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2.6.3 薬理試験概要表

2.6.3.1 薬理試験：一覧表

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
Primary Pharmacodynamics					
In vitro potency of setmelanotide on human melanocortin receptors: MC1R, MC3R, MC4R & MC5R and Mouse MC2R	In vitro	In vitro	[redacted], France	IRC-022493 on human MC1345R & mouse MC2R	4.2.1.1-1
In vitro potency of setmelanotide on rat melanocortin 4 receptors (MC4R)	In vitro	In vitro	[redacted], France	IRC-022493 on rat MC4	4.2.1.1-2
Biochemical characterization of human, rat, mouse, cynomolgus, rhesus macaque, and dog MCRs (MC1R-MC5R) with setmelanotide, α-MSH, and LY2112688.	In vitro	In vitro	[redacted], USA	RM-493-PH-027	4.2.1.1-3
MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. NOTE: In vitro pharmacology at the MC4R receptor also included in this publication.	In vitro	In vitro	Institute for Experimental Pediatric Endocrinology, Charité – Universitätsmedizin Berlin, Germany	Clément 2018	4.3
Effect of increasing SC infusion pump doses on body weight and food and water intake in normal and obese C57BL/6 mice	Mouse	SC Infusion	[redacted], USA	BIM-22493-005	4.2.1.1-4
Effect of increasing SC infusion pump doses on body weight and food and water intake in diet induced obese Sprague-Dawley rats	Rat	SC Infusion	[redacted], USA	BIM-22493-003	4.2.1.1-5

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
Effect of time of administration and number of SC injections on body weight and food and water intake in lean and diet induced obese Sprague-Dawley rats	Rat	SC Injection	[redacted], USA	BIM-22493-004	4.2.1.1-6
Evaluation of a melanocortin-4 receptor (MC4R) agonist (setmelanotide) in *Mc4r* deficiency	Mouse	SC Injection	University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Wellcome Trust-MAC Institute of Metabolic Science, Cambridge, United Kingdom	Collet 2017	4.3
Effect of increasing SC infusion pump doses on body weight and food and water intake in normal Sprague-Dawley rats	Rat	SC Infusion	[redacted], USA	BIM-22493-002	4.2.1.1-7
Dose-response comparison of the effect of SC infusion of setmelanotide versus LY2112688 (Lilly) and structurally related compounds on body weight gain in normal Sprague-Dawley rats	Rat	SC Infusion	[redacted], USA	BIM-22493-016	4.2.1.1-8
Effect of various doses of setmelanotide by SC injection on acute food intake in normal lean Sprague-Dawley rats	Rat	SC Injection	[redacted], USA	BIM-22493-007	4.2.1.1-9
Effect of increasing SC doses on body weight and food and water intake in normal Sprague-Dawley rats	Rat	SC Injection	[redacted], USA	BIM-22493-001	4.2.1.1-10

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
Effect of increasing SC infusion pump doses on body weight and food and water intake in obese Zucker rats	Rat	SC Infusion	[redacted], USA	BIM-22493-006	4.2.1.1-11
Magel2-null mice are hyper-responsive to setmelanotide, a MC4R agonist	*Magel2*-null Mouse	IP Injection	Department of Medical Genetics, University of Alberta, Edmonton, AB, Canada	RM-493-PH-026/ Bischof 2016	4.2.1.1-12
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: This report includes a publication by Kievit 2013	Monkey	SC Infusion	Oregon National Primate Research Center Beaverton, OR, USA	RM-493-PH-007	4.2.1.1-13
Potency and tolerance study by SC injection in beagle dogs	Dog	SC Injection	[redacted], France	32587 TSC	4.2.1.1-14
Effects of chronic setmelanotide treatment on energy and glucose metabolism	Mouse	SC Infusion	[redacted], USA	BIM-22493-009	4.2.1.1-15
Determine whether setmelanotide acts as an insulin sensitizer independently of weight loss and if this effect is dependent on the MC4 receptor (in C57BL/6J and *Mc4r* knockout mice)	Mouse	SC Injection	[redacted], USA	BIM-22493-008	4.2.1.1-16
Secondary Pharmacodynamics					

