表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Noteworthy Findings:								
Died or Sacrificed Moribund – Toxicity Animals (Dosing Phase)	1	2	3	1	0	0	1	2
Clinical Signs (Dosing Phase) [b]:								
Limited Use, Hind Legs	-	-	-	-	2	-	7	3
Limited Use, Left Hind Leg	-	-	-	-	1	-	2	-
Limited Use, Right Hind Leg(s)	-	-	-	-	2	-	2	1
Kinking, Tail	-	-	14	-	13	9	19	18
Altered Ambulation, Front Legs	-	-	-	-	-	-	1	-
Altered Ambulation, Hind Digit(s)	-	-	-	-	-	-	-	1
Altered Ambulation, Hind Legs	-	-	-	-	11	4	19	19
Altered Ambulation, Right Hind Leg	-	-	-	-	-	1	-	1
Valgus, Front Legs	-	-	-	-	2	-	11	13
Valgus, Front Paws	-	-	-	-	-	-	1	-
Valgus, Hind Legs	-	-	-	-	-	-	1	8
Valgus, Left Front Leg	-	-	-	-	2	-	7	7
Valgus, Right Front Leg	-	-	-	-	-	-	6	5
Valgus, Tail	-	-	-	-	-	-	-	1
Clinical Signs (Recovery Phase) [b]:								
Kinking, Tail	-	-	NA	NA	NA	NA	4	5
Altered Ambulation, Hind Legs	-	-	NA	NA	NA	NA	5	5
Valgus, Front Legs	-	-	NA	NA	NA	NA	5	5
Valgus, Front Paws	-	-	NA	NA	NA	NA	1	0
Valgus, Hind Legs	-	-	NA	NA	NA	NA	0	1
Valgus, Left Front Leg	-	-	NA	NA	NA	NA	2	2

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Body Weight Change (Dosing Phase):								
Days 1 - 183 (g)	-	-	-	-	-	-	-	-
Body Weight Change (Recovery Phase):								
Dosing Day 183 – Recovery Day 28 (g)	-	11	-	-	-	-	-	-6*
Food Consumption (Dosing and Recovery Phase):	-	-	-	-	-	-	-	-
Hematology								
Dosing Day 86/87								
White blood cell count ($\times 10^3/\mu L$)	-	3.74	-	-	-	-	-	4.89*
Absolute lymphocyte count ($\times 10^3/\mu L$)	-	2.47	-	-	-	-	-	3.38*
Dosing Day 177								
White blood cell count ($\times 10^3/\mu L$)	-	4.27	-	-	-	-	-	5.19
Absolute lymphocyte count ($\times 10^3/\mu L$)	-	2.55	-	-	-	-	-	3.38*
Clinical Chemistry								
Dosing Day 86/87								
Creatinine (mg/dL)	-	0.8	-	-	-	-	-	0.8*
Inorganic Phosphorus (mg/dL)	6.4	5.4	-	-	-	-	7.1*	6.0*
Alkaline Phosphatase (U/L)	63	40	-	-	81	-	97	58*
Dosing Day 177								
Creatinine (mg/dL)	-	0.8	-	-	-	-	-	0.7*
Cholesterol (mg/dL)	277	-	-	-	-	-	209*	-
Triglycerides (mg/dL)	113	-	-	-	56*	-	47*	-
Alkaline Phosphatase (U/L)	70	35	-	-	87	-	82*	49*

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Urine Chemistry								
Dosing Day 177								
Urine Volume (mL)	-	5.5	-	-	-	13.2*	-	8.9*
Urine Gamma Glutamyltransferase-to-urine Creatinine Ratio	-	7.31	-	-	-	9.94*	-	10.91*
Macroscopic Observations (Dosing Phase) [b]:								
No. Examined	15	15	15	15	15	15	15	15
Joint, Other								
Abnormal Shape	0	0	3	0	11	6	13	14
Tail								
Abnormal Shape	0	0	13	0	12	9	14	11
Bone, Other								
Abnormal Shape	0	0	3	0	6	0	6	2
Femur Bone								
Abnormal Shape	0	0	0	0	5	0	3	2
Sternum Bone								
Abnormal Shape	0	0	0	0	0	2	2	3
Macroscopic Observations (Recovery Phase) [b]:								
No. Examined	5	5	0	0	0	0	5	5
Joint, Other								
Abnormal Shape	0	0	NA	NA	NA	NA	5	5
Tail								
Abnormal Shape	0	0	NA	NA	NA	NA	5	5
Bone, Other								
Abnormal Shape	0	0	NA	NA	NA	NA	1	0

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Macroscopic Observations (Recovery Phase) (cont'd) [b]**:**								
No. Examined	5	5	0	0	0	0	5	5
Femur Bone								
Abnormal Shape	0	0	NA	NA	NA	NA	0	2
Sternum Bone								
Abnormal Shape	0	0	NA	NA	NA	NA	1	2
Organ Weights	-	-	-	-	-	-	-	-
Histopathology (Dosing Phase) [b]**:**								
No. Examined	15	15	15	15	15	15	15	15
Joint, Other:								
Growth Plate Thickness, Increased								
Minimal	0	0	1	-	4	3	1	4
Slight	0	0	2	-	7	2	6	9
Moderate	0	0	1	-	-	-	6	1
Growth Plate Dysplasia								
Minimal	0	0	-	-	1	3	3	2
Slight	0	0	3	-	10	3	6	12
Moderate	0	0	1	-	-	-	3	-
Tail:								
Growth Plate Thickness, Increased								
Minimal	0	0	12	-	8	9	5	7
Slight	0	0	1	-	3	-	6	4
Moderate	0	0	-	-	-	-	3	-

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Histopathology (Dosing Phase) (cont'd) [b]**:**								
No. Examined	15	15	15	15	15	15	15	15
Tail:								
Growth Plate Dysplasia								
Minimal	0	0	-	-	-	-	-	2
Slight	0	0	-	-	-	-	1	-
Femur:								
Growth Plate Thickness, Increased								
Minimal	0	0	0	0	2	0	1	1
Slight	0	0	0	0	2	0	1	1
Moderate	0	0	0	0	0	0	1	0
Growth Plate Dysplasia								
Minimal	0	0	0	0	1	0	0	0
Slight	0	0	0	0	1	0	0	2
Moderate	0	0	0	0	1	0	0	0
Sternum:								
Growth Plate Thickness, Increased								
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	2	0
Growth Plate Dysplasia								
Minimal	0	0	0	0	0	0	1	1
Slight	0	0	0	0	0	0	1	1

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Histopathology (Dosing Phase) (cont'd) [b]:								
No. Examined	15	15	15	15	15	15	15	15
Bone, Other:								
Growth Plate Thickness, Increased								
Minimal	0	0	0	0	0	0	1	0
Growth Plate Dysplasia								
Minimal	0	0	0	0	1	0	1	0
Histopathology (Recovery Phase) [b]:								
No. Examined	5	5	0	0	0	0	5	5
Joint, Other:								
Growth Plate Thickness, Increased	0	0	NA	NA	NA	NA	2	1
Growth Plate Dysplasia	0	0	NA	NA	NA	NA	5	5
Tail:								
Growth Plate Thickness, Increased	0	0	NA	NA	NA	NA	5	5
Growth Plate Dysplasia	0	0	NA	NA	NA	NA	1	0
Femur:								
Growth Plate Thickness, Increased	0	0	NA	NA	NA	NA	0	2
Growth Plate Dysplasia	0	0	NA	NA	NA	NA	0	2
Sternum:								
Growth Plate Thickness, Increased	0	0	NA	NA	NA	NA	0	1
Growth Plate Dysplasia	0	0	NA	NA	NA	NA	1	2
Bone, Other:								
Growth Plate Thickness, Increased	0	0	NA	NA	NA	NA	0	0
Growth Plate Dysplasia	0	0	NA	NA	NA	NA	1	0

表 2.6.7.7-2 BMN 111 の Sprague Dawley ラットにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	50	50	150	150	500	500
Number of Animals	20	20	15	15	15	15	20	20
Number of Recovery Animals	5	5	0	0	0	0	5	5
Total Sperm Count, Motility, and Morphology:								
Total Sperm Count - Change (Dosing Phase)	-	NA	-	NA	-30.5%	NA	-26.5%	NA
Total Sperm Count - Change (Recovery Phase)	-	NA	-	NA	-	NA	-42.7%	NA
Dual Energy X-Ray Absorptiometry (DEXA) [c]	-	-	-	-	-	-	-	-

-, No noteworthy findings; ADA, antidrug antibody; AUC, area under the plasma concertation-time curve; BMC, bone mineral content; BMD, bone mineral density; GLP, Good Laboratory Practice; NA, not applicable; DEXA, dual-energy X-ray absorptiometry; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; SD, Sprague Dawley; TK, toxicokinetics.

* $p \leq 0.05$ Statistical significance is based on actual data (not on the percent differences).

a) At 50 µg/kg, 10/13 males and 9/14 females were ADA positive on Day 176. At 150 µg/kg, 11/15 males and 11/15 females were ADA positive on Day 176. At 500 µg/kg, 5/19 males and 12/24 females were ADA positive on Day 176, and 1/5 males and 3/5 females were ADA positive on Day 211.

b) These values represent the number of incidences that each was observed.

c) BMC and BMD observed at Week 13 of dosing phase relative to the pre-dose phase values for whole body and right femur measurements. Relationship of BMC and BMD measurements BMN 111 administration not evaluated.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験

Report Title: A 26-Week Subcutaneous Injection Toxicity Study of BMN 111 in the Juvenile Rats Followed by a 6-Week Recovery

Species/Strain: Rat/Sprague Dawley

Initial Age: 7 days

Date of First Dose: 09 January 2012

Duration of Dosing: 26 weeks

Duration of Post-dose: 6 weeks

Method of Administration: SC

Vehicle/Formulation: BMN 111 placebo vehicle 2 or 0.005 mol/L citrate buffer solution, pH 5.5 ± 0.2 (citric acid monohydrate, sodium citrate dehydrate, L-methionine, trehalose dihydrate, D-mannitol and polysorbate 80 in water for injection)

Study No.: [BMN111-11-052]

Location in CTD: 4.2.3.2

Test Article: BMN 111

GLP Compliance: Yes

NOAEL: 10 µg/kg/day

TK								
Daily Dose (µg/kg/day)	**0 (Control)**		**10**		**30**		**90**	
Number of Animals (Subset D) [a]	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Days 7/188 postpartum (Day 1/182)	**3/6**	**3/6**	**18/9**	**18/9**	**18/9**	**18/9**	**18/9**	**18/9**
T_{max} (min) Day 1	NA	NA	5.0	NA	5.0	5.0	5.0	5.0
Day 182	NA	NA	30	15	15	15	15	5.0
C_{max} (pg/mL) Day 1	NA	NA	3290	0	2953	240	2803	3210
Day 182	NA	NA	680	527	3857	1987	26,150	16,900
AUC_{0-t} (pg·min/mL) Day 1	NA	NA	NC	0	NC	NC	NC	NC
Day 182	NA	NA	22,842	10,133	140,208	84,208	734,877	459,917
Anti-Drug Antibodies								
Number of Animals (Subset D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Days 188/230 postpartum	**6**	**6**	**9**	**9**	**9**	**9**	**9**	**9**
Incidence [b]								
N Positive (% Positive)								
Day 188pp	0 (0)	0 (0)	5 (55.6)	7 (77.8)	6 (66.7)	4 (44.4)	6 (66.7)	5 (55.6)
Day 230pp	0 (0)	0 (0)	2 (22.2)	5 (55.6)	4 (44.4)	6 (66.7)	2 (22.2)	5 (55.6)

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Pre-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Died or Sacrificed Moribund – Toxicity Animals (Pre-weaning)	0	0	0	0	0	1	1	0
Died or Sacrificed Moribund – Toxicity Animals (Post-weaning -Main)	0	0	1	0	0	0	0	2
Died or Sacrificed Moribund – Toxicity Animals (Post-weaning -Recovery)	1	0	2	4	0	0	2	1
Died or Sacrificed Moribund – Toxicity Animals (Post-weaning -Reproductive)	1	0	0	0	0	1	0	0

AUC, area under the plasma concertation-time curve; C_{max}, maximum observed plasma concentration; F, female; GLP, Good Laboratory Practice; M, male; NA, not applicable; NC, not calculated; NOAEL, no-observed-adverse-effect level; pp, postpartum; SC, subcutaneous, SD; Sprague Dawley; T_{max}, time to peak plasma concentration; TK, toxicokinetics.

a) TK: Subset D comprised of 3 controls and 18 BMN 111 animals on Day 1, and 6 controls and 9 BMN 111 animals on Day 182; 3 animals/sex/group/timepoint.

b) Screened and confirmed positive samples.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Pre-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9	10/16/20/9
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Noteworthy Findings								
Clinical Observations (Subset A and B combined) [a]								
Post weaning								
Abnormal Gait	-	-	-	-	-	-	21	6
Abnormal Hindpaw	-	-	-	-	-	-	23	8
Bent tail	-	-	-	-	-	-	16	1
Firm swelling (hindpaw/hindlimb)	-	-	-	-	-	-	22	9
Hunched Posture	-	-	-	-	-	-	14	9
Limited usage (hindlimb)	-	-	-	-	-	-	13	3
Prominent Backbone	-	-	-	-	-	-	8	4
Red skin (forepaws/forelimb or hindpaws)	-	-	-	-	-	-	3	3
Splayed Foot	-	-	-	-	-	-	17	2
Stiff Hindpaw	-	-	-	-	-	-	24	14
Thin body condition	-	-	-	1	-	3	12	12
Body Weight (% change) (Subset A and B combined)								
Post weaning								
Day 21-182 pp	1082.9	-	1077.6	-	1179.0	-	1028.5	-
Day 182-224 pp	4.9	-	5.1	-	3.6	-	0.9 C	-

-, no noteworthy findings; F, female; M, male; pp, postpartum.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
a) These values represent the number of incidences that each was observed.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Food Consumption (total per interval) (g/animal) (Subset A and B combined)								
Post weaning								
Day 28-189 pp	5166.1	-	-	-	5355.1	-	4887.6	-
Day 189-230 pp	1387.9	-	-	-	1501.0	-	1185.7	-
Crown-rump length (cm) (Subset A/B combined)								
Post weaning								
Day 63 pp	19.60	16.98	-	-	-	-	19.88	17.67 C
Day 231 pp	24.47	20.00	-	-	-	-	25.92 C	21.43 C

-, no noteworthy findings; F, female; M, male; pp, postpartum.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Tail length (cm) (Subset A and B combined)								
Post weaning								
Day 56 pp	18.92	17.06	-	-	-	-	18.94	17.52 A
Day 231 pp	24.13	20.39	-	-	-	-	27.50 F	22.90 C

-, no noteworthy findings; F, female; M, male; pp, postpartum.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/15/20/9
Functional Observation Battery (Arena)								
Week 24/25 (Subset B)								
Ataxic Gait								
None	16	16	14	13	16	15	7**	14
Slight	0	0	0	0	0	0	6**	1
Moderate	0	0	0	0	0	0	1**	0
Falls over	0	0	0	0	0	0	1**	0
Overall Gait Incapacity								
None	16	16	14	13	16	15	6***	12
Slight	0	0	0	0	0	0	6***	2
Moderate	0	0	0	0	0	0	2***	1

F, female; M; male.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Significantly different from control group [Group 1] value, Fisher's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D) Post-weaning	M	F	M	F	M	F	M	F
	10/16/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/15/20/9
Functional Observation Battery								
Week 24/25 (Subset B)								
Locomotor activity level								
Very Slight	1	-	0	-	0	-	0*	-
Slight	3	-	3	-	4	-	9*	-
Moderate	12	-	11	-	12	-	5*	-
Arousal								
Severely decreased	1	-	0	-	0	-	0	-
Moderately decreased	3	-	3	-	4	-	9	-
Moderately Increased	4	-	2	-	3	-	1	-
Week 30/31 (Subset B)								
Impaired Gait								
None	16	16	14	13	16	15	3*** ü	12⌂
Gait impeded due to injured hindlimb								
None	16	16	14	13	16	15	4*** ü	13⌂
Slight	0	0	0	0	0	0	7*** ü	1⌂
Moderate	0	0	0	0	0	0	1*** ü	0

