

**Results:**

**Table 3. Results of the bacterial reversion test of NK-104-lactone [direct method: -S9]** Exp. No.3846 (144-019)

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>a)</sup>	0	117	10	28	22	6
Test substance	2.44	118				3
	4.88	109				6
	9.77	116	6			4
	19.5	109	10			5
	39.1	106	13	26	21	5
	78.1	90 <sup>b)</sup>	9	20	14	1 <sup>c)</sup>
	156		7 <sup>b)</sup>	27	18	
	313		7 <sup>b)</sup>	25	25	
	625 <sup>d)</sup>			32	20 <sup>d)</sup>	
	1250 <sup>d)</sup>			22 <sup>d)</sup>	19 <sup>d)</sup>	
	Positive control compound		AF-2	NaN <sub>3</sub>	AF-2	AF-2
Dose (µg/plate)		0.01	0.5	0.01	0.1	80
Mean revertant colonies per plate		521	340	132	637	572

AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide      NaN<sub>3</sub>: Sodium azide      9-AA: 9-Aminoacridine hydrochloride

<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Growth inhibition was observed  
<sup>c)</sup>: Visible precipitation was occurred

(Sponsor, M4, 3846, p38)

**Table 4. Results of the bacterial reversion test of NK-104-lactone [activation method: +S9]** Exp. No.3846 (144-019)

Compound	Dose (µg/plate)	Mean revertant colonies per plate					
		TA100	TA1535	WP2uvrA	TA98	TA1537	
DMSO <sup>a)</sup>	0	113	9	31	32	7	
Test substance	9.77	125	10	33		6	
	19.5	117	10	36		6	
	39.1	129	9	27	24	8	
	78.1	118	11	27	28	12	
	156	148	11	26	37	6 <sup>d)</sup>	
	313	124 <sup>d)</sup>	11 <sup>d)</sup>	22 <sup>d)</sup>	33	8 <sup>d)</sup>	
	625				32 <sup>d)</sup>		
	1250 <sup>d)</sup>				27 <sup>d)</sup>		
	Positive control compound		2-AA	2-AA	2-AA	2-AA	2-AA
	Dose (µg/plate)		1	2	10	0.5	2
Mean revertant colonies per plate		840	310	756	290	163	

2-AA: 2-Aminoanthracene

<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Growth inhibition was observed  
<sup>d)</sup>: Visible precipitation was occurred

(Sponsor, M4, 3846, p39)

Study validity: A reproducible or dose-related increase in colonies to twice the level in the solvent controls was judged as positive.

**3847 – Chromosomal aberration test in cultured mammalian cells on NK-104 lactone**

**Key findings:**

- NK104 was negative for chromosomal aberrations in CHL cells, both with and without metabolic activation.

Volume #, and page #: M4, 3847

Conducting laboratory and location: (b) (4)

Date of study initiation: August 13, 1998

GLP compliance: Yes.

QA reports: yes (X) no ( )

Drug, lot number, and purity: YT-00213-193-B, 99.5% purity

**Methods:**

Strains/species/cell line: Chinese hamster lung (CHL cells) fibroblast cell line.

Doses used in definitive study: See study results.

Basis of dose selection:

Table 1. Results of growth inhibition test on NK-104-lactone [direct method]				Exp. No. 3847 (144-020)			
[direct method: 24 hrs]				[direct method: 48 hrs]			
Compound	Dose (µg/mL)	Survival (%)	[Mean]	Compound	Dose (µg/mL)	Survival (%)	[Mean]
Saline <sup>a</sup>	0	100.0	[100.0]	Saline <sup>a</sup>	0	100.0	[100.0]
		100.0				100.0	
Test substance	0.488	97.7	[97.0]	Test substance	0.0610	102.0	[101.3]
		96.3				100.6	
	0.977	93.2	[94.7]		0.122	94.9	[96.4]
		96.1				98.0	
	1.95	92.6	[92.3]		0.244	98.0	[97.8]
		92.1				97.6	
	3.91	86.5	[88.9]		0.488	96.8	[95.8]
		91.2				94.9	
	7.81	68.7	[68.7]		0.977	82.1	[78.6]
		68.7				75.1	
	15.6	54.3	[53.6]		1.95	69.6	[70.8]
		52.8				72.0	
	31.3	41.8	[44.6]		3.91	63.3	[61.4]
		47.4				59.6	
	62.5	37.0	[37.2]		7.81	25.7	[25.9]
		37.4				26.2	
	125	11.7	[11.9]		15.6	13.3	[13.8]
		12.1				14.3	
	250	4.0	[3.6]		31.3	3.7	[3.4]
		3.3				3.1	

50% Growth inhibition dose was as follows:  
 [direct method: 24 hrs]-----21.4 (µg/ml.)  
 [direct method: 48 hrs]-----3.84 (µg/mL)  
<sup>a</sup>: Solvent control

(Sponsor, M4, 3847, p33)

**Table 2. Results of growth inhibition test on NK-104-lactone [activation method]**

Exp. No. 3847 (144-020)

[activation method: -S9]				[activation method: +S9]				
Compound	Dose (µg/ml.)	Survival (%)	[Mean]	Compound	Dose (µg/ml.)	Survival (%)	[Mean]	
Saline <sup>a)</sup>	0	100.0	[100.0]	Saline <sup>a)</sup>	0	100.0	[100.0]	
Test substance	0.977	100.0		Test substance	62.5	93.7	[96.6]	
		99.4	[98.2]				99.4	
	1.95	101.5	[101.1]		125	97.6	[96.8]	
		100.6					95.9	
	3.91	93.6	[96.5]		250	74.8	[73.8]	
		99.3					72.8	
	7.81	96.3	[93.9]		500 <sup>b)</sup>	42.3	[41.6]	
		91.5					41.0	
	15.6	65.4	[65.4]		1000 <sup>b)</sup>	16.6	[14.6]	
		65.4					12.6	
	31.3	55.8	[55.7]		2000 <sup>b)</sup>	6.0	[5.8]	
		55.6					5.5	
62.5	50.4	[51.1]						
	51.8							
125	35.6	[35.7]						
	35.7							
250	11.8	[11.1]						
	10.3							
500 <sup>b)</sup>	5.0	[4.9]						
	4.7							

50% Growth inhibition dose was as follows:  
 [activation method: -S9] — 49.2 (µg/mL)  
 [activation method: +S9] — 433 (µg/mL)

<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Visible precipitation was occurred at the end of exposure period

(Sponsor, M4, 3847, p34)

Negative controls: Vehicle controls were treated with physiological saline

Positive controls: For the direct method, mitomycin C (MMC) was employed. For the metabolic activation method, cyclophosphamide (CP) was used.

