inspections were requested for three studies. Two controlled clinical studies, RM-493-012 and RM-493-015, are pertinent to the claimed indication. [redacted] (b) (4) All studies are ongoing.

RM-493-012
Study RM-493-012 is an open-label Phase 3 pivotal study with a double-blind placebo-controlled withdrawal period (that will allow subjects to serve as their own control to assess any reversal effects on weight and hunger to confirm any drug effects) to assess safety and efficacy of setmelanotide in subjects with pro-opiomelanocortin (POMC) deficiency obesity or Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) genetic mutation (pediatric, adolescents and adults).

The study contains two cohorts of subjects: a pivotal cohort and a supplemental cohort. As indicated in the Statistical Analysis Plan (SAP), the efficacy analysis to support this NDA is to be based on pivotal cohort subjects that had completed the study.

The primary objective was to evaluate the effect on body weight change in subjects with POMC deficiency obesity after 1 year of treatment with setmelanotide. Key secondary objectives were to assess the effect of 1 year of treatment with setmelanotide on safety and tolerability (including blood pressure and heart rate) and hunger in subjects ≥12 years of age Subjects who completed setmelanotide treatment in this study were eligible to continue in a separate extension study, RM-493-022.

The primary endpoint per protocol was the proportion of subjects in the full analysis set who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment, compared to

the proportion from historical data (at most, 5% responders in the null population).

RM-493-015
Study RM-493-015 is an open-label phase 3 pivotal study with a double-blind placebo-controlled withdrawal period (that will allow patients to serve as their own control to assess any reversal effects on weight and hunger to confirm any drug effects) to assess safety and efficacy of setmelanotide in subjects with leptin receptor (LEPR) deficiency obesity.

The study contains two cohorts of subjects: pivotal and supplemental.

The primary objective was to evaluate the effect on body weight change in subjects with LEPR deficiency obesity due to rare bi-allelic or loss-of-function mutations after 1 year of treatment with setmelanotide.

Key secondary objectives were to assess the effect of 1 year of treatment with setmelanotide on safety and tolerability (including blood pressure and heart rate) and hunger in ubjects ≥12 years of age.

The primary endpoint per protocol was the proportion of subjects in the full analysis set who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment, compared to the proportion from historical data (at most, 5% responders in the null population).

Subjects who complete setmelanotide treatment were eligible to continue setmelanotide treatment in a separate extension study RM-493-022.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. **James Swain, MD**
   Honor Health Research Institute
   10210 N. 92nd Street, Suite 100
   Scottsdale, AZ 85258-4523
   Study: RM-493-012 **Site:** 006

Dates of inspection: August 3 – 7, 2020

There (b) (4) screened and enrolled into the study; (b) (4) completed the study. There were (b) (4) records reviewed.

The institutional review board of record was (b) (4)

This was Dr. Swain's first clinical trial involving an investigational drug product. The study subject was referred to him. He was contacted by the sponsor who was knowledgeable of a potential patient with the gene mutation under investigation in the Phoenix area.

The source records were attributable, legible, contemporaneous, original and accurate. The electronic systems used during the study were: 1) (b) (4) Electronic Data Capture (EDC), provided by the sponsor; 2) (b) (4), the electronic health record used by (b) (4) and 3) (b) (4) the e-Diary for subject. The site had access to their data located in the portal throughout the clinical trial.

The subject was confirmed to have the PCSK1 genetic mutation. The subject was enrolled into the extension study after completion of the RM493-012 study.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

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3. Rhythm Pharmaceuticals, Inc. / Sponsor
222 Berkeley Street, Suite 1200
Boston, MA 02116-3733

Dates of inspection: June 8 – 17, 2020

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/contract research organization (CRO), deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

In addition, due to the inability to inspect as many sites as initially anticipated due to the COVID-19 pandemic, all Monitoring Plans and all monitoring reports for all sites for

Studies RM-493-012, RM-493-015, [redacted] were collected.

Onsite inspection focused on five sites:

- Study RM-493-012: Site 003/Dr. Clement/France and Site 008/Dr. DeWaele/Belgium
- Study RM-493-015: Site 002/Dr. Clement/France and Site 004/Dr Farooqi/United Kingdom
- [redacted]

Additional remote focus of review was Study RM-493-012 Site 004/Dr. Bahm/Canada and Site 001/Dr. Kuehnen/Germany and Study RM-493-015 Site 002/ Dr. Clement/France.

To date, there have been no terminations or suspensions of investigators or study sites.

Rhythm Pharmaceuticals, Inc (Rhythm) entered into an agreement with the CRO [redacted] to transfer responsibility of study start-up, data management services, site monitoring, project management and communications as reported in the Master Service Agreement (MSA) effective January 11, 2016. Over the course of study start-up and the first year of Study RM-493-012, there was substantial CRO staff turnover, which raised concerns regarding the management of sites and monitoring reports being completed in a timely manner. Rhythm hired a contractor, [redacted], to conduct a GCP audit. Based on the results of the audit, Rhythm decided to transfer the clinical oversite responsibilities to the CRO [redacted] Rhythm remained very engaged in all trial activities and had adequate sponsor oversight.