-, no noteworthy findings; F, female; M, male; ü, based on 12 animals; ⌂, based on 14 animals.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Significantly different from control group [Group 1] value, Fisher's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset B)	M	F	M	F	M	F	M	F
Week 30/31	10/16/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/13/20/9	10/15/20/9
Overall Gait Incapacity								
None	16	16	14	13	16	15	4***	12
Slight	0	0	0	0	0	0	7***	3
Moderate	0	0	0	0	0	-	2***	0
Locomotor activity level								
Slight	6	-	0*	-	7	-	8	-
Moderate	10	-	14*	-	9	-	5	-
Arousal								
Moderately decreased	6	-	0*	-	7	-	8	-
Normal	9	-	12*	-	8	-	5	-
Moderately increased	1	-	2*	-	1	-	0	-
Body position								
Lying on Side/Curled Up	5	-	3	-	3	-	10*	-
Sitting/standing	11	-	11	-	13	-	3*	-
Rearing	1	-	2	-	2	-	1	-
Rearing								
Mean value	3.0	-	4.7	-	3.3	-	1.1A	-
Toe pinch								
Moderate	16	-	14	-	16	-	5***	-
Rapid	0	-	0	-	0	-	8***	-

-, no noteworthy findings; F, female; M, male.
*, **, ***: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Fisher's test).
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset B)	M	F	M	F	M	F	M	F
Week 13/14	10/16/20/6	10/16/20/6	10/16/20/6	10/13/20/9	10/16/20/6	10/15/20/9	10/14/20/9	10/16/20/9
Motor activity								
Total activity counts								
Mean	242.7	-	311.5	-	269.9	-	197.9	-
Linear time contrast								
Mean	-77.0	-	-68.9	-	-63.6	-	-51.9B	-
Week 24/25								
Total activity counts								
Mean	239.0	-	230.6$	-	217.9	-	110.2C	-
Linear time contrast								
Mean	-68.2	-	-60.6$	-	-58.1	-	-22.8C	-
Week 30/31								
Total activity counts								
Mean	185.8	-	242.1$	-	227.1	-	118.1&	-
Linear time contrast								
Mean	-47.8	-	-52.7$	-	-55.3	-	-27.7B&	-

-, no noteworthy findings; F, female; M, male; $, based on 14 animals; &, based on 13 animals.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Cincinnati water maze [a] (Subset B)								
Swimming ability performance								
Mean (seconds)								
End of treatment								
Trial 1	9.8	-	13.6	-	9.9	-	24.9	-
Trial 3	5.3	-	6.4	-	5.7	-	17.4 F	-
Trial 4	7.1	-	5.8	-	5.4	-	15.9 F	-
End of recovery								
Trial 1	12.0	-	10.9	-	7.8	-	14.8	-
Trial 3	6.5	-	5.4	-	7.6	-	14.8 D	-
Trial 4	5.6	-	7.4	-	6.1	-	13.6 F	-
Path A								
End of treatment								
First trial (seconds)	120	-	123	-	128	-	205 A	-
Last trial (seconds)	70	-	66	-	98	-	111	-
% Difference between first and last trials	-42	-	-46	-	-23	-	-46	-
End of recovery								
First trial (seconds)	137	-	134	-	126	-	179	-
Last trial (seconds)	105	-	106	-	85	-	78	-
% Difference between first and last trials	-24	-	-21	-	-33	-	-56	-

-, no noteworthy findings; F, female; M, male.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).
a) The tests could not be performed for some males at 90 μg/kg/day due to their difficulty swimming, which was considered related to the severity of the clinical condition of the hind limbs/hind paws of these animals.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/16/20/9	10/16/20/9	10/15/20/9	10/15/20/9	10/16/20/9
Path B								
End of treatment								
First trial (seconds)	233	-	196	-	223	-	250	-
Last trial (seconds)	17	-	16	-	17	-	26 A	-
% Difference between first and last trials	-93	-	-92	-	-92	-	-90	-
End of recovery								
First trial (seconds)	165	-	168	-	204	-	167	-
Last trial (seconds)	18	-	21	-	33	-	23	-
% Difference between first and last trials	-89	-	-88	-	-84	-	-86	-
Hematology (Subset A)								
End of treatment								
Absolute neutrophil count ($10^3/\mu L$)	-	1.030	-	0.714	-	0.985	-	1.608
Clinical Chemistry (Subset A)								
End of treatment								
Phosphorus (mg/dL)	6.00	-	6.62	-	6.75	-	6.98 A	-
Alkaline phosphatase (U/L)	49.2	-	52.4	-	48.1	-	66.8 B	-
Creatinine (mg/dL)	0.36	-	0.32	-	0.31	-	0.29 A	-
Biochemical Markers of Bone Turnover (Subset A)								
Day 21 pp								
P1NP (ng/mL)	389.170	339.878	348.791	328.004	317.743	314.903	317.901	254.908 A
Week 16								
TRACP-5b (U/L)	3.269	5.219	4.089	5.854	3.797	5.615	4.497 B	6.356

-, no noteworthy findings; F, female; M, male; P1NP, procollagen type 1 N-terminal propeptide; pp, postpartum; TRACP-5b, tartrate-resistant acid phosphatase-5b.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	9/16/20/9
Radiological evaluation (Subset A and B combined)								
Week 16 (Treatment period)								
Calcaneum Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape (R and/or L)	-	-	-	-	-	-	22	6
Femur Distal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	14	-
Femur Proximal								
Increased radiolucency, metaphysis and/or physis and/or head, and/or periosteal reaction and/or displacement fracture, physis (R and/or L)	-	-	-	-	6	6	24	20
Humerus Proximal								
Increased radiolucency, physis, proximal (R and/or L)	-	-	-	-	1	-	14	6
Metatarsal I Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape, bent, proximal (R and/or L)	-	-	-	-	-	-	21	4
Olecranon								
Increased radiolucency, physis (R and/or L)	-	-	-	-	15	6	22	22
Radius								
Increased radiolucency, physis proximal and/or distal (R and/or L)	-	-	-	-	-	-	2	5

-, no noteworthy findings; F, female; L, left; M, male; R, right.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (μg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/16/20/6**	**10/16/20/6**	**10/16/20/9**	**10/13/20/9**	**10/16/20/9**	**10/15/20/9**	**10/14/20/9**	**9/16/20/9**
Tibia Distal								
Increased radiolucency, metaphysis and/or physis and/or displacement/fracture and/or periosteal reaction (R and/or L)	-	-	-	-	12	-	24	21
Tibia Proximal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	13	-
Week 26 (End of treatment)								
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/16/20/6**	**10/16/20/6**	**9/14/20/9**	**10/13/20/9**	**10/16/20/9**	**10/15/20/9**	**10/14/20/9**	**9/15/20/9**
Calcaneum Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape (R and/or L)	-	-	-	-	-	-	22	5⌂
Caudal Vertebrae								
Reduced intervertebral space and/or scoliosis/kyphosis and/or increased radiolucency, physis, cranial and/or caudal, and/or abnormal shape	-	-	-	-	-	1	19	-

-, no noteworthy findings; F, female; L, left; M, male; R, right; ⌂, based on 24 animals.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	9/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	9/15/20/9
Femur Distal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	18	-
Femur Proximal								
Increased radiolucency, metaphysis and/or physis and/or head, and/or periosteal reaction and/or displacement fracture, physis, and/or femoral neck abnormal shape, bent (R and/or L)	-	-	-	-	9	5	24	22
Humerus								
Increased radiolucency, physis and/or metaphysis and/or focal bone loss, metaphysis, proximal and/or caudal (R and/or L)	-	-	-	-	-	-	4	1
Metatarsal I Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape, bent, proximal (R and/or L)	-	-	-	-	-	-	20	3
Olecranon								
Increased radiolucency, physis (R and/or L)	-	-	-	2	14	9	23	22
Radius/Ulna Distal								
Increased radiolucency, physis and/or metaphysis (R and/or L)	-	-	-	-	-	-	3	2

-, No noteworthy findings; F, female; L, left; M, male; R, right.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/16/20/6**	**10/16/20/6**	**9/14/20/9**	**10/13/20/9**	**10/16/20/9**	**10/15/20/9**	**10/14/20/9**	**9/15/20/9**
Tibia Distal								
Increased radiolucency, metaphysis and/or physis and/or displacement/fracture, physis (cranial) and/or periosteal reaction (R and/or L)	-	-	-	-	9	-	23	21
Tibia Proximal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	18	-
Week 32 (End of recovery)								
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/15/20/6**	**10/16/20/6**	**10/14/20/9**	**10/13/20/9**	**10/16/20/9**	**10/15/20/9**	**10/13/20/9**	**9/15/20/9**
Calcaneum Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape (R and/or L)	-	-	-	-	-	-	11	1
Caudal Vertebrae								
Reduced intervertebral space and/or scoliosis/kyphosis and/or increased radiolucency, physis, cranial and/or caudal, and/or abnormal shape	-	-	-	-	-	-	12	1
Femur Distal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	10	-

-, no noteworthy findings; F, female; L, left; M, male; R, right.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/15/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/13/20/9	9/15/20/9
Femur Proximal								
Increased radiolucency, metaphysis and/or physis and/or head, and/or periosteal reaction and/or displacement fracture, physis and/or metaphysis, proximal and/or caudal, and/or femoral neck abnormal shape, bent, and/or luxation, femoral head (R and/or L)	-	-	-	-	5	-	13	13
Humerus Proximal								
Increased radiolucency, physis and/or metaphysis, proximal and/or focal bone loss, metaphysis, proximal and/or caudal (R and/or L)	-	-	-	-	-	-	2	-
Metatarsal I Proximal								
Increased radiolucency, metaphysis and/or physis, and/or abnormal shape, bent, proximal (R and/or L)	-	-	-	-	-	-	7	1
Olecranon								
Increased radiolucency, physis (R and/or L)	-	-	-	-	8	-	13	1
Radius/Ulna Distal								
Increased radiolucency, physis and/or metaphysis (R and/or L)	-	-	-	-	-	-	2	-

-, no noteworthy findings; F, female; L, left; M, male; R, right.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/15/20/6**	**10/16/20/6**	**10/14/20/9**	**10/13/20/9**	**10/16/20/9**	**10/15/20/9**	**10/13/20/9**	**9/15/20/9**
Tibia Distal								
Increased radiolucency, metaphysis and/or physis, physeal scar visible and/or displacement/fracture, physis, cranial and/or periosteal reaction, cranial, and/or physeal scar visible (R and/or L)	-	-	-	-	3	-	13	10
Tibia Proximal								
Increased radiolucency, metaphysis (R and/or L)	-	-	-	-	-	-	10	-
Radiological evaluation- Cube root ratio (Subset B)								
Week 6 (Treatment period)								
Number of Animals	**16**	**16**	**16**	**16**	**16**	**15**	**14**	**16**
Right Tibia								
Length	5.460	-	5.416	-	5.508	-	5.586 A	-
Week 16 (Treatment period)								
Number of Animals	**16**	**16**	**16**	**13**	**16**	**15**	**14**	**16**
Right Femur								
Length	4.715	5.100	4.703	5.147	4.756	5.187	4.995 C	5.374 C
Right Tibia								
Length	5.338	5.771	5.253	5.713	5.323	5.801	5.634 D	5.944
Lumbar Spine								
Length	6.288	6.663	6.285	6.671	6.373	6.807	6.653 C	6.917 B

-, no noteworthy findings; F, female; L, left; M, male; R, right.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Week 26 (End of treatment)								
Number of Animals	**16**	**16**	**14**	**13**	**16**	**15**	**14**	**14**
Right Femur								
Length	4.727	5.177	4.762	5.280	4.766	5.300	5.080 C	5.592 C
Width	0.446	-	0.439	-	0.432	-	0.420	-
Right Humerus								
Length	3.741	4.089	3.735	4.148	3.716	4.099	3.917 B	4.211
Right Tibia								
Length	5.241	5.721	5.213	5.807	5.205	5.755	5.431 A	5.950 A
Lumbar Spine								
Length	6.240	6.630	6.308	6.663	6.376	6.737	6.902 C	7.085 F
Skull								
Length	5.808	-	5.884	-	5.790	-	6.073 B	-
End of recovery								
Number of Animals	**15**	**16**	**14**	**13**	**16**	**15**	**13**	**15**
Right Femur								
Length	4.726	5.199	4.769	5.326	4.773	5.314	5.153 C	5.632 C
Width	0.474	-	0.454	-	0.468	-	0.447	-
Right Humerus								
Length	3.747	4.073	3.737	4.163	3.729	4.098	3.938 B	4.231 A
Right Tibia								
Length	5.255	5.719	5.219	5.848	5.228	5.691	5.442	5.968 A
Lumbar Spine								
Length	6.273	6.615	6.302	6.700	6.405	6.719	6.961 C	7.168 F
Skull								
Length	5.870	-	5.885	-	5.827	-	6.116 A	-

-, no noteworthy findings; F, female; M, male.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/16/20/9
Densitometry (Subset B)								
DEXA- *In vivo*								
Week 14/15 (Treatment period)								
Lumbar spine - Global (L1-L4)								
BMC (g)	0.714	-	0.736	-	0.736	-	0.659	-
BMD (g/cm^2)	0.2637	-	0.2673	-	0.2672	-	0.2425 B	-
Right Femur-Global								
Area (cm^2)	-	1.593	-	1.591	-	1.606	-	1.683 B
BMC (g)	0.690	-	0.684	-	0.694	-	0.622 A	-
BMD (g/cm^2)	0.3270	-	0.3292	-	0.3261	-	0.2902 C	-
Right Femur-Proximal								
Area (cm^2)	-	0.502	-	0.495	-	0.512	-	0.553 C
BMC (g)	0.249	-	0.247	-	0.254	-	0.227	-
BMD (g/cm^2)	0.3863	0.3512	0.3909	0.3519	0.3870	0.3482	0.3365 C	0.3283 B
Right Femur-Mid								
BMC (g)	0.138	-	0.132	-	0.136	-	0.128	-
BMD (g/cm^2)	0.3101	-	0.3078	-	0.3073	-	0.2904 A	-
Right Femur-Distal								
BMC (g)	0.208	-	0.207	-	0.204	-	0.174 C	-
BMD (g/cm^2)	0.3410	-	0.3445	-	0.3400	-	0.2934 C	-
Week 25/26 (End of treatment period)								
Lumbar spine - Global (L1-L4)								
Area (cm^2)	3.033	2.188	3.132$	2.180	3.126	2.242	3.214	2.340⌂
BMD (g/cm^2)	0.2914	0.2659	0.3019$	0.2641	0.2910	0.2733	0.2574 C	0.2568⌂

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

-, no noteworthy findings; BMC, bone mineral content; BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; F, female; M, male; ⌂, based on 15 animals; $, based on 14 animals.