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
In vitro pharmacology: Diversity profile	Panel of off-target receptors and enzymes	In vitro	[redacted], France	791318b	4.2.1.2-1
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: Observation of lack of Penile erection is described in this report. This report includes a publication by Kievit 2013 Key issue: Effects of setmelanotide on penile Erection and other animal behavior	Monkey	SC Infusion	Oregon National Primate Research Center Beaverton, OR, USA	RM-493-PH-007	4.2.1.1-13
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: Observation of lack of skin pigmentation is described in this report This report includes a publication by Kievit 2013 Key issue: Skin hyper-pigmentation induced by setmelanotide	Monkey	SC Infusion	Oregon National Primate Research Center Beaverton, OR, USA	RM-493-PH-007	4.2.1.1-13
Safety Pharmacology					
Effect of setmelanotide on cloned hERG potassium channels expressed in human embryonic kidney cells	HEK cells	In vitro	[redacted], USA	RM-493-TOX-010	4.2.1.3-1

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
Effect on heart rate and blood pressure of two MC4R agonists: BIM22497 (LY2112688) and setmelanotide	Rat	SC Bolus	Ipsen [redacted], France	EXP783_788_794/CV02	4.2.1.3-2
Effects on heart rate and blood pressure of a 5-day SC bolus administration of setmelanotide and BIM22497 in telemetered rats	Rat	SC Bolus	Ipsen [redacted], France	EXP863_864_CVECG01	4.2.1.3-3
Role of sympathetic tone on CV effects after SC bolus administration in conscious rats	Rat	SC Bolus	Ipsen [redacted], France	EXP837/CV02	4.2.1.3-4
Effects on heart rate and blood pressure of a 14-day SC infusion of setmelanotide in telemetered rats	Rat	SC Infusion	Ipsen [redacted], France	EXP853_CVECG01	4.2.1.3-5
A CV telemetry study of multiple-dose setmelanotide in conscious naïve cynomolgus male and female monkeys	Monkey	SC Infusion	[redacted], Canada	RM-493-PH-003	4.2.1.3-6
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: This report includes a publication by Kievit 2013	Monkey	SC Infusion	Oregon National Primate Research Center Beaverton, OR, USA	RM-493-PH-007	4.2.1.1-13
A CV safety pharmacology study using radio-telemetry in conscious male Göttingen minipigs with toxicokinetic assessments	Göttingen Minipig	SC Bolus Injection and Infusion	[redacted] Canada	RM-493-PH-005	4.2.1.3-7

Test Article: Setmelanotide					
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number/Reference**	**Location in eCTD**
A pharmacological safety assessment of the effect of setmelanotide on the central nervous system in Sprague-Dawley rats	Rat	SC Infusion	[redacted], Canada	RM-493-PH-001	4.2.1.3-8
A pharmacological assessment of the effect of setmelanotide on the respiratory system of Sprague-Dawley rats	Rat	SC Infusion	[redacted], Canada	RM-493-PH-002	4.2.1.3-9
Effect of increasing SC infusion pump doses on liver enzymes in normal and obese C57BL/6J mice	Mouse	SC Infusion	[redacted], USA	BIM-22493-015	4.2.1.3-10
Pharmacodynamic Drug Interactions					
Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice.	Mouse	SC Bolus Injection	Division of Metabolic Diseases, Department of Medicine, Technische Universitat Munchen, Munich, Germany	Clemmensen 2015	4.3

Definitions: BIM22497 = LY2112688; CV = cardiovascular; GLP-1 = glucagon-like peptide-1; HEK = human embryonic kidney; hERG = human ether-à-go-go-related gene; IP = intraperitoneal; MCR = melanocortin receptor; MC1R, MC2R, MC3R, MC4R & MC5R = melanocortin type 1, type 2, type 3, type 4 and type 5 receptor; SC = subcutaneous.