[redacted]

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

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Central Doc. Rm./ NDA 213793
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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: 9/30/2020 **Date consulted:** 7/21/2020

From: Jacquline Yancy, Ph.D., Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

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

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Drug: IMCIVREE (setmelanotide) injection, for subcutaneous use

NDA: 213793

Applicant: Rhythm Pharmaceuticals

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and pediatric patients 6 years of age and older.

Materials Reviewed:

- Applicant's draft labeling submitted March 27, 2020.
- Applicant's clinical summary and overview submitted in application,

- DPMH review of Belviq XR, NDA 208524, Miriam Dinatale, M.D., May 26, 2016. DARRTS Reference ID: 3937014[1]
- DPMH review of Qsymia, NDA 022580/017, Jeanine Best, MSN, July 20, 2020. DARRTS Reference ID: 4643393[2]

Consult Question: "Is the PLLR language in the PI acceptable?

INTRODUCTION AND BACKGROUND

On March 27, 2020, the applicant (Rhythm Pharmaceuticals) submitted an NDA for a new molecular entity (NME) IMCIVREE (setmelanotide), a melanocortin 4 receptor (MC4R) agonist peptide developed to treat proopiomelanocortin (POMC), including PCSK1, deficiency obesity and leptin receptor (LEPR) deficiency obesity. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) consulted the Division of Pediatric and Maternal Health (DPMH) on August 7, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Rare Genetic Disorders of Obesity (RGDO)

Several single-gene disorders result in severe, early-onset obesity. These monogenic forms of early-onset obesity show the biological importance of the mutant gene in body-weight control. The main genes affected in these monogenic disorders (leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), prohormone convertase 1 (PCSK1), melanocortin 4 receptor (MC4R), brain-derived neurotrophic factor (BDNF) and neurotrophic tyrosine kinase receptor type 2 (NTRK2)) encode hormones or neurotransmitters and their hypothalamic receptors of the highly conserved leptin-melanocortin pathway, which is critical for the regulation of food intake and body weight.[3] The MC4R pathway mutations cause rare genetic disorders of obesity that start early in childhood, progress over time and can become life-threatening in severity. There are no approved treatments for the obesity and insatiable hunger associated with these rare genetic disorders of obesity (RGDO).

There are no previous DPMH reviews for Setmelanotide.

Setmelanotide Drug Characteristics

Drug Class	MC4R agonist
Mechanism of Action	Setmelanotide is a MC4 receptor agonist. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4 receptor, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.
Molecular Weight	1117.3 g/mol
Half-life	Approximately 11 hours
Protein Binding	79.1%
Bioavailability	N/A

[1] The Belviq XR consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] The Qsymia Hydrochloride consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[3] Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. Nat Clin Pract Endocrinol Metab. 2008;4:569–577.

Serious Adverse Reactions as listed in the proposed labeling	• Hyperpigmentation • Depression • Spontaneous penile erection
Formulation	Injection 10 mg/ml solution in multi-dose vial; contains 10mg benzyl alcohol preservative

REVIEW

PREGNANCY

Obesity and Pregnancy

Obesity is a complex health issue resulting from a combination of causes and individual factors such as behavior and genetics.[4] The CDC reports a U.S. prevalence of obesity of 42.4% in 2017 to 2018. The prevalence of obesity during this time period was 40.0% among young adults aged 20 to 39 years and 44.8% among middle-aged adults aged 40 to 59 years.[5] Obese pregnant women are at an increased risk of adverse pregnancy complications and adverse maternal and fetal outcomes. These risks increase with increasing degrees of maternal obesity. Approximately 25% of pregnancy complications, including gestational hypertension, preeclampsia, gestational diabetes, and preterm birth, and approximately 32% of large for gestational age neonates are attributable to excessive gestational weight gain.[6] Maternal obesity also increases the risk for congenital malformations, including neural tube defects, cardiac malformations, orofacial defects, and limb reduction abnormalities.[7]

Optimally, women should achieve weight loss to control obesity prior to pregnancy, and even small weight reductions before pregnancy may improve pregnancy outcomes. The current evidence related to weight loss and obstetric and neonatal outcomes in all pregnant women is limited. Weight loss in obese women during pregnancy is not recommended due to the potential risks to the fetus.[8] Low maternal weight gain and weight loss in pregnancy have been associated with restrictions in fetal growth, specifically increased risk of small for gestational age (SGA).[9,10] The 2009 Institute of Medicine (IOM) guidelines recommend a total pregnancy weight gain of 11 to 20 lbs. for obese women.[11] Inadequate weight gain and gestational weight loss is not encouraged for obese pregnant women.[9] ACOG recommends that diet and exercise counseling be guided by the patient's body mass index and IOM recommendations for pregnancy weight gain.