A, B, C; $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test)

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/15/20/9
Right Femur-Global								
Area (cm^2)	-	1.686	-	1.688	-	1.728	-	1.831 C
BMC (g)	0.881	0.557	0.885	0.564	0.907	0.567	0.727 C%	0.549
BMD (g/cm^2)	0.3765	0.3299	0.3813	0.3337	0.3750	0.3281	0.3036 C%	0.2994 C
Right Femur-Proximal								
Area (cm^2)	0.698	0.518	0.682	0.520	0.741	0.554 A	0.744%	0.628 C
BMC (g)	0.303	0.199	0.306	0.203	0.320	0.210	0.245 C%	0.206
BMD (g/cm^2)	0.4348	0.3828	0.4480	0.3903	0.4314	0.3782	0.3271 C%	0.3287 C
Right Femur-Mid								
BMC (g)	0.184	0.111	0.181	0.110	0.183	0.109	0.158 C%	0.104
BMD (g/cm^2)	0.3731	0.2762	0.3767	0.2755	0.3727	0.2742	0.3334 C%	0.2613 A
Right Femur-Distal								
BMC (g)	0.244	0.180	0.243	0.183	0.245	0.181	0.189 C%	0.169
BMD (g/cm^2)	0.3864	0.3662	0.3902	0.3682	0.3819	0.3638	0.3003 F%	0.3396 B
Week 31/32 (End of recovery)								
Lumbar spine - Global (L1-L4)								
Area (cm^2)	3.148	2.241	3.267	2.249	3.248	2.328	3.307&	2.442 B
BMD (g/cm^2)	0.2995	0.2712	0.3119	0.2761	0.2994	0.2822	0.2693 B&	0.2646
Right Femur-Global								
Area (cm^2)	2.387	1.725	2.365	1.724	2.438	1.768	2.460@	1.834 B
BMC (g)	0.929	0.584	0.930	0.589	0.947	0.593	0.783 C@	0.553
BMD (g/cm^2)	0.3887	0.3375	0.3928	0.3408	0.3881	0.3352	0.3172 C@	0.3013 C

-, no noteworthy findings; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male; &, based on 13 animals; %, based on 12 animals; @, based on 11 animals.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/16/20/9
Right Femur-Proximal								
Area (cm^2)	0.687	0.524	0.674$	0.522	0.742 D	0.553	0.786 D@	0.603 C⌂
BMC (g)	0.310	0.207	0.311$	0.209	0.328	0.216	0.271@	0.202⌂
BMD (g/cm^2)	0.4505	0.3937	0.4609$	0.3998	0.4426	0.3906	0.3419 C@	0.3340 F⌂
Right Femur-Mid								
BMC (g)	0.198	0.119	0.194$	0.117	0.198	0.118	0.165 C@	0.108⌂
BMD (g/cm^2)	0.3895	0.2882	0.3924$	0.2855	0.3914	0.2871	0.3385 C@	0.2656 B⌂
Right Femur-Distal								
BMC (g)	0.253	0.186	0.253$	0.188	0.252	0.187	0.205 C@	0.174⌂
BMD (g/cm^2)	0.3944	0.3685	0.3964$	0.3755	0.3927	0.3641	0.3156 C@	0.3423 A⌂
pQCT- *In vivo*								
Week 14/15 (Treatment period)								
Right Proximal Tibia - Metaphysis								
Total								
BMC (mg/mm)	11.924	-	11.824	-	11.841	-	9.705 C	-
BMD (mg/cm^3)	515.03	-	529.83	-	513.93	-	444.11 E	-
Trabecular								
BMC (mg/mm)	2.393	2.626	2.443	2.737	2.298	2.647	1.544 C	2.309
BMD (mg/cm^3)	206.12	456.51	218.16	486.38	199.33	481.83	141.25 E	409.79
Cortical/Subcortical								
BMC (mg/mm)	9.533	-	9.382	-	9.544	-	8.161 C	-
BMD (mg/cm^3)	823.96	-	841.36	-	829.34	-	747.33 E	-

-, no noteworthy findings; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male; pQCT, peripheral quantitative computed tomography; ⌂, based on 15 animals; $, based on 14 animals; @, based on 11 animals.

A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/16/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/14/20/9	10/15/20/9
Right Proximal Tibia - Diaphysis								
Cortical								
Area (mm^2)	6.666	-	6.538	-	6.728	-	6.023 B	-
BMC (mg/mm)	8.163	-	8.053	-	8.253	-	7.317 C	-
Thickness (mm)	0.8451	-	0.8529	-	0.8583	-	0.7829 C	-
Week 25/26 (End of treatment period)								
Right Proximal Tibia - Metaphysis								
Total								
Area (mm^2)	21.743	-	21.497$	-	21.959	-	20.517&	-
BMC (mg/mm)	13.342	9.244	13.520$	9.216	13.204	9.095	9.984 C&	8.561
BMD (mg/cm^3)	616.13	875.11	630.88$	890.92	603.32	886.77	487.08 C&	808.25 B
Trabecular								
BMD (mg/cm^3)	233.71	-	246.81$	-	234.43	-	164.75 E&	-
Cortical/Subcortical								
BMC (mg/mm)	10.983	8.543	11.185$	8.613	10.778	8.424	8.085 C&	7.655 A
BMD (mg/cm^3)	943.93	1039.21	933.48$	1020.48	928.49	1044.15	900.26 B&	996.82 A
Right Proximal Tibia - Diaphysis								
Total								
Area (mm^2)	10.268	6.576	10.316$	6.628	10.421	6.493	9.256 B&	6.136
Cortical								
Area (mm^2)	7.923	5.281	8.009$	5.205	7.968	5.154	6.748 C&	4.762 C
BMC (mg/mm)	10.061	6.632	10.190$	6.555	10.108	6.479	8.415 C&	5.953 E
BMD (mg/cm^3)	1269.83	-	1272.38$	-	1268.60	-	1246.17 C&	-
Thickness (mm)	0.9454	0.8061	0.9571$	0.7819	0.9393	0.7864	0.8243 C&	0.7383 C
Periosteal circumference (mm)	11.3475	9.0819	11.3764$	9.1179	11.4363	9.0300	10.7754 B&	8.7719

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

-, no noteworthy findings; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male; $, based on 14 animals; &, based on 13 animals.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/16/20/6	10/16/20/6	10/14/20/9	10/13/20/9	10/16/20/9	10/15/20/9	10/13/20/9	10/15/20/9
Week 31/32 (End of recovery)								
Right Proximal Tibia - Metaphysis								
Total								
Area (mm^2)	20.954	-	20.314	-	20.759	-	18.592 A	-
BMC (mg/mm)	13.564	9.441	13.549	9.441	13.311	9.215	10.162 C	8.236 B
BMD (mg/cm^3)	650.58	890.51	669.73	910.19	644.20	900.20	547.02 C	829.37 B
Trabecular								
BMC (mg/mm)	2.176	-	2.039	-	2.088	-	1.562 B	-
BMD (mg/cm^3)	233.34	-	241.02	-	229.94	-	163.85 E	-
Cortical/Subcortical								
BMC (mg/mm)	-	8.764	-	8.905	-	8.567	-	7.430 B
BMD (mg/cm^3)	-	-	-	-	-	-	-	-
Right Proximal Tibia - Diaphysis								
Total								
Area (mm^2)	10.687	6.702	10.529	6.762	10.714	6.626	9.255 C	6.081 B
Cortical								
Area (mm^2)	8.279	5.319	8.296	5.298	8.282	5.262	6.839 C	4.818 C
BMC (mg/mm)	10.623	6.741	10.696	6.714	10.598	6.655	8.621 C	6.055 C
BMD (mg/cm^3)	1283.25	1267.90	1289.47	1266.68	1280.04	1264.77	1260.44 C	1256.11
Thickness (mm)	0.9708	0.7988	0.9889	0.7875	0.9698	0.7953	0.8398 C	0.7591 A
Periosteal circumference (mm)	11.5763	9.1674	11.4932	9.2072	11.5930	9.1218	10.7723 C	8.7345 B

-, no noteworthy findings; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9
Gross pathology								
Day 189 pp (Subset A)								
Bone - Acetabulum, Right								
Thickening	-	-	-	-	-	-	2	1
Joint - Femoroacetabular								
Enlargement	-	-	-	-	-	-	1	2
Thickening	-	-	-	-	-	-	-	2 [a]
Bone - Femur, Right								
Area depressed	-	-	-	-	-	1	-	1
Area raised	-	-	-	-	-	-	1	1
Area dark	-	-	-	-	1	-	1	-
Discoloration pale	-	-	-	-	-	-	-	2
Enlargement	-	-	-	-	-	-	2	-
Fracture	-	-	-	-	-	-	1	1
Small	-	-	-	-	-	-	-	2 [a]
Surface irregular	-	-	-	-	-	-	1	3 [a]
Bone - Tibia, Left								
Area raised	-	-	-	-	-	-	5	-
Enlargement	-	-	-	-	-	-	3	-
Bone - Tibia, Right								
Bent	-	-	-	-	-	-	1	-
Joint - Tibiotarsal								
Enlargement	-	-	-	-	-	-	3	-
Area raised	-	-	-	-	-	-	5	-

-, no noteworthy finding; F, female; M, male; pp, postpartum.
a) Includes preterminal animal 4509, which was found dead on Day 187 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9
Gross pathology								
Day 231 pp (Subset B)								
Bone - Femur, Right								
Area depressed	-	-	-	-	1	-	2	3
Area raised	-	-	-	-	-	-	1	1
Discoloration pale	-	-	-	-	1	-	3	3
Enlargement	-	-	-	-	1	-	2	-
Fracture	-	-	-	-	-	-	3	2
Soft	-	-	-	-	-	-	1	1
Joint Femoroacetabular								
Enlargement	-	-	-	-	-	-	3	-
Joint Tibiotarsal								
Enlargement	-	-	-	-	1	-	10	-
Bone - Tibia, Left								
Bent	-	-	-	-	-	-	2[a]	-
Enlargement	-	-	-	-	-	-	8	-
Bone - Tibia, Right								
Bent	-	-	-	-	-	-	6[a]	-

-, no noteworthy finding; F, female; M, male; pp, postpartum.
a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Histopathology								
Day 189 pp (Subset A)								
Bone - Femur, Left								
Degeneration/necrosis/fissure: physeal/epiphyseal femoral head								
Slight	-	-	-	-	2	1	1	-
Marked	-	-	-	-	-	-	2	2
Severe	-	-	-	-	-	-	4	1
Necrosis: Bone								
Moderate	-	-	-	-	-	-	3	2
Marked	-	-	-	-	1	-	3	1
Severe	-	-	-	-	-	-	2	2 [a]
Fibrosis periosteal: neck								
Moderate	-	-	-	-	-	-	5	1
Marked	-	-	-	-	-	-	2	1 [a]
Severe	-	-	-	-	-	-	1	5
Hypertrophy/hyperplasia: articular cartilage: proximal								
Slight	-	-	-	-	1	-	2	2
Moderate	-	-	-	-	-	-	4	4 [a]
Decreased metaphyseal/epiphyseal cancellous Bone								
Minimal	-	-	-	-	-	-	2	-
Slight	-	-	-	-	-	-	8	-

-, no noteworthy finding; F, female; M, male; pp, postpartum.

a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Physeal persistence: trochanter								
Minimal	5	4	6	1	5	4	-	6[a]
Slight	1	1	-	1	2	1	3	2
Moderate	-	-	-	-	1	-	7	-
Increased hypertrophic zone/primary spongiosa: physis								
Minimal	-	-	-	-	2	4	1	1
Slight	-	-	-	-	6	4	8	1
Moderate	-	-	-	-	-	-	-	2
Marked	-	-	-	-	1	-	-	2
Fibrosis: endosteal								
Moderate	-	-	-	-	-	-	2	-
Cartilage persistence/hypertrophy								
Moderate	-	-	-	-	2	-	1	-
Bone-Acetabulum								
Degeneration/necrosis: cartilage/Bone								
Moderate	-	-	-	-	-	-	2	2
Marked	-	-	-	-	-	-	6	2[a]
Severe	-	-	-	-	-	-	-	1

-, no noteworthy finding; F, female; M, male.
a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Physeal/cartilage persistence/formation								
Minimal	-	-	-	-	-	-	-	1 [a]
Slight	-	-	-	-	1	-	-	1
Moderate	-	-	-	-	-	-	-	1
Marked	-	-	-	-	-	-	3	-
Periosteal Bone formation								
Minimal	-	-	-	-	-	-	1	-
Slight	-	-	-	-	-	-	2	1
Moderate	-	-	-	-	1	-	1	-
Joint Femoroacetabular								
Degeneration/fibrosis: chronic								
Minimal	-	-	-	-	-	1	-	1
Moderate	-	-	-	-	-	-	1	4
Marked	-	-	-	-	-	-	5	3 [a]
Severe	-	-	-	-	-	-	3	-
Bone - Tibia, Left								
Disorganized cartilage/bone growth: physeal/metaphyseal-distal								
Moderate	-	-	-	-	-	-	2	2 [a]
Marked	-	-	-	-	-	-	4	-
Severe	-	-	-	-	-	-	4	1
Physeal persistence/thickening: distal								
Minimal	-	-	-	-	2	-	-	2 [a]
Slight	-	-	-	-	-	-	-	2 [a]
Moderate	-	-	-	-	1	-	-	2

-, no noteworthy finding; F, female; M, male.
a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Periosteal Bone formation: distal								
Slight	-	-	-	-	-	-	6	-
Moderate	-	-	-	-	-	-	3	1
Marked	-	-	-	-	-	-	1	-
Decreased metaphyseal/epiphyseal cancellous Bone: proximal								
Minimal	1	-	-	-	-	-	3	-
Slight	-	-	-	-	-	-	7	-
Increased hypertrophic zone: physis								
Minimal	-	-	-	-	-	-	10	5 [a]
Bone - Calcaneum								
Physeal persistence/thickening								
Minimal	-	-	-	-	-	-	-	1 [a]
Slight	-	-	-	-	-	-	3	2
Moderate	-	-	-	-	-	-	3	-
Marked	-	-	-	-	-	-	1	-
Decreased metaphyseal cancellous Bone								
Minimal	-	-	-	-	-	-	2	-
Moderate	-	-	-	-	-	-	4	-
Bone Metatarsus-1, Left								
Physeal persistence/thickening:								
Slight	-	-	-	-	-	-	3 [a]	-
Moderate	-	-	-	-	-	-	2	-
Marked	-	-	-	-	-	-	1	-

-, no noteworthy findings; F, female; M, male.
a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Decreased cancellous/cortical Bone								
Slight	-	-	-	-	-	-	3	-
Joint Tibiotarsal								
Inflammation articular/peri-articular								
Slight	-	-	-	-	-	-	3	-
Moderate	-	-	-	-	-	-	3	-
Marked	-	-	-	-	-	-	1	1
Inflammation: tenosynovial								
Slight	-	-	-	-	-	-	3	-
Marked	-	-	-	-	-	-	2	1
Bone - Humerus, Left								
Decreased metaphyseal/epiphyseal cancellous Bone: proximal								
Slight	-	-	-	-	-	-	2	-
Increased hypertrophic zone: physis								
Minimal	-	-	-	-	-	-	4	-
Joint-Humeroscapular for Scapula								
Physeal persistence/thickening: scapula								
Minimal	2	2	2	1	2	2	2	1
Slight	-	-	-	-	-	-	1	1
Marked	-	-	-	-	-	-	2	-

-, no noteworthy finding; F, female; M, male.
a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Bone - Radius, Left								
Increased hypertrophic zone/primary-spongiosa: physis								
Minimal	-	-	-	-	-	-	-	4 [a]
Slight	-	-	-	-	-	-	5	-
Moderate	-	-	-	-	-	-	4	-
Bone - Ulna, Left								
Increased hypertrophic zone/primary spongioza: physis								
Minimal	-	-	-	-	-	-	3	9 [a]
Slight	-	-	-	-	-	-	2	-
Moderate	-	-	-	-	-	-	5	-
Decreased metaphyseal cancellous bone								
Minimal	-	-	-	-	-	-	3	-
Slight	-	-	-	-	-	-	2	-
Bone – Sternum								
Increased hypertrophic zone: physis								
Minimal	-	-	-	-	-	-	6	5 [a]
Slight	-	-	-	-	-	-	3	1

-, no noteworthy finding; F, female; M, male.

a) As applicable, includes preterminal animals 4504, 4509, and 4520, which were found dead on Day 112, Day 187, and Day 152 postpartum, respectively.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Bone - Vertebrae, Caudal								
Thickening: physis								
Slight	-	-	-	-	-	-	3	-
Moderate	-	-	-	-	-	-	3	-
Day 231 pp (Subset B)								
Bone - Femur, Left								
Degeneration/necrosis/fissure: physeal/epiphyseal femoral head								
Minimal	-	-	-	-	-	-	2	2
Slight	-	-	-	-	1	-	1	2
Moderate	-	-	-	-	2	-	2	-
Necrosis: Bone								
Severe	-	-	-	-	-	-	6 [a]	5
Fibrosis periosteal: neck								
Moderate	-	-	-	-	-	-	6 [a]	1
Marked	-	-	-	-	-	-	-	2
Hypertrophy/hyperplasia: articular cartilage: proximal								
Slight	-	-	-	-	2	-	-	-
Moderate	-	-	-	-	-	-	3	-
Marked	-	-	-	-	-	-	1 [a]	-

-, no noteworthy finding; F, female; M, male; pp, postpartum.
a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Decreased metaphyseal/epiphyseal cancellous bone								
Minimal	-	-	-	-	-	-	2	-
Slight	-	-	-	-	-	-	7[a]	-
Moderate	-	-	-	-	-	-	2	-
Physeal persistence: trochanter								
Minimal	2	-	-	-	2	-	-	-
Woven bone-osteoid accumulation								
Moderate	-	-	-	-	-	-	2[a]	-
Bone - Acetabulum								
Degeneration/necrosis: cartilage/bone								
Moderate	-	-	-	-	-	-	1	1
Marked	-	-	-	-	-	-	5[a]	2

-, no noteworthy finding; F, female; M, male.

a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Decreased cancellous Bone								
Slight	-	-	-	-	-	-	3	-
Moderate	-	-	-	-	-	-	3	-
Joint Femoroacetabular								
Degeneration/fibrosis: chronic								
Slight	-	-	-	-	1	-	1	-
Moderate	-	-	-	-	-	-	3	3
Marked	-	-	-	-	-	-	2 [a]	-
Severe	-	-	-	-	-	-	3	5
Bone - Tibia, Left								
Disorganized cartilage/bone growth: physeal/metaphyseal-distal								
Moderate	-	-	-	-	-	-	-	3
Marked	-	-	-	-	-	-	4 [a]	-
Severe	-	-	-	-	-	-	7	1
Physeal persistence/thickening: distal								
Slight	-	-	-	-	-	-	-	2

-, no noteworthy finding; F, female; M, male.
a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Periosteal Bone formation								
Slight	-	-	-	-	-	-	2	-
Moderate	-	-	-	-	-	-	3	-
Decreased metaphyseal/epiphyseal cancellous bone: proximal								
Minimal	-	-	-	-	-	-	5	-
Slight	-	-	-	-	-	-	2[a]	-
Moderate	-	-	-	-	-	-	2	-
Bone - Calcaneum								
Physeal persistence/thickening								
Minimal	-	-	-	-	-	-	3	-
Slight	-	-	-	-	-	-	4	-
Moderate	-	-	-	-	-	-	2[a]	-
Decreased metaphyseal cancellous bone								
Slight	-	-	-	-	-	-	3[a]	-
Moderate	-	-	-	-	-	-	3	-
Bone Metatarsus-1, Left								
Decreased cancellous/cortical Bone								
Minimal	-	-	-	-	-	-	2	-

-, no noteworthy finding; F, female; M, male.
a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Joint Tibiotarsal								
Inflammation articular/peri-articular								
Slight	-	-	-	-	-	-	2 [a]	-
Moderate	-	-	-	-	-	-	2	-
Inflammation: tenosynovial								
Slight	-	-	-	-	-	-	3	1
Bone - Humerus, Left								
Decreased metaphyseal/epiphyseal cancellous bone: proximal								
Minimal	-	-	-	-	-	-	2 [a]	-
Slight	-	-	-	-	-	-	3	-

-, no noteworthy finding; F, female; M, male.
a) Includes preterminal animal 4016, which was found dead on Day 201 postpartum.