**Results:**

**Table 3. Chromosome aberration test on CHL cells treated with NK-104-lactone [direct method: 24 hrs]**

Exp. No. 3847 (144-020)

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations						Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	etc	csb	csc	oth				
Saline <sup>a)</sup>	0	200	0	0	0	0	0	0	0.0-	0.0-	0.5-	-
Test substance	6.25	200	1	1	0	0	0	0	1.0-	0.5-	0.5-	-
	12.5	200	0	1	0	0	0	0	0.5-	0.5-	0.0-	-
	25.0	200	0	3	0	0	0	0	1.5-	1.5-	1.0-	-
	50.0	Toxic										
MMC <sup>b)</sup>	0.05	200	6	30	80	0	0	0	50.0+	49.0+	0.0-	+

ctb: Chromatid break    etc: Chromatid exchange    csb: Chromosome break    csc: Chromosome exchange    oth: others

<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Mitomycin C)

(Sponsor, M4, 3847, p35)

**Table 4. Chromosome aberration test on CHL cells treated with NK-104-lactone [direct method: 48 hrs]** Exp. No. 3847 (144-020)

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations						Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse	oth				
Saline <sup>a)</sup>	0	200	0	0	0	0	0	0	0.0-	0.0-	0.0-	-
Test substance	1.56	200	2	0	0	0	0	0	1.0-	0.0-	1.5-	-
	3.13	200	0	1	0	0	0	0	0.5-	0.5-	0.5-	-
	6.25	200	1	2	0	0	0	0	1.5-	1.0-	0.5-	-
	12.5	Toxic										
MMC <sup>b)</sup>	0.025	200	12	43	92	0	1	0	58.0+	56.0+	0.0-	+

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Mitomycin C)

(Sponsor, M4, 3847, p36)

**Table 6. Chromosome aberration test on CHL cells treated with NK-104-lactone [activation method: +S9]** Exp. No. 3847 (144-020)

Compound	Dose (µg/ml.)	Number of Cells	Number of cells with structural aberrations						Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse	oth				
Saline <sup>a)</sup>	0	200	0	0	0	0	0	0	0.0-	0.0-	0.0-	-
Test substance	100	200	1	0	1	0	0	0	1.0-	0.5-	0.0-	-
	200	200	0	0	0	0	0	0	0.0-	0.0-	0.5-	-
	400	200	0	1	1	0	0	0	1.0-	1.0-	0.5-	-
	800 <sup>d)</sup>	Toxic										
Cp <sup>b)</sup>	12.5	200	10	24	105	0	1	0	59.5+	57.5+	0.0-	+

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Cyclophosphamide)  
<sup>d)</sup>: Visible precipitation was occurred at the end of exposure period

(Sponsor, M4, 3847, p38)

Study validity (comment on replicates, counting method, criteria for positive results, etc.): A negative result was less than 5% aberrant cells. Suspicious was 5-10% aberrant cells. Positive was >10% aberrant cells. Less than 50% live cells per culture was determined to be cytotoxic.

There were no (false) positive results of structural aberrations or polyploidy among untreated and solvent-treated controls. There were no false negatives, as all the positive controls produced expected chromosomal aberrations. Metabolic activity was required by cyclophosphamide for a positive response.

**Table 5. Chromosome aberration test on CHL cells treated with NK-104-lactone [activation method: -S9]** Exp. No. 3847 (144-020)

Compound	Dose (µg/ml.)	Number of Cells	Number of cells with structural aberrations						Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse	oth				
Saline <sup>a)</sup>	0	200	0	1	0	0	0	0	0.5-	0.5-	0.0-	-
Test substance	25.0	200	2	1	0	0	0	0	1.5-	0.5-	0.0-	-
	50.0	200	2	1	1	0	0	0	2.0-	1.0-	0.0-	-
	100	200	1	3	1	0	0	0	2.5-	2.0-	0.0-	-
	200	Toxic										
Cp <sup>b)</sup>	12.5	200	1	3	2	0	0	0	2.5-	2.0-	0.0-	-

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Cyclophosphamide)

(Sponsor, M4, 3847, p37)

**RF9964 – Two-week repeated dose oral toxicity study with 8-OH-NK-104 Ca salt in rats**

The toxicities of the major hydroxylated metabolite of NK-104 were evaluated in an acute, repeat-dose study in male rats.

**GROUP ASSIGNMENTS**

Group	Test article	Dose (mg/kg) BID	Volume (mL/kg)	Concentration (mg/mL)	Number of animals
1	Control (Vehicle)	0	20	0	6 males
2	8-OH NK-104 Ca salt	200	20	1.0	6 males
3	8-OH NK-104 Ca salt	400	20	2.0	6 males

(Sponsor, M4, RF9964, p8)

No animals survived to the planned 2 and 1 week end-point (for 200 and 400 mg/kg/day, respectively). The effects on kidneys were the primary end-points. Rats in both dose groups lost weight dramatically compared to controls. Alkaline phosphatase (ALP) was increased 2-fold in the high-dose 400 mg/kg/day group. Lactate dehydrogenase (LDH) was increased 4 to 5 fold, blood urea nitrogen (BUN) was also increased 2 to 3-fold, aspartate transaminase (AST) increased 10 to 16-fold, alanine transaminase (ALT) was increased 10 to 20-fold in the 200 and 400 NK-104 mg/kg/day dose groups versus controls, respectively.

