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2.6.5 薬物動態試験

2.6.5.1 薬物動態試験： 一覧表

Type of Study	Test System	Method of Administration	Facility	Study Number	Location
Absorption					
Absorption after single dose	Rabbit	Ocular topical	[redacted]	[redacted]	4.2.2.2-1
Absorption after repeat dose	Rabbit	Ocular topical (7 days)	[redacted]	[redacted]	4.2.3.2-1
	Rabbit	Ocular topical (26 weeks)	[redacted]	[redacted]	4.2.3.2-3
	Monkey	Ocular topical (7 days)	[redacted]	[redacted]	4.2.3.2-5
	Monkey	Ocular topical (39 weeks)	[redacted]	[redacted]	4.2.3.2-8
	Rat	Intravenous (28 days)	[redacted]	[redacted]	4.2.3.2-10
	Dog	Intravenous (28 days)	[redacted]	[redacted]	4.2.3.2-12

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2.6.5.1 薬物動態試験： 一覧表（続き）

Type of Study	Test System	Method of Administration	Facility	Study Number	Location
Distribution					
Ocular distribution after single dose	Rabbit	Ocular topical	[redacted]	[redacted]	4.2.2.2-1
Ocular distribution after repeat dose	Rabbit	Ocular topical	[redacted]	[redacted]	4.2.2.3-1
Systemic distribution after single dose	Rat	Intravenous	[redacted]	[redacted]	4.2.2.3-2
Distribution *in vitro*	n/a	*In vitro* binding to human, beagle, rat plasma	[redacted]	[redacted]	4.2.2.3-3
	n/a	*In vitro* binding to melanin	[redacted]	[redacted]	4.2.2.3-4
Metabolism					
In vivo metabolism after single dose	Rabbit	Ocular topical	[redacted] Japan	[redacted]	4.2.2.4-1

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2.6.5.1 薬物動態試験： 一覧表（続き）

Type of Study	Test System	Method of Administration	Facility	Study Number	Location
In vitro Metabolism of AR-13324	n/a	*In vitro* Male and female dog, monkey, mouse, rat, rabbit, human liver microsomes Rat and human liver S9 fractions Rabbit, pig, dog, monkey, human corneas Rabbit, rat, dog, monkey, human plasma	[redacted]	[redacted]	4.2.2.4-2
CYP450 Data	n/a	*In vitro* Inhibition of CYP450 enzyme activity (screening study)	[redacted]	[redacted]	4.2.1.1-3
Excretion					
Urine and feces excretion after repeat dose	Rabbit	Ocular topical	[redacted]	[redacted]	4.2.2.3-1
Urine and feces excretion after single dose	Rat	Intravenous	[redacted]	[redacted]	4.2.2.3-2
Pharmacokinetic Drug Interactions					
None					

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2.6.5.2 分析方法及びバリデーション試験

Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Noteworthy Findings	Report Number
Rat/plasma	AR-13323, Netarsudil, AR-13503, and AR-13534	1.00–1000 ng/mL	LC-MS/MS/ Chiral column	All analytes unstable in whole blood at room temperature, but stable 2 h kept on ice. Stable for 6 h in plasma kept in ice. Validated for selectivity, sensitivity, calibration curve fitting, accuracy, precision, recovery, matrix factor, dilution, hemolysis effects, whole blood stability, and carryover. Analyte stability demonstrated for freeze/thaw, extract storage conditions and reinjection reproducibility. Long-term matrix stability was also established:105 days at -70°C. All analytes stable at -70°C for 281 days; AR-13324 and AR-13323 stable at -70°C for 435 days.	[redacted] Used in: [redacted] [redacted] Unvalidated method used in: [redacted] [redacted] (long-term stability)
Rabbit/plasma	AR-13323, Netarsudil, AR-13503, and AR-13534	1.00–1000 ng/mL	LC-MS/MS/ Chiral column	Stable for 2 h in whole blood kept on ice. Stable for 24 h in plasma kept in ice. Validated for selectivity, sensitivity, calibration curve fitting, accuracy, precision, recovery, matrix factor, dilution, hemolysis effects, whole blood stability, and carryover. Analyte stability demonstrated for freeze/thaw, extract storage conditions and reinjection reproducibility. Long-term matrix stability was also established: 42 days at -70°C.	[redacted] Used in: [redacted] [redacted] [redacted]

Confidential

2.6.5.2 分析方法及びバリデーション試験（続き）

Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Noteworthy Findings	Report Number
Rabbit/Plasma				All analytes stable at -70°C for 92 days; AR-13324 and AR-13323 stable at -70°C for 203 days.	[redacted] (long-term stability)
Dog/Plasma	AR-13323, Netarsudil, AR-13503, and AR-13534	1.00–1000 ng/mL	LC-MS/MS/ Chiral column	Not stable in whole blood at room temperature, but stable 1 h kept on ice. Stable for 24 h in plasma kept in ice. Validated for selectivity, sensitivity, calibration curve fitting, accuracy, precision, recovery, matrix factor, dilution, hemolysis effects, whole blood stability, and carryover. Analyte stability demonstrated for freeze/thaw, extract storage conditions and reinjection reproducibility. Long-term matrix stability was also established: 23 days at -20°C and 24 days at -70°C All analytes stable at -70°C for 317 days; AR-13324, AR-13503, and AR-13534 stable at -20°C for 242 days.	[redacted] Used in: [redacted] Unvalidated method used in: [redacted] [redacted] [redacted] (long-term stability)

Confidential

2.6.5.2 分析方法及びバリデーション試験（続き）

Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Noteworthy Findings	Report Number
Monkey/ Plasma	Netarsudil	0.100–100 ng/mL	LC-MS/MS	AR-13324 stable in plasma at least 24 h at room temperature, in whole blood at room temperature or on ice for at least 2 h. Method selective, linear, accurate, precise, and rugged. Analyte stability demonstrated for freeze/thaw, extract storage conditions and reinjection reproducibility. Long-term matrix stability was also established: 76 days at -20°C and at -70°C	[redacted] Used in: [redacted] [redacted]
Monkey/ Plasma	AR-13323, Netarsudil, AR-13503, and AR-13534	1.00–1000 ng/mL	LC-MS/MS/ Chiral column	All analytes not stable in whole blood at room temperature, but stable 2 h kept on ice. Stable for 16 h in plasma kept in ice. Validated for selectivity, sensitivity, calibration curve fitting, accuracy, precision, recovery, matrix factor, dilution, hemolysis effects, whole blood stability, and carryover. Analyte stability demonstrated for freeze/thaw, extract storage conditions and reinjection reproducibility. Long-term matrix stability was also established: 35 days at -20°C and 85 days at -70°C All analytes stable at -70°C for 192 days.	[redacted] Used in: [redacted] [redacted] [redacted] (long-term stability)

Confidential

2.6.5.2 分析方法及びバリデーション試験（続き）

Species/ Sample Matrix	Analytes	Calibration Range	Type of Assay	Noteworthy Findings	Report Number
Rabbit/ Cornea and Aqueous humor	Netarsudil AR-13503	0.1–25 ng/mL (Cornea) 0.2–50 ng/mL (Aqueous humor)	LC-MS/MS	Validated for selectivity, specificity, sensitivity, calibration curve fitting, accuracy, precision, carryover, matrix effect, recovery, reproducibility, and dilution. Analyte stability demonstrated for room temperature, freeze/thaw, processed sample and reinjection reproducibility. Long-term matrix stability was also established: 18 and 19 days at -80°C for cornea homogenate and aqueous humor, respectively.	[redacted]

Confidential

2.6.5.3 薬物動態試験： 吸収：点眼投与

2.6.5.3.1 ウサギ単回点眼

Test Article: ^{14}C-AR-13324

Study No.	[redacted]	Location: 4.2.2.2-1	
Title	Ocular Tissue Distribution Study of Total Radioactivity in Dutch-Belted Male Rabbits Following a Single Topical Ocular Administration of [^{14}C]AR-13324		
Species	Dutch Belted Rabbit	Method of Administration	Topical ocular dose to both eyes, single 35 µL/eye/dose
Gender (M/F) / Number of Animals	M / 3 (per each timepoint)	Dose	0.014 mg/animal
Feeding Conditions	Fed	Radionuclide	^{14}C
Vehicle/Formulation	0.02% ^{14}C-STN1013900 Ophthalmic Solution	Specific Activity	2146 MBq/mmol
Sampling Time	0.25, 0.5, 1, 4, 8, 24, 48 h post dosing		

Tissues/ Time (h)	Radioactivity Concentration (ng eq./g) [1]							PK Parameter [2]			
	0.25	0.5	1	4	8	24	48	T_{max} (h)	C_{max} (ng eq./g)	$T_{1/2}$ (h)	$AUC_{0\text{-inf}}$ (ng eq.·h/g)
Blood	0.701 ±0.06938	0.663 ±0.06913	0.611 ±0.03378	0.307 ±0.03730	0.266 ±0.05890	0.416 ±0.3998	0.0898 ±0.02079	0.25	0.700	27.2	19.3
Plasma	0.818 ±0.1194	0.880 ±0.06411	0.788 ±0.1805	0.482 ±0.1366	0.476 ±0.1822	0.719 ±1.0552	0.0708 ±0.05162	0.5	0.880	16.4	26.1

eq.: Equivalent to ^{14}C-AR-13324.