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Bone - Sternum								
Increased hypertrophic zone: physis								
Slight	-	-	-	-	-	-	2	-
Bone - Vertebrae, Caudal								
Thickening: physis								
Slight	-	-	-	-	-	-	2	-
Moderate	-	-	-	-	-	-	7	-
Decreased cancellous Bone								
Slight	-	-	-	-	-	-	6	-
Moderate	-	-	-	-	-	-	2	-
Bone measurements (mm)								
Day 189 pp (Subset A)								
Right Femur								
Length	42.61	37.23	42.99	37.58	43.38	37.39	45.29C	38.87C
Width	5.15	4.09	5.12	4.23	4.99	4.05	4.44C	3.90
Right Tibia								
Length	46.94	41.19	46.88	41.25	48.22	41.53	51.38C	44.73C
Width	4.06	3.33	4.00	3.16	3.85	3.13	3.61B	3.11
Right Radius								
Length	29.05	25.77	28.32	26.20	29.41	26.04	30.14	27.09C

-, no noteworthy finding; F, female; M, male; pp, postpartum.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/15/20/6	10/16/20/6	9/14/20/9	10/12/20/9	10/16/20/9	10/15/20/9	10/13/20/9	8/15/20/9
Day 231 pp (Subset B)								
Right Femur								
Length	43.76	37.31	44.14	37.27	44.36	37.44	46.28E	38.97C
Width	5.35	4.30	5.33	4.30	5.35	4.22	4.80C	4.00C
Right Tibia								
Length	48.89	41.73	48.52	41.62	49.38	42.04	52.24F	44.45C
Width	4.11	3.26	4.15	3.27	4.12	3.18	3.87A	3.15
Right Radius								
Length	29.55	25.99	29.70	25.98	29.80	26.28	30.79C	26.95C
Densitometry (Subset B)								
DEXA - *Ex vivo*								
Week 25/26 (End of treatment period)								
Number of Animals	**10**	**10**	**9**	**10**	**10**	**10**	**10**	**8**
Right Femur-Global								
BMC (g)	0.84	-	0.82	-	0.82	-	0.64C	-
BMD (g/cm^2)	0.309	0.279	0.301	0.282	0.298	0.274	0.250C	0.255C
Right Femur-Proximal								
Area (cm^2)	-	0.67	-	0.70	-	0.71A	-	0.72B
BMC (g)	0.29	-	0.28	-	0.29	-	0.23E	-
BMD (g/cm^2)	0.321	0.287	0.315	0.291	0.303A	0.280	0.248C	0.259E
Right Femur-Mid								
Area (cm^2)	0.61	-	0.61	-	0.60	-	0.53C	-
BMC (g)	0.19	-	0.19	-	0.18	-	0.15C	-
BMD (g/cm^2)	0.313	-	0.305	-	0.302	-	0.272C	-

-, no noteworthy finding; BMC, bone mineral content; BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; F, female; M, male; pp, postpartum.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/15/20/6	10/16/20/6	9/14/20/9	10/12/20/9	10/16/20/9	10/15/20/9	10/13/20/9	8/15/20/9
Number of Animals	**10**	**10**	**9**	**10**	**10**	**10**	**10**	**8**
Right Femur-Distal								
Area (cm^2)	0.53	-	0.53	-	0.53	-	0.49A	-
BMC (g)	0.19	-	0.18	-	0.19	-	0.14C	-
BMD (g/cm^2)	0.361	0.346	0.348	0.356	0.354	0.343	0.281C	0.318B
Week 31/32 (End of recovery)								
Number of Animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Right Femur-Global								
BMD (g/cm^2)	0.317	0.284	0.326	0.290	0.328	0.292	0.280C	0.262A
Right Femur-Proximal								
Area (cm^2)	0.93	-	0.95	-	1.01A	-	1.02A	-
BMD (g/cm^2)	0.323	0.294	0.331	0.299	0.330	0.297	0.276C	0.267B
Right Femur-Mid								
Area (cm^2)	0.63	0.49	0.66	0.49	0.65	0.49	0.59A	0.46B
BMC (g)	0.21	0.13	0.22	0.13	0.22	0.13	0.18B	0.11B
BMD (g/cm^2)	0.332	0.257	0.336	0.257	0.344	0.266	0.300B	0.241A
Right Femur-Distal								
Area (cm^2)	-	-	-	-	-	-	-	-
BMC (g)	0.20	0.15	0.21	0.16	0.22	0.16	0.17A	0.14
BMD (g/cm^2)	0.363	0.347	0.383	0.361	0.380	0.359	0.323C	0.324

-, no noteworthy finding; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/15/20/6	10/16/20/6	9/14/20/9	10/12/20/9	10/16/20/9	10/15/20/9	10/13/20/9	8/15/20/9
pQCT - *Ex vivo*								
Week 25/26 (End of treatment period)								
Number of Animals	10	10	9	10	10	10	10	8
Right Femur Diaphysis								
Total								
Area (mm^2)	15.18	9.35	14.60	9.87	13.67	9.60	10.45C	8.44
Cortical								
Area (mm^2)	9.67	6.35	9.39	6.68	8.97	6.30	7.00C	5.70A
BMC (mg/mm)	12.91	8.37	12.58	8.69	12.03	8.26	9.23C	7.37
BMD (mg/cm^3)	1335.7	1319.3	1340.3	1302.0	1341.8	1310.3	1318.1B	1292.5B
Thickness (mm)	0.876	0.748	0.870	0.766	0.868	0.727	0.782C	0.707
Periosteal circumference (mm)	13.794	10.831	13.531	11.124	13.089	10.968	11.421C	10.277
Endosteal circumference (mm)	8.291	6.131	8.065	6.311	7.636	6.400	6.505C	5.834
L4 Lumbar Vertebral Body								
Total								
BMC (mg/mm)	7.12	6.13	7.50	6.23	6.96	5.96	5.93B [a]	5.96
BMD (mg/cm^3)	680.95	703.78	683.26	711.81	685.79	672.27A	616.19B [a]	671.26A

BMC, bone mineral content; BMD, bone mineral density; F, female; M, male; pQCT, peripheral quantitative computed tomography.
a) n = 9
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/15/20/6	10/16/20/6	9/14/20/9	10/12/20/9	10/16/20/9	10/15/20/9	10/13/20/9	8/15/20/9
pQCT - *Ex vivo*								
Week 31/32 (End of recovery)								
Number of Animals	10	10	10	10	10	10	10	10
Right Femur Diaphysis								
Total								
Area (mm^2)	15.65	10.29	15.71	10.17	16.05	10.12	12.50C	9.03A
Cortical								
Area (mm^2)	10.19	6.96	10.31	6.89	10.40	6.80	8.10C	5.79C
BMC (mg/mm)	13.87	9.17	13.97	9.00	14.07	8.98	10.80C	7.54C
BMD (mg/cm^3)	1360.2	1320.1	1355.9	1306.5	1353.1	1320.6	1333.6C	1301.9
Thickness (mm)	0.916	0.782	0.927	0.778	0.923	0.771	0.815C	0.682C
Periosteal circumference (mm)	14.011	11.347	14.032	11.296	14.182	11.269	12.500C	10.638A
L4 Lumbar Vertebral Body								
Total								
BMC (mg/mm)	7.43	-	7.86	-	7.34	-	6.23A	-
BMD (mg/cm^3)	662.65	-	697.71	-	675.12	-	606.54A	-
Trabecular								
BMD (mg/cm^3)	300.51	-	338.40	-	320.65	-	262.05	-

-, no noteworthy finding; BMC, bone mineral content; BMD, bone mineral density; F, female; M, male; pQCT, peripheral quantitative computed tomography.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Biomechanical testing (Subset A and B)								
Week 25/26 (End of treatment period)								
Right Femur-3-point bending								
Peak load (N)	202.41$	160.40	193.19	158.07	178.47A	156.36	127.02C	128.44C
Stiffness (N/mm)	409	453	398	451	368	437	266C	372B
Modulus (MPa)	6525	-	6749	-	7194	-	8034B	-
AUC (N-mm)	169$	73	162	73	136	82	100D	56A
Right Femur - Femoral neck shear								
Peak load (N)	175.68%	142.86	170.81	145.43	163.96$	119.47B	[a]	[a]
Stiffness (N/mm)	523.35$	525.55	447.65	556.35	412.46$	445.64A	[a]	[a]
L4 Lumbar Vertebral Body - Compression								
Peak load (N)	481.24	430.43	476.96	440.91	445.86	386.21	304.74C$	353.88A
Apparent strength (MPa)	45.88	49.48	43.41	50.44	43.81	43.57	31.66C$	39.82B
Yield load (N)	435.01	412.60	439.46	413.62	409.80	366.72	290.50E$	333.84A
Yield stress (MPa)	41.42	47.44	40.07	47.32	40.25	41.33	30.22B$	37.64B
Stiffness (N/mm)	4832.62	4760.20	4723.69	5053.38	4724.72	4144.11	3466.88A$	3802.38
Modulus (MPa)	1657.26	1907.08	1528.10	1989.73	1653.38	1669.79	1273.44D$	1527.82
AUC (N-mm)	43.05	31.04	42.24	33.09	37.61	29.91	23.18F$	26.07
Toughness (MPa)	1.14	1.02	1.07	1.11	1.04	0.94	0.68C$	0.82A

-, no noteworthy findings; F, female; M, male; $, based on 9 animals; %, based on 8 animals.
a) No data are available.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Post-weaning	**10/10/20/6**	**10/10/20/6**	**9/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**10/10/20/9**	**8/10/20/9**
Week 31/32 (End of recovery)								
Right Femur - 3-point bending								
Peak load (N)	214.37	175.83	217.06	172.91	228.22	165.14	165.33B	141.73B
Ultimate stress (MPa)	-	229.83	-	222.31	-	212.49	-	202.16B
Stiffness (N/mm)	455	-	482	-	489	-	357B	-
Right Femur-Femoral neck shear								
Stiffness (N/mm)	626.20$	589.42	557.48	604.67	509.48$	532.78$	320.00@	339.09C &
L4 Lumbar Vertebral Body - Compression								
Peak load (N)	474.56	-	572.09A$#	-	511.28$	-	388.00	-
Yield load (N)	440.65	-	541.40A$#	-	486.76$	-	367.41	-
Yield stress (MPa)	39.46	-	47.85A$#	-	45.07$	-	35.86	-
AUC (N-mm)	37.76	-	45.23$	-	40.37$	-	27.43A	-
Histomorphometry								
Day 189 pp (Subset A)								
Growth plate thickness measurements (µm)	150	127	150	134	158	131	164A	146A

-, no noteworthy findings; F, female; M, male; $, based on 9 animals; &, based on 3 animals; @, based on 2 animals; #, in the absence of consistent changes in densitometry at that site at that dose level, differences were considered incidental.

A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).

表 2.6.7.7-3 BMN 111 の幼若ラットにおける 26 週間皮下投与毒性試験及び 6 週間回復性試験（続き）

Daily Dose (µg/kg/day)	0 (Control)		10		30		90	
Number of Animals (Subset A/B/C/D)	M	F	M	F	M	F	M	F
Post-weaning	10/10/20/6	10/10/20/6	9/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	10/10/20/9	8/10/20/9
Day 189 pp (Subset A)								
Static bone parameters – Proximal Tibia								
Bone volume (BV/TV [%])	16.7	-	14.9	-	13.3	-	4.8C	-
Mineralized volume (Md.V/TV [%])	16.7	-	14.9	-	13.3	-	4.7C	-
Osteoid volume (OV/BV (%))	0.11	-	0.10	-	0.12	-	1.07E	-
Trabecular thickness (Tb.Th [µm])	75	-	79	-	69	-	58E	-
Trabecular separation (Tb.Sp [µm])	484	-	476	-	472	-	1317C	-
Trabecular number (Tb.N [mm^{-1}])	2.23	-	1.87	-	1.94	-	0.80C	-
Osteoid surface (OS/BS [%])	21.9	-	19.9	-	20.9	-	34.1B	-
Osteoblast surface (Ob.S/BS [%])	21.6	-	19.8	-	20.7	-	33.0B	-
Day 231 pp (Subset A)								
Static bone parameters – Proximal Tibia								
Bone volume (BV/TV [%])	14.4	-	17.1	-	15.3	-	7.1B	-
Mineralized volume (Md.V/TV [%])	14.3	-	17.1	-	15.3	-	7.1B	-
Osteoid volume (OV/BV [%])	0.06	-	0.10	-	0.05	-	0.26D	-

-, no noteworthy findings; F, female; M, male.
A, B, C: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunnett's test).
D, E, F: $p < 0.05$, $p < 0.01$, $p < 0.001$ (Significantly different from control group [Group 1] value, Dunn's test).

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験

Report Title: 28-Day Repeat-Dose Subcutaneous Injection Toxicity and Toxicokinetic Study of BMN 111 in Cynomolgus Monkeys with 7-Day Recovery

Species/Strain: Cynomolgus monkeys/*Macaca fascicularis*

Initial Age: 2-3 years

Date of First Dose: 17 May 2011 (males), 19 May 2011 (females)

Duration of Dosing: 28 days

Duration of Post-dose: 7 days

Method of Administration: SC

Vehicle/Formulation: 0.005 mol/L citrate buffer solution, pH 5.5 containing 5.25% (w/v) sucrose, 1.5% (w/v) mannitol, 0.727 mg/mL methionine, and 0.005% (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.