**GROSS FINDINGS**

Group	Dose	Findings	Incidence (%)
1	Control (vehicle)	*)	0/6 (0)
2	200mg/kg x 2/day	Staining around perineum	1/6 (16.7)
		Swelling of adrenal gland	2/6 (33.3)
		Atrophy of thymus	1/6 (16.7)
3	400mg/kg x 2/day	Atrophy of thymus	5/6 (83.3)
		Congestion of liver	5/6 (83.3)
		Congestion of lung	5/6 (83.3)
		Staining around perineum	5/6 (83.3)
		Swelling of adrenal gland	5/6 (83.3)
*) : No abnormality			

(Sponsor, M4, RF9964, p25)

Histopathological findings: Drastic body weight decreases in a short period of time (<2 weeks) confounded organ weight comparisons. Forestomach hyperkeratosis, (3/4 and 3/5), splenic atrophy (2/4, 5/5), decreased zymogen granules in pancreas (3/4, 5/5), degeneration of midlobular hepatocytes (2/5, 5/5), and degeneration of proximal renal tubular epithelium (3/4, 5/5) were observed at 200 and 400 mg/kg/day NK-104 dose levels versus none (0/6) in controls, respectively.

Centrilobular vacuolar degeneration of hepatocytes (4/5), focal necrosis of liver (2/5), and hepatocellular necrosis (3/5) were observed at 400 mg/kg/day NK-104 versus none (0/6) in controls.

Liver and kidney appeared to be the major target organs, with the more severe effects at lower doses being found in the kidney. No NOAEL was identified in this study.

**Impurities**

The NK-104 (b) (4) which are process impurities, are present in the drug substance at concentrations that exceed the ICH Q3A qualification threshold for the drug substance. Kowa has attempted to qualify the NK-104 (b) (4) in the following manner: 1) The Sponsor verified exposure in a relevant non-clinical species by administering supra-physiological doses of the (b) (4) alone to mice (they recorded ~100-fold higher levels of the (b) (4) in mice than those concentrations recorded in humans after administration of the maximum recommended human dose of 4 mg/day NK-104), and in particular they measured uptake by the bone (for conduct of a bone-specific gene-tox study), 2) The Sponsor performed the required gene-tox assays (Ames, chromosomal aberration, an *in vivo* mouse micronucleus assay), 3) The Sponsor performed a dedicated 30-day toxicity study by administering the (b) (4) alone (a 14-90 day study is suggested by the guidance) in a single relevant species. Therefore, Kowa has attempted to qualify the (b) (4) process impurities in compliance with the guidance on impurities in drug substances, ICH Q3A.

**RF9501 – Single dose toxicity study of UK-4 (relative substance of NK-104) in mice by oral administration**

This study was designed to evaluate an oxidized form of NK-104 that was formed upon extended storage of lot# 104P-9202. This degradants (b) (4), was present a (b) (4) but (b) (4) of the drug substance.

**DOSE GROUP ASSIGNMENTS**

Group	Drug	Dose (mg/kg)	Volume (mL/kg)	Concentration (w/v%)	Number of animals	
					Males	Females
1	Control (0.5% CMC)	-	40	-	5	5
2	(b) (4)	(b) (4)	20	1.25	5	5
3	(b) (4)	(b) (4)	20	2.5	5	5
4	(b) (4)	(b) (4)	20	5.0	5	5
5	(b) (4)	(b) (4)	40	5.0	5	5
6	NK-104	300	20	2.5	5	5
7	NK-104	1000	20	5.0	5	5
8	(b) (4)	(b) (4)	10	1.25	5	5

(Sponsor, M4, RF9501, p5)

One mortality occurred in a female in the 1000 mg/kg group, and most male and all female animals died (8/10) in the 2000 mg/kg dose group. Forestomach thickening was observed at a greater rate in males for (b) (4) (5/5) than in NK-104 controls (2/5) at the 1000 mg/kg dose, whereas female rates were identical (4/5) in both groups. The results of this study indicate that (b) (4) has a lower maximum tolerated dose than NK-104, but that they are roughly equally likely to cause forestomach thickening. This finding indicates that (b) (4) is likely to have pharmacodynamic effects on HMG-CoA reductase similar to (b) (4) NK-104.

**RFG2519 – Single dose toxicity study of NK-104 (b) (4) in rats by oral administration**

Doses of 250, 500, 1000 mg/kg were administered. Staining around the perineum was found in high-dose females which resolved during the observation period (14 days). A transient decreased in food consumption was found in mid-dose males and high-dose rats. Body weight was not affected. Histopathology was unremarkable. Plasma concentrations of the optical isomer increased with dose but appeared to show saturation of absorption. Females appeared to have greater exposure than males. The acute toxicity (b) (4) was less than that of the NK-104.