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[4] https://www.cdc.gov/obesity/adult/causes.html, accessed 8/13/2020

[5] https://www.cdc.gov/obesity/data/adult html, accessed 8/13/2020

[6] Santos S, Voerman E, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American, and Australian cohorts. *BJOG*, 2019; 126(8):984-995

[7] https://www.uptodate.com/contents/obesity-in-pregnancy-complications-and-maternal-management/print?source=history_widget, accessed 8/13/2020

[8] Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. Cochrane Database Syst Rev. 2013;(1):CD009334. Published 2013 Jan 31. doi:10.1002/14651858.CD009334.pub2

[9] *ACOG Practice Bulletin No 156: Obesity in Pregnancy. Obstetr & Gynec*, 2015; 126(6):E112-26

[10] Goldstein RF, Abell SK, Ranasinha S, et al. Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis. JAMA. 2017;317(21):2207–2225. doi:10.1001/jama.2017.3635

[11] Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

The primary weight management strategies during pregnancy are dietary control, exercise, and behavior modification in order to avoid excessive gestational weight gain. Weight loss medications are not recommended during the time of conception or during pregnancy because of safety concerns and adverse maternal and fetal effects.[12]

Nonclinical Experience
Data from embryo-fetal development and pre/postnatal development studies in rats and rabbits exposed to setmelanotide during organogenesis, at dose exposures 11 and 0.4 times respectively the exposure at the recommended human dose of 3 mg, reveal no evidence of adverse developmental effects.

The reader is referred to the full pharmacology/toxicology review by Shaji Theodore, PhD

Review of Pharmacovigilance Database
There were no pregnancy exposures reported during the setmelanotide clinical development program.

The product is not approved for any indications in any country at the time, therefore, there are no global pharmacovigilance data available.

Review of Literature
DPMH conducted a review of published literature in PubMed, Embase, and Briggs and Freeman and no publications were found evaluating the use of Setmelanotide in pregnant women. DPMH also searched Micromedex for Setmelanotide summary information. No information was found.

Reviewer comment:
Animal reproduction studies do not show evidence of adverse developmental effects. Therefore, formal pregnancy testing and contraception are not necessary for setmelanotide labeling. Since minimal weight gain, and not weight loss, is currently recommended for all pregnant women, there is no benefit for a weight-loss medication during pregnancy. Setmelanotide injection solution is provided in a multi-dose vial containing 10 mg of the preservative benzyl alcohol, which is a theoretical risk for the fetus. As there may be accidental or intentional exposure to setmelanotide during pregnancy, and there are no clinical data describing adverse developmental effects, DPMH would recommend labeling state that setmelanotide is not recommended for use during pregnancy [redacted] (b) (4) *In addition, a "Clinical Considerations" section, which describes the importance of minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who are already overweight or obese, should be included in the labeling.*

LACTATION
Nonclinical Experience
Dose-related setmelanotide concentrations were observed in rat milk 2 hours after subcutaneous injection in the preweaning phase of a pre- and post-natal development study in rats. Mean setmelanotide concentrations in rat milk were 12.0, 83.0, and 106.0 ng/mL at doses of 0.5, 3.0,

[12] *ACOG Practice Bulletin No 156: Obesity in Pregnancy. Obstetr & Gynec*, 2015; 126(6):E112-26

and 5.0 mg/kg/day, respectively. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups on post-natal Day 11.

The reader is referred to the full pharmacology/toxicology review by Shaji Theodore, PhD.

Review of Literature
DPMH conducted a review of published literature in PubMed, Embase, LactMed, and Medications in Mother's Milk regarding the use of setmelanotide and lactation. No publications were located.

Reviewer comment
The animal pre/post-natal development study shows that setmelanotide is excreted at low levels in the milk of rats treated during the preweaning lactation period. Therefore, setmelanotide is likely to be present in human milk, however, due to species-specific lactation physiology, the exact amount transferred to human milk cannot be determined. However, no quantifiable setmelanotide concentration was found in the plasma of nursing rat pups, suggesting that the drug may not be absorbed from the gastrointestinal tract. DPMH recommends including language in the labeling advising the clinician to consider the benefit-risk of breastfeeding while using this drug along with any potential adverse effects on the breastfed child.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
In nonclinical studies, there were no effects of setmelanotide on fertility in male rats (3.0 mg/kg/day, approximately 9 times the human AUC from a 3.0 mg dose) or female rats (5.0 mg/kg/day, approximately 11 times the human AUC from a 3.0 mg dose) following subcutaneous administration.

Review of Literature:
DPMH conducted a literature search in PubMed, Embase, and Micromedex regarding the use of Setmelanotide and fertility. No publications were located.

Reviewer comment:
The applicant has not included a subsection 8.3 in labeling. Given the lack of adverse effects on fertility in animal studies, and the lack of adverse developmental outcomes demonstrated with setmelanotide use in pregnancy (animal or human), DPMH agrees with the applicant that subsection 8.3 should be omitted from labeling.

DISCUSSION AND CONCLUSIONS

Pregnancy
Setmelanotide is proposed as a treatment for patients with RGDO due to specific genetic defects that impact the functioning of the MC4R pathway. (b) (4) [redacted] Benzyl alcohol is present in setmelanotide multiple-dose vials. Because of the potential exposure of benzyl alcohol to the

fetus, DPMH recommends labeling state that setmelanotide is not recommended for use during pregnancy. The labeling should include clinical considerations regarding weight loss during pregnancy.

DPMH recommends the Division consider a drug utilization review to evaluate use of the drug in the first three years after approval with the assistance of OSE. If there is demonstration of prevalent use in females of reproductive potential, regardless if they have the RGDO disorder, DPMH recommends the Division consider a postmarketing requirement study to evaluate use of setmelanotide in females of reproductive potential and pregnancy and infant outcomes.