Study No.: [BMN111-11-019]

Location in CTD: 4.2.3.2

Test Article: BMN 111

GLP Compliance: Yes

NOAEL: 300 µg/kg/day

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20 (Low)**	**20 (Low)**	**90 (Mid)**	**90 (Mid)**	**300 (High)**	**300 (High)**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Toxicokinetics:								
Day 2:								
$AUC_{0\text{-}600m}$ (pg·min/mL)	NA	NA	173,981	36,738	584,163	734,463	4,782,214	4,879,861
C_{max} (pg/mL)	NA	NA	2803	1618	14,875	17,400	83,814	96,607
T_{max} (min)	NA	NA	5.00	5.00	5.00	10.0	15.0	15.0
$t_{1/2}$ (min)	NA	NA	29.1	NA	26.7	23.3	34.7	31.8
Day 28:								
$AUC_{0\text{-}600m}$ (pg·min/mL)	NA	NA	214,004	51,706	954,619	736,388	11,646,607	10,673,021
C_{max} (pg/mL)	NA	NA	3320	2034	18,813	16,600	132,071	144,357
T_{max} (min)	NA	NA	5.00	5.00	15.0	15.0	15.0	15.0
$t_{1/2}$ (min)	NA	NA	28.0	26.8	22.8	22.2	83.6	79.1

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Noteworthy Findings:								
Died or Sacrificed Moribund Animals (Dosing Phase)	0	0	0	0	0	0	0	0
Died or Sacrificed Moribund Animals (Recovery Phase)	0	0	0	0	0	0	0	0
Clinical Signs	-	-	-	-	-	-	-	-
Body Weights	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Electrocardiographic Measurements (Dosing Phase)[a]:								
Heart Rate (beats/minute)								
Dosing Day 1								
2 hours post-dose	131	134	-	-	-	-	42%**	33%*
3 hours post-dose	139	125	-	-	-	-	33%*	30%*
4 hours post-dose	131	137	-	-	-	-	29%	18%
5 hours post-dose	127	141	-	-	-	-	28%	9%
Dosing Day 8								
2 hours post-dose	133	133	-	-	-	-	14%	21%
3 hours post-dose	141	138	-	-	-	-	7%	13%
4 hours post-dose	130	138	-	-	-	-	13%	5%
5 hours post-dose	142	144	-	-	-	-	13%	3%

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Electrocardiographic Measurements (Dosing Phase) [a]:								
Heart Rate (beats/minute)								
Dosing Day 15								
2 hours post-dose	129	125	-	-	-	-	13%	22%
3 hours post-dose	126	120	-	-	-	-	15%	22%
4 hours post-dose	125	128	-	-	-	-	12%	16%
5 hours post-dose	126	132	-	-	-	-	3%	11%
Dosing Day 22								
2 hours post-dose	140	133	-	-	-	-	24%	17%
3 hours post-dose	130	130	-	-	-	-	16%	14%
4 hours post-dose	126	138	-	-	-	-	20%	8%
5 hours post-dose	136	137	-	-	-	-	13%	2%
cGMP (pmol/mL) [a]:								
Dosing Day 2								
30 minutes post-dose	4.68	4.58	-	-	618.80%*	708.73%*	1452.35%*	978.82%*
60 minutes post-dose	1.11	4.26	-	-	705.41%*	469.72%*	3782.88%*	669.95%*
Dosing Day 28								
30 minutes post-dose	3.55	5.53	-	-	607.89%*	461.84%*	859.72%*	715.73%*
60 minutes post-dose	3.92	6.86	-	-	405.36%*	257.00%*	622.19%*	460.06%*

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
CTX-II (pg/mL) [a]:								
Dosing Day 29	123.60	95.24	-	-	-	-	175.57%*	81.04%
Recovery Day 7	144.21	145.22	NA	NA	NA	NA	184.31%*	55.49%
Bone Measurements (Dosing Phase) [a]:								
Growth Plate								
Multiplication Area (mm^2)	5.017	3.341	-	-	42.5%	67.8%*	67.7%	52.5%*
Multiplication Height (µm)	236.032	181.521	-	-	50.2%*	70.4%*	90.6%*	48.0%*
Hypertrophy Area (mm^2)	1.960	1.320	-	-	217.8%	293.8%*	242.6%	272.2%*
Hypertrophy Height (µm)	93.150	71.202	-	-	242.5%	311.5%*	282.9%	279.6%*
Sum of All Zones at the Growth Plate								
Area (mm^2)	-	8.545	-	-	-	71.2%*	-	66.5%*
Height (µm)	679.061	458.062	-	-	54.8%*	79.4%*	64.1%*	68.8%*
Bone Measurements (Recovery Phase) [a]:								
Growth Plate								
Multiplication Area (mm^2)	-	3.096	NA	NA	NA	NA	-	89.3%*
Multiplication Height (µm)	200.770	170.781	NA	NA	NA	NA	44.5%*	83.9%*
Hypertrophy Area (mm^2)	-	-	NA	NA	NA	NA	-	-
Hypertrophy Height (µm)	-	-	NA	NA	NA	NA	-	-
Sum of All Zones at the Growth Plate								
Area (mm^2)	-	7.961	NA	NA	NA	NA	-	56.1%*
Height (µm)	-	429.853	NA	NA	NA	NA	-	55.4%*

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Femur Bone Histology (Recovery Phase)[b]:								
Disorganized, Femur, Physis, Proliferative Zone								
Minimal	0	0	NA	NA	NA	NA	1	1
Thickness Increased, Femur, Physis, Proliferative Zone								
Minimal	0	0	NA	NA	NA	NA	0	3
Disorganized, Femur, Physis, Hypertrophic/Calcified Zone								
Minimal	0	0	NA	NA	NA	NA	1	2
Thickness Increased, Femur, Physis, Hypertrophic/Calcified Zone								
Minimal	0	0	NA	NA	NA	NA	1	2
Mild	0	0	NA	NA	NA	NA	0	1
Vascular Invasion Decreased, Femur, Primary Spongiosa								
Minimal	0	0	NA	NA	NA	NA	0	1

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (μg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Organ Weights	-	-	-	-	-	-	-	-
Histopathology (Dosing Phase) [b]:								
No. Examined	4	4	4	4	4	4	4	4
Sternum bone:								
Increased Thickness, Growth Plate								
Minimal	0	0	3	2	1	4	1	3
Slight	0	0	1	2	3	0	3	1
Subcutan Site A:								
Infiltrate, Lymphocyte/Macrophage								
Minimal	1	1	1	1	2	2	4	1
Infiltrate, Neutrophil								
Minimal	0	1	0	1	0	0	0	0
Slight	0	0	0	0	0	1	0	0
Infiltrate, Eosinophil								
Minimal	1	1	0	0	1	3	2	1
Inflammation, Granulomatous								
Minimal	0	0	0	0	1	0	0	0
Fibroplasia								
Minimal	0	2	1	0	1	0	0	1
Slight	1	0	0	0	0	0	0	0
Hemorrhage								
Minimal	0	0	0	0	0	1	0	0
Edema								
Minimal	0	0	0	1	0	0	0	0

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Organ Weights	-	-	-	-	-	-	-	-
Histopathology (Dosing Phase) [b]:								
No. Examined	4	4	4	4	4	4	4	4
Subcutan Site B:								
Infiltrate, Lymphocyte/Macrophage								
Minimal	0	1	3	0	3	1	3	3
Slight	0	0	0	0	0	0	1	0
Infiltrate, Neutrophil								
Minimal	1	2	1	1	1	1	1	0
Slight	0	0	0	0	0	1	1	1
Infiltrate, Eosinophil								
Minimal	0	0	1	0	1	2	1	0
Slight	0	0	0	0	0	0	1	1
Inflammation, Granulomatous								
Minimal	0	1	0	0	0	0	0	0
Fibroplasia								
Minimal	1	1	1	0	0	0	1	0
Hemorrhage								
Minimal	0	0	0	0	1	1	0	0
Edema								
Minimal	0	0	0	0	0	0	0	1
Slight	0	0	0	0	0	0	1	0

表 2.6.7.7-4 BMN 111 のカニクイザルにおける 28 日間反復皮下投与毒性・トキシコキネティクス試験及び 7 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20 (Low)	20 (Low)	90 (Mid)	90 (Mid)	300 (High)	300 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Recovery Phase) [b]:								
No. Examined	3	3	0	0	0	0	3	3
Sternum bone:								
Increased Thickness, Growth Plate								
Minimal	0	0	NA	NA	NA	NA	3	3
Subcutan Site A:								
Infiltrate, Lymphocyte/Macrophage								
Minimal	0	0	NA	NA	NA	NA	1	0
Fibroplasia								
Minimal	1	0	NA	NA	NA	NA	0	0
Regeneration, Panniculus Muscle								
Minimal	1	0	NA	NA	NA	NA	0	0
Subcutan Site B:								
Infiltrate, Lymphocyte/Macrophage								
Minimal	0	0	NA	NA	NA	NA	0	1
Inflammation, Granulomatous								
Minimal	0	0	NA	NA	NA	NA	1	0
Fibroplasia								
Minimal	0	0	NA	NA	NA	NA	1	0

-, no noteworthy findings; $AUC_{0\text{-}600m}$, area under the plasma concentration-time curve from minute 0 to minute 600; cGMP, cyclic guanosine monophosphate; C_{max}, maximum observed plasma concentration; CTX-II, C-terminal telopeptide of type II collagen; GLP, Good Laboratory Practice; NA, not applicable; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; $t_{1/2}$, elimination half-life; T_{max}, time to peak plasma concentration.

* $p \leq 0.05$ Statistical significance is based on actual data (not on the percent differences).

** $p \leq 0.01$ Statistical significance is based on actual data (not on the percent differences).

a) For controls, group means are shown. For treated groups, percent difference from controls is shown.

b) These values represent the number of incidences that each was observed.

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験

Report Title: 26-Week Repeat-Dose Toxicity and Toxicokinetic Study of Subcutaneous Administration of BMN 111 in Cynomolgus Monkeys with a 28-Day Recovery

Species/Strain: Cynomolgus monkeys/*Macaca fascicularis*

Initial Age: 2-3 years

Date of First Dose: 05 July 2011 (males), 12 July 2011 (females)

Duration of Dosing: 26 weeks

Duration of Post-dose: 28 days

Method of Administration: SC

Vehicle/Formulation: 0.005 mol/L citrate buffer solution, pH 5.5 containing 5.8% (w/v) trehalose dihydrate, 1.5% (w/v) mannitol, 0.727 mg/mL methionine, and 0.005% (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.

Study No. [BMN111-11-035]

Location in CTD: 4.2.3.2

Test Article: BMN 111

GLP Compliance: Yes

NOAEL: 90 µg/kg

Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
TK [a]:								
Day 1:								
AUC_{0-t} (pg·min/mL)	NA	NA	177,306	NC	1,210,900	849,038	5,670,936	2,898,932
Day 85:								
AUC_{0-t} (pg·min/mL)	NA	NA	52,663	NC	1,906,966	675,250	18,290,136	19,089,486
Day 176:								
AUC_{0-t} (pg·min/mL)	NA	NA	39,100	NC	574,854	426,156	4,081,291	14,867,791
Noteworthy Findings:								
Died or Sacrificed Moribund-Toxicity Animals (Dosing Phase)	0	0	0	0	0	0	0	0
Died or Sacrificed Moribund-Toxicity Animals (Recovery Phase)	0	0	NA	NA	NA	NA	0	0

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Body Weight Change (Dosing Phase):								
Days 1 - 183 (g)	-	-	-	-	-	-	-	-
Body Weight Change (Recovery Phase):								
Dosing Day 183 – Recovery Day 28 (g)	-	-	-	-	-	-	-	-
Clinical Signs (Dosing Phase) [b]:								
Limited Use, Hips	-	-	-	-	-	-	3	1
Decreased Range of Motion, Hind Legs	-	-	-	-	-	-	1	-
Clinical Signs (Recovery Phase) [b]:								
Limited Use, Hips	-	-	-	-	-	-	2	1
Food Consumption (Dosing and Recovery Phases)	-	-	-	-	-	-	-	-
Clinical Pathology (Dosing and Recovery Phases)	-	-	-	-	-	-	-	-
Organ Weights (Dosing and Recovery Phases)	-	-	-	-	-	-	-	-
Macroscopic Observations (Dosing Phase):								
No. Examined	4	4	4	4	4	4	4	4
Femur, Proximal end								
Abnormal Shape	0	0	0	0	0	0	1	0
Macroscopic Observations (Recovery Phase):	-	-	-	-	-	-	-	-
No. Examined	3	3	0	0	0	0	3	3
Histopathology (Dosing Phase) [b]:								
No. Examined	4	4	4	4	4	4	4	4
Sternum								
Growth Plate Thickness, Increased								
Minimal	0	0	2	1	3	4	2	4
Slight	0	0	0	0	1	0	2	0

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20	20	90	90	300	300
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Recovery Phase) [b]:	-	-	-	-	-	-	-	-
No. Examined	3	3	0	0	0	0	3	3
Tibia, Femur, and Humerus Lengths (Week 13 to pre-dose phase):								
Tibia, Medial	21.38	5.32	-	-	-	20.75*	36.18*	21.73*
Tibia, Central	19.70	7.26	-	-	28.85*	23.71*	33.55*	23.82*
Tibia, Lateral	17.01	8.28	-	-	26.18*	22.81*	29.92*	22.19*
Femur, Medial	9.38	17.74	-	-	-	-	-	37.27*
Femur, Central	7.95	15.95	-	-	-	-	-	-
Femur, Lateral	9.90	16.41	-	-	-	-	-	-
Humerus Medial	9.85	11.96	-	-	19.91*	-	25.70*	-
Humerus, Central	16.59	13.75	-	-	26.55*	22.90*	32.97*	22.75*
Humerus, Lateral	11.96	12.01	-	-	22.67*	-	29.49*	-
Tibia, Femur, and Humerus Lengths (Week 25 to pre-dose phase):								
Tibia, Medial	16.16	7.85	-	-	-	18.15*	29.76*	23.18*
Tibia, Central	16.87	9.54	-	-	-	20.11*	29.66*	23.32*
Tibia, Lateral	16.13	9.66	-	-	-	19.45*	26.87*	21.60*
Femur, Medial	12.27	21.09	-	-	-	-	-	-
Femur, Central	10.89	19.48	-	-	-	-	-	-
Femur, Lateral	12.58	18.25	-	-	-	-	-	-
Humerus Medial	9.02	12.32	-	-	18.60*	-	21.93*	-
Humerus, Central	13.92	13.47	-	-	23.26*	-	26.70*	-
Humerus, Lateral	12.85	12.92	-	-	22.11*	-	27.25*	-

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Proximal Tibia Growth Plate:								
No. Examined	7	7	4	4	4	4	7	7
Growth Plate Height – Central (mm)								
Week 13	0.34	0.26	0.48	0.65	1.00*	0.43	0.83*	0.67*
Week 25	0.17	0.24	0.23	0.48	0.83*	0.43	0.87*	0.76*
Bone Mineral Content and Bone Mineral Density	-	-	-	-	-	-	-	-

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
BioMarkers [c]:								
P1NP (µg/L) - Day 85	1690.12	1531.01	-	-	+19.4%	+18.6%	+34.9%	+40.7%
P1NP (µg/L) - Day 176	-	1254.84	-	-	-	+19.7%	-	+57.6%
P1NP (µg/L) - Day 183	-	1081.25	-	-	-	+25.5%	-	+60.9%
BSAP (UL) - Day 85	379.13	322.49	-	-	-	+36.9%	+35.2%	+38.2%
BSAP (UL) - Day 176	448.08	-	-	-	-	-	+35.2%	-
BSAP (UL) - Day 183	-	299.96	-	-	-	+20.7%	-	+27.6%
Osteocalcin (ng/mL)	-	-	-	-	-	-	-	-
CTX-II (pg/mL) - Day 85	156.24	130.57	-	-	+52.8%	+82.4%*	+88.3%*	+62.1%*
CTX-II (pg/mL) - Day 176	182.55	127.07	-	-	-	+29.4%	+41.5%	+29.3%
CTX-II (pg/mL) - Day 183	-	104.93	-	-	-	+31.0%	-	+46.4%
NTx (nmol BCE) – Day 85	144.09	-	+48.2%*	-	+40.6%*	-	+46.5%*	-
Femur and Lumbar Vertebrae Mechanical Strength	-	-	-	-	-	-	-	-
Lumbar Vertebrae, Foramen Magnum, and Skull Measurements	-	-	-	-	-	-	-	-
Femur Histopathology (Dosing Phase) [b]:								
No. Examined	4	4	4	4	4	4	4	4
Femur, Physis, Proliferative Zone, Disorganized								
Minimal	0	0	0	0	1	0	1	3
Mild	0	0	0	0	0	1	0	0
Femur, Physis, Proliferative Zone, Thickness Increased								
Minimal	0	0	2	3	3	2	1	1
Mild	0	0	2	0	1	0	3	2
Moderate	0	0	0	0	0	1	0	1

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Femur Histopathology (Dosing Phase) [b]**:**								
No. Examined	4	4	4	4	4	4	4	4
Femur, Physis, Hypertrophic/Calcified Zone, Disorganized								
Mild	0	0	0	0	1	1	0	0
Femur, Physis, Hypertrophic/Calcified Zone, Thickness Increased								
Minimal	0	0	3	4	3	3	2	1
Mild	0	0	0	0	1	0	2	3
Marked	0	0	0	0	0	1	0	0
Femur, Primary Spongiosa, Thickness Increased								
Minimal	0	0	3	2	3	2	1	2
Mild	0	0	0	0	0	1	3	2
Femur Histopathology (Recovery Phase) [b]**:**								
No. Examined	3	3	0	0	0	0	3	3
Femur, Physis, Proliferative Zone, Thickness Increased								
Minimal	0	0	NA	NA	NA	NA	2	0
Femur and Parietal Bone Histomorphometry:								
Growth Plate, Area (mm^2) - Day 183	3.26	2.31	+5.5%	+37.7%	+16.6%	+96.0%	+46.3%	+121.2%
Growth Plate, Height (µm) - Day 183	160.86	110.24	-	+28.2%	+1.5%	+84.5%	+21.4%	+104.1%
Growth Plate, Area (zones sum; mm^2) - Day 183	10.91	8.32	+13.4%	-	+32.1%*	-	+29.2%*	+41.6%
Parietal bone thickness (µm)	-	-	-	-	-	-	-	-
Bone volume/tissue volume (%)	-	-	-	-	-	-	-	-

表 2.6.7.7-5 BMN 111 のカニクイザルにおける 26 週間反復皮下投与毒性・トキシコキネティクス試験及び 28 日間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	20	20	90	90	300	300
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Cyclic Guanosine Monophosphate Analysis [d]:								
Week 13 - 30 min post-dose (pmol/mL)	-	-	-	-	-	-	+31.291	+32.632
Week 13 - 60 min post-dose (pmol/mL)	-	-	-	-	-	-	+41.393	+27.205
Week 26 - 30 min post-dose (pmol/mL)	-	-	-	-	-	+17.407	+21.864	+31.992
Week 26 - 60 min post-dose (pmol/mL)	-	-	-	-	-	-	+30.616	+26.388
Atrial Natriuretic Peptide/ Brain Natriuretic Peptide	-	-	-	-	-	-	-	-
Spermatogenesis Staging	-	NA	-	NA	-	NA	-	NA

-, no noteworthy findings; ADA, antidrug antibody; AUC, area under the plasma concentration-time curve; BSAP, bone-specific alkaline phosphatase; CTX-II, C-terminal telopeptide of type II collagen; GLP, Good Laboratory Practice; NA, not applicable; NC, not calculated; NOAEL, no-observed-adverse-effect level; NTx, cross linked N-telopeptide of type I collagen; P1NP, procollagen type 1 N-terminal propeptide ; SC, subcutaneous; TK, toxicokinetics.