2.6.3.2 効力を裏付ける試験

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
In vitro potency of setmelanotide on human melanocortin receptors: MC1R, MC3R, MC4R & MC5R and Mouse MC2R	CHO-K1 cells expressing hMC1, MC3, MC4 and MC5Rs, Y1 cells expressing mMC2R	In vitro	-	3 separate experiments (n = 3) for MC4, a single experiment for MC1 (n = 4), MC3 (n = 4) and MC5 (n = 4), 2 experiments (n = 5) for MC2	The Ki and EC_{50} with hMC4R are 2.1 nmol/L for the binding of [^{125}I]-(Tyr^{2})-(Nle^{4}-D-Phe^{7})-α-MSH ([^{125}I]-NDP-α-MSH) and 0.27 nmol/L in the Gαs/adenylyl cyclase signaling mediated cAMP accumulation assay, respectively. Activation of other MC receptors requires concentrations that are 18 to 5,900 fold or higher than for MC4R: Setmelanotide displays no activity in a cAMP stimulation assay for the mMC2R (ACTH receptor).	IRC-022493 on human MC1345R & mouse MC2R/ 4.2.1.1-1
In vitro potency of setmelanotide on rat melanocortin 4 receptors (MC4R)	CHO-K1 cells expressing rMC4R	In vitro	-	3 separate experiments (n = 2 for binding, n =4 for cAMP)	The Ki and EC_{50} with rMC4R are comparable to those for hMC4R.	IRC-022493 on rat MC4/ 4.2.1.1-2

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Biochemical characterization of human, rat, mouse, cynomolgus, rhesus macaque, and dog MCRs (MC1R-MC5R) with setmelanotide, α MSH, and LY2112688.	HEK293 cells	In vitro	-	6 separate experiments	Setmelanotide did not stimulate MC2R (ACTH receptor) in any species. The EC_{50}s of setmelanotide at MC4Rs of the 6 species were comparable (range: 0.210 to 3.053 nmol/L). Similarly, the EC_{50}s at MC3Rs were also comparable (range: 0.335 to 1.307 nmol/L). With MC1Rs, the EC_{50}s ranged 0.830 to 26.60 nmol/L, with the lowest EC_{50} values for rat and human (0.830 and 1.730 nmol/L, respectively), and the highest EC_{50} values for mouse and rhesus monkey (26.04 and 26.60 nmol/L, respectively). No stimulation of transiently expressed MC5Rs of human, mouse and rat was observed, while EC_{50} values of 2.492, 7.784, and 29.25 nmol/L were recorded with transiently expressed dog, cynomolgus, and rhesus MC5Rs, respectively.	RM-493-PH-027/ 4.2.1.1-3

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. NOTE: In vitro pharmacology at the MC4R receptor also included in this publication.	HEK293 cells	In vitro	-	7 separate experiments (n = 3) for Gαs, 4 separate experiments (n = 3) for NFAT	For the Gαs signaling, setmelanotide was about 5-fold more potent (EC_{50}: 3.9 ± 1.7 nmol/L) than α-MSH (EC_{50}: 23 ± 7 nmol/L) or LY2112688 (EC_{50}: 14 ± 4 nmol/L). Setmelanotide was about 50 to 100-fold more potent in the NFAT signaling assay (EC_{50}: 5.9 ± 1.8 nmol/L) compared to α-MSH (EC_{50}: 480 ± 260 nmol/L) or LY2112688 (EC_{50}: 330 ± 190 nmol/L). In addition, the setmelanotide induced NFAT activation could not be blocked by the antagonist AgRP (100 nmol/L), whereas both α-MSH and LY2112688 effects were completely blocked.	Clément 2018/ 4.3
Effect of increasing SC infusion pump doses on body weight and food and water intake in normal and obese C57BL/6 mice	Mouse/ C57BL/6	SC Infusion	0.22, 0.67 or 2.00 mg/kg/day	Male/ 5-7	DIO mice showed a dose-related tendency toward decreased body weight gain relative to vehicle control across all dose groups for the 14-day treatment period, whereas normal mice showed a dose-related decrease in body weight gain over the only first 4 days of dosing period, with partial reversal of this effect by Day 14. In the DIO mice, treatment with setmelanotide reversed the impairment of glucose clearance in a dose-dependent fashion. At 0.67 and 2.00 mg/kg/day, glucose clearance was normalized after setmelanotide treatment.	BIM-22493-005/ 4.2.1.1-4