Lactation

The animal pre/post-natal developmental study shows that setmelanotide is excreted at low levels in the milk of rats, however, no quantifiable setmelanotide concentration was found in the plasma of nursing rat pups, suggesting that the drug may not be absorbed from the gastrointestinal tract. However, benzyl alcohol is present in setmelanotide multiple-dose vials. Because benzyl alcohol is rapidly metabolized by a lactating woman, benzyl alcohol exposure in the breastfed infant is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drug. Setmelanotide lactation labeling should include the recommendation to not breastfeed.

Females and Males of Reproductive Potential

Animal data do not indicate an adverse effect from setmelanotide on fertility. There are no clinical data on setmelanotide's effects on human fertility. There are no data indicating setmelanotide has teratogenic potential, therefore, no pregnancy testing or contraceptive use during treatment is required. DPMH recommends that 8.3 be omitted from labeling.

Risk with Benzyl Alcohol Preservative used in Multi-dose Vials

Although the drug is not intended for use in pediatric populations less than six years of age, patients with RGDO are often diagnosed before 5 years of age. Therefore, the warning language about risk of benzyl alcohol exposure to infants is being recommended. DPMH has included the boilerplate language from the Labeling Review Tool in the labeling recommendations below for subsections 5.X and 8.4.

LABELING RECOMMENDATIONS

DPMH revised highlights and subsections 5.X, 8.1, 8.2, 8.4, and Section 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on September 24, 2020. DPMH recommendations are below and reflect the discussions with DDLO. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* Not recommended when breastfeeding (8.2)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.X Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative

IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, [redacted] (b) (4) The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (IMCIVREE contains 10 mg of benzyl alcohol per mL) *[see Use in Specific Populations (8.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMCIVREE contains the preservative benzyl alcohol. Because benzyl alcohol is rapidly metabolized by a pregnant woman, benzyl alcohol exposure in the fetus is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.4)]*. [redacted] (b) (4)

There are no available data with IMCIVREE in pregnant women to inform a drug associated risk for major birth defects and miscarriage or adverse maternal or fetal outcomes. For the general US population, weight loss offers no potential benefit to a pregnant woman and may result in fetal harm *(see Clinical Considerations)*. In animal reproduction studies, setmelanotide subcutaneously administered to pregnant rats from before mating to the end of organogenesis was not teratogenic at 11 times clinical exposure at the maximum recommended human dose (MRHD) of 3 mg, [redacted] (b) (4) Setmelanotide subcutaneously administered to pregnant rabbits during the period of organogenesis was not teratogenic at clinical [redacted] (b) (4) . Setmelanotide administered subcutaneously to pregnant rats during organogenesis through lactation did not result in adverse developmental effects at 7 times [redacted] (b) (4) the MRHD, [redacted] (b) (4) (*see Data*).

The estimated background risk of birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal obesity increases the risk for congenital malformations, including neural tube defects, cardiac malformations, oral clefts, and limb reduction defects. In addition, weight loss during pregnancy may result in fetal harm including increased risk of small for gestational age. Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

Embryo-fetal development was evaluated in female rats administered setmelanotide subcutaneously during mating to end of major organogenesis (14 days prior to mating to gestation day 17) at doses of 0.5, 3, and 5 mg/kg/day, resulting in exposures up to 11 times the human exposure at MRHD of 3mg, based on AUC. Dose-related decreases in maternal food intake and body weight gain were observed during the premating period but not during gestation. No evidence of embryo-fetal toxicity was observed. (b) (4)

Embryo-fetal development was evaluated in pregnant rabbits subcutaneously administered setmelanotide during organogenesis (gestation days 7 to 19) at doses of 0.05, 0.1, and 0.2 mg/kg/day, resulting in clinically relevant exposures at the MRHD, based on AUC. Decreases in maternal food consumption and body weight were observed at all doses. Increases in embryo-fetal resorptions and post-implantation losses were observed at ≥ 0.1 mg/kg/day, in the presence of significant maternal toxicity, and fetal body weights were 7% lower than controls at 0.2 mg/kg/day.

Pre- and post-natal development was evaluated in rats subcutaneously administered setmelanotide during the period of organogenesis and continuing to weaning (gestation day 6 to lactation day 21) at doses of 0.5, 3.0, and 5.0 mg/kg/day, which resulted in exposures up to 7 times the human exposure at the MRHD, based on AUC. Pup body weights at birth were 9% lower than controls at 3.0 and 5.0 mg/kg/day, which was consistent with reduced maternal body weight gain and food consumption during gestation. No adverse setmelanotide-related effects on pup survival, growth, maturation, visual function, neurobehavioral performance, or reproductive performance were observed up to the highest dose.

8.2 Lactation

Risk Summary

IMCIVREE from multiple-dose vials contains the preservative benzyl alcohol. Because benzyl alcohol is rapidly metabolized by a lactating woman, benzyl alcohol exposure in the breastfed infant is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs *[see Warnings and Precautions (5.x) and Use in Specific Populations (8.4)]*. (b) (4) .

There is no information on the presence of setmelanotide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. However, setmelanotide is present in the milk of rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Data

Dose-related setmelanotide concentrations were observed in milk 2 hours after subcutaneous injection in the preweaning phase of a pre- and post-natal development study in rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups on post-natal Day 11.