* $p \leq 0.05$ Statistical significance is based on actual data.

a) Positive ADAs were detected in several animals at Day 85 and/or Day 176. The incidence was 7/8 at 20 µg/kg, 2/8 at 90 µg/kg, and 5/14 at 300 µg/kg.

b) These values represent the number of incidences that each was observed.

c) For controls, group means shown. For BMN 111 groups, percent difference from controls shown.

d) Change versus predose value.

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験

Report Title: 44-Week Repeat-Dose Toxicity and Toxicokinetic Study Following Daily Subcutaneous Administration of BMN 111 in Cynomolgus Monkeys with a 13-Week Recovery

Species/Strain: Cynomolgus monkeys/*Macaca fascicularis*

Duration of Dosing: 44 weeks

Study No. [BMN111-11-043]

Initial Age: 4-5 years

Duration of Post-dose: 13 weeks

Location in CTD: 4.2.3.2

Date of First Dose: 04 October 2011 (males), 18 October 2011 (females)

Method of Administration: SC

Test Article: BMN 111

Vehicle/Formulation: 0.005 mol/L citrate buffer solution, pH 5.5 containing 5.8% (w/v) trehalose dihydrate, 1.5% (w/v) mannitol, 0.727 mg/mL methionine, and 0.005% (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP

GLP Compliance: Yes

NOAEL: 25 µg/kg

Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**25 (Low)**	**25 (Low)**	**75 (Mid)**	**75 (Mid)**	**250 (High)**	**250 (High)**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
TK:								
Day 2								
C_{max} (pg/mL)	NA	NA	3600	1460	19,800	7550	76,600	82,200
$AUC_{0\text{-}6h}$ (pg·hr/mL)	NA	NA	1380	NA	17,200	5700	90,600	91,400
T_{max} (hr)	NA	NA	0.0830	0.0830	0.167	0.167	0.214	0.202
$t_{1/2}$ (hr)	NA	NA	NA	NA	0.535	0.421	0.532	0.492
Week 4								
C_{max} (pg/mL)	NA	NA	2350	2440	20,300	19,800	87,900	138,000
$AUC_{0\text{-}6h}$ (pg·hr/mL)	NA	NA	1000	1340	20,200	14,500	138,000	190,000
T_{max} (hr)	NA	NA	0.0830	0.139	0.250	0.167	0.226	0.286
$t_{1/2}$ (hr)	NA	NA	NA	NA	0.598	0.326	0.754	0.638

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**25 (Low)**	**25 (Low)**	**75 (Mid)**	**75 (Mid)**	**250 (High)**	**250 (High)**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
TK (cont'd):								
Week 12								
C_{max} (pg/mL)	NA	NA	1690	2040	30,600	9160	99,600	274,000
$AUC_{0\text{-}6h}$ (pg·hr/mL)	NA	NA	NA	1270	26,500	11,500	173,000	312,000
T_{max} (hr)	NA	NA	0.167	0.139	0.333	0.208	0.357	0.286
$t_{1/2}$ (hr)	NA	NA	NA	NA	0.621	0.780	0.711	0.725
Week 44								
C_{max} (pg/mL)	NA	NA	1170	NA	9,490	7490	154,000	201,000
$AUC_{0\text{-}6h}$ (pg·hr/mL)	NA	NA	NA	NA	11,000	6670	368,000	254,000
T_{max} (hr)	NA	NA	0.167	NA	0.438	0.167	0.398	0.293
$t_{1/2}$ (hr)	NA	NA	NA	NA	0.595	0.555	1.07	0.957
Noteworthy Findings:								
Died or Sacrificed Moribund Animals (Dosing Phase)	0	0	0	0	0	0	0	0
Died or Sacrificed Moribund Animals (Recovery Phase)	0	0	0	0	0	0	0	0
Clinical Signs (Dosing Phase) [c]								
Limited use of hindlimbs	0	0	0	0	2	0	5	2
Decreased range of motion	0	0	0	0	0	0	5	0
Hypoactive	0	1	0	0	1	0	3	0
Dorsal Recumbency	0	0	0	0	0	0	1	0
Lateral Recumbency	0	0	0	0	0	0	3	0

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Clinical Signs (Recovery Phase) [c]								
Limited use of hindlimbs	0	0	NA	NA	NA	NA	2	0
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Ophthalmic Examinations	-	-	-	-	-	-	-	-
Menstruation Assessment	NA	-	NA	-	NA	-	NA	-
BP Determination	-	-	-	-	-	-	-	-
Electrocardiogram Measurements (Dosing Phase) [a]								
PR (msec)	-	-	-	-	-	-	-	-
QRS (msec)	-	-	-	-	-	-	-	-
QT (msec)	-	-	-	-	-	-	-	-
QTc (msec)	-	-	-	-	-	-	-	-
HR (beats/minute)								
Day 1								
Block 1	134	131	-10.4%	-8.4%	-2.2%	+28.2%*	-10.4%	+29.0%**
Block 2	105	111	-1.9%	-16.2%	-1.9%	+19.8%	-13.3%	+13.5%
Day 19								
Block 1	130	134	-3.8%	-13.4%	-6.2%	+28.4%	-13.1%	+15.7%
Block 2	99	106	-4.0%	-9.4%	-4.0%	+25.5%	-11.1%	+7.5%
Day 80								
Block 1	131	129	-6.1%	-20.2%	-7.6%	+21.7%*	-3.1%	+22.5%*
Block 2	112	110	-8.0%	-13.6%	-8.9%	+17.3%	-8.9%	+7.3%

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Electrocardiogram Measurements (Dosing Phase)[a]								
HR(beats/minute)								
Day 164								
Block 1	134	142	-6.7%	-12.7%	-6.7%	+21.1%	+2.2%	+27.5%
Block 2	108	122	0.0%	-13.1%	-10.2%	+13.9%	+1.9%	+10.7%
Day 248								
Block 1	123	135	-2.4%	-8.1%	-12.2%	+11.1%	+15.4%	+27.4%*
Block 2	106	116	+0.9%	-12.1%	-9.4%	+11.2%	+5.7%	+12.1%
Day 305								
Block 1	122	146	-1.6%	-15.1%	-1.6%	+1.4%	+27.0%*	+32.2%*
Block 2	116	132	-6.9%	-13.6%	-12.1%	+1.5%	+10.3%	+9.8%
ECG Measurements (Recovery Phase)[a]								
PR (msec)	-	-	NA	NA	NA	NA	-	-
QRS (msec)	-	-	NA	NA	NA	NA	-	-
QT (msec)	-	-	NA	NA	NA	NA	-	-
QTc (msec)	-	-	NA	NA	NA	NA	-	-
HR (beats/minute)								
Day 17								
Block 1	124	134	NA	NA	NA	NA	-1.6%	+11.2%
Block 2	111	106	NA	NA	NA	NA	-0.9%	+13.2%

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
cGMP (pmol/mL) [a]								
Week 4								
Pre-dose	9.014	8.917	+7.4%	+27.3%	+3.7%	+13.6%	+3.5%	+31.8%
30 minutes post-dose	8.133	7.01	+55.7%	+110.7%	+264.4%	+556.6%	+461.6%	+706.3%
60 minutes post-dose	6.588	6.576	+108.8%	+145.0%	+561.7%	+338.8%	+658.4%	+604.9%
Week 12								
Pre-dose	11.439	10.525	-14.0%	+14.8%	-12.8%	+29.5%	+4.4%	+35.1%
30 minutes post-dose	9.416	8.807	+19.1%	+121.6%	+197.7%	+161.1%	+546%	+665.0%
60 minutes post-dose	7.431	6.462	+119.9%	+70.8%	+258.6%	+238.7%	+739.7%	+883.3%
Week 24								
Pre-dose	14.867	9.675	-47.3%	+59.9%	-18.1%	+5.4%	+95.7%	-8.6%
30 minutes post-dose	12.562	7.829	+20.3%	+66.4%	+91.9%	+120.9%	+225.7%	+762.0%
60 minutes post-dose	13.160	7.798	+9.1%	+33.7%	+70.3%	+71.8%	+442.3%	+679.5%
Week 44								
Predose	10.684	7.376	-21.0%	+14.8%	-27.6%	+26.7%	-9.1%	-14.3%
30 minutes post-dose	9.042	5.974	-2.0%	+38.9%	+95.2%	+214.2%	+432.8%	+793.8%
60 minutes post-dose	8.759	5.066	-16.9%	+26.4%	+95.6%	+139.4%	+392.2%	+1096.9%

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Antibody Analysis [b]								
Week 4	ND	ND	ND	ND	ND	D	ND	ND
Week 12	ND	ND	D	D	D	D	D	D
Week 24	ND	ND	D	D	D	ND	ND	ND
Week 44	ND	ND	ND	D	D	D	ND	ND
Atrial Natriuretic Peptide and Brain Natriuretic Peptide	-	-	-	-	-	-	-	-
Testosterone Concentration and Inhibin-B	-	NA	-	NA	-	NA	-	NA
Hematology	-	-	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-	-	-
Clinical Chemistry	-	-	-	-	-	-	-	-
Urinalysis - Day 304								
pH [a]	7.4	7.4	+2.7%	+2.7%	+5.4%	+1.4%	0.0%	-10.8%*
Urine Chemistry	-	-	-	-	-	-	-	-
Biomarker Analysis								
P1NP (µg/L)	-	-	-	-	-	-	-	-
NTx (nmol BCE)	-	-	-	-	-	-	-	-
Osteocalcin (ng/mL)	-	-	-	-	-	-	-	-
BSAP (U/L)	-	-	-	-	-	-	-	-
CTX-I	-	-	-	-	-	-	-	-

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Biomarker Analysis								
CTX-II (pg/mL) [a]								
Predose	86.62	29.39	+10.2%	+333.1%	+5.2%	+76.8%	-9.9%	+73.3%
Dosing Week 12	115.34	58.74	+14.7%	+2.0%	+88.0%	+16.3%	+69.1%	+55.8%
Dosing Week 24	124.22	44.46	+2.5%	+6.5%	+40.2%	+27.6%	+63.2%	+78.5%
Dosing Week 36	126.73	40.14	-29.3%	-6.1%	+25.8%	+33.9%	+51.0%	+59.5%*
Dosing Week 44	119.59	29.55	-2.7%	-2.8%	+60.7%	+72.7%	+53.4%	+82.2%*
Recovery	134.29	29.72	NA	NA	NA	NA	+11.5%	+83.0%
BMC/BMD	-	-	-	-	-	-	-	-
Bone Length (Dosing Phase - Day 308) [a]								
Tibia (mm)								
Medial	131.61	120.14	+1.8%	-2.7%	+9.2%	-1.6%	+6.5%	-0.1%
Central	130.39	118.87	+1.8%	-2.9%	+8.9%	-1.6%	+5.4%	+0.2%
Lateral	127.86	116.29	+1.8%	-3.2%	+7.8%	-2.0%	+3.9%	-0.3%
Femur (mm)								
Medial	146.03	132.4	+3.4%	-1.1%	+7.4%	-2.2%	-5.6%	-0.8%
Central	142.13	128.86	+2.9%	-0.9%	+7.3%	-2.1%	-5.3%	-0.9%
Lateral	145.60	131.37	+2.6%	-0.9%	+6.7%	-1.5%	-4.0%	-0.6%
Humerus (mm)								
Medial	122.34	114.63	+5.3%	+1.9%	+6.9%	-0.8%	+9.3%	+3.4%
Central	126.93	119.14	+5.2%	+1.7%	+6.7%	-1.1%	+8.8%	+2.2%
Lateral	126.69	119.23	+4.8%	+1.3%	+5.6%	-2.2%	+7.5%	+1.3%

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Bone Length (Recovery Phase-Day 354 - Males, Day 353-Females)[a]								
Tibia (mm)								
Medial	131.2	121.23	NA	NA	NA	NA	+12.1%	+3.1%
Central	129.37	119.5	NA	NA	NA	NA	+11.6%	+3.1%*
Lateral	126.63	117.37	NA	NA	NA	NA	+10.5%	+1.9%
Femur (mm)								
Medial	147.4	133.27	NA	NA	NA	NA	-0.8%	+3.6%
Central	143.67	130.27	NA	NA	NA	NA	-0.7%	+3.1%
Lateral	146.57	132.77	NA	NA	NA	NA	0.0%	+3.4%
Humerus (mm)								
Medial	122.93	115.37	NA	NA	NA	NA	+12.9%	+2.9%
Central	128	119.27	NA	NA	NA	NA	+12.5%	+2.7%
Lateral	126.43	119.77	NA	NA	NA	NA	+11.7%	+1.2%
Growth Plate Thickness (Dosing Phase - Day 308)								
Tibia (mm)								
Medial	0.17	0.00	0.08	0.05	0.38	0.13	0.39	0.19
Central	0.00	0.00	0.00	0.00	0.08	0.00	0.10	0.00
Lateral	0.00	0.00	0.00	0.00	0.18	0.00	0.27*	0.03
Growth Plate Thickness (Recovery Phase-Day 354 - Males, Day 353-Females)[c]								
Tibia (mm)								
Medial	0.20	0.00	NA	NA	NA	NA	0.17	0.07
Central	0.00	0.00	NA	NA	NA	NA	0.00	0.00
Lateral	0.00	0.00	NA	NA	NA	NA	0.00	0.00

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Bone Measurements								
L1-L4 vertebrae (mm)	-	-	-	-	-	-	-	-
Foramen Magnum (mm)	-	-	-	-	-	-	-	-
Skull (mm)	-	-	-	-	-	-	-	-
Femur Bend Strength	-	-	-	-	-	-	-	-
L3 Vertebrae Compression	-	-	-	-	-	-	-	-
Bone Histopathology (Dosing Phase - Day 309)[c]								
Femur, Epiphysis								
Thickness Increased, trabecular bone								
Minimal	1	0	2	1	1	1	0	2
Mild	1	0	2	1	2	1	2	0
Moderate	0	0	0	0	0	0	1	0
Femur, Metaphysis								
Thickness Increased, trabecular bone								
Minimal	0	0	0	0	2	0	1	3
Mild	1	0	1	0	1	1	1	0
Femur, Physis								
Closure Incomplete								
Minimal	0	0	0	1	0	0	0	1
Moderate	0	1	0	0	0	0	0	0
Proliferation, Chondrocyte, proliferative zone								
Minimal	2	0	1	1	3	2	2	2
Mild	0	0	0	0	1	0	2	1