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Effect of increasing SC infusion pump doses on body weight and food and water intake in diet induced obese Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Infusion	0.08, 0.34 or 1.34 mg/kg/day	Male/ 8	By Day 14, dose related decreases in body weight gain relative to vehicle control of 22 to 53 g were seen in normal lean rats and of 29 to 60 g were seen in DIO rats. Furthermore, a dose-related decrease in food intake relative to vehicle control of 35 to 68 g was seen in lean rats and of 64 to 93 g was seen in obese rats.	BIM-22493-003/ 4.2.1.1-5
Effect of time of administration and number of SC injections on body weight and food and water intake in lean and diet induced obese Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Injection	0.67 mg/kg/day	Male/ 8	The greatest effect on decrease in body weight gain and food consumption was seen when setmelanotide was administered SC TID in DIO rats, but with relatively similar effects when administered QD in the evening.	BIM-22493-004/ 4.2.1.1-6
Evaluation of a melanocortin-4 receptor (MC4R) agonist (setmelanotide) in *Mc4r* deficiency	Mouse/ *Mc4r* Knockout	SC Injection	1.34 mg/kg/day	n = 8 for *Mc4r*+/+ and *Mc4r*+/-, n = 3 for *Mc4r*-/-	*Mc4r* +/+ and *Mc4r* +/- mice lost weight with setmelanotide, with WT mice being the most sensitive to the treatment, while *Mc4r*-/- mice do not respond.	Collet 2017/ 4.3
Effect of increasing SC infusion pump doses on body weight and food and water intake in normal Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Infusion	0.04-1.34 mg/kg/day	Male/ 8	Setmelanotide at doses ranging administered via SC infusion was effective in decreasing the rate of body weight gain and suppressing appetite in normal Sprague-Dawley rats.	BIM-22493-002/ 4.2.1.1-7

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Dose-response comparison of the effect of SC infusion of setmelanotide versus LY2112688 (Lilly) and structurally related compounds on body weight gain in normal Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Infusion	0.04, 0.08, 0.17, 0.34, 0.67 or 1.34 mg/kg/day	Male/ 8	Setmelanotide administered via SC infusion is more potent than LY2112688 in decreasing the rate of body weight gain.	BIM-22493-016/ 4.2.1.1-8
Effect of various doses of setmelanotide by SC injection on acute food intake in normal lean Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Injection	0.11 mg/kg to 2.79 mg/kg	Male/ 8	Single acute doses of setmelanotide administered via SC injection resulted in significant dose-related decreases in food intake in normal, lean rats, with decreases in food intake of 3 to 4 g seen 6 hours post-dose.	BIM-22493-007/ 4.2.1.1-9
Effect of increasing SC doses on body weight and food and water intake in normal Sprague-Dawley rats	Rat/ Sprague-Dawley	SC Injection	0.04, 0.08, 0.17, 0.34, 0.67 or 1.34 mg/kg/day	Male/ 8	The effect of setmelanotide in decreasing body weight gain and food intake was similar when administered via either SC injection or SC infusion for 7 days in normal, lean rats.	BIM-22493-001/ 4.2.1.1-10

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Effect of increasing SC infusion pump doses on body weight and food and water intake in obese Zucker rats	Rat/ Zucker	SC Infusion	0.06 or 0.56 mg/kg/day	Male/ 8	Significant decreases in body weight gain relative to vehicle control of -35 and -60 g were seen in the 0.06 and 0.56 mg/kg/day groups, respectively ($p < 0.0001$ except Day 1 in each dose group, Dunnett's test [two-tailed]), on Day 7. A similar dose-related decrease in food intake was observed by the end of the 7-day treatment period.	BIM-22493-006/ 4.2.1.1-11
Magel2-null mice are hyper-responsive to setmelanotide, a MC4R agonist	*Magel2*-null Mouse	IP Injection	0.04, 0.1, 0.2 or 1 mg/kg	Male/ 6	*Magel2*-null mice were found to be hypersensitive to the appetite suppressing and metabolic effects of acutely administered setmelanotide. Setmelanotide increased energy expenditure, significant lowered RER in WT and *Magel2*-null mice, with reduced food intake.	RM-493-PH-026/ 4.2.1.1-12/ Bischof 2016
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: This report includes a publication by Kievit 2013 Effects in lean non-human primates	Monkey/ Rhesus	SC Infusion	0.17, 0.5 or 1.5 mg/kg/day	Male/ 3, Female/ 3	0.5 and 1.5 mg/kg/day of setmelanotid significantly decreased in food intake in normal lean monkeys. In all 3 dose groups, no change in glucose tolerance, fasting glucose, or fasting insulin levels were seen.	RM-493-PH-007/ 4.2.1.1-13