8.4 Pediatrics

IMCIVREE is not approved for use in neonates or infants. Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and low birth weight infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (IMCIVREE contains 10 mg of benzyl alcohol) *[see Warnings and Precautions (5.X)]*.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients who may become pregnant to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Population (8.1)]*.

Lactation

Advise patients that treatment with IMCIVREE is not recommended for use while breastfeeding *[see Use in Specific Population (8.2)]*.

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/s/

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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)

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

Date of This Review:	September 10, 2020
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 213793
Product Name, Dosage Form, and Strength:	Imcivree (setmelanotide) injection, 10 mg/mL
Total Product Strength:	10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Rhythm Pharmaceuticals
FDA Received Date:	August 7, 2020
OSE RCM #:	2020-612-1
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised Instruction for Use (IFU), Patient Prescribing Information (PPI) container label, and carton labeling received on August 7, 2020 for Imcivree. The Division of Diabetes, Lipid Disorders, and Obesity requested that we review the revised IFU, PPI, container label and carton labeling for Imcivree (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised PPI, container label, and carton labeling are acceptable from a medication error perspective. Our evaluation of the proposed IFU identified areas of vulnerability that may lead to medication errors. We ask that the Division convey the comments in section 2.1 below to Rhythm Pharmaceuticals so that recommendations are implemented prior to approval of this NDA.

2.1 INSTRUCTION FOR USE (IFU) COMMENTS TO RHYTHM PHARMACEUTICALS

Our evaluation of the proposed IFU identified areas of vulnerability that may lead to medication errors. We request that a revised IFU incorporating the following recommendations be submitted for agency review:

1- Under Figure B consider:

   a- specifying the size of syringe and needle gauge that can measure and deliver the labeled doses as stated in the prescribing information (i.e., 1 mL).

   b- labeling the parts of the syringe since lay users may be unfamiliar with parts of a syringe (i.e., barrel, plunger).

2- The images of syringes in Figure G are difficult to read. Consider enlarging this figure and adding the syringe marking (i.e. 0.1 mL, 0.2 mL and 0.3 mL).

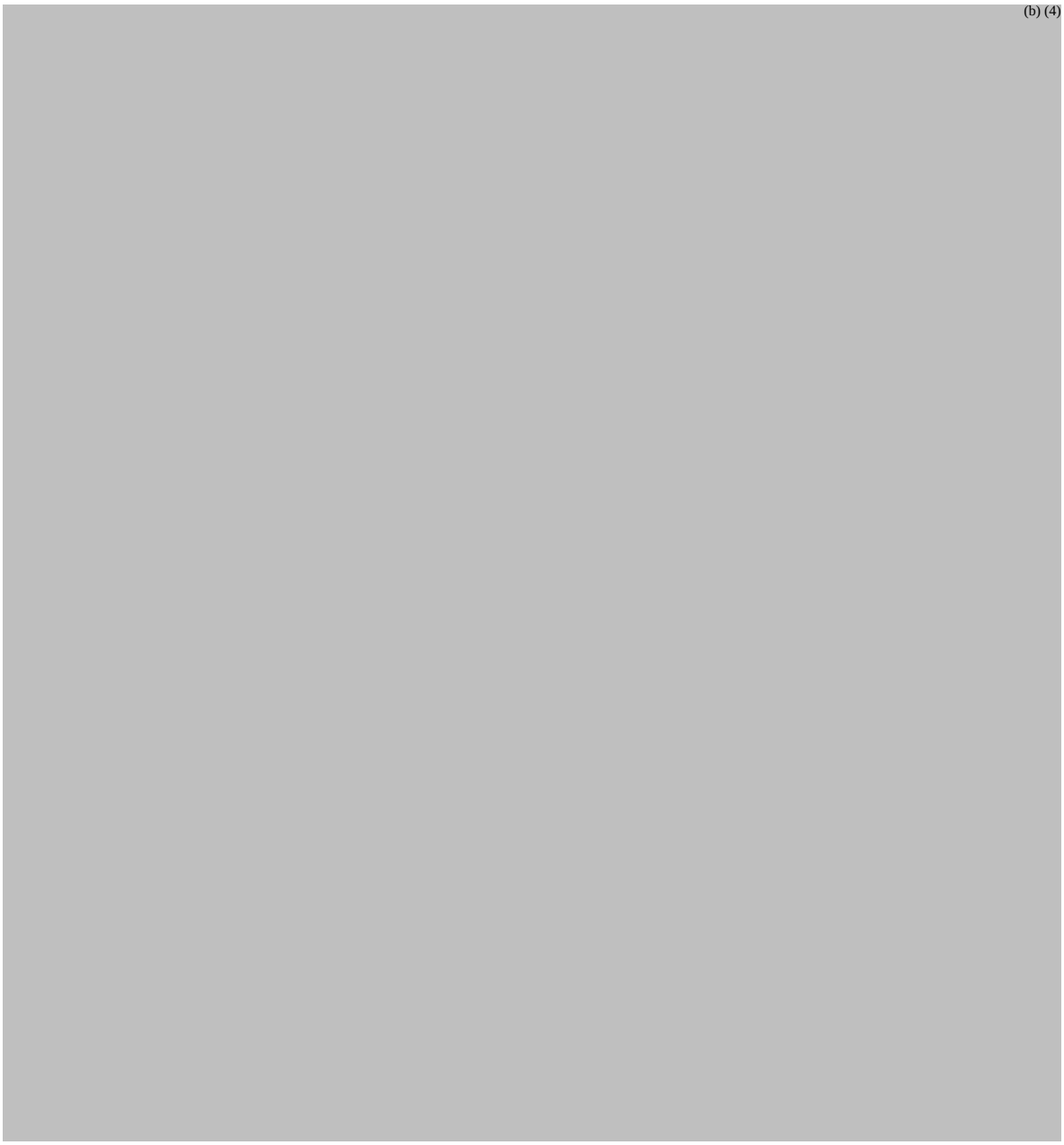
(b) (4)