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**25 (Low)**	**25 (Low)**	**75 (Mid)**	**75 (Mid)**	**250 (High)**	**250 (High)**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Bone Histopathology (Recovery Phase - Day 92) [c]								
Femur, Epiphysis								
Thickness Increased, trabecular bone								
Minimal	0	0	NA	NA	NA	NA	2	2
Mild	0	0	NA	NA	NA	NA	0	1
Femur, Metaphysis								
Thickness Increased, trabecular bone								
Moderate	0	0	NA	NA	NA	NA	0	1
Femur, Physis								
Closure Incomplete								
Minimal	0	0	NA	NA	NA	NA	1	0
Moderate	0	0	NA	NA	NA	NA	0	2
Proliferation, Chondrocyte, proliferative zone								
Minimal	0	0	NA	NA	NA	NA	3	3
Femur Histomorphometry (Dosing Phase - Day 309) [a]								
Growth Plate								
Multiplication Area (mm^2)	4.00	-	-6.5%	-	+6.3%	-	+72.0%*	-
Multiplication Height (µm)	160.26	-	-14.3%	-	-1.7%	-	+53.3%*	-
Hypertrophy Area (mm^2)	1.47	-	-40.8%	-	-8.2%	-	+68.7%	-
Hypertrophy Height (µm)	60.00	-	-40.0%	-	-13.5%	-	+54.5%	-
Sum of All Zones at the Growth Plate								
Area (mm^2)	11.10	-	-16.8%	-	+6.8%	-	+62.7%*	-
Height (µm)	409.36	-	-23.4%	-	-9.5%	-	+38.3%*	-

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**25 (Low)**	**25 (Low)**	**75 (Mid)**	**75 (Mid)**	**250 (High)**	**250 (High)**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Femur Histomorphometry (Recovery Phase - Day 400) [a]								
Growth Plate								
Multiplication Area (mm^2)	4.36	NA	NA	NA	NA	NA	-2.5%	NA
Multiplication Height (µm)	181.22	NA	NA	NA	NA	NA	-20.2%	NA
Hypertrophy Area (mm^2)	1.18	NA	NA	NA	NA	NA	-53.4%	NA
Hypertrophy Height (µm)	53.45	NA	NA	NA	NA	NA	-44.8%	NA
Sum of All Zones at the Growth Plate								
Area (mm^2)	11.74	NA	NA	NA	NA	NA	-20.3%	NA
Height (µm)	456.16	NA	NA	NA	NA	NA	-36.0%*	NA
Calvaria Histomorphometry	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Macroscopic Observations (Dosing Phase)								
Femur								
Abnormal shape	0	0	0	0	0	0	1	1
Depressed area	0	0	0	0	1	0	2	0
Raised Area	0	0	0	0	1	0	3	2
Fracture	0	0	0	0	0	0	2	0
Thickened joint capsule	0	0	0	0	0	0	1	0
Bone, Other (pelvis, tibia, patella, humerus, scapula, and/or ulna)								
Abnormal shape	0	0	0	0	0	0	1	0
Depressed area	0	0	0	0	1	0	2	0
Raised Area	0	0	0	0	0	0	0	1
Shallow acetabulum	0	0	0	0	0	0	2	0
Luxation	0	0	0	0	0	0	0	1

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Macroscopic Observations (Recovery Phase) [c]								
Femur								
Depressed area (articular cartilage erosion)	0	0	NA	NA	NA	NA	2	0
Raised Area (periarticular bone growth)	0	0	NA	NA	NA	NA	2	0
Bone, Other (pelvis and/or tibia)								
Depressed area	0	0	NA	NA	NA	NA	2	0
Histopathology (Dosing Phase) [c]								
Number Examined	1	1	0	0	1	0	2	1
Bone, Other (pelvis, tibia, humerus, scapula, and/or tibia)								
Increased Thickness, Growth Plate								
Slight	0	0	0	0	0	0	2	0
Moderate	0	0	0	0	0	0	0	1
Erosion, Articular Cartilage								
Minimal	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	1	0	2	0
Exostosis								
Minimal	0	0	0	0	0	0	0	1
Fracture								
Minimal	0	0	0	0	0	0	1	0
Fibrosis, Joint Capsule								
Moderate	0	0	0	0	1	0	1	0
Marked	0	0	0	0	0	0	1	0
Hyperplasia, Synovium								
Slight	0	0	0	0	1	0	0	0

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Dosing Phase)(cont'd) [c]								
Number Examined	4	4	4	4	4	4	4	4
Sternum								
Increased Thickness, Growth Plate								
Minimal	0	0	0	4	0	4	0	4
Subcutaneous								
Injection Site, A								
Fibrosis								
Minimal	1	0	2	0	1	1	1	0
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	1
Granuloma, hair shaft								
Minimal	0	0	0	0	0	1	0	0
Hemorrhage								
Minimal	0	0	0	0	0	1	0	0
Slight	0	0	0	0	0	0	0	2
Infiltrate, eosinophils								
Minimal	0	0	0	1	0	1	0	1
Infiltrate, mononuclear cell								
Minimal	1	0	2	2	3	2	2	2
Slight	0	0	0	0	0	1	1	1
Moderate	0	0	0	0	0	0	0	1
Inflammation, acute								
Minimal	0	0	0	0	0	1	0	0

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Dosing Phase)(cont'd) [c]								
Number Examined	4	4	4	4	4	4	4	4
Subcutaneous								
Injection Site, B								
Fibrosis								
Minimal	0	1	2	2	1	1	1	1
Slight	0	0	0	0	0	0	1	2
Granuloma, hair shaft								
Minimal	0	1	1	0	0	0	1	0
Hemorrhage								
Minimal	0	0	0	0	1	0	0	2
Slight	0	0	0	0	0	0	1	0
Infiltrate, eosinophils								
Minimal	0	0	1	0	1	1	1	1
Infiltrate, mononuclear cell								
Minimal	1	0	3	3	3	3	1	3
Slight	1	0	1	0	0	0	2	1
Injection Site, C								
Fibrosis								
Minimal	0	0	0	1	2	0	0	0
Slight	0	0	0	0	0	1	0	1
Granuloma, hair shaft								
Minimal	0	0	1	0	0	0	0	1

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Dosing Phase)(cont'd) [c]								
Number Examined	4	4	4	4	4	4	4	4
Subcutaneous								
Injection Site, C								
Hemorrhage								
Minimal	1	0	0	1	0	0	0	0
Slight	0	0	0	0	1	0	0	0
Infiltrate, eosinophils								
Minimal	0	0	1	0	1	0	2	1
Infiltrate, mononuclear cell								
Minimal	1	0	3	1	3	2	3	1
Slight	0	0	0	0	0	1	1	2
Injection Site, D								
Fibrosis								
Minimal	0	0	0	2	0	2	0	1
Slight	0	1	0	0	1	1	0	1
Granuloma, hair shaft								
Minimal	0	0	0	0	0	1	0	0
Hemorrhage								
Minimal	0	2	0	1	0	0	0	2
Slight	0	0	0	0	1	0	0	0
Infiltrate, eosinophils								
Minimal	0	0	0	1	1	0	1	1

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Dosing Phase)(cont'd) [c]								
Number Examined	4	4	4	4	4	4	4	4
Subcutaneous								
Injection Site, D								
Infiltrate, mononuclear cell								
Minimal	1	0	2	3	1	0	3	1
Slight	0	0	0	1	1	2	0	1
Injection Site, E								
Hemorrhage								
Minimal	0	0	1	0	0	0	1	1
Slight	1	0	0	0	1	1	0	0
Infiltrate, mononuclear cell								
Minimal	0	0	0	0	0	0	1	1
Inflammation, acute								
Minimal	2	0	1	0	2	1	1	2
Slight	1	0	0	0	0	0	0	0

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	0 (Control)	0 (Control)	25 (Low)	25 (Low)	75 (Mid)	75 (Mid)	250 (High)	250 (High)
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
Histopathology (Recovery Phase) [c]								
Number Examined	3	3	NA	NA	NA	NA	3	3
Subcutaneous								
Injection Site, A								
Infiltrate, mononuclear cell								
Minimal	0	0	NA	NA	NA	NA	0	1
Injection Site, B								
Infiltrate, mononuclear cell								
Minimal	0	1	NA	NA	NA	NA	1	2
Injection Site, C								
Infiltrate, mononuclear cell								
Minimal	0	1	NA	NA	NA	NA	1	0
Injection Site, D								
Fibrosis								
Minimal	0	0	NA	NA	NA	NA	1	0
Infiltrate, mononuclear cell								
Minimal	0	0	NA	NA	NA	NA	0	1
Male Reproductive Assessment	-	NA	-	NA	-	NA	-	NA
Staging of Spermatogenesis	-	NA	-	NA	-	NA	-	NA

表 2.6.7.7-6 BMN 111 のカニクイザルにおける 44 週間反復皮下投与（連日）毒性・トキシコキネティクス試験及び 13 週間回復性試験（続き）

-, no noteworthy findings; $AUC_{0\text{-}6h}$, area under the plasma concentration-time curve from time 0 to 6 hours; BSAP, bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; BP, blood pressure; cGMP, cyclic guanosine monophosphate; C_{max}, maximum observed plasma concentration; CTX-I, C-terminal telopeptide of type I collagen; CTX-II, C-terminal telopeptide of type II collagen; D, detected; ECG, electrocardiogram; GLP, Good Laboratory Practice; HR, heart rate; NA, not applicable; ND, not detected; NTx, cross linked N-telopeptide of type I collagen; P1NP, procollagen type 1 N-terminal propeptide; SC, subcutaneous; $t_{1/2}$, elimination half-life; T_{max}, time to peak plasma concentration; TK, toxicokinetics.

* $p \leq 0.05$ Statistical significance based on actual data.

** $p \leq 0.01$ Statistical significance based on actual data.

a) For controls, group means shown. For BMN 111 groups, percent difference from controls shown.

b) No antibodies to BMN 111 detected in controls. Incidence of animals testing positive for anti-BMN 111 antibodies was low at Week 4. Incidence of animals testing positive for anti-BMN 111 antibodies increased as study went on, with increasing incidence at Weeks 12 and 24, and with the majority of animals observed with an immune response by Week 44.

c) These values represent the number of incidences that each was observed.

2.6.7.8 *In Vitro* 遺伝毒性試験

In vitro 遺伝毒性試験は実施しなかった。

2.6.7.9 *In Vivo* 遺伝毒性試験

In vivo 遺伝毒性試験は実施しなかった。

2.6.7.10 がん原性試験

がん原性試験は実施しなかった。

2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

表 2.6.7.11-1 生殖発生毒性試験：重要な試験以外の試験

Test Article: BMN 111

Test System	Method of Administration	Duration, Administration Schedule (Number per Group)	Doses (µg/kg)	Noteworthy Findings	Study/Report Number
Rabbit, Hra: (NZW) SPF	SC	Daily, GD 7-19 (8F/group)	0, 45, 135, 240	• Clinical effects limited to soft/liquid feces. • Treatment with 240 µg/kg had an effect on embryo-fetal viability and fetal weights. • Higher incidence of resorption observed in the 240 µg/kg group. • Average number of resorptions for 240 µg/kg group was increased. • Percent post-implantation loss for the 240 µg/kg group was increased, but was within historical control ranges. • A dose of 240 µg/kg was selected for the definitive embryo-fetal toxicity study (BMN111-14-081).	[BMN111-14-055]

F, female; GD, gestation day; NZW, New Zealand White; SC, subcutaneous; SPF, specific pathogen-free.

2.6.7.12 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

表 2.6.7.12-1 BMN 111 のラットにおける受胎能及び着床までの初期胚発生に関する皮下投与試験

Report Title: Study of Fertility and Early Embryonic Development to Implantation of BMN 111 Administered by Subcutaneous Injection in Rats

Species/Strain: Rat/Sprague Dawley

Duration of Dosing: Males: 4 weeks prior to mating
Females: 15 days prior to mating through day 7 of gestation

Study No.: [BMN111-14-060]

Location in CTD: 4.2.3.5.1

Initial Age: 71 days male, 66 days females

Day of Mating: Day 0

Design similar to ICH 4.1.1: Yes

Date of First Dose: 23 Dec 2014

Method of Administration: SC

Test Article: BMN 111

Day of C-Section: Day 13 of gestation

Vehicle/Formulation: BMN 111 vehicle control solution 2 (0.005 mol/L citrate buffer solution, pH 5.5 +/- 0.2)

GLP Compliance: Yes

The No Observed Adverse Effect Level (NOAEL): F_0 males: 90 µg/kg, F_0 females: 90 µg/kg, F_1 Litters: 540 µg/kg

Daily Dose (µg/kg)		0 (Vehicle)	90	270	540
Males	TK: AUC_{0-t} (ng·min/mL) Day 1/Day 50	NA	196/406	1490/2660	2620/4250
	No. Evaluated	25	25	25	25
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations: Testes/epididymides, small	1	1	2	2
	Body Weight (%) [a]	463.9	99.4	95.3*	94.5*
	Food Consumption (%) [a]	27.9	100.0	97.8	98.2
	Mean No. Days Prior to Mating	1.8	2.2	3.4	4.7*
	No. of Males that Mated	25	25	23	22
	No. of Fertile Males	22	21	22	20

AUC, area under the plasma concentration-time curve; -, no noteworthy findings; NA, not applicable; SC, subcutaneous; TK, toxicokinetics.
* $p < 0.05$; Dunnett's Test. Statistical significance is based on actual data (not on the percent differences).
a) After 4 weeks of dosing. For controls, group means are shown. For BMN 111 groups, percent differences from controls are shown.

表 2.6.7.12-1 BMN 111 のラットにおける受胎能及び着床までの初期胚発生に関する皮下投与試験（続き）

Daily Dose (µg/kg)		0 (Vehicle)	90	270	540
Females	TK: AUC_{0-t} (ng·min/mL) Day 1/Day 7 of gestation	-	91.7/617	352/854	1280/3000
	No. Evaluated	25	25	25	25
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations:				
	Premating:				
	Irregular Gait	0	0	3	12**
	Hunched Posture	0	0	2	8**
	Limited Use of Hindlimbs	0	0	2	3
	Gestation:				
	Hunched Posture	0	0	13*	22**
	Irregular Gait	0	0	4	18**
	Necropsy Observations	-	-	-	-
	Premating Body Weight g (%) [a]	257.7	100.0	99.7	99.1
	Gestation Body Weight g (%) [a]	314.7	101.0	99.4	99.4
	Premating Food Consumption g (%) [a]	17.8	100.6	98.3	97.8
	Gestation Food Consumption g (%) [a]	21.3	101.9	99.1	99.5
	Mean No. Estrous Cycles/14 days	3.1	3.2	3.3	3.2
	Mean No. Days Prior to Mating	1.8	2.2	3.6	5.2*
	No. of Females Sperm Positive	25	25	25	24
	No. of Pregnant Females	22	21	23	22
	No. Aborted or with Total Resorption of Litter	0	1	0	0
	Mean No. Corpora Lutea	15.5	14.6	14.6	14.8
	Mean No. Implantations	15.1	13.9	12.6	14.3
	Mean % Preimplantation Loss	2.0	7.5	14.8	3.2
	Mean No. Viable Conceptuses	14.6	13.3	12.0	13.8
	Mean No. Non-Viable Conceptuses	0.5	0.6	0.6	0.5
	Mean % Post-implantation Loss	3.6	8.1	5.4	3.5

表 2.6.7.12-1 BMN 111 のラットにおける受胎能及び着床までの初期胚発生に関する皮下投与試験（続き）

AUC, area under the plasma concentration-time curve; GLP, Good Laboratory Practice; -, no noteworthy findings; TK, toxicokinetics.
a) At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown.
* $p < 0.05$; **, $p < 0.01$; Dunnett's Test. Statistical significance is based on actual data (not on the percent differences).