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Chronic treatment with a melanocortin 4 receptor agonist causes weight loss and improves CV function in diet induced obese macaques Note: This report includes a publication by Kievit 2013 Effects in obese (DIO) non-human primates	Monkey/ Rhesus	SC Infusion	0.5 mg/kg/day	Male/ 12	Treatment with setmelanotide at 0.5 mg/kg/day for 8 weeks was effective in decreasing food intake, body weight, and fat mass and improving glucose homeostasis, insulin sensitivity, and leptin levels in obese (DIO) rhesus macaques.	RM-493-PH-007/ 4.2.1.1-13
Potency and tolerance study by SC injection in beagle dogs	Dog	SC Injection	0.02, 0.05, 0.17, 0.5, 1.67 or 5.0 mg/kg/day	Male/ 3 and Female/ 3	Treatment with setmelanotide resulted in dose-dependent decrease in body weight gain and food consumption, with a progressive or rapid return in food intake during the washout periods.	32587 TSC/ 4.2.1.1-14
Effects of chronic setmelanotide treatment on energy and glucose metabolism	Mouse/ C57BL/6J	SC Infusion	0.11, 0.45 or 1.12 mg/kg/day	Male/ 8	In DIO mice, setmelanotide inhibited feeding, decreased body weight and fat mass, improved glucose clearance, and enhances both hepatic and insulin sensitivity.	BIM-22493-009/ 4.2.1.1-15

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Determine whether setmelanotide acts as an insulin sensitizer independently of weight loss and if this effect is dependent on the MC4 receptor (in C57BL/6J and *Mc4r* knockout mice)	Mouse/ C57BL/6J and *Mc4r* knockout	SC Injection	13.41 mg/kg	Male/ 8 for DIO mice, 6 for *Mc4r* knockout mice	In DIO mice, setmelanotide 13.41 mg/kg acutely enhanced glucose tolerance and insulin tolerance. In contrast, neither glucose nor insulin tolerance was improved in *Mc4r* knockout mice. Setmelanotide increased GIR and reduced HGP but did not affect Rd. Immunoblotting analysis of proteins that mediate insulin signaling in liver samples showed increased [redacted], and [redacted] consistent with enhanced insulin sensitivity.	BIM-22493-008/ 4.2.1.1-16

Definitions: α-MSH = alpha-melanocyte-stimulating hormone; ACTH = adrenocorticotropic hormone; AgRP = agouti-related peptide; cAMP = cyclic adenosine monophosphate; CHO = Chinese hamster ovary; CV = cardiovascular; DIO = diet-induced obesity; EC_{50} = 50% Effective concentration; Gαs = G-protein alpha subunit for stimulating adenylate cyclase; GIR = glucose infusion rates; h = human; HEK = human embryonic kidney; HGP = hepatic glucose production; IP = intraperitoneal; [^{125}I]-NDP-α-MSH = [^{125}I]-(Tyr^{2})-(Nle^{4}-D-Phe^{7})-α-MSH; Ki = inhibitory constant; m = mouse; MCR = melanocortin receptor; MC1R, MC2R, MC3R, MC4R & MC5R = melanocortin type 1, type 2, type 3, type 4 and type 5 receptor; NFAT= nuclear factor of activated T cells; QD = once daily; r = rat; Rd = glucose disappearance rate; RER = respiratory gas exchange ratio; SC = subcutaneous; TID = three times daily; WT = wild-type.

2.6.3.3 副次的薬理試験

Test Article: Setmelanotide						
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/ Location in eCTD/Reference**
Diversity receptor and enzyme profiling with >80 receptor binding and enzyme assays at 1 µmol/L concentration of setmelanotide.	Individual receptor expressing cell lines	In vitro	1 µmol/L	NA	None of the 16 enzymes assayed were inhibited or stimulated at 1 µmol/L setmelanotide (referred to as IRC-022493 in report). Setmelanotide at 1 µmol/L inhibited ligand binding by <20% at 64 of the 70 off-target receptors, by 20-50% at 5 receptors (muscarinic, NK2, sigma, thyrotropin-releasing hormone, and gamma-aminobutyric acid [GABA] transporter), and by 59% at opioid receptors. The clinical C_{max} for unbound setmelanotide with current clinical daily dose of 3 mg is approximately 55-fold less than the 1 µmol/L concentration used in these receptor binding assays.	791318b/ 4.2.1.2-1
Behavior effects: Penile erection, stretching, yawning, muscular stiffness	Monkey/ Rhesus	SC Infusion	0.17 mg/kg/day for 8 weeks; 0.5 mg/kg/day for 1 and 8 weeks	Male/ 8	No behavior effects, including stretching, yawning and penile erection, were seen. The lack of muscular stiffness was also observed by the increase in activity during the treatment period.	RM-493-PH-007/ 4.2.1.1-13
Skin hyper-pigmentation	Monkey/ Rhesus	SC Infusion	0.17 mg/kg/day for 8 weeks; 0.5 mg/kg/day for 1 and 8 weeks	Male/ 8	No skin tanning, or coat color changes were observed.	RM-493-PH-007/ 4.2.1.1-13