1) Each value represents mean±SD (n=3).

2) Each PK parameter was calculated using average radioactivity concentration.

Confidential

2.6.5.3.2 ウサギ 7 日間反復点眼

Test Article: AR-13324

Study No.	[redacted]		Location: 4.2.3.2-1		
Title	A 7-Day Ocular Toxicity Study of AR-13324 Ophthalmic Solutions in Dutch Belt Rabbits with a 7-Day Recovery (GLP)				
Species	Dutch Belted Rabbit		Method of Administration	Topical ocular dose to both eyes, QD and QID, 7 days, 30 µL/eye/dose	
Gender (M/F) / Number of Animals	M / 5 or 8, F / 5 or 8 (per each dose)		Dose	24, 48, 96 µg/animal/day	
Feeding Conditions	Fed		Analyte	Netarsudil, AR-13503	
Vehicle/Formulation	0.04%, 0.08% STN1013900 Ophthalmic Solution		Analysis Method	LC-MS/MS	
Sample	Plasma				
Sampling Time	Day 1: 0.5, 1, 2, 4 and 16 h after administration (QD), 0.5, 1, 2, 4 and 16 h after the fourth administration (QID) Day 7: Pre-dose, 0.5, 1, 2, 4 and 16 h after administration (QD), Pre-dose (prior to the first administration), 0.5, 1, 2, 4 and 16 h after the fourth administration (QID)				

PK parameter / Analyte		Netarsudil[1)]					
Gender		Male			Female		
Formulation Concentration (%)		0.04[2)]	0.08[2)]	0.04[3)]	0.04[2)]	0.08[2)]	0.04[3)]
Method of Administration		QD	QD	QID	QD	QD	QID
Dose (µg/animal/day)		24	48	96	24	48	96
Day 1	C_{max} (ng/mL)[4)]	0.109±0.1055	1.58±2.313	3.30±8.487	0.106±0.1176	0.232±0.1400	0.681±0.7148
	$AUC_{0\text{-}16h}$ (ng·h/mL)[4)]	0.0613±0.05737	1.628±2.8911	2.615±4.1466	0.0752±0.07492	1.017±0.8161	2.227±3.1645
	T_{max} (h)[4)]	0.7±0.29	0.5±0	3.4±5.70	0.7±0.29	0.9±0.75	0.6±0.24
	$T_{1/2}$ (h)	NC	NC	NC	NC	NC	NC

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2.6.5.3.2 ウサギ 7 日間反復点眼（続き）

Test Article: AR-13324

PK parameter / Analyte		Netarsudil[1]					
Gender		Male			Female		
Formulation Concentration (%)		0.04[2]	0.08[2]	0.04[3]	0.04[2]	0.08[2]	0.04[3]
Method of Administration		QD	QD	QID	QD	QD	QID
Dose (μg/animal/day)		24	48	96	24	48	96
Day 7	C_{max} (ng/mL)[4]	0.146±0.1363	0.526±0.09938	1.01±0.602	0.503±0.5304	0.441±0.5149	1.56±1.0697
	$AUC_{0\text{-}16h}$ (ng·h/mL)[4]	0.2902±0.35821	3.739±1.9009	5.348±4.9845	1.017±1.617	0.9231±1.0323	3.499±2.0974
	T_{max} (h)[4]	1±0.9	5±6.3	1.6±1.58	1±0.7	1±0.7	0.9±0.56
	$T_{1/2}$ (h)	NC	NC	NC	NC	NC	NC

QD: Once a day.

QID: Four times a day.

NC: Not calculated.

1) The sum of the measured values of Netarsudil concentration and AR-13503 concentration was regarded as the Netarsudil concentration.

2) n=5.

3) n=8.

4) Each value represents mean±SD (n=5 for 0.04% and 0.008% QD, n=8 for 0.004% QID).

Confidential

2.6.5.3.3 ウサギ 26 週間反復点眼

Test Article: AR-13324

Study No.	[redacted]	Location: 4.2.3.2-3	
Title	A 3/6-Month Ocular Toxicity Study with AR-13324 Ophthalmic Solutions in Dutch Belted Rabbits (GLP)		
Species	Dutch Belted Rabbit	Method of Administration	Topical ocular dose to both eyes, BID, 26 weeks 35 µL/eye/dose
Gender (M/F) / Number of Animals	M / 5, 7, 9 or 11, F /5, 7, 9 or 11 (per each day or dose)	Dose	28, 56 µg/animal/day
Feeding Conditions	Fed	Analyte	Netarsudil, AR-13323, AR-13534, AR-13503
Vehicle/Formulation	0.02%, 0.04% STN1013900 Ophthalmic Solution	Analysis Method	LC-MS/MS
Sample	Plasma		
Sampling Time	Day 1, Week 12, Week 26: 0.5, 1 h after the second administration		

		Plasma Concentration (ng/mL)							
Formulation Concentration (%)		0.02				0.04			
Dose (µg/animal/day)		28				56			
Gender		Male[1)]		Female[1)]		Male[2)]		Female[2)]	
Time (h)		0.5	1	0.5	1	0.5	1	0.5	1
Day 1	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	1.51[3)]	BLQ	BLQ	1.05[3)]	1.19–1.53[4)]	1.03–1.50[4)]	1.02–1.40[5)]	1.18–1.60[5)]
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

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2.6.5.3.3 ウサギ 26 週間反復点眼（続き）

Test Article: AR-13324

		Plasma Concentration (ng/mL)							
Formulation Concentration (%)		0.02				0.04			
Dose (μg/animal/day)		28				56			
Gender		Male[1)]		Female[1)]		Male[2)]		Female[2)]	
Time (h)		0.5	1	0.5	1	0.5	1	0.5	1
Week 12	Netarsudil	BLQ	BLQ	BLQ	BLQ	2.09[3)]	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Week 26	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

BID: Twice a day.

BLQ: Below the lower limit of quantification (<1.00 ng/mL).

1) n=9 (Day 1 and Week 12), n=5 (Week 26).

2) n=11 (Day 1 and Week 12), n=7 (Week 26).

3) n=1.

4) Plasma concentration range of 2 animals.

5) Plasma concentration range of 3 animals.

Confidential

2.6.5.3.4 サル 7 日間反復点眼

Test Article: AR-13324

Study No.	[redacted]			Location: 4.2.3.2-5			
Title	A 7-Day Ocular Toxicity Study of AR-13324 in Cynomolgus Monkeys with a 7-Day Recovery Period						
Species	Cynomolgus Monkey		Method of Administration	Topical ocular dose to both eyes, QID, 7 days 30 µL/eye/dose			
Gender (M/F) / Number of Animals	M / 3 or 5, F / 3 or 5 (per each dose)		Dose	24, 96, 288 µg/animal/day			
Feeding Conditions	Fed		Analyte	Netarsudil			
Vehicle/Formulation	0.01%, 0.04%, 0.12% STN1013900 Ophthalmic Solution		Analysis Method	LC-MS/MS			
Sample	Plasma						
Sampling Time	Day 1: Pre-dose (prior to the first administration), 0.5, 1, 2, 4, 8 and 15 h after the fourth administration Day 7: Pre-dose (prior to the first administration), 0.5, 1, 2, 4, 8 and 15 h after the fourth administration						
PK parameter / Analyte		Netarsudil					
Gender		Male			Female		
Formulation Concentration (%)		0.01[1)]	0.04[1)]	0.12[2)]	0.01[1)]	0.04[1)]	0.12[2)]
Dose (µg/animal/day)		24	96	288	24	96	288
Day 1	C_{max} (ng/mL)[3)]	NC	NC	0.232±0.0597	NC	NC	0.232±0.0651[5)]
	AUC_{0-t} (ng·h/mL)[3)]	NC	NC	0.849±0.527	NC	NC	0.990±0.524[5)]
	T_{max} (h)[4)]	NC	NC	0.5	NC	NC	0.5[5)]
	$T_{1/2}$ (h)[3)]	NC	NC	NC	NC	NC	NC

Confidential

2.6.5.3.4 サル 7 日間反復点眼（続き）

Test Article: AR-13324

PK parameter / Analyte		Netarsudil					
Gender		Male			Female		
Formulation Concentration (%)		0.01[1)]	0.04[1)]	0.12[2)]	0.01[1)]	0.04[1)]	0.12[2)]
Dose (μg/animal/day)		24	96	288	24	96	288
Day 7	C_{max} (ng/mL)[3)]	NC	NC	NC	NC	NC	NC
	AUC_{0-t} (ng·h/mL)[3)]	NC	NC	NC	NC	NC	NC
	T_{max} (h)[4)]	NC	NC	NC	NC	NC	NC
	$T_{1/2}$ (h)[3)]	NC	NC	NC	NC	NC	NC

QID: Four times a day.

NC: Not calculated.

1) n=3.

2) n=5.

3) Each value represents mean±SD.

4) Each value represents mean.

5) n=4.