**Table 9. Plasma concentrations and toxicokinetic parameters of NK-104 (b) after single oral administration of NK-104 (b) rats**

Dose	No.	Plasma Concentration (µg/mL)					C <sub>max</sub> (µg/mL)	AUC (µg.hr/mL)
		Time after Dosing (hr)						
		1	2	4	6	8		
250 mg/kg	male							
	5M1	43.3	71.2	76.8	70.1	51.1	76.8	494.9
	5M2	65.2	76.2	126.5	114.5	87.9	126.5	749.4
	5M3	123.9	110.1	106.1	80.5	46.0	123.9	708.3
	Mean	77.5	85.8	103.1	88.3	61.7	109.1	650.9
	S.D.	41.7	21.2	25.0	23.2	22.9	28.0	136.6
250 mg/kg	female							
	5F1	93.3	108.4	83.2	85.6	68.2	108.4	661.5
	5F2	144.9	125.8	150.8	124.5	77.4	150.8	961.7
	5F3	176.6	205.2	178.0	164.3	123.0	205.2	1292.1
	Mean	138.3	146.5	137.3	124.8	89.5	154.8	971.8
	S.D.	42.1	51.6	48.9	39.4	29.4	48.5	315.4
500 mg/kg	male							
	6M1	81.8	112.7	98.1	119.7	93.0	119.7	779.5
	6M2	116.7	87.0	127.2	122.8	111.9	127.2	859.5
	6M3	183.8	128.6	144.0	132.0	93.4	183.8	1001.9
	Mean	128.8	109.5	123.1	124.8	99.4	136.9	880.3
	S.D.	41.1	20.8	23.2	6.4	10.8	23.6	112.6
500 mg/kg	female							
	6F1	188.7	174.0	189.8	164.5	163.6	189.8	1313.9
	6F2	203.5	212.6	255.0	243.8	224.0	255.0	1744.0
	6F3	179.5	152.1	185.5	216.7	192.7	216.7	1404.6
	Mean	187.9	179.6	210.1	208.3	193.4	220.5	1487.5
	S.D.	13.5	30.6	38.9	40.3	30.2	32.8	226.7
1,000 mg/kg	male							
	7M1	142.4	187.9	167.2	154.3	109.7	187.9	1177.3
	7M2	224.7	209.8	188.9	145.6	130.1	224.7	1336.6
	7M3	148.7	154.3	183.1	139.1	135.4	183.1	1155.0
	Mean	169.3	184.7	179.7	146.3	123.1	198.6	1223.6
	S.D.	48.0	26.9	11.3	7.6	13.6	22.8	108.2
1,000 mg/kg	female							
	7F1	217.4	201.8	185.0	193.0	221.6	221.6	1497.5
	7F2	266.7	299.2	312.4	317.0	---	317.0	1637.4*
	7F3	214.4	247.5	263.7	269.3	261.5	269.3	1913.0
	Mean	232.8	249.5	253.7	239.7	241.5	269.3	1689.3
	S.D.	29.3	48.8	64.3	62.6	28.2	47.7	209.6

---: No sample because of animal died  
 \*: AUC value calculated up to 6 hours after dosing  
 Mean and S.D. value was calculated by excepted for this data.

(Sponsor)

**G2520 – One-month oral toxicity of NK-104 (b) (4) (impurity) in rat**

NK-104(b) (4) is identified as an impurity found in trace amounts of NK-104 (amount not specified). The (b) (4) was given by oral gavage (0.5% CMC-Na) at (b) (4) g to Wistar rats. Body weight gain and food consumption were unremarkable, in fact standard toxicity parameters were all unremarkable except liver weights (absolute, relative). Relative (to body) liver weights were increased in high-dose males and females. However no remarkable correlative change in clinical chemistry or hematology or histopathology (control, high-dose only) is observed. Therefore the NOAEL=10 mg/kg for the (b) (4) in this one month rat study. Generally this would suggest that NK-104(b) (4) has less toxicity than that of NK-104. Since limited amounts of this impurity is present in NK-104 it is considered to contribute minimally to the toxicity of the parent in rats.

**3844 – Mutagenicity testing of NK-104(b) (4) in bacterial reverse mutation assays**

NK-104(b) (4) was not mutagenic in an Ames assay in the following strains:

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<i>Salmonella typhimurium</i> TA100	(histidine-requiring mutant, base-pair substitution type)
<i>Salmonella typhimurium</i> TA98	(histidine-requiring mutant, frameshift type)
<i>Salmonella typhimurium</i> TA1535	(histidine-requiring mutant, base-pair substitution type)
<i>Salmonella typhimurium</i> TA1537	(histidine-requiring mutant, frameshift type)
<i>Escherichia coli</i> WP2 <i>uvrA</i>	(tryptophan-requiring mutant, base-pair substitution type)

(Sponsor, M4, 3844, p17)

DOSE RANGE-FINDING, DIRECT METHOD, -S9

Compound	Dose (µg/plate)	Mean revertant colonies per plate						
		TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537		
DMSO <sup>a)</sup>	0	110	12	25	25	8		
NK-104(b)	(b) (4)	94	11	23	23	6		
		104	10	24	26	7		
		106	11	23	27	7		
		99	12	25	22	8		
		101	8	20	25	7		
		98 <sup>b)</sup>	10 <sup>b)</sup>	26	24 <sup>b)</sup>	7 <sup>b)</sup>		
		63 <sup>b)</sup>	10 <sup>b)</sup>	23 <sup>b)</sup>	29 <sup>b)</sup>	4 <sup>b)</sup>		
		53 <sup>b)</sup>	10 <sup>b)</sup>	19 <sup>b)</sup>	24 <sup>b)</sup>	4 <sup>b)</sup>		
		Positive control compound		AF-2	NaN <sub>3</sub>	AF-2	AF-2	9-AA
		Dose (µg/plate)		0.01	0.5	0.01	0.1	80
Mean revertant colonies per plate		478	397	140	751	407		
AF-2: 2-(2-Fury 1)-3-(5-nitro-2-fury 1)acrylamide		NaN <sub>3</sub> : Sodium azide		9-AA: 9-Aminoacridine hydrochloride				
a): Solvent control								
b): Growth inhibition was observed								

(Sponsor, M4, 3844, p35)