Definitions: Admin = administration; C_{max} = maximal concentration; GABA = gamma-aminobutyric acid; NA = not applicable; No. = number; SC = subcutaneous.

2.6.3.4 安全性薬理試験

							Test Article: Setmelanotide
Organ Systems Evaluated	**Species/ Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP Compliance[1]**	**Study Number/ Location in eCTD/Reference**
Cardiovascular (hERG channel current inhibition)	Human embryonic kidney cells (HEK293)	In vitro	0.01 and 0.3 mg/mL	NA	Setmelanotide inhibited hERG current by (mean ± SEM, n = 3) 1.6 ± 0.4% at 0.01 mg/mL and 9.2 ± 0.4% at 0.3 mg/mL (~300 µmol/L) compared to 0.8 ± 0.8 % for vehicle control and 80.3 ± 2.8% for 60 nmol/L terfenadine (positive control). The highest tested strength of 300 mol/L is about 17,500 fold higher than clinical C_{max} exposure with a 3 mg dose.	Yes	RM-493-TOX-010/ 4.2.1.3-1
Cardiovascular	Rat/ Sprague-Dawley	SC Bolus	0.01, 0.03, 0.1, 0.3, or 3 mg/kg	Male/ 7 or 8	Setmelanotide and LY2112688 caused similar dose-dependent increases in HR and MBP in the rat. The dose of setmelanotide devoid of significant CV effect was 0.01 mg/kg. Rather than the rat model, the non-human primate model of CV activity was more predictive of setmelanotide induced human CV effects.	No	EXP783_788_794/CV02/ 4.2.1.3-2

Test Article: Setmelanotide							
Organ Systems Evaluated	**Species/ Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP Compliance[1]**	**Study Number/ Location in eCTD/Reference**
Cardiovascular	Rat/ Sprague-Dawley	SC Bolus	0.67 mg/kg x 5 days	Male/ 5	Setmelanotide or LY2112688 induced similar increases in HR in the rat. Maximum effects occurred within the 3 hours after the first administration and then progressively decreased on the following days. A transient increase of MBP was observed after each injection. Rather than the rat model, the non-human primate model of CV activity was more predictive of setmelanotide induced human CV effects.	No	EXP863_864_CVECG01/ 4.2.1.3-3
Cardiovascular	Rat/ Sprague-Dawley	SC Bolus	0.3 mg/kg	Male/ 7	Inhibition of α- and β-adrenergic receptors with infusion of terazosin and propranolol, respectively, antagonized the HR and MBP effects of setmelanotide, indicating that the CV effects of setmelanotide in the rat are related to increased sympathetic tone. Rather than the rat model, the non-human primate model of CV activity was more predictive of setmelanotide induced human CV effects.	No	EXP837/CV02/ 4.2.1.3-4

Test Article: Setmelanotide							
Organ Systems Evaluated	**Species/ Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP Compliance[1]**	**Study Number/ Location in eCTD/Reference**
Cardiovascular	Rat/ Sprague-Dawley	SC infusion	0.67 mg/kg/day for 14 days	Male/ 6	Slow infusion rate to minimize peak plasma concentration of setmelanotide did not eliminate increases in heart rate and the transient increase in MBP. Rather than the rat model, the non-human primate model of CV activity was more predictive of setmelanotide induced human CV effects.	No	EXP853_CVECG01/ 4.2.1.3-5
Cardiovascular	Monkey/ Cynomolgus	SC infusion	2.5, 12, and 25 mg/kg/day for 3 days	Male/ 4 Female/ 4	No deaths, treatment related clinical signs, or biologically significant changes in systolic pressures, heart rate or electrocardiographic interval duration or waveforms after setmelanotide administration at doses up to 25 mg/kg/day for 3 days in this GLP study. The highest tested dose is 50-fold higher than a dose which showed marked weight loss efficacy in obese Rhesus.	Yes	RM-493-PH-003/ 4.2.1.3-6