Confidential

2.6.5.3.5 サル９ヵ月間反復点眼

Test Article: AR-13324

Study No.	[redacted]	Location: 4.2.3.2-8	
Title	A 9-Month GLP Ocular Toxicity Study of AR-13324 Ophthalmic Solutions following Topical Ocular Administration in Cynomolgus Monkeys with a 4-Week Recovery Phase		
Species	Cynomolgus Monkey	Method of Administration	Topical ocular dose to both eyes, BID, 39 weeks 35 µL/eye/dose
Gender (M/F) / Number of animals	M / 10 or 6, F / 10 or 6 (per each day)	Dose	28, 56 µg/animal/day
Feeding Conditions	Fed	Analyte	Netarsudil AR-13323, AR-13534, AR-13503
Vehicle/Formulation	0.02%, 0.04% STN1013900 Ophthalmic Solution	Analysis Method	LC-MS/MS
Sample	Plasma		
Sampling Time	Day 1, Week 13, Week 39: 15, 30 min after the second administration		

		Plasma Concentration (ng/mL)							
Formulation Concentration (%)		0.02				0.04			
Dose (µg/animal/day)		28				56			
Gender		Male		Female		Male		Female	
Time (min)		15	30	15	30	15	30	15	30
Day 1[1)]	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

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2.6.5.3.5 サル９ヵ月間反復点眼（続き）

Test Article: AR-13324

		Plasma Concentration (ng/mL)							
Formulation Concentration (%)		0.02				0.04			
Dose (μg/animal/day)		28				56			
Gender		Male		Female		Male		Female	
Time (min)		15	30	15	30	15	30	15	30
Week 13 [1)]	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Week 39 [2)]	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13323	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13534	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

BID: Twice a day

BLQ: Below the lower limit of quantification (<1.00 ng/mL).

1) n=10 (per each gender).

2) n=6 (per each gender).

Confidential

2.6.5.4 薬物動態試験： 吸収：静脈内投与

2.6.5.4.1 ラット 28 日間反復静脈内投与

Test Article: AR-13324 [redacted]

Study No.	[redacted]	Location: 4.2.3.2-10	
Title	A 28-Day GLP Intravenous Toxicity Study of AR-13324 in Rats with a 14-Day Recovery		
Species	Sprague Dawley Rat	Method of Administration	iv bolus injection, QD, 28 days
Gender (M/F) / Number of Animals	M / 3, F / 3 (per each dose)	Dose	0.04–0.07 mg/kg/day (as netarsudil), 0.16–0.21 mg/kg/day (as netarsudil), 0.59–0.74 mg/kg/day (as netarsudil)
Feeding Conditions	Fed	Analyte	Netarsudil, AR-13323, AR-13503, AR-13534
Vehicle/Formulation	Saline/Solution ([redacted])	Analysis Method	LC-MS/MS
Sample	Plasma		
Sampling Time	Day 1, Day 28: Pre-dose, 10, 30 min, 2, 4, 8, 24 h after administration		

Dose (mg/kg/day)	0.04–0.07		0.16–0.21		0.59–0.74	
Gender	Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[1)]	Female[1)]
PK parameter for Netarsudil (Day 1/ Day 28)						
AUC_{0-t} (ng·h/mL)	4.5982 / 1.8522	4.4868 / 3.9119	30.8279 / 20.7398	19.9858 / 16.8155	103.0820 / 101.8679	104.7314 / 91.8564
AUC_{0-24h} (ng·h/mL)	4.9412 / 3.6147	4.8268 / 4.2849	37.5239 / 24.2798	23.0258 / 19.4555	130.8420 / 125.7879	138.6514 / 121.5364
T_{max} (h)	0.167 / 0.167	0.167 / 0.167	0.167 / 0.167	0.167 / 0.167	0.167 / 0.167	0.167 / 0.167
C_{max} (ng/mL)	4.74 / 4.06	4.39 / 4.39	19.7 / 18.2	9.80 / 12.6	64.9 / 64.5	59.4 / 57.0
$T_{1/2, e}$[2)] (h)	0.49 / NC	0.49 / 0.54	2.7 / 1.8	2.0 / 1.7	3.6 / 3.1	3.8 / 3.7

Confidential

2.6.5.4.1 ラット 28 日間反復静脈内投与（続き）

Test Article: AR-13324 [redacted]

Dose (mg/kg/day)	0.04–0.07		0.16–0.21		0.59–0.74	
Gender	Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[1)]	Female[1)]
PK parameter for Netarsudil (Day 1/ Day 28)						
V_z[3)] (L)	10.1 / NC	10.5 / 12.9	24.2 / 21.9	29.1 / 25.2	30.0 / 26.8	30.7 / 33.9
Cl[4)] (L/h)	14.5 / NC	14.8 / 16.7	6.2 / 8.3	10.0 / 10.5	5.8 / 6.1	5.5 / 6.3
PK parameter for AR-13323 (Day 1/ Day 28)						
$AUC_{0\text{-}t}$ (ng·h/mL)	NC / NC	NC / NC	NC / NC	NC / NC	1.4031 / 1.3702	1.1428 / 1.0412
$AUC_{0\text{-}24h}$ (ng·h/mL)	NC / NC	NC / NC	0.2268 / 0.1211	NC / NC	2.4681 / 2.4727	2.2078 / 1.5587
T_{max} (h)	NC / NC	NC / NC	0.167 / 0.167	NC / NC	0.167 / 0.167	0.167 / 0.167
C_{max} (ng/mL)	NC / NC	NC / NC	0.680 / 0.363	NC / NC	3.12 / 3.04	2.51 / 2.30
$T_{1/2,\ e}$[2)] (h)	NC / NC	NC / NC	NC / NC	NC / NC	NC / NC	NC / NC
Ratio AR-13323 $AUC_{0\text{-}t}$ and Netarsudil $AUC_{0\text{-}t}$[5)]	NC / NC	NC / NC	NC / NC	NC / NC	0.014 / 0.013	0.011 / 0.017
Ratio AR-13323 C_{max} and Netarsudil C_{max}[5)]	NC / NC	NC / NC	0.035 / NC	NC / NC	0.048 / 0.047	0.042 / 0.040
PK parameter for AR-13503 (Day 1/ Day 28)						
$AUC_{0\text{-}t}$ (ng·h/mL)	NC / NC	NC / NC	0.0718 / NC	0.333 / 0.2724	3.6233 / 4.2597	2.1649 / 6.9281
$AUC_{0\text{-}24h}$ (ng·h/mL)	NC / NC	NC / NC	0.2150 / NC	0.7083 / 0.9849	5.2033 / 4.6027	6.2524 / 6.9281
T_{max} (h)	NC / NC	NC / NC	0.167 / NC	0.167 / 0.5	0.5 / 0.167	0.5 / 0.167
C_{max} (ng/mL)	NC / NC	NC / NC	0.860 / NC	1.00 / 0.950	1.99 / 7.00	5.45 / 4.10
$T_{1/2,\ e}$[2)] (h)	NC / NC	NC / NC	NC / NC	NC / NC	2.9 / 0.45	NC / 9.0

PK parameter for AR-13534 was not calculated because all the plasma concentrations were below the lower limit of quantification.

Each PK parameter was calculated using average concentration.

QD: Once a day.

Confidential

NC: Not calculated.

1) n=3.

2) Apparent plasma elimination phase half-life.

3) Volume of distribution of terminal elimination phase.

4) Total systemic clearance from plasma.

5) Consistent with a [redacted]

Confidential

2.6.5.4.2 イヌ 28 日間反復静脈内投与

Test Article: AR-13324 [redacted]

Study No.	[redacted]	Location: 4.2.3.2-12	
Title	A 28 Day GLP Intravenous Toxicity Study of AR-13324 in Beagle Dogs with a 2-Week Recovery		
Species	Beagle Dog	Method of Administration	iv bolus injection, QD, 28 days
Gender (M/F) / Number of Animals	M / 3 or 5, F / 3 or 5 (per each dose)	Dose	0.04–0.05 mg/kg/day 0.15–0.18 mg/kg/day 0.53–0.67 mg/kg/day
Feeding Conditions	Fed	Analyte	Netarsudil, AR-13323, AR-13503, AR-13534
Vehicle/Formulation	Saline/Solution ([redacted])	Analysis Method	LC-MS/MS
Sample	Plasma		
Sampling Time	Day 1, Day 7, Day 28: Pre-dose, 10, 30 min, 2, 4, 8, 24 h after administration		

Dose (mg/kg/day)		0.04–0.05		0.15–0.18		0.53–0.67	
Gender		Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[2)]	Female[2)]
PK parameter for Netarsudil							
AUC_{0-t} (ng·h/mL)	Day 1	10.11±3.177	11.15±4.693	29.57±1.755	57.60±19.999	281.61±62.025	209.18±43.359
	Day 7	39.33±20.581	31.55±20.784	49.54±23.263	110.99±34.763	426.88±97.210	309.38±83.903
	Day 28	42.10±20.241	28.21±20.616	34.31±4.081	108.61±27.838	481.68±151.932	334.79±96.125
AUC_{0-24h} (ng·h/mL)	Day 1	17.31±7.620	16.16±9.259	47.49±6.127	65.47±6.736	281.61±62.025	209.18±43.359
	Day 7	42.71±14.766	41.07±12.923	59.78±15.274	110.99±34.763	426.88±97.210	309.38±83.903
	Day 28	46.28±13.003	36.63±13.463	54.65±11.099	108.61±27.838	481.68±151.932	334.79±96.125