**DOSE RANGE-FINDING, METABOLIC ACTIVATION, +S9**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>o)</sup>	0	114	14	28	27	11
NK-104 <sup>(b)</sup> (b) (4)	(b) (4)	103	13	21	29	12
	(b) (4)	122	14	34	28	8
	(b) (4)	128	13	29	31	9
	(b) (4)	109	13	34	31	12
	(b) (4)	94	10	26	34	11
	(b) (4)	94 <sup>o)</sup>	10	21	33	8
	(b) (4)	81 <sup>o)</sup>	10 <sup>o)</sup>	23 <sup>o)</sup>	22 <sup>o)</sup>	10 <sup>o)</sup>
	(b) (4)	78 <sup>o)</sup>	10 <sup>o)</sup>	16 <sup>o)</sup>	23 <sup>o)</sup>	4 <sup>o)</sup>
Positive control compound	2-AA	2-AA	2-AA	2-AA	2-AA	
Dose (µg/plate)	1	2	10	0.5	2	
Mean revertant colonies per plate	625	336	710	213	148	
2-AA: 2-Aminoanthracene						
<sup>o)</sup> : Solvent control						
<sup>o)</sup> : Growth inhibition was observed						

(Sponsor, M4, 3844, p36)

**DOSE RANGE-FINDING, DIRECT METHOD, -S9**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>o)</sup>	0	103	12	23	18	8
NK-104 <sup>(b)</sup> (b) (4)	(b) (4)	98	12		13	12
	(b) (4)	87	12		22	10
	(b) (4)	96	10	19	19	8
	(b) (4)	104	6	22	13	12
	(b) (4)	100	7	23	17 <sup>o)</sup>	9 <sup>o)</sup>
	(b) (4)	74 <sup>o)</sup>	7 <sup>o)</sup>	17	16 <sup>o)</sup>	9 <sup>o)</sup>
	(b) (4)			19 <sup>o)</sup>		
	(b) (4)			17 <sup>o)</sup>		
Positive control compound	AF-2	NaN <sub>3</sub>	AF-2	AF-2	9-AA	
Dose (µg/plate)	0.01	0.5	0.01	0.1	80	
Mean revertant colonies per plate	569	409	148	696	335	
AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide      NaN <sub>3</sub> : Sodium azide      9-AA: 9-Aminoacridine hydrochloride						
<sup>o)</sup> : Solvent control						
<sup>o)</sup> : Growth inhibition was observed						

(Sponsor, M4, 3844, p37)

**MAIN STUDY, METABOLIC ACTIVATION, +S9**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>o)</sup>	0	136	14	24	32	11
NK-10 <sup>(b)</sup> (b) (4)	(b) (4)	121				
	(b) (4)	137				
	(b) (4)	121	16	23	34	10
	(b) (4)	124	15	24	25	6
	(b) (4)	109	9	20	26	9
	(b) (4)	104 <sup>o)</sup>	10	19	23	7
	(b) (4)		7 <sup>o)</sup>	18	25 <sup>o)</sup>	8 <sup>o)</sup>
	(b) (4)		7 <sup>o)</sup>	15 <sup>o)</sup>	20 <sup>o)</sup>	5 <sup>o)</sup>
	Positive control compound	2-AA	2-AA	2-AA	2-AA	2-AA
	Dose (µg/plate)	1	2	10	0.5	2
Mean revertant colonies per plate	587	361	717	209	160	
2-AA: 2-Aminoanthracene						
<sup>o)</sup> : Solvent control						
<sup>o)</sup> : Growth inhibition was observed						

(Sponsor, M4, 3844, p38)

**3845 – Chromosomal aberration test in cultured mammalian cells on NK-104**  
 (b) (4)

A chromosomal aberration assay was performed using Chinese hamster lung fibroblast (CHL) cells. NK-104 (b) (4) was negative for chromosomal aberrations in this analysis.

**DOSE RANGE-FINDING FOR CYTOTOXICITY, DIRECT METHOD, 24 AND 48 HOURS (GROWTH INHIBITION)**

[direct method: 24 hrs]				[direct method: 48 hrs]			
Compound	Dose (µg/mL)	Survival (%)	[Mean]	Compound	Dose (µg/mL)	Survival (%)	[Mean]
Saline <sup>a)</sup>	0	100.0	[100.0]	Saline <sup>a)</sup>	0	100.0	[100.0]
NK-104 (b) (4)	(b) (4)	100.0		NK-104 (b) (4)	(b) (4)	100.0	
		96.1	[94.9]			88.9	[91.2]
		93.6				93.4	
		82.4	[80.9]			83.0	[83.3]
		79.5				83.6	
		76.3	[74.9]			61.3	[63.1]
		73.6				64.8	
		70.6	[69.2]			45.7	[44.5]
		67.8				43.3	
		66.1	[65.5]			22.7	[20.9]
		64.8				19.2	
		57.7	[56.5]			14.1	[14.3]
		55.2				14.4	
		44.8	[42.1]			12.0	[12.0]
39.5		12.0					
8.5	[7.0]	0.6	[0.3]				
5.5		0.0					

50% Growth inhibition dose was as follows:  
 [direct method: 24 hrs]-----394 (µg/mL)  
 [direct method: 48 hrs]-----106 (µg/mL)  
<sup>a)</sup>: Solvent control

(Sponsor, M4, 3845, p33)

**DOSE RANGE-FINDING FOR CYTOTOXICITY(GROWTH INHIBITION) DIRECT AND WITH METABOLIC ACTIVATION**

[activation method: -S9]				[activation method: +S9]			
Compound	Dose (µg/mL)	Survival (%)	[Mean]	Compound	Dose (µg/mL)	Survival (%)	[Mean]
Saline <sup>a)</sup>	0	100.0	[100.0]	Saline <sup>a)</sup>	0	100.0	[100.0]
NK-104 (b) (4)	(b) (4)	100.0		NK-104 (b) (4)	(b) (4)	100.0	
		103.9	[104.5]			97.7	[99.2]
		105.2				100.6	
		98.9	[99.9]			86.9	[87.3]
		100.8				87.8	
		99.5	[97.9]			79.7	[79.5]
		96.4				79.3	
		92.3	[89.2]			77.7	[77.7]
		86.1				77.7	
		80.4	[82.5]			69.5	[68.5]
		84.7				67.5	
		72.1	[73.2]			63.0	[63.2]
		74.3				63.4	
		32.4	[32.5]			37.1	[36.9]
32.6		36.7					
12.4	[11.8]	13.6	[13.7]				
11.1		13.8					