Test Article: Setmelanotide							
Organ Systems Evaluated	**Species/ Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP Compliance[1]**	**Study Number/ Location in eCTD/Reference**
Cardiovascular	Monkey/ Rhesus	SC Infusion	0.17 mg/kg/day for 8 weeks; 0.5 mg/kg/day for 1 and 8 weeks	Male/ 8	No increase in HR and no effect on systolic BP was seen. In the obese animals the HR remained lower 4 weeks post-dose. Paralleling the decrease in HR, a significant decrease in diastolic BP also was seen in both obese and lean animals. Increases in BP and significant increases in HR were seen among the same animals infused with LY2112688.	No	RM-493-PH-007/ 4.2.1.1-13
Cardiovascular	Minipig/ Göttingen	SC injection and infusion over 24 hours	0.5 mg/kg	Male/ 4	Mild, non-adverse, reversible positive chronotropic effect of setmelanotide at 0.5 mg/kg by bolus injection or infusion see in this exploratory study.	No	RM-493-PH-005/ 4.2.1.3-7
Central nervous system	Rat/ Sprague-Dawley	SC infusion	10, 60, or 120 mg/kg	Male/ 8	Single 24-hour SC infusions of setmelanotide at doses up to 120 mg/kg did not affect qualitative or quantitative functional FOB or motor activity parameters. Reddening of the pinnae and paws were noted at 60 and 120 mg/kg up to 24 hours post-end of infusion.	Yes	RM-493-PH-001/ 4.2.1.3-8

							Test Article: Setmelanotide
Organ Systems Evaluated	**Species/ Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP Compliance[1]**	**Study Number/ Location in eCTD/Reference**
Respiratory system	Rat/ Sprague-Dawley	SC infusion	10, 60, or 120 mg/kg	Male/ 6	Single 24-hour SC infusions had no effect on tidal volume, respiratory rate and derived minute volume at doses up to 120 mg/kg/day.	Yes	RM-493-PH-002/ 4.2.1.3-9
Hepatic	Mouse/ C57BL/6J	SC infusion pump	0.168, 0.503 and 1.51 mg/kg/day for 14 days	Male/ 7-8	ALT elevated above normal range in lean mice possibly related to restricted diet. No increases in liver enzymes above normal range in obese mice at any dose level. Also, in toxicology studies (described in Module 2.6.6) no liver toxicity observed after 26-week repeat-dosing study in rats and 39-week study in monkey.	No	BIM-22493-015/ 4.2.1.3-10

Definitions: Admin. = administration; ALT = alanine transaminase; LY2112688 = a MC4R agonist that was studied in a Ph-1 study and used as comparator; C_{max} = maximal concentration; CV = cardiovascular; FOB = functional observation battery; GLP = Good Laboratory Practice; HEK = human embryonic kidney; hERG = human ether-à-go-go-related gene; HR = heart rate; MC4R = melanocortin type 4 receptor; MBP = mean blood pressure; NA = not applicable; No. = number; SC = subcutaneous; SEM = standard error of the mean.

[1]An entry of "Yes" indicates that the study includes a GLP compliance statement.

2.6.3.5 薬力学的薬物相互作用試験

						Test Article: Setmelanotide
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses**	**Gender and No. per Group**	**Noteworthy Findings**	**Study Number/Location in eCTD/Reference**
Co-administration with liraglutide (a GLP-1 receptor agonist) to investigate for combined benefits of simultaneously targeting MC4R and GLP-1 receptor	Mouse/ C57BL/6	SC bolus injection	Setmelanotide: 4 mg/kg/day and Liraglutide: 0.038 mg/kg/day for 5 days; and 22 days	Male/ 8	Co-treatment of DIO mice with setmelanotide and liraglutide improved body weight loss and enhances glycemic control and cholesterol metabolism beyond what can be achieved with either mono-therapy. The superior metabolic efficacy of this co-administration therapy was attributed to the anorectic and glycemic actions of both drugs, along with the ability of setmelanotide to increase energy expenditure.	Clemmensen 2015/ 4.3

Definitions: SC = subcutaneous; DIO = diet-induced obesity GLP-1 = glucagon-like peptide-1; MC4R = melanocortin type 4 receptor.

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