Confidential

2.6.5.4.2　　イヌ 28 日間反復静脈内投与（続き）

Test Article: AR-13324 [redacted]

Dose (mg/kg/day)		0.04–0.05		0.15–0.18		0.53–0.67	
Gender		Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[2)]	Female[2)]
T_{max} (h)	Day 1	0.167±0	0.167±0	0.167±0	0.167±0	0.167±0	0.167±0
	Day 7	0.167±0	0.389±0.1923	0.167±0	0.167±0	0.167±0	0.167±0
	Day 28	0.167±0	0.167±0	0.167±0	0.167±0	0.167±0	0.167±0
C_{max} (ng/mL)	Day 1	3.18±0.287	4.56±0.555	11.4±2.20	11.8±0.12	52.7±11.21	41.8±3.42
	Day 7	4.96±0.724	5.60±0.185	13.2±1.29	14.1±2.14	67.8±6.53	51.3±6.74
	Day 28	5.56±0.609	4.76±0.650	13.1±0.36	14.5±1.46	63.3±11.17	51.5±4.41
$T_{1/2, e}$[3)] (h)	Day 1	11.1±7.51	4.3±2.46	9.9±4.04	12.2±3.04	9.5±2.11	9.5±0.76
	Day 7	16.7±7.99	17.4±6.96	6.2±3.73	14.0±6.88	10.5±2.11	12.3±1.16
	Day 28	18.3±7.77	29.4±21.47	11.1±5.95	12.0±3.87	13.0±2.64	12.6±2.13
V_z[4)] (L)	Day 1	36.7±6.80	23.0±2.81	46.9±2.98	41.8±2.87	29.0±5.17	40.6±10.10
	Day 7	24.3±2.56	24.1±4.30	28.7±5.12	26.4±2.01	20.2±2.11	32.7±9.36
	Day 28	22.9±2.07	29.6±5.02	40.2±8.34	25.4±1.88	21.1±5.07	30.5±8.65
Cl[5)] (L/h)	Day 1	2.83±3.386	4.33±1.833	3.58±1.157	2.45±0.424	2.19±0.516	2.96±0.651
	Day 7	1.30±0.936	1.06±0.486	3.75±1.395	1.53±0.702	1.40±0.377	1.87±0.623
	Day 28	1.01±0.541	1.02±0.787	3.13±1.740	1.59±0.567	1.15±0.337	1.74±0.650

Confidential

2.6.5.4.2 イヌ 28 日間反復静脈内投与（続き）

Test Article: AR-13324 [redacted]

Dose (mg/kg/day)		0.04–0.05		0.15–0.18		0.53–0.67	
Gender		Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[2)]	Female[2)]
PK parameter for AR-13323							
AUC_{0-t} (ng·h/mL)	Day 1	NC	NC	NC	NC	1.65±1.118	1.03±0.094
	Day 7	NC	NC	NC	NC	1.81±0.995	1.00±0.146
	Day 28	NC	NC	NC	NC	2.61±1.389	1.06±0.072
AUC_{0-24h} (ng·h/mL)	Day 1	NC	NC	NC	NC	2.68±1.171	1.97±0.117
	Day 7	NC	NC	NC	NC	2.90±1.029	1.94±0.280
	Day 28	NC	NC	NC	NC	3.82±1.504	1.81±0.632
T_{max} (h)	Day 1	NC	NC	NC	NC	0.167±0	0.167±0
	Day 7	NC	NC	NC	NC	0.167±0	0.167±0
	Day 28	NC	NC	NC	NC	0.167±0	0.167±0
C_{max} (ng/mL)	Day 1	NC	NC	NC	NC	2.68±0.400	2.25±0.240
	Day 7	NC	NC	NC	NC	3.02±0.267	2.19±0.327
	Day 28	NC	NC	NC	NC	2.83±0.516	2.27±0.165
$T_{1/2, e}$[3)] (h)	Day 1	NC	NC	NC	NC	1.4[8)]	NC
	Day 7	NC	NC	NC	NC	1.5[8)]	NC
	Day 28	NC	NC	NC	NC	1.8±0.25[1)]	NC
Ratio AR-13323 AUC_{0-t} and Netarsudil AUC_{0-t}[6)]	Day 1	NC	NC	NC	NC	0.0055±0.00227	0.0051±0.00139
	Day 7	NC	NC	NC	NC	0.0041±0.00124	0.0034±0.000628
	Day 28	NC	NC	NC	NC	0.0053±0.00238	0.0030±0.000764

Confidential

2.6.5.4.2 イヌ 28 日間反復静脈内投与（続き）

Test Article: AR-13324 [redacted]

Dose (mg/kg/day)		0.04–0.05		0.15–0.18		0.53–0.67	
Gender		Male[1)]	Female[1)]	Male[1)]	Female[1)]	Male[2)]	Female[2)]
Ratio AR-13323 C_{max} and Netarsudil C_{max}[6)]	Day 1	NC	NC	NC	NC	0.051±0.00336	0.054±0.00317
	Day 7	NC	NC	NC	NC	0.045±0.00292	0.043±0.00182
	Day 28	NC	NC	NC	NC	0.045±0.00270	0.044±0.00107
PK parameter for AR-13503							
$AUC_{0\text{-}t}$ (ng·h/mL)	Day 1	NC	NC	NC	NC	NC	NC
	Day 7	NC	NC	NC	NC	7.81[7)]	12.62±9.635
	Day 28	NC	NC	NC	NC	14.25±11.572	31.51±12.791
$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	NC	NC	NC	NC	NC	NC
	Day 7	NC	NC	NC	NC	16.21[7)]	20.97±5.153
	Day 28	NC	NC	NC	NC	23.15±6.884	33.80±8.086
T_{max} (h)	Day 1	NC	NC	NC	NC	NC	NC
	Day 7	NC	NC	NC	NC	2.1[7)]	3.7±4.03
	Day 28	NC	NC	NC	NC	6.4±2.19	6.8±2.68
C_{max} (ng/mL)	Day 1	NC	NC	NC	NC	NC	NC
	Day 7	NC	NC	NC	NC	1.26[7)]	1.50±0.223
	Day 28	NC	NC	NC	NC	1.51±0.201	1.80±0.288
$T_{1/2,\ e}$[3)] (h)	Day 1	NC	NC	NC	NC	NC	NC
	Day 7	NC	NC	NC	NC	NC	NC
	Day 28	NC	NC	NC	NC	NC	25.6[8)]

PK parameter for AR-13534 was not calculated because all the plasma concentrations were below the lower limit of quantification.

Confidential

Each PK parameter represents mean±SD.

QD: Once a day.

NC: Not calculated.

1) n=3.

2) n=5.

3) Apparent plasma elimination phase half-life.

4) Volume of distribution of terminal elimination phase.

5) Total systemic clearance from plasma.

6) Consistent with a [redacted]

7) n=2.

8) n=1.

Confidential

2.6.5.5 薬物動態試験： 分布

2.6.5.5.1 ウサギ単回点眼時の眼組織分布

Test Article: ^{14}C-AR-13324

Study No.	[redacted]				Location: 4.2.2.2-1									
Title	Ocular Tissue Distribution Study of Total Radioactivity in Dutch-Belted Male Rabbits Following a Single Topical Ocular Administration of [^{14}C]AR-13324													
Species	Dutch Belted Rabbit				Method of Administration				Topical ocular dose to both eyes, single 35 µL/eye/dose					
Gender (M/F) / Number of Animals	M / 3 (per each timepoint)				Dose				0.014 mg/animal					
Feeding Conditions	Fed				Radionuclide				^{14}C					
Vehicle/Formulation	0.02% ^{14}C-STN1013900 Ophthalmic Solution				Specific Activity				2146 MBq/mmol					
Analysis Method	Liquid Scintillation Counting													
Sampling Time	0.25, 0.5, 1, 4, 8, 24, 48 h post dosing													
Ocular Tissues/Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		0.5		1		4		8		24		48	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Aqueous Humor	1.56 ±0.854	3.03 ±1.523	2.14 ±1.141	2.43 ±0.434	3.05 ±0.771	4.46 ±2.426	14.2 ±0.76	20.6 ±0.64	16.3 ±6.16	22.6 ±6.04	12.6 ±4.32	12.9 ±4.35	3.22 ±1.271	3.94 ±0.882
Vitreous Humor	7.27 ±4.265	4.43 ±2.688	2.67 ±1.205	3.59 ±1.346	1.56 ±0.547	2.82 ±0.859	1.67 ±0.163	1.76 ±0.476	2.62 ±1.801	1.66 ±0.224	0.530 ±0.2859	0.869 ±0.5263	0.249 ±0.1988	0.263 ±0.2326
Conjunctiva	2442 ±276.0	3292 ±362.2	1918 ±307.9	2352 ±383.0	1068 ±306.0	1373 ±1048.3	269 ±55.0	321 ±86.4	291 ±117.5	365 ±139.3	104 ±59.6	133 ±58.4	32.9 ±11.12	70.7 ±33.72