50% Growth inhibition dose was as follows:  
 [activation method: -S9]-----427 (µg/mL)  
 [activation method: +S9] -----409 (µg/mL)  
<sup>a)</sup>: Solvent control

(Sponsor, M4, 3845, p34)

**DIRECT METHOD, 24 HOURS**

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations					Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse				
Saline <sup>a)</sup>	0	200	1	1	0	0	0	0.5-	0.5-	0.5-	-
NK-104(b)	(b) (4)	200	0	2	0	0	0	1.0-	1.0-	0.0-	-
		200	1	1	1	0	0	1.5-	1.0-	0.5-	-
		200	2	8	4	0	0	6.5 ±	6.0 ±	0.5-	±
		200	0	1	2	0	0	1.5-	1.5-	0.0-	-
		Toxic	200	10	40	83	0	0	53.0+	52.0+	1.0-

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Mitomycin C)

(Sponsor, M4, 3845, p35)

**DIRECT METHOD, 48 HOURS**

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations					Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse				
Saline <sup>a)</sup>	0	200	0	2	1	0	0	1.5-	1.5-	0.5-	-
NK-104(b)	(b) (4)	200	0	0	1	0	0	0.5-	0.5-	0.5-	-
		200	1	2	1	0	1	2.5-	2.0-	0.5-	-
		200	0	6	4	0	0	4.0-	4.0-	0.0-	-
		Toxic	200	3	49	99	0	1	59.0+	59.0+	0.5-

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Mitomycin C)

(Sponsor, M4, 3845, p36)

**METABOLIC ACTIVATION METHOD, -S9**

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations					Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement	
			gap	ctb	cte	csb	cse					oth
Saline <sup>a)</sup>	0	200	0	2	1	0	0	1.5-	1.5-	0.0-	-	
NK-104(b)	(b) (4)	200	1	0	0	0	0	0.5-	0.0-	0.0-	-	
		200	0	2	0	1	0	1.5-	1.5-	0.5-	-	
		200	1	1	1	0	0	1.5-	1.0-	0.5-	-	
		Toxic	200	0	5	0	0	0	2.5-	2.5-	0.0-	-
		CP <sup>b)</sup>	12.5	200	0	5	0	0	0	2.5-	2.5-	0.0-

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Cyclophosphamide)

(Sponsor, M4, 3845, p37)

**METABOLIC ACTIVATION METHOD, +S9**

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations					Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse				
Saline <sup>a)</sup>	0	200	0	0	0	0	0	0.0-	0.0-	0.0-	-
NK-104(b)	(b) (4)	200	0	0	0	0	0	0.0-	0.0-	0.0-	-
		200	0	0	0	0	0	0.0-	0.0-	0.5-	-
		200	0	2	0	0	0	1.0-	1.0-	0.5-	-
		Toxic	200	0	37	92	0	0	53.5+	53.5+	1.0-

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others  
<sup>a)</sup>: Solvent control  
<sup>b)</sup>: Positive control (Cyclophosphamide)

(Sponsor, M4, 3845, p38)

**CONFIRMATIVE ASSAY WITH METABOLIC ACTIVATION, +S9**

Compound	Dose (µg/mL)	Number of Cells	Number of cells with structural aberrations						Total (+gap) (%)	Total (-gap) (%)	Polyploid cells (%)	Final judgement
			gap	ctb	cte	csb	cse	oth				
Saline <sup>a)</sup>	0	200	0	0	0	0	0	0	0.0-	0.0-	0.5-	-
NK-104 <sup>(b) (4)</sup>	(b) (4)	200	2	3	1	0	0	0	3.0-	2.0-	0.0-	-
		200	2	7	3	0	0	0	6.0±	5.0±	0.5-	±
		200	2	9	6	0	0	0	8.0±	7.0±	0.5-	±
		200	1	6	5	1	1	0	7.0±	6.5±	1.0-	±
		200	2	6	1	0	0	0	4.5-	3.5-	1.5-	-
		200	0	4	2	0	0	0	3.0-	3.0-	0.5-	-
		200	3	1	7	0	0	0	5.5±	4.0-	0.5-	-
MMC <sup>b)</sup>	0.05	200	13	42	103	0	0	0	62.0+	59.5+	0.5-	+

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others

<sup>a)</sup>: Solvent control

<sup>b)</sup>: Positive control (Mitomycin C)

(Sponsor, M4, 3845, p39)

**RFG2524 – Mouse micronucleus of NK-104<sup>(b) (4)</sup>**

A single dose of 250, 500 or 750 mg/kg was given to CD-1 mice the high-dose was estimated to be an MTD. No significant difference was found in micronucleated cells in the NK-104<sup>(b) (4)</sup> treated group.

(b) (4)

**RFG2521 – Single dose toxicity study of NK-104<sup>(b) (4)</sup> in rats by oral administration**

The same doses were tested. In the high-dose females 3/5 animals died, no mortality was observed in males. Gross necropsy findings were similar to those of NK-104 although histopathology was not performed. Findings included inflation of the stomach, accumulation of food and invagination of the intestine. In females given<sup>(b) (4)</sup> decreased locomotion, ptosis, diarrhea, staining around the perineum and decreased body weight gain were observed. In rats given<sup>(b) (4)</sup> decreased food consumption was observed which resolved during the 14 day observation period.