[a] Fanari, M. Label and Labeling Review for Imcivree (NDA 213793). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 July 15. RCM No.: 2015-612.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 7, 2020

Patient Prescribing Information and IFU available in EDR
\\CDSESUB1\evsprod\NDA213793\0021\m1\us\114-labeling\draft\labeling

(b) (4)



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/s/

MELINA N FANARI
09/10/2020 12:20:15 PM

SEVAN H KOLEJIAN
09/10/2020 12:44:50 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 30, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Patricia Madara, RPM
DDLO

Subject: QT Consult to NDA 213793 (SDN 006)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 4/1/2020 regarding the Division's QT related question. We reviewed the following materials:

- Sponsor's QT evaluation report (Submission 0006; link);
- Previous IRT review for IND 112595 dated 12/16/2016 in DARRTS (link);
- Proposed labeling (Submission 0006; link); and
- Study reports for RM-493-012, RM-493-014, and RM-493-015 reports (Submission 0006).

1 Responses for the Division

Request from the Division: Setmelanotide is a melanocortin 4 receptor (MC4R) agonist peptide developed to treat proopiomelanocortin (POMC) and leptin receptor (LepR) deficiency obesity. These are extremely rare diseases and setmelanotide has received breakthrough therapy designation for these indications. On 3/27/20, a new NME NDA was submitted which will receive priority review (8-month clock).

Upon initial review of the current submission, IRT noted that the sponsor provided a QT report based on pooled data from 57 patients across different trials that do not appear to provide adequate quality or large exposure margin. (b) (4)

Please provide advice to the sponsor regarding an appropriate path to evaluate the arrhythmogenic potential of this product to exclude a small mean effect (>10 msec). A placebo-

controlled QT study in healthy subjects is feasible and this drug is not intended for an immediately life-threatening disease condition.

We intend to request the Sponsor to submit results of a thorough TQT as a post-marketing requirement (PMR).

Previously Rhythm agreed to conduct the [redacted] (b) (4) Please provide any additional guidance necessary for the PMR.

IRT's response:

1. *We recommend that the sponsor conducts a thorough QT study. The TQT study can be designed using concentration-QTc analysis as the primary analysis. Additionally, we have the following comments:*
   - *When submitting the TQT study protocol, please include the following together with the protocol:*
     - *A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (https://www.fda.gov/media/129685/download)*
     - *Statistical analysis plan*
     - *Investigator's Brochure*
   - *For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).*
2. We propose the following language for the PMR. Our proposal is only a suggestion and we defer the final decision to the Division.

   Conduct a thorough QT study to evaluate the effect of setmelanotide on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, and its Questions and Answers (R3).
3. The available data are not adequate to support [redacted] (b) (4)

[redacted]

2 BACKGROUND

2.1 Product Information

Setmelanotide is a melanocortin 4 receptor (MC4R) agonist peptide developed to treat proopiomelanocortin (POMC) and leptin receptor (LepR) deficiency obesity. The proposed therapeutic dose for adults is a starting dose of 2 mg once daily (QD) subcutaneous (SC) injection for 2 weeks; if well-tolerated, the dose can increase to 3 mg QD SC injection after the first 2 weeks of treatment. For patients aged 6 to (b) (4) years, the starting dose is 1 mg QD SC injection for 2 weeks followed by dose escalation to 2 mg QD or 3 mg QD, based on tolerability and efficacy.

2.2 Sponsor's position related to the question

Previously the sponsor proposed (b) (4)

In the current submission, the sponsor provided an analysis of setmelanotide impact on the QTc interval using PK/ECG data from 57 patients with monogenic obesity in studies RM-493-012, RM-493-014, and RM-493-015. Refer to section 2.5 for a summary of the current submission.

2.3 Nonclinical Cardiac Safety

The IC50 for the effect of setmelanotide on hERG potassium current was estimated to be greater than 300 µg/mL, the maximum concentration tested. In addition, an extensive, multi-day cardiovascular telemetry study with setmelanotide administered by SC continuous infusion was performed in cynomolgus monkeys. No setmelanotide-related effects were noted on the ECG parameters (PR, QRS, QT, and QTc intervals) following the administration at doses of 2.5, 12, and 25 mg/kg/day. In both these studies, there were extremely large exposure/concentration margins to the approximate Cmax (~20 ng/mL) of the 1.5 mg SC injection dose (the dose being considered at the time of this comparison).