Confidential

2.6.5.5.1 ウサギ単回点眼時の眼組織分布（続き）

Test Article: ^{14}C-AR-13324

Ocular Tissues/Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		0.5		1		4		8		24		48	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Cornea	2605 ±2299.4	3972 ±770.1	3666 ±2991.0	3578 ±731.0	2204 ±2051.1	2593 ±2660.8	2485 ±807.4	2743 ±1540.3	2079 ±214.1	2652 ±938.8	1228 ±498.0	1144 ±575.9	288 ±122.9	311 ±64.7
Iris/Ciliary Body	955 ±1479.1	64.2 ±35.56	82.5 ±51.68	47.6 ±17.97	72.1 ±72.93	85.1 ±75.65	466 ±698.7	224 ±181.1	107 ±43.9	416 ±544.1	202 ±71.5	148 ±64.9	309 ±272.5	289 ±27.9
Lens	1.77 ±2.314	1.77 ±1.227	1.49 ±0.385	1.25 ±0.565	1.73 ±0.869	1.33 ±1.120	0.757 ±0.6087	1.12 ±0.678	0.724 ±0.4479	0.815 ±0.1327	0.608 ±0.05388	0.660 ±0.2186	0.556 ±0.05631	0.705 ±0.1125
Retinal-Choroid-Plexus	79.8 ±91.64	24.1 ±7.21	24.1 ±13.58	50.3 ±31.83	13.6 ±3.08	39.0 ±13.08	27.6 ±8.14	26.7 ±5.85	23.7 ±10.65	29.8 ±8.16	36.7 ±24.39	28.6 ±8.97	22.5 ±12.99	20.1 ±4.80

Confidential

2.6.5.5.1 ウサギ単回点眼時の眼組織分布（続き）

Test Article: ^{14}C-AR-13324

Pharmacokinetic parameter/Tissue	Left/Right	Aqueous Humor	Vitreous Humor	Conjunctiva	Cornea	Iris/Ciliary Body	Lens	Retinal-Choroid-Plexus
C_{max} (ng eq./g)	Right	22.6	4.43	3292	3972	416	1.77	50.3
	Left	16.3	7.27	2442	3666	955	1.77	79.8
T_{max} (h)	Right	8	0.25	0.25	0.25	8	0.25	0.5
	Left	8	0.25	0.25	0.5	0.25	0.25	0.25
AUC_{0-t} (ng eq.·h/g)	Right	613	50.7	12390	69605	11555	37.0	1298
	Left	510	51.2	9525	63387	10845	32.8	1390
$T_{1/2}$ (h)	Right	15.7	15.0	17.4	12.9	112	83.3	67.8
	Left	16.6	12.2	12.8	13.8	NC	98.6	204

eq.: Equivalent to ^{14}C-AR-13324.

NC: Not calculated.

Radioactivity concentration represents mean±SD (n=3).

Each PK parameter was calculated using average radioactivity concentration.

Confidential

2.6.5.5.2 ウサギ反復点眼時の眼組織分布

Test Article: ^{14}C-AR-13324

Study No.	[redacted]	Location: 4.2.2.3-1	
Title	Tissue Distribution and Excretion Profile Study of Total Radioactivity in Dutch-Belted Male Rabbits Following Single and Repeated Dose Topical Ocular Administration of [^{14}C]Netarsudil		
Species	Dutch Belted Rabbit	Method of Administration	Topical ocular dose to both eyes, single and 7 days, 35 µL/eye/dose
Gender (M/F) / Number of Animals	M / 3 (per each timepoint)	Dose	0.014 mg/animal
Feeding Conditions	Fed	Radionuclide	^{14}C
Vehicle/Formulation	0.02% ^{14}C-STN1013900 Ophthalmic Solution	Specific Activity	2146 MBq/mmol
Analysis Method	Liquid Scintillation Counting		
Sampling Time	Single dose: 0.25, 1, 6, 24, 48, 96, 168 h post dosing Repeated dose: 48, 96, 168 h post dosing (QD, 7 days)		

Ocular Tissues (single dose)/ Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		1		6		24		48		96		168	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Aqueous Humor	0.0431 ±0.07464	BLQ	4.03 ±1.184	1.78 ±1.577	18.4 ±5.69	18.0 ±4.02	17.1 ±1.53	22.6 ±10.45	3.22 ±1.438	4.48 ±1.293	BLQ	BLQ	BLQ	BLQ
Vitreous Humor	6.25 ±5.574	27.6 ±35.23	2.03 ±2.239	1.45 ±1.372	0.479 ±0.7326	2.34 ±3.133	0.591 ±0.5847	0.331 ±0.5729	0.00822 ±0.01424	BLQ	0.0337 ±0.0583	0.551 ±0.8643	0.343 ±0.5945	0.0869 ±0.15051
Cornea	2639 ±527.1	5159 ±2596.0	4352 ±1031.6	5564 ±1601.5	3686 ±480.7	4222 ±189.1	1217 ±399.1	1748 ±556.9	233 ±118.1	397 ±19.8	102 ±51.7	164 ±65.5	72.0 ±26.01	129 ±7.0
Conjunctiva	2139 ±607.4	4982 ±2661.7	1704 ±1063.4	1878 ±1086.7	536 ±160.0	376 ±225.1	178 ±124.0	130 ±38.6	80.1 ±53.37	79.4 ±47.23	31.5 ±23.21	41.3 ±25.44	22.6 ±8.19	19.8 ±19.00

Confidential

2.6.5.5.2 ウサギ反復点眼時の眼組織分布（続き）

Test Article: ^{14}C-AR-13324

Ocular Tissues (single dose) / Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		1		6		24		48		96		168	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Nictitating Membrane	1624 ±384.0	2931 ±333.9	1808 ±545.0	1272 ±138.7	509 ±306.9	671 ±291.7	358 ±77.5	190 ±108.5	164 ±ND	160 ±117.2	150 ±128.8	230 ±48.5	131 ±55.5	120 ±134.3
Optic Nerve	39.5 ±47.92	49.7 ±62.95	4.20 ±5.524	1.18 ±2.046	8.18 ±14.171	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Lens	0.633 ±0.6959	0.515 ±0.3259	0.128 ±0.0865	0.0961 ±0.16653	0.0407 ±0.07057	0.0457 ±0.07913	0.379 ±0.2548	0.204 ±0.2728	0.275 ±0.1922	0.235 ±0.2453	0.00825 ±0.01429	0.314 ±0.5430	BLQ	BLQ
Iris/Ciliary Body	14.9 ±10.08	92.6 ±115.95	12.7 ±4.69	15.2 ±4.27	31.4 ±14.28	23.8 ±11.10	60.6 ±16.91	70.5 ±34.83	86.8 ±45.96	125 ±66.0	31.4 ±32.41	61.5 ±32.35	21.8 ±33.96	28.3 ±44.75
Retinal-Choroid-Plexus	15.4 ±8.07	38.6 ±38.68	19.9 ±22.46	18.0 ±13.53	5.31 ±4.315	23.6 ±34.94	3.10 ±2.062	0.904 ±0.3842	1.16 ±1.069	1.64 ±2.583	20.0 ±34.69	0.0895 ±0.15509	50.8 ±47.18	44.3 ±39.98
Sclera	365 ±72.6	524 ±203.1	287 ±67.1	466 ±172.9	203 ±20.4	180 ±29.9	86.9 ±73.79	126 ±43.5	62.3 ±5.90	50.4 ±18.60	48.3 ±20.81	48.5 ±7.91	40.9 ±9.13	33.8 ±5.45
Ocular Tissues (repeated dose, 7 days)/Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		1		6		24		48		96		168	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Aqueous Humor	–	–	–	–	–	–	–	–	18.9 ±4.08	18.1 ±5.86	21.9 ±5.00	20.6 ±6.15	11.3[1)]	21.1 ±1.56
Vitreous Humor	–	–	–	–	–	–	–	–	0.481 ±0.3680	0.205 ±0.0275	3.42 ±3.145	0.379 ±0.1735	1.09 ±1.484	1.67 ±2.326

Confidential

2.6.5.5.2 ウサギ反復点眼時の眼組織分布（続き）

Test Article: ^{14}C-AR-13324

Ocular Tissues (repeated dose, 7 days)/Time (h)	Radioactivity Concentration (ng eq./g)													
	0.25		1		6		24		48		96		168	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Cornea	–	–	–	–	–	–	–	–	1359 ±426.3	1509 ±686.7	3176 ±760.0	3854 ±597.5	2439 ±644.7	3807 ±1163.9
Conjunctiva	–	–	–	–	–	–	–	–	198 ±109.5	159 ±62.1	455 ±140.1	569 ±153.0	329[1)]	186 ±24.7
Nictitating Membrane	–	–	–	–	–	–	–	–	259 ±242.9	120 ±108.8	1734[1)]	808 ±952.0	1531 ±77.3	1324 ±464.3
Optic Nerve	–	–	–	–	–	–	–	–	38.5 ±64.28	BLQ	8.22 ±14.242	7.67 ±13.287	58.4 ±101.07	7.19 ±12.453
Lens	–	–	–	–	–	–	–	–	1.08 ±0.921	1.18 ±1.176	3.30 ±2.761	1.64 ±0.401	2.38 ±1.535	2.17 ±0.856
Iris/Ciliary Body	–	–	–	–	–	–	–	–	105 ±42.8	196 ±87.6	165 ±134.0	304 ±82.2	252 ±371.8	237 ±354.4
Retinal-Choroid-Plexus	–	–	–	–	–	–	–	–	6.01 ±3.880	7.76 ±7.313	86.0 ±114.28	20.1 ±8.25	308 ±333.2	336 ±311.8
Sclera	–	–	–	–	–	–	–	–	166 ±75.8	157 ±85.0	273 ±40.2	331 ±94.3	422 ±142.3	418 ±49.8

QD: Once a day.