**G2522 – One-month repeated dose toxicity study of NK-104<sup>(b) (4)</sup> by oral administration in rats**

NK-104<sup>(b) (4)</sup> is identified as an impurity found in trace amounts of NK-104 (amount not specified). The<sup>(b) (4)</sup> was given by oral gavage (0.5% CMC-Na) at<sup>(b) (4)</sup> to Wistar rats. Body weight gain and food consumption were unremarkable, in fact standard toxicity parameters were all unremarkable except liver weights (absolute, relative). Relative (to body) liver weights were increased in high-dose males and females. However no remarkable correlative change in clinical chemistry or hematology or histopathology (control, high-dose only) is observed. Therefore the NOAEL=10 mg/kg for the<sup>(b) (4)</sup> in this one month rat study.

In one month toxicity studies of NK-104 in rats, hypertrophy of forestomach, hyperkeratosis of mucosal epithelium of forestomach, acanthosis, infiltration of monocytes into mucous membranes and edema of submucosal tissue were observed at ≥mg/kg. In addition the<sup>(b) (4)</sup> groups resulted in increased cholinesterase activity and decreases in triglycerides in males and increases in GPT, GOT and necrosis of skeletal muscle in females were observed. Generally this would suggest that NK-104<sup>(b) (4)</sup> has less toxicity than that of NK-104. Since limited amounts of this impurity is

present in NK-104 it is considered to contribute minimally to the toxicity of the parent in rats.

Toxicokinetics:

28 Day Oral Toxicology Study in Rats – Toxicokinetic Analyses of NK-104 <sup>(b) (4)</sup>							
NK-104 <sup>(b) (4)</sup>		(b) (4)					
Day 1	C <sub>max</sub> (µg/mL)	0.144	0.18	0.90	2.21	16.1	32.2
	AUC (µg h/mL)	0.68	0.90	4.49	8.17	59.8	128.9
Day 28	C <sub>max</sub> (µg/mL)	0.242	0.353	2.48	4.07	17.7	27.3
	AUC (µg h/mL)	1.05	1.98	8.16	12.53	101.3	147

**4278 – Mutagenicity testing of NK-104<sup>(b) (4)</sup> in bacterial reverse mutation assays**

The NK-104<sup>(b) (4)</sup> was studied in an Ames assay, with the following cells:

<i>Salmonella typhimurium</i> TA100	(histidine-requiring mutant, base-pair substitution type)
<i>Salmonella typhimurium</i> TA98	(histidine-requiring mutant, frameshift type)
<i>Salmonella typhimurium</i> TA1535	(histidine-requiring mutant, base-pair substitution type)
<i>Salmonella typhimurium</i> TA1537	(histidine-requiring mutant, frameshift type)
<i>Escherichia coli</i> WP2 <i>uvrA</i>	(tryptophan-requiring mutant, base-pair substitution type)

(Sponsor, M4, 4278, p18)

The NK-104<sup>(b) (4)</sup> was negative in an Ames assay, both with and without metabolic activation.

(b) (4)

**DOSE RANGE-FINDING FOR CYTOTOXICITY (GROWTH INHIBITION), DIRECT METHOD**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537
DMSO <sup>a)</sup>	0	120	11	22	18	7
Test substance	(b) (4)	116	8	29	20	7
		130	11	21	19	6
		126	19	22	20	6
		139	12	24	24	7
		127 <sup>b)</sup>	13	25	17 <sup>b)</sup>	6
		103 <sup>b)</sup>	11 <sup>b)</sup>	32 <sup>b)</sup>	18 <sup>b)</sup>	5 <sup>b)</sup>
		77 <sup>b)</sup>	10 <sup>b)</sup>	30 <sup>b)</sup>	22 <sup>b)</sup>	4 <sup>b)</sup>
		56 <sup>b)</sup>	12 <sup>b)</sup>	17 <sup>b)</sup>	12 <sup>b)</sup>	6 <sup>b)</sup>
Positive control compound		AF-2	NaN <sub>3</sub>	AF-2	AF-2	9-AA
Dose (µg/plate)		0.01	0.5	0.01	0.1	80
Mean revertant colonies per plate		551	485	143	529	370
		AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide		NaN <sub>3</sub> : Sodium azide	9-AA: 9-Aminoacridine hydrochloride	
		a): Solvent control		b): Growth inhibition was observed		

(Sponsor, M4, 4278, p36)

**DOSE RANGE-FINDING FOR CYTOTOXICITY (GROWTH INHIBITION) METABOLIC ACTIVATION**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537
DMSO <sup>a)</sup>	0	102	16	24	33	14
Test substance	(b) (4)	106	14	23	22	17
		121	13	21	22	15
		107	9	24	26	13
		107	18	25	22	12
		106	17	30	27	14
		93	16	29	23	17
		71 <sup>b)</sup>	12	27	27	14 <sup>b)</sup>
		65 <sup>b)</sup>	11 <sup>b)</sup>	17 <sup>b)</sup>	22 <sup>b)</sup>	11 <sup>b)</sup>
Positive control compound		2-AA	2-AA	2-AA	2-AA	2-AA
Dose (µg/plate)		1	2	10	0.5	2
Mean revertant colonies per plate		705	366	864	324	148
		2-AA: 2-Aminoanthracene				
		a): Solvent control				
		b): Growth inhibition was observed				

(Sponsor, M4, 4278, p37)

**DIRECT METHOD**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>a)</sup>	0	117	8	21	20	6
Test substance	(b) (4)	115			21	
		116			16	
		112	13	24	17	9
		117	11	23	19	7
		115	11	21	21	7
		104 <sup>b)</sup>	12	26	18 <sup>b)</sup>	8
			9 <sup>c)</sup>	29 <sup>c)</sup>		5 <sup>c)</sup>
			9 <sup>c)</sup>	28 <sup>c)</sup>		8 <sup>c)</sup>
Positive control compound		AF-2	NaN <sub>3</sub>	AF-2	AF-2	9-AA
Dose (µg/plate)		0.01	0.5	0.01	0.1	80
Mean revertant colonies per plate		469	454	150	573	418
AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide		NaN <sub>3</sub> : Sodium azide		9-AA: 9-Aminoacridine hydrochloride		
a): Solvent control						
b): Growth inhibition was observed						