Reviewer's Comment: *Plasma binding was approximately 50%. The ratio between the highest concentration tested in the hERG study (300 ug/mL) and free Cmax at the 3 mg QD dose (~20 ng/mL assuming PK linearity) is greater than 10000-fold.*

2.4 Clinical Cardiac Safety

Not provided.

2.5 Summary results of prior QTc assessments

Studies RM-493-012, RM-493-014 and RM-493-015 are three Phase 2/3 studies of setmelanotide for the treatment of very rare forms of genetic obesity. Studies RM-493-012 and RM-493-015 used placebo-control. These studies used a dose titration schedule in a variable open label titration phase (up to 12 weeks) to reach a maximum dose of 2.5 mg QD or 3 mg QD (if necessary). 12-lead ECGs were collected at screening, predose and 8 hours postdose (during

titration only) at each dose titration visit, Days 85, 183, and 365 (triplicate ECG in study RM-493-015). In addition, the sponsor included ABPM measurements at screening, Day 183, and Day 365.

14 patients in study RM-493-012, 30 in study RM-493-030, and 13 in study RM-493-015 provided ECG data. The sponsor did not examine the data systematically for quality and/or anomalies. The sponsor provided summary statistics of QTcF, ΔQTcF, QTcB, and ΔQTcB, likely based on the 12-lead ECG data. The sponsor concluded that the available data give no indication of any systematic QT prolongation, in that mean/median data for both QTcB and QTcF.

Reviewer's comment: *The sponsor did not provide placebo data for comparison. The three studies do not provide adequate exposure margin to waive the need of a positive control, and the ECG quality were sub-optimal. The reviewers do not agree with the sponsor's conclusion as these data were not adequate to support a QT assessment to exclude a small mean effect on the QTc interval.*

2.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

NAN ZHENG
07/30/2020 11:05:50 AM

CHRISTINE E GARNETT
07/30/2020 11:23:55 AM

LABEL 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:	July 15, 2020
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 213793
Product Name, Dosage Form, and Strength:	Imcivree (setmelanotide) injection, 10 mg/mL
Total Product Strength:	10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Rhythm Pharmaceuticals
FDA Received Date:	March 27, 2020 and June 10, 2020
OSE RCM #:	2020-612
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

As part of the 505(b)(1) NDA for Imcivree (setmelanotide) injection, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Imcivree Prescribing Information (PI), Patient Prescribing Information (PPI), Instruction for Use (IFU), container label and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF MATERIAL REVIEWED

Imcivree was designated breakthrough therapy for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older. It is intended for once daily patient self-administration and will be provided in a 1 mL multi-dose (b) (4) vial. In addition, Imcivree is intended to be dispensed from specialty pharmacies only.

We note that since Imcivree will be provided in a 1 mL vial presentation (b) (4) there is a risk of wrong dose medication errors associated with the design of this product. We are concerned that patients might misinterpret the entire vial as a single dose and administer the contents of the entire vial instead of the recommended dose of 0.1 mL, 0.2 ml or 0.3 mL. This concern was shared with the clinical team in DDLO and based on feedback provided, the clinical impact of a patient administering a wrong

dose (i.e. contents of entire vial) appears minimal. Per the clinical team, animal data of 50x human doses showed no cardiovascular involvement. Thus, we determined that the residual risk association with potential wrong dose medication errors associated with the design of this product is minimal. Furthermore, we note that the residual risk can be further mitigated through appropriate labeling of the product.

Our review of the proposed Instruction for Use (IFU) concluded that as currently formatted, the IFU information is presented in such a manner that could lead to confusion and mediation errors. We note that the IFU uses graphical symbols that are not in FDA recognized consensus standards. It incorporates (b) (4) that creates clutter and decreases readability, the 2-column format of the IFU has steps that appear to not be in sequence and contains figures located in close proximity to unrelated steps. The IFU also (b) (4)

In response to a request by DMEPA to provide data or information to support the Imcivree product user interface, we note that the Applicant provided "external use testing". However, this testing appeared to be focused on patient's subjective feedback on clarity and likeability of the product. The testing did not provide data, such as data from a human factors (HF) validation study, that indicates that the proposed IFU has been optimized and supports safe and effective use. For these reasons, we request the Applicant revise the Imcivree IFU to incorporate the basic design principles outlined in section 4.1 below prior to DMEPA conducting a comprehensive review of the IFU. These recommendations also incorporate those provided by the Patient Labeling Team (PLT) in the Division of Medical Policy Programs.

4 CONCLUSION AND RECOMMENDATIONS

Overall, the Imcivree product interface has the potential for risk of wrong dose medication errors. However, based on the low clinical impact of wrong dose errors we do not object to the product as designed in this circumstance and defer to DDLO to determine if the potential public health benefit of this product outweighs these risks for dosing errors.

Our evaluation of the proposed Imcivree Prescribing Information (PI), Patient Prescribing Information (PPI), Instruction for Use (IFU) and container label and carton labeling identified areas of vulnerability that may lead to medication errors. We ask that the Division convey Table 3 and the comments in section 4.1 below in its entirety to Rhythm Pharmaceuticals so that recommendations are implemented prior to approval of this NDA.