BLQ: Below the lower limit of quantification (less than 2-fold background value).

eq.: Equivalent to ^{14}C-AR-13324.

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ND: Not determined.

–: Not collected of samples.

Each value represents mean±SD (n=3).

1) n=2

Confidential

2.6.5.5.3 ラット単回静脈内投与時の全身組織分布

Test Article: ^{14}C-AR-13324

Study No.	[redacted]				Location: 4.2.2.3-2					
Title	Excretion Mass Balance and Quantitative Whole-Body Autoradiography in Long-Evans Rats Following a Single Intravenous Dose of [^{14}C]AR-13324									
Species	Long-Evans Rat				Method of Administration		Single iv bolus injection			
Gender (M/F) / Number of Animals	M / 1 (per each timepoint)				Dose		1 mg/kg (3.7 MBq/kg)			
Feeding Conditions	Fed				Radionuclide		^{14}C			
Vehicle/Formulation	Saline/Solution				Specific Activity		2146 MBq/mmol			
Analysis Method	Quantitative Whole-Body Autoradiography: Tissue Distribution									
Time (h)	0.5	1	4	8	24	72	96	120	144	168
Blood and Plasma Concentrations (µg eq./g)										
Blood	0.236	0.173	0.061	0.034	0.016	0.009	0.007	0.006	0.005	0.004
Plasma	0.260	0.192	0.056	0.029	0.014	0.006	0.004	BLQ	BLQ	BLQ
Blood to Plasma Ratio	0.91	0.90	1.09	1.17	1.14	1.50	1.75	ND	ND	ND
Tissue Concentrations (µg eq./g)										
Vascular/Lymphatic										
Blood (cardiac)	0.315	0.196	0.064	0.032	0.018	BLQ	BLQ	BLQ	BLQ	BLQ
Bone Marrow	1.296	1.378	1.060	0.828	0.215	0.063	0.081	0.102	0.033	0.039
Lymph Node	0.744	1.111	0.760	0.488	0.467	0.141	0.128	0.077	0.051	0.073
Spleen	3.020	3.152	2.353	1.308	0.519	0.199	0.233	0. 242	0.144	0.131
Thymus	0.431	0.468	0.521	0.345	0.224	0.088	0.064	0.056	0.032	0.059

Confidential

2.6.5.5.3 ラット単回静脈内投与時の全身組織分布（続き）

Test Article: ^{14}C-AR-13324

Tissue Concentrations (μg eq./g)										
Time (h)	0.5	1	4	8	24	72	96	120	144	168
Excretory/Metabolic										
Bile (in duct)	21.322	14.400	7.285	6.023	0.343	0.041	0.027	BLQ	0.019	0.035
Kidney (cortex)	5.408	3.768	1.790	0.966	0. 323	0.124	0.106	0.088	0.041	0.059
Kidney (medulla)	4.072	3.172	1.263	0.583	0.278	0.087	0.065	0.053	0.022	0.033
Liver (high[1)])	9.810	8.347	4.791	2.564	2.762	0.715	0.967	1.538	1.072	2.120
Liver (low[1)])	6.577	6.580	3.176	1.427	0.400	0.131	0.142	0.097	0.088	0.042
Liver (total[1)])	6.996	6.918	3.005	1.806	0.476	0.265	0.271	0.170	0.149	0.161
Urinary Bladder	1.577	1.098	2.071	0.703	0.063	BLQ	BLQ	0.013	BLQ	0.017
Urinary Bladder (contents)	27.933	6.022	2.837	1.152	0.102	BLQ	BLQ	BLQ	BLQ	BLQ
Central Nervous System										
Brain (cerebellum)	0.019	BLQ	0.013	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Brain (cerebrum)	0.020	BLQ	0.016	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Brain (medulla)	0.024	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Meninges	0.545	0.233	0.328	0.201	0.131	0.233	0.116	0.239	0.095	0.182
Spinal Cord	0.027	0.012	0.015	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Endocrine										
Adrenal Gland (cortex)	13.555	13.464	14.868	11.646	12.129	11.277	10.647	11.658	7.296	10.268
Adrenal Gland (medulla)	6.048	6.038	5.518	4.844	3.675	2.742	4.613	3.798	5.334	2.019
Pituitary Gland	1.618	2.433	1.829	1.668	0.875	0.425	0.389	0.113	0.257	0.044
Thyroid	5.311	5.758	1.469	1.162	0.338	0.093	0.065	0.099	0.200	0.055

Confidential

2.6.5.5.3 ラット単回静脈内投与時の全身組織分布（続き）

Test Article: ^{14}C-AR-13324

Tissue Concentrations (μg eq./g)										
Time (h)	0.5	1	4	8	24	72	96	120	144	168
Secretory										
Exorbital Lacrimal Gland	0.747	0.942	0.852	0.584	0.545	0.419	0.352	0.337	0.301	0.424
Intraorbital Lacrimal Gland	0.714	0.840	1.055	0.641	0.552	0.494	0.246	0.330	0.252	0.353
Harderian Gland	0.459	0.398	0.403	0.281	0.169	0.048	0.034	0.015	BLQ	0.017
Mammary Gland Region	0.399	0.424	0.116	0.109	0.073	BLQ	BLQ	BLQ	BLQ	0.011
Pancreas	1.958	1.841	1.498	0.773	0.124	0.047	0.047	0.028	0.023	0.030
Salivary Gland	1.610	1.667	1.269	0.621	0.236	0.067	0.290	0.110	0.075	0.038
Fatty										
Adipose (brown)	1.382	0.943	0.444	0.266	0.070	0.017	0.033	0.015	BLQ	0.019
Adipose (white)	0.141	0.214	0.093	0.109	0.029	BLQ	BLQ	BLQ	BLQ	BLQ
Dermal										
Skin (non-pigmented)	0.405	0.389	0.303	0.287	0.065	0.043	0.020	0.012	0.011	0.011
Skin (pigmented)	0.373	0.332	0.274	0.142	0.080	0.040	0.068	0.021	0.013	0.015
Reproductive										
Epididymis	0.184	0.129	0.143	0.085	0.073	0.018	0.026	BLQ	BLQ	BLQ
Preputial Gland	0.779	0.925	1.143	0.590	0.517	0.662	0.458	0.685	0.475	1.225
Prostate Gland	0.409	0.340	0.206	0.173	0.157	BLQ	0.018	0.025	BLQ	0.014
Seminal Vesicles	0.152	0.112	0.087	0.166	0.041	0.012	0.011	0.014	BLQ	0.030

Confidential

2.6.5.5.3 ラット単回静脈内投与時の全身組織分布（続き）

Test Article: ^{14}C-AR-13324

Tissue Concentrations (μg eq./g)										
Time (h)	0.5	1	4	8	24	72	96	120	144	168
Testis	0.049	0.040	0.042	0.034	0.029	0.032	0.049	0.021	0.030	0.020
Skeletal/Muscular										
Bone	0.073	0.036	0.092	0.027	0.018	BLQ	BLQ	BLQ	BLQ	BLQ
Periosteum	1.365	0.925	0.554	0.193	0.211	0.235	0.166	0.083	0.076	0.187
Heart	2.623	1.555	0.286	0.129	0.044	0.016	0.015	0.015	BLQ	0.014
Skeletal Muscle	1.362	0.685	0.317	0.125	0.021	BLQ	0.015	BLQ	BLQ	BLQ
Respiratory										
Lung (high[1)])	24.551	12.035	10.575	5.855	2.451	9.030	137.813[2)]	0.538	1.659	4.808
Lung (low[1)])	2.405	4.094	2.018	0.894	0.197	0.053	0.068	0.024	0.012	0.019
Lung (total[1)])	3.160	4.502	2.687	1.206	0.295	0.243	1.890	0.048	0.030	0.057
Nasal Turbinates	0.079	0.348	0.325	0.013	0.038	BLQ	BLQ	BLQ	BLQ	BLQ
Alimentary Canal										
Cecum	1.161	1.214	0.523	4.421	1.023	0.025	0.011	BLQ	BLQ	BLQ
Cecum (contents)	0.049	0.164	7.422	27.944	2.599	0.071	0.029	0.028	BLQ	BLQ
Colon	0.872	0.996	0.756	0.369	0.300	0.022	0.027	0.014	BLQ	BLQ
Colon (contents)	BLQ	0.048	0.743	1.930	3.025	0.073	0.035	0.024	BLQ	BLQ
Esophagus	0.650	0.636	0.466	0.090	0.023	BLQ	BLQ	BLQ	BLQ	BLQ
Oral Mucosa	0.501	0.443	0.331	0.124	0.044	0.013	0.018	0.013	BLQ	BLQ
Small Intestine	2.824	2.569	0.496	0.372	0.137	BLQ	0.015	BLQ	BLQ	0.025

Confidential

2.6.5.5.3 ラット単回静脈内投与時の全身組織分布（続き）

Test Article: ^{14}C-AR-13324

Tissue Concentrations (µg equivalents/g)										
Time (h)	0.5	1	4	8	24	72	96	120	144	168
Alimentary Canal										
Small Intestine (contents)	79.107	22.819	33.604	12.741	0.588	0.030	0.018	0.013	BLQ	0.017
Stomach (gastric mucosa)	2.044	1.310	0.563	0.332	0.060	0.021	0.033	0.016	BLQ	0.021
Stomach (contents)	4.087	2.556	0.144	0.107	0.022	BLQ	BLQ	BLQ	BLQ	BLQ
Ocular										
Eye (lens)	BLQ	BLQ	BLQ	BLQ	0.013	BLQ	BLQ	BLQ	BLQ	BLQ
Eye (Uvea)	0.949	1.249	1.270	0.886	1.308	1.117	1.182	1.111	1.004	0.947

BLQ: Below quantification limit (<0.001 µg eq./g for blood and plasma, <0.011 µg eq./g for tissues).

eq.: Equivalent to ^{14}C-AR-13324.