2.6.7.13 生殖発生毒性試験：胚・胎児発生に関する試験

表 2.6.7.13-1 BMN 111 のラットにおける胚・胎児発生に関する皮下投与試験

Report Title: An Embryo-Fetal Development Study of BMN 111 Administered by Subcutaneous Injection in Rats

Species/Strain: Rat/Sprague Dawley
Initial Age: 67 to 72 days of age
Date of First Dose: 21 Dec 2014
Day of C-Section: Day 21 of gestation

Duration of Dosing: Days 6 to 17 of gestation
Day of Mating: Day 0
Method of Administration: SC
Vehicle/Formulation: BMN 111 vehicle control solution 2 (0.005 mol/L citrate buffer solution, pH 5.5 +/- 0.2) aqueous solution

Study No.: [BMN111-14-061]
Location in CTD: 4.2.3.5.2
Design similar to ICH 4.1.3: Yes
Test Article: BMN 111
GLP Compliance: Yes

The No Observed Adverse Effect Level (NOAEL): F_0 females: 540 µg/kg; F_1 Litters: 540 µg/kg
Special Features: TK

Daily Dose (µg/kg)		0 (Vehicle)	90	270	540
Dams/Does	TK: AUC_{0-t} (ng·min/mL) Day 6/Day 17 of gestation	NA	216/530	1170/1750	1520/3950
	No. Pregnant	24	25	25	24
	No. Died or Sacrificed Moribund	0[b]	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight (%)[a]	373.4	98.3	100.5	99.4
	Food Consumption (%)[a]	22.2	99.1	103.2	103.6
	Mean No. Corpora Lutea	12.6	12.3	13.2	12.8
	Mean No. Implantations	11.9	11.3	12.2	12.0
	Mean % Preimplantation Loss	4.1	8.9	7.6	5.8

AUC, area under the plasma concentration-time curve; GLP, Good Laboratory Practice; -, no noteworthy findings; NA, not applicable; SC, subcutaneous; SD, Sprague Dawley; TK, toxicokinetics.

a) End of dosing period. For controls, group means shown. For BMN 111, percent differences from controls shown. Statistical significance based on actual data.
b) Excludes Dam No. 5001, which delivered and was euthanized on Day 21 of gestation.

表 2.6.7.13-1 BMN 111 のラットにおける胚・胎児発生に関する皮下投与試験（続き）

Daily Dose (μg/kg)		0 (Vehicle)	90	270	540
Litters	No. Litters Evaluated	23	25	25	24
	No. Live Fetuses	258	272	290	277
	Mean No. Resorptions	0.7	0.4	0.6	0.4
	No. of Litters with Dead Fetuses	0	0	0	0
	Mean % Post-implantation Loss	5.6	3.7	5.1	3.9
	Mean Fetal Body Weight (g)	5.82	5.93	5.80	5.85
	Fetal Sex Ratios (% males)	45.9	46.3	48.5	45.6
	Fetal Anomalies:				
	Gross External	-	-	-	-
	Visceral Anomalies				
	Brain: Ventricles moderate dilation				
	No. Fetuses (%)	1 (0.8)	0	0	0
	No. Litters (%)	1 (4.3)	0	0	0
	Vessels: Interrupted Aortic Arch with Patent Ductus Arteriosis				
	No. Fetuses (%)	0	1 (0.8)	0	0
	No. Litters (%)	0	1 (4.0)	0	0
	Skeletal Anomalies				
	Skull: Zygomatic Incompletely ossified				
	No. Fetuses (%)	6 (4.4)	10 (6.8)	4 (2.7)	11 (7.6)
	No. Litters (%)	3 (13.0)	6 (24.0)	2 (8.0)	5 (20.8)
	Skull: Parietal Incompletely ossified				
	No. Fetuses (%)	2 (1.5)	0	0	3 (2.1)
	No. Litters (%)	1 (4.3)	0	0	3 (12.5)

表 2.6.7.13-1 BMN 111 のラットにおける胚・胎児発生に関する皮下投与試験（続き）

Daily Dose (µg/kg)		0 (Vehicle)	90	270	540
Litters	No. Litters Evaluated	23	25	25	24
	Skeletal Anomalies				
	Skull: Squamosal Incompletely ossified				
	No. Fetuses (%)	7 (5.2)	8 (5.5)	2 (1.3)	10 (6.9)
	No. Litters (%)	4 (17.4)	4 (16.0)	1 (4.0)	5 (20.8)
	Total Affected Fetuses (Litters)	13 (8)	15 (9)	12 (9)	19 (11)

-, no noteworthy findings.

表 2.6.7.13-2 BMN 111 のウサギにおける胚・胎児発生に関する皮下投与試験

Report Title: An Embryo-Fetal Development Study of BMN 111 by Subcutaneous Injection in Rabbits

Species/Strain: Rabbit/ Hra:(NZW)SPF

Duration of Dosing: Main: Days 7 to 19 of gestation
TK: Days 7 to 20 of gestation

Study No.: [BMN111-14-081]

Location in CTD: 4.2.3.5.2

Initial Age: 5-6 months of age

Day of Mating: Day 0

Design similar to ICH 4.1.3: Yes

Date of First Dose: 02 Feb 2015

Method of Administration: SC

Test Article: BMN 111

Day of C-Section: Day 29 of gestation

Vehicle/Formulation: BMN 111 vehicle control solution 2 (0.005 mol/L citrate buffer solution, pH 5.5 +/- 0.2) aqueous solution

GLP Compliance: Yes

The No Observed Adverse Effect Level (NOAEL): F_0 females: 240 µg/kg; F_1 Litters: 240 µg/kg

Special Features: TK/ fetal TK

Daily Dose (µg/kg)		0 (Vehicle)	45	135	240
Dams/Does	TK: AUC_{0-t} (ng·min/mL) Day 7/19	NA	7920/5950	27,100/24,900	60,300/58,000
	Fetal Plasma Concentration (ng/mL) Day 20	NA	LOQ	0.253	0.460
	No. Pregnant	20	19	19	19
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations				
	Injection site red/purple	++	++	++	++
	Ungroomed Coat	+	+	+	+
	Necropsy Observations	-	-	-	-
	Body Weight kg (%) [a]	3.44	101.5	100.0	100.6
	Food Consumption g (%) [a]	164.5	96.5	92.3	94.9
	Mean No. Corpora Lutea	10.1	9.9	10.4	10.3
	Mean No. Implantations	9.6	9.3	9.6	9.6
	Mean % Preimplantation Loss	5.3	6.4	7.2	7.2

AUC, area under the plasma concentration-time curve; GLP, Good Laboratory Practice; LOQ, limit of quantitation (LOQ, 0.100 ng/mL); +, Mild; ++, Moderate; -, no noteworthy findings; NA, not applicable; NZW, New Zealand White; SC, subcutaneous; SPF, specific pathogen-free; TK, toxicokinetics.

a) End of dosing period. For controls, group means shown. For BMN 111 groups, percent differences from controls shown. Statistical significance based on actual data.

表 2.6.7.13-2 BMN 111 のウサギにおける胚・胎児発生に関する皮下投与試験（続き）

Daily Dose (mg/kg)		0 (Vehicle)	45	135	240
Litters	No. Litters Evaluated	20	19	19	19
	No. Live Fetuses	178	172	177	178
	Mean No. Resorptions	0.6	0.2	0.3	0.2
	No. of Litters with Dead Fetuses	1	0	0	0
	Mean % Post-implantation Loss	7.7	2.2	3.4	2.4
	Mean Fetal Body Weight (g)	42.29	41.43	41.28	41.47
	Fetal Sex Ratios (% males)	49.2	55.1	51.0	50.8
	Fetal Anomalies:				
	Gross External	-	-	-	-
	Visceral Anomalies	-	-	-	-
	Skeletal Anomalies				
	Hyoid: Ala, Angulated				
	No. Fetuses (%)	2 (1.1)	5 (2.9)	0 (0.0)	7 (3.9)**
	No. Litters (%)	2 (10.0)	5 (26.3)	0 (0.0)	4 (21.0)
	Sternal Centra: Incompletely Ossified				
	No. Fetuses (%)	0 (0.0)	0 (0.0)	5 (2.8)**	0 (0.0)
	No. Litters (%)	0 (0.0)	0 (0.0)	3 (15.8)**	0 (0.0)
	Total Affected Fetuses (Litters)	14 (8)	12 (11)	11 (8)	13 (9)

-, no noteworthy findings.
* $p < 0.05$; ** $p < 0.01$; Fisher Exact Test.

2.6.7.14 生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

表 2.6.7.14-1 BMN 111 のラットにおける出生前及び出生後の発生並びに母体の機能に関する皮下投与試験

Report Title: A Subcutaneous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of BMN 111 in Rats, Including Postnatal Behavioral/Functional Evaluation

Species/Strain: Rat/Sprague Dawley

Duration of Dosing: Days 6 of gestation through Day 20 postpartum

Study No.: [BMN111-18-103]

Location in CTD: 4.2.3.5.3

Initial Age: 82 to 91 days of age

Day of Mating: Day 0

Design similar to ICH 4.1.2?: Yes

Date of First Dose: 12 Dec 2018

Method of Administration: SC

Test Article: BMN 111

Litters Not Culled

Vehicle/Formulation: BMN 111 vehicle control solution 2 (0.005 mol/L citrate buffer solution, pH 5.5 +/- 0.2)

GLP Compliance: Yes

The No Observed Adverse Effect Level (NOAEL): F_0 females: 540 µg/kg; F_1 males: 540 µg/kg; F_1 females: 540 µg/kg

Special Features: Postnatal Behavioral/Functional Evaluation

Daily Dose (µg/kg/day)		0 (Control)	90	270	540
F_0 Females:	TK: Concentration of BMN 111 (ng/mL)				
	GD 6 (Plasma)	-	0.00	0.00	0.00
	LD 14 (Plasma)	-	1.52	16.9	28.2
	LD 14 (Milk)	-	0.0904	0.299	0.896
	No. Pregnant	24	24	24	24
	No. Died or Sacrificed Moribund (Gestation)	0	1 [a]	0	0
	No. Aborted or with Total Res. of Litter	0	0	0	0
	Mean Duration of Gestation (days)	22.8	22.6	22.7	22.4
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Organ Weights	-	-	-	-
	Gestation Body Weight GD 21 (%) [b]	386.2 g	-0.08	+1.24	-1.55
	Lactation Body Weight LD 21 (%) [b]	318.6 g	+4.08	+4.02	+2.70
	Gestation Food Consumption GD 6-18 (%) [b]	71.7 g/animal	+0.56	-0.42	-0.42
	Gestation Food Consumption GD 18-21 (%) [b,c]	27.8 g/animal	0.00	+3.60	+2.52
	Lactation Food Consumption LD 1-14 (%) [b,d]	53.4 g/animal	+0.94	-0.94	-0.56

表 2.6.7.14-1 BMN 111 のラットにおける出生前及び出生後の発生並びに母体の機能に関する皮下投与試験（続き）

-, no noteworthy findings; GD, Gestation Day; GLP, Good Laboratory Practice; LD, Lactation Day; SC, subcutaneous; TK, toxicokinetics.
a) Rat 1130 was euthanized on GD 22 due to adverse clinical observations.
b) End of gestation or lactation. For controls, group means shown. For BMN 111 groups, percent differences from controls shown. Statistical significance based on actual data.
c) Excludes values for dams that were in the process of delivering or had delivered.
d) Because it is presumed that the pups begin to consume maternal food after Day 14 of lactation, maternal food consumption values were not tabulated on Days 14 to 21 of lactation.

表 2.6.7.14-1 BMN 111 のラットにおける出生前及び出生後の発生並びに母体の機能に関する皮下投与試験（続き）

Daily Dose (µg/kg/day)		0 (Control)	90	270	540
F_1 Litters: Preweaning	TK [a]				
	No. Litters Evaluated	24	23	24	24
	Mean No. of Implantations	13.1	13.2	13.0	13.0
	Mean No. Pups/Litter	12.5	12.6	12.3	12.4
	Mean No. Liveborn Pups/Litter	12.2	12.6*	12.3	12.4*
	No. of Litters with Stillborn Pups	4	0	0	0
	Total Litter Loss LDs 1-4 N [b]	0	0	0	0
	Total Litter Loss LDs 5-21 N [b]	0	0	0	0
	Mean Pup Weight/Litter LD 4 (g)	10.0	10.0	10.0	9.9
	Mean Pup Weight/Litter LD 21(g)	44.0	43.9	45.5	43.6
	Pup Sex Ratios (% males)	53.2	47.5	50.1	50.4
	Pup Clinical Observations	-	-	-	-
	Reflex and Physical Development	-	-	-	-
	Pup Necropsy Observations	-	-	-	-

-, no noteworthy findings; BQL, Below quantitation level; LD, Lactation Day; PND, Postnatal Day; TK, toxicokinetics.
* $p < 0.05$.
a) All individual pup concentrations of BMN 111 in plasma were BQL on PND 1 and PND 14. Individual pup concentrations of BMN 111 in milk (collected on PND 14 were BQL in all pups in 90 and 270 µg/kg/day groups, and in 3/4 pups in 540 µg/kg/day group. One pup in the 540 µg/kg/day group had a BMN 111 concentration of 0.137 ng/mL in milk collected on PND 14.
b) Excludes pups euthanized on PND 1 or PND 14 for blood collection.

表 2.6.7.14-1 BMN 111 のラットにおける出生前及び出生後の発生並びに母体の機能に関する皮下投与試験（続き）

Daily Dose (µg/kg/day)		0 (Control)	90	270	540
F_1 Males: Postweaning	No. Evaluated Postweaning	24	24	24	24
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Organ Weights	-	-	-	-
	Body Weight PND 113 (%)[a]	611.6 g	+0.26	+0.29	+2.55
	Body Weight Change PND 22-113 (g)[b]	+559.1	+561.0	+559.0	+576.5
	Food Consumption PND 22-92 (%)[c]	59.4 g/animal	-1.35	-1.52	+1.01
	Mean Age of Preputial Separation (days)	43.5	43.2	43.3	43.9
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.5	3.0	2.2	3.1
	No. of Males that Mated	24	21	23	24
	No. of Fertile Males	21	20	21	21

-, no noteworthy findings; PND, Postnatal Day.

a) End of postweaning period. For controls, group means shown. For BMN 111 groups, percent differences from controls shown. Statistical significance based on actual data.

b) From weaning to end of the postweaning period.

c) From weaning to cohabitation. Because food consumption values were recorded at weekly intervals, based on each rat's day postpartum, PND 92 was the last day in which the youngest rats had food consumption values recorded before cohabitation.

表 2.6.7.14-1 BMN 111 のラットにおける出生前及び出生後の発生並びに母体の機能に関する皮下投与試験（続き）

Daily Dose (µg/kg/day)		0 (Control)	90	270	540
F_1 Females: Postweaning	No. Evaluated	24	24	24	24
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Organ Weights	-	-	-	-
	Premating Body Weight PND 92 (%) [a]	305.9 g	0.00	+2.39	+1.14
	Premating Body Weight Change PND 22-92 (g) [b]	+255.8	+255.4	+261.2	+259.9
	Premating Food Consumption PND 22-92 (%) [a,b]	43.4 g/animal	-4.84	-2.30	-1.61
	Gestation Body Weight GD 14 (%) [a]	391.6 g	+1.17	+2.99	+1.07
	Gestation Body Weight Change GD 0-14 (g)	+79.2 g	+89.4	+86.4	+83.8
	Gestation Food Consumption GD 0-14 (%) [a]	26.9 g/animal	+5.58	+5.95	+4.83
	Mean Age of Vaginal Patency (days)	31.2	31.8	31.6	31.1
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. of Days Prior to Mating	2.5	3.4	2.2	3.1
	No. of Females Sperm Positive	24	22	22	23
	No. of Pregnant Females	21	21	22	21
	Mean No. Corpora Lutea	19.0	17.8	18.4	18.8
	Mean No. Implantations	16.9	16.5	17.3	16.3
	Mean % Preimplantation Loss	8.2	6.8	5.9	12.4
F_2 Litters	Mean No. Live Conceptus/Litter	16.2	15.6	16.5	15.7
	No. of Litters with Dead Conceptuses	10	12	12	8
	No. of Dead Conceptuses	15	19	16	12
	Mean % Post-implantation Loss	4.4	5.4	4.4	3.7

-, no noteworthy findings; GD, Gestation Day; PND, Postnatal Day.

a) End of premating or gestation period. For controls, group means shown. For BMN 111 groups, percent differences from controls shown. Statistical significance based on actual data.

b) From weaning to cohabitation. Because body weight and food consumption values were recorded at weekly intervals, based on each rat's day postpartum, PND Day 92 was the last day in which the youngest rats had body weight or food consumption values recorded before cohabitation.

2.6.7.15 新生児を用いた試験

新生児を用いた試験は実施しなかった。

2.6.7.16 局所刺激性試験

局所刺激性試験は実施しなかった。

2.6.7.17 その他の毒性試験

その他の毒性試験は実施しなかった。