[a] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), Patient Prescribing Information (PPI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Instructions on correct needle type for administration are missing.	Prevent administration errors.	Add the following statement to the 2nd paragraph in section 2.2: 'Instruct patients to use a 1 mL syringe with a needle appropriate for subcutaneous injection.'
Full Prescribing Information-Section 17 Patient Counseling Information			
1.	Guidance on instructing patients/caregivers on proper subcutaneous technique.	Prevent product administration errors.	Add the following statements prior to the Administration Section: 'Healthcare practitioners should instruct patients and caregivers on how to prepare and administer the correct dose of Imcivree and assess their ability to inject subcutaneously to ensure the proper administration of Imcivree [see Instructions for Use].' 'Instruct patients to use a 1 mL syringe with a needle appropriate for subcutaneous injection.'
Patient Information			
1.	The "How should I use Imcivree?" section bullet #5 should be more prominent in the section.	Prevent patient self-administration without proper training.	Bullet # 5 in the 'How should I use Imcivree' should be relocated to after bullet #2 in this section.

Table 3. Identified Issues and Recommendations for Rhythm Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
ALL Carton Labeling and Container Labels			
1.	Established name lacks prominence compared to proprietary name and has a bolded letter 'l'.	Per 21 CFR 201.10(g)(2).	The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2). In addition, the same font size and color should be utilized for all letters in the established name.
Carton Labeling			
1.	Strength statement lacks prominence compared to proprietary and established name.	Per 21 CFR 201.15(a)(6)	Increase the prominence of the strength presentation statement.
2.	Product has different expiration date after patient first use. There is no space for end user to write the beyond-use date.	Reduce risk for deteriorated drug medication errors.	Revise the statement (b) (4) to: 'Date of first opening ___/____/____. Discard unused portion 30 days after first opening'.
3.	Statement alerting that vial contains multiple doses is missing.	Avoid risk of wrong dose medication errors.	Consider adding the following statement to the principal display panel: 'Vial contains multiple doses'
4.	Net quantity statement 'One 1 mL vial' is too prominent.	Competes with other important information on the principle display panel.	Decrease the prominence (e.g., unbold text) of the net quantity statement so that it is less prominent than the strength presentation.
5.	Usual dosage statement requires revisions.	Per 21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the Dosage and Administration statement to read:

Table 3. Identified Issues and Recommendations for Rhythm Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"Recommended Dosage: See prescribing information."
6.	Storage statements (Protect from light and Do not freeze) are repeated.	Reduce redundancy and clutter.	Consider removing the (b) (4) section since it is already listed at the bottom of the storage section.
7.	Store in original container statement is missing.	Prevent product deterioration.	Consider adding the following statement after the 'Protect from light' and 'Do not freeze" statements in the storage section: 'Store in the original carton'

4.1 INSTRUCTION FOR USE (IFU) COMMENTS TO RHYTHM PHARMACEUTICALS

Our evaluation of the proposed Instruction for Use (IFU) determined that the IFU is confusing, error prone and has not been tested for optimization. In order to conduct a comprehensive review of the IFU we request that a revised IFU incorporating the following recommendations be submitted for agency review:

1- Remove the (b) (4)

2- To improve readability and comprehension, we request that the 2-column format be revised to a 1-column format for steps throughout the IFU.

3- The IFU contains too much information that could lead to decreased patient comprehension. Revise the IFU to streamline important information and reduce redundant information.

4- [redacted] (b) (4) removed from the IFU.

5- The proposed IFU incorporates recommendations related to the use of [redacted] (b) (4) Revise the IFU to recommend the use of a 1 mL syringe with a needle appropriate for subcutaneous injection for product administration.

Additionally, we refer you to *the Guidance for Industry Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format, July 2019* for general recommendations for developing the content and format of an Instructions for Use (IFU).[b]

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-and-drug-device

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imcivree received on March 27, 2020 from Rhythm Pharmaceuticals.

Product Name	Imcivree
Initial Approval Date	N/A
Active Ingredient	setmelanotide
Indication	The treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older.
Route of Administration	subcutaneous
Dosage Form	injection
Strength	10 mg/ mL
Dose and Frequency	For adults (b) (4) the starting dose of IMCIVREE is a 2-mg once daily subcutaneous injection for 2 weeks. After 2 weeks, if IMCIVREE is well-tolerated, the dose can be increased to a 3-mg once daily subcutaneous injection. For patients aged 6 to (b) (4) years, the starting dose of IMCIVREE is a 1-mg once daily subcutaneous injection for 2 weeks. If tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If healthy weight (50th to 90th percentile) is not achieved with the 2-mg once daily subcutaneous injection and additional weight loss is desired, the dose may be increased to 3 mg once daily.
How Supplied	(b) (4) 1 mL vial; 1 vial per carton
Storage	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 12, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, setmelanotide and IND 112595. Our search did not identify any previous relevant reviews.

APPENDIX G. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Imcivree labels and labeling submitted by Rhythm Pharmaceuticals.

- Container Label and Carton Labeling received on March 27, 2020
- Prescribing Information (Image not shown) received on March 27, 2020, available from \\CDSESUB1\evsprod\NDA213793\0006\m1\us\114-label\1141-draft-label
- Patient Prescribing Information and Instruction for Use received on June 10, 2020, available from \\CDSESUB1\evsprod\NDA213793\0013\m1\us\114-labeling\draft\labeling

G.2 Label and Labeling Images

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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