ND: Not determined.

ULOQ: >87.156 µg eq./g.

1) Terms 'high, 'low', 'total' refer to tissue areas with high concentration focal points, areas of lower concentration, and total tissue area, respectively.

2) Value is above the upper limit of quantification.

Confidential

2.6.5.6 薬物動態試験： 蛋白結合及びメラニン結合

2.6.5.6.1 蛋白結合

Test Article: AR-13324 and AR-13503

Study No.	[redacted]	Location: 4.2.2.3-3	
Title	*In Vitro* Binding of AR-13324 and AR-13503 to Human, Beagle, and Rat Plasma		
Study System	*In vitro*		
Sample	Rat, Dog, Human Plasma		
Analyte	Netarsudil, AR-13503		
Analysis Method	Ultrafiltration, LC-MS		
Concentration Tested	Species	Netarsudil Percent Bound	AR-13503 Percent Bound
10 µmol/L	Human	>97.3	60.7±1.2
	Dog	>97.3	43.1±1.2
	Rat	>97.3	47.7±0.3
100 µmol/L	Human	>99.8	67.3±2.2
	Dog	>99.8	42.4±0.7
	Rat	>99.8	49.9±0.6
1000 µmol/L	Human	99.97±0.003	70.9±2.0
	Dog	99.96±0.006	45.4±0.2
	Rat	99.95±0.003	49.6±1.1

Each value represents mean or mean±SE (n=3).

Confidential

2.6.5.6.2 メラニン結合

Test Article: AR-13324, AR-13503, Chloroquine and Ciprofloxacin

Study No.	[redacted]		Location: 4.2.2.3-4		
Title	Binding of AR-13324 and AR-13503 to Melanin *In Vitro*				
Study System	*In vitro*				
Sample	Cuttlefish melanin				
Analyte	Netarsudil, AR-13503				
Analysis Method	Ultrafiltration, LC-MS				
Concentration Tested	Species	Netarsudil Kd B_{max}	AR-13503 Kd B_{max}	Chloroquine[1)] Kd B_{max}	Ciprofloxacin[1)] Kd B_{max}
AR-13324: 0–75 µmol/L; AR-13503: 0–134 µmol/L; Chloroquine: 0–77 µmol/L; Ciprofloxacin: 0–201 µmmol/L	Cuttlefish melanin	23 µmol/L 725 nmol/mg	20 µmol/L 672 nmol/mg	14 µmol/L 458 nmol/mg	35 µmol/L 909 nmol/mg

Kd: Binding constant, B_{max}: Maximum binding.

1) Positive control.

Confidential

2.6.5.7 薬物動態試験： 妊娠又は授乳動物における試験

なし

2.6.5.8 薬物動態試験： その他の分布試験

なし

Confidential

2.6.5.9 薬物動態試験： 代謝：*In Vivo*

2.6.5.9.1 ウサギ単回点眼時の代謝

Test Article: AR-13324

Study Number		[redacted]		Location: 4.2.2.4-1		
Title		白色ウサギにおける STN1013900 点眼液点眼後の角膜中及び房水中ネタルスジル並びに AR-13503 濃度の評価				
Species		Japanese White Rabbit		Method of Administration	Topical ocular dose to both eyes, single, 50 µL/eye	
Gender (M/F) / Number of animals		M / 2 (per each time point)		Dose	10 µg/eye	
Feeding Condition		Fed		Analyte	Netarsudil, AR-13503	
Vehicle/Formulation		0.02% STN1013900 Ophthalmic Solution		Analysis Method	LC-MS/MS	
Sample		Cornea and Aqueous humor				
Tissue Concentrations (ng/g or mL)						
Time (h)		0.5	1	2	4	8
Cornea	Netarsudil	3210±657	3390±1440	2530±1260	1110±290	790±329
	AR-13503	101±12.3	176±48.5	146±79.1	131±42.3	66.6±28.3
Aqueous Humor	Netarsudil	BLQ	BLQ	BLQ	BLQ	BLQ
	AR-13503	0.121±0.140	1.03±0.354	2.02±1.18	2.08±0.749	0.672±0.193

Each value represents mean±SD (n=4).

BLQ: Below the lower limit of quantification (<0.2 ng/mL).

Confidential

2.6.5.10 薬物動態試験： 代謝：*In Vitro*

2.6.5.10.1 代謝物プロファイル

Test Article: AR-13324 and AR-13503

Study No.	[redacted]	Location: 4.2.2.4-2
Title	*In Vitro* Metabolism of AR-13324	
Study Systems	Liver microsomes of dog, monkey, mouse, rat, male rabbit, pooled male and female human liver microsomes (AR-13324) Liver microsomes of dog, monkey, mouse, rat, male rabbit, pooled male and female human liver microsomes (AR-13503) Liver S9 fractions from human and Aroclor 1254-induced Sprague-Dawley rat Human liver microsomes Cornea homogenate from rabbit, pig, dog, monkey, and human Plasma from rat, rabbit, dog, monkey, and human	
Analyte	Netarsudil and AR-13503	
Analysis Method	LC-MS and HPLC	

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2.6.5.10.1 代謝物プロファイル（続き）

Test Article: AR-13324 and AR-13503

Metabolism of AR-13324 by Liver Microsomes of Dog, Monkey, Mouse, Rat, Rabbit and Human Liver Microsomes - 1 hour incubation			
Initial Concentration: 20 µmol/L			
Species	Gender	Netarsudil (µmol/L)	AR-13503 (µmol/L)
Dog	F	20.50±4.73	0.72±0.47
	M	23.30±4.03	0.84±0.53
Monkey	F	9.37±3.01	10.47±4.37
	M	11.63±3.14	8.85±3.75
Mouse	F	2.68±0.40	16.11±6.43
	M	5.07±1.66	17.32±7.54
Rat	F	20.66±6.19	3.17±1.48
	M	13.86±3.12	5.24±1.68
Rabbit	M	1.30±0.87	13.19±5.35
Human	M/F	8.20±0.94	7.49±2.59

Metabolism of AR-13324 by Human Liver S9 Fractions - 2 hours incubation		
Initial Concentration: 20 µmol/L		
Time (min)	Netarsudil (µmol/L)	AR-13503 (µmol/L)
0	22.78±2.99	-0.31±0.13
15	20.75±2.33	1.61±1.45
30	18.38±1.65	2.81±0.98
45	16.67±2.12	4.01±0.95
60	14.63±1.48	5.09±1.72
90	9.86±2.99	7.15±2.37
120	7.68±1.60	9.41±3.53

Confidential

2.6.5.10.1 代謝物プロファイル（続き）

Test Article: AR-13324 and AR-13503

Metabolism of AR-13503 by Liver Microsomes of Dog, Monkey, Mouse, Rat, Rabbit and Human Liver Microsomes - 1 hour incubation		
Initial Concentration: 20 μmol/L		
Species	Sex	AR-13503 (μmol/L)
Dog	F	21.57±0.66
	M	20.98±1.94
Monkey	F	20.97±2.83
	M	22.03±3.03
Mouse	F	21.59±3.35
	M	22.36±3.41
Rat	F	21.76±5.30
	M	21.52±5.51
Rabbit	M	22.15±6.18
Human	M/F	22.91±7.00

Metabolism of AR-13324 by Human Liver Microsomes - 2 hours incubation		
Initial Concentration: 20 μmol/L		
Time (min)	Netarsudil (μmol/L)	AR-13503 (μmol/L)
0	21.00±3.17	-0.31±0.13
15	19.83±3.17	2.06±0.51
30	16.74±1.76	4.16±1.04
45	13.95±1.76	6.22±1.48
60	14.44±1.24	7.41±1.19
90	7.37±2.21	10.16±2.97
120	4.17±1.07	11.63±3.23

Confidential

2.6.5.10.1 代謝物プロファイル（続き）

Test Article: AR-13324 and AR-13503

Metabolism of AR-13324 by Aroclor 1254-Induced Rat S9 Extract		
Initial Concentration: 20 µmol/L		
Time (min)	Netarsudil (µmol/L)	AR-13503 (µmol/L)
0	22.47±2.48	-0.31±0.13
15	22.04±3.21	0.19±0.34
30	21.80±2.24	0.52±0.24
45	21.02±2.79	0.77±0.40
60	20.95±2.15	1.04±0.76
90	15.98±4.00	1.45±0.49
120	15.62±2.07	1.89±0.87

Metabolism of AR-13324 by Pig, Rabbit, Dog, Monkey and Human Corneas					
Initial Concentration: 200 µmol/L					
Time (min)	Percent Remaining of Netarsudil				
	Pig	Rabbit	Dog	Monkey	Human
0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0
15	88.1±2.2	93.7±4.9	85.5±2.0	98.3±2.4	84.1±1.0
30	79.0±1.9	83.3±5.6	74.9±2.4	92.5±1.0	76.1±2.5
60	67.3±4.0	70.2±6.7	62.2±3.0	82.0±1.2	71.8±2.5
90	60.4±3.8	58.8±8.3	49.4±2.7	75.5±2.7	66.7±4.5
120	54.4±5.0	48.5±7.7	39.5±1.4	68.2±3.7	66.0±5.5
180	44.5±4.6	36.9±7.4	ND	58.5±4.1	63.8±5.0
240	36.3±3.5	29.9±4.5	23.4±1.7	48.4±4.2	60.5±5.3

Confidential

2.6.5.10.1 代謝物プロファイル（続き）

Test Article: AR-13324 and AR-13503

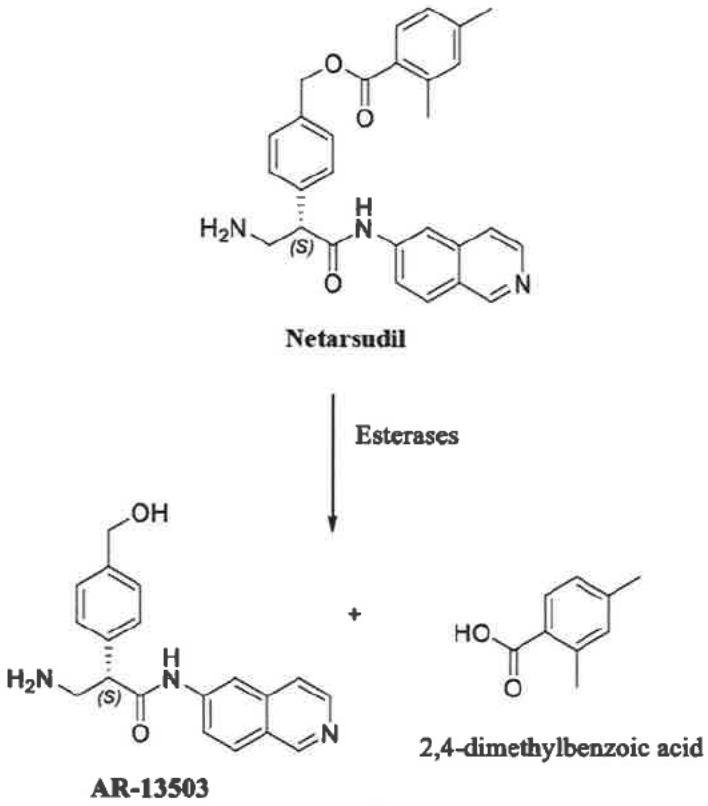
Metabolism of AR-13324 by Rabbit, Human, Monkey, Dog and Rat Plasma (mixed gender)					
Initial Concentration: 100 μmol/L					
Time (min)	Percent Remaining of Netarsudil				
	Rabbit	Human	Monkey	Dog	Rat
0	100	100	100	100	100
15	78	94	101	94	95
30	54	92	98	93	91
90	26	89	91	92	91
120	22	88	97	92	90
180	17	88	96	89	88

Each value represents mean or mean±SD.

ND: Not determined.

Confidential

2.6.5.11 薬物動態試験： 推定代謝経路



Confidential

2.6.5.12 薬物動態試験： 薬物代謝酵素の誘導／阻害

2.6.5.12.1 薬物代謝酵素の誘導

なし

Confidential

2.6.5.12.2 薬物代謝酵素の阻害

Test Article: AR-12432, AR-13165 (di-HCl salt), AR-13084 and AR-13324 (di-HCl salt)

Study No.	[redacted]	Location: 4.2.1.1-3	
Title	Non-Kinase Selectivity Profiling of the Rho Kinase Inhibitors AR-12432, AR-13165, AR-13084 and AR-13324 (CYP450 Data Only)		
Study Systems	*In vitro* Inhibition of CYP450 1A2, 2C19, 2C9, 2D6, 3A4		
Analyte	Each substrate metabolite		
Analysis Method	Enzyme activity (Spectrofluorimetric quantitation)		
Percent Inhibition Recorded at 10 µmol/L Test Compound Concentration			
Cytochrome P450s	AR-13165[1)]	AR-13084[2)]	Netarsudil
1A2	93	15	88
2C19	100	78	100
2C9	72	25	80
2D6	90	65	92
3A4	86	38	84

1) AR-13165 is the racemic mixture of AR-13323 and AR-13324.

2) AR-13084 is the racemic mixture of the active metabolites of AR-13323 and AR-13324.

Confidential

2.6.5.13 薬物動態試験： 排泄

2.6.5.13.1 ウサギ単回及び反復点眼時の排泄

Test Article: ^{14}C-AR-13324

Study No.	[redacted]	Location: 4.2.2.3-1	
Title	Tissue Distribution and Excretion Profile Study of Total Radioactivity in Dutch-Belted Male Rabbits Following Single and Repeated Dose Topical Ocular Administration of [^{14}C]Netarsudil		
Species	Dutch Belted Rabbit	Method of Administration	Topical ocular dose to both eyes, QD, 7 days 35 µL/eye/dose
Gender (M/F) / Number of Animals	M / 4	Dose	0.014 mg/animal
Feeding Conditions	Fed	Radionuclide	^{14}C
Vehicle/Formulation	0.02% ^{14}C-STN1013900 Ophthalmic Solution	Specific Activity	2146 MBq/mmol
Analysis Method	Liquid Scintillation Counting	Sample	Urine, feces and cage wash

Time (h)[1)]	Percent of Dose Recovered					
	Single Dose			Repeated Dose (7 days)		
	Urine	Feces	Total[1)]	Urine	Feces	Total[1)]
0–24	9.88±5.953	48.49±5.95648	61.81±7.749	–	–	–
0–48	11.99±6.710	57.95±3.214	73.78±7.039	–	–	–
0–72	12.40±6.770	60.86±2.832	77.31±7.711	–	–	–
0–96	12.43±6.773	61.58±2.934	78.06±8.017	–	–	–
0–120	12.43±6.77	61.78±2.839	78.27±7.905	–	–	–
0–144	12.43±6.77	61.81±2.820	78.29±7.859	–	–	–
0–168	12.43±6.77	61.81±2.819	78.29±7.856	15.99±1.565[2)]	52.54±3.135[2)]	73.84±5.067[2)]

QD: Once a day.

Confidential

–: Not evaluated.

Each value represents mean±SD (n=4).

1) The sum of dose recovered in urine, feces, and cage wash samples.

2) Time after the first administration of repeated dose.

Confidential

2.6.5.13.2 ラット単回静脈内投与時の排泄

Test Article: ^{14}C-AR-13324

Study number	[redacted]							Location: 4.2.2.3-2			
Title	Excretion Mass Balance and Quantitative Whole-Body Autoradiography in Long-Evans Rats Following a Single Intravenous Dose of [^{14}C]AR-13324										
Species	Long-Evans Rat							Method of Administration		Single iv bolus injection	
Gender (M/F) / Number of Animals	M/3							Dose		1 mg/kg	
Feeding Conditions	Fed							Radionuclide		^{14}C	
Vehicle/Formulation	Saline/Solution							Specific Activity		2146 MBq/mmol	
Analysis Method	Liquid Scintillation Counting							Sample		Urine, feces, cage rinse, cage wash and cage wipe	
Excretion Route	Percent of Dose Recovered										
	Pre-dose	0–8 h	8–24 h	24–48 h	48–72 h	72–96 h	96–120 h	120–144 h	144–168 h	Subtotal	Total[3)]
Urine	BLQ	7.2±2.6	5.6±1.4	0.8±0.1	0.4±0.1	0.2±0.0	0.1±0.0	0.1±0.0	BLQ	14.4±2.8[1)]	91.0±0.5
Feces	BLQ	0.2±0.1	65.8±0.7	6.9±2.1	1.6±0.5	0.7±0.2	0.4±0.1	0.3±0.1	0.2±0.0	75.9±2.2[1)]	
Cage Rinse	–	–	0.4±0.0	0.1±0.0	BLQ	0.1±0.0	BLQ	BLQ	–	0.6±0.0[2)]	
Cage Wash	–	–	–	–	–	–	–	–	0.1±0.0[2)]	0.1±0.0[1)]	
Cage Wipe	–	–	–	–	–	–	–	–	0.1±0.1[2)]	0.1±0.1[1)]	

–: Not evaluated.

Each value represents mean±SD (n=3).

BLQ: Below the limit of detection or a value <500 dpm.

1) Dose recovered from 0-168 h.

2) Dose recovered from 0-144 h.

3) The sum of dose recovered in all samples.

Confidential

2.6.5.14　薬物動態試験：　排泄：胆汁中

なし

2.6.5.15　薬物動態試験：　薬物相互作用

なし

2.6.5.16　薬物動態試験：　その他

なし

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