(Sponsor, M4, 4278, p38)

**METABOLIC ACTIVATION**

Compound	Dose (µg/plate)	Mean revertant colonies per plate				
		TA100	TA1535	WP2uvrA	TA98	TA1537
DMSO <sup>a)</sup>	0	109	12	30	27	15
Test substance	(b) (4)	102				10
		106				11
		115	12	25	30	9
		113	17	24	34	13
		85	14	23	30	6
		70 <sup>b)</sup>	10	25	24	12 <sup>b)</sup>
			13	23 <sup>c)</sup>	26	
			9 <sup>c)</sup>	14 <sup>c)</sup>	24 <sup>c)</sup>	
Positive control compound		2-AA	2-AA	2-AA	2-AA	2-AA
Dose (µg/plate)		1	2	10	0.5	2
Mean revertant colonies per plate		857	389	850	316	173
2-AA: 2-Aminoanthracene						
a): Solvent control						
b): Growth inhibition was observed						

(Sponsor, M4, 4278, p39)

**4315 (144-025) – Chromosomal aberration test in cultured mammalian cells on NK-**

(b) (4)

**Key findings:**

- Cells were treated by the direct method for 24h at 75, 150, 300, 600 µg/mL and for 48h at 37.5, 75, 150, 300 µg/mL.
- Cells were treated by activation method ±S9 at 188, 375, 750, 1500 µg/mL.
- Results indicate dose-related structural aberrations by direct (24h) and activation methods ±S9 with the NK-104<sup>(b) (4)</sup> (impurity).

**Direct method 24 h: aberrations –gaps were 1% at 75 µg/mL, 1.5% at 150 µg/mL and 6.5% at 300 µg/mL (70% cytotoxicity). A confirmatory test reveals structural aberrations of 0.5% at 150 µg/mL, 4.5% at 225 µg/mL and 6% at 300 µg/mL.**

**Direct method 48 h: Findings were unremarkable**

**Metabolic Activation –S9:** structural aberrations were 1% at 188 µg/mL, 3.5% at 375 µg/mL and 7.5% at 750 µg/mL (~70% cytotoxicity). In a confirmatory test structural aberrations were 1.5% at 300 µg/mL, 1.5% at 450 µg/mL, 5.5% at 600 µg/mL and 57% at 750 µg/mL.

**Metabolic Activation +S9:** structural aberrations were 0.5% at 375 µg/mL and 23% at 750 µg/mL (~40% cytotoxicity) In a confirmatory test structural aberrations 6.5% at 600 µg/mL and 50.5% at 750 µg/mL. A second confirmatory test results in polyploidy of 5% at 600 and 675 µg/mL, 8% at 750 µg/mL and 10.8% at 825 µg/mL (cytotoxicity 40-80%).

**$D_{20}$  values and TR values calculated from the aforesaid results are shown in the following:**

Test system	Type of aberration	$D_{20}$ value	TR value [concerned dose]
Metabolic activation method with +S9 treatment	Structural aberration	0.779	24.7 [750 µg/mL]
Metabolic activation method with -S9 treatment*	Structural aberration	0.537	60.0 [750 µg/mL]
Metabolic activation method with +S9 treatment*	Structural aberration	0.562	52.7 [750 µg/mL]

\*: Confirmatory test

(Sponsor)

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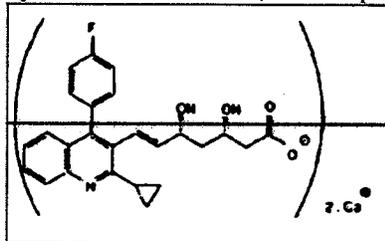
Conducting laboratory and location: (b) (4)

Date of study initiation: 1/7/99-6/22/99

GLP compliance: Y

QA reports: yes (x) no ( )

Drug, lot number, and purity: YT-00298-158B; 99.7% purity



(Sponsor)

50% cytotoxicity was obtained at 287 µg/mL by the direct method with 24h treatment, 139 µg/mL after 48 h treatment by direct method, 834 µg/mL –S9 by the activation method (3 days) and 684 µg/mL +S9 by the activation method. A precipitate was seen at 1080 µg/mL by either direct or activation method. The study appears to be valid and demonstrates reproducible dose related structural aberrations.

**G2525 – Micronucleus test of NK-104<sup>(b) (4)</sup> by single oral administration in mice**

**Key Study Findings:**

- The NK-104 <sup>(b) (4)</sup> was evaluated in an *in vivo/in vitro* micronucleus assay after single oral administration in mice.
- NK-104 <sup>(b) (4)</sup> was negative in this assay, both with and without metabolic activation.

**GROUP ASSIGNMENTS**

Group No.	Test article name	Dose (mg/kg)	Dose volume (mL/kg)	Concentration (w/v%)	Number of animals used* Males	Specimen preparation time (hr)
1	0.5%CMC-Na	—	20	—	6	24
2	NK-104 <sup>(b) (4)</sup>	(b)	20	(b)	6	24
3	NK-104 <sup>(b) (4)</sup>	(b)	20	(b)	6	24
4	NK-104 <sup>(b) (4)</sup>	(b)	25	(b)	6	24
5	0.5%CMC-Na	—	20	—	6	48
6	NK-104 <sup>(b) (4)</sup>	(b)	20	(b)	6	48
7	NK-104 <sup>(b) (4)</sup>	(b)	20	(b)	6	48
8	NK-104 <sup>(b) (4)</sup>	(b)	25	(b)	6	48
9	0.5%CMC-Na	—	20	—	6	72
10	NK-104 <sup>(b) (4)</sup>	(b)	20	(b) (4)	6	72
11	NK-104 <sup>(b) (4)</sup>	(b)	20	(b)	6	72
12	NK-104 <sup>(b) (4)</sup>	(b)	25	(b)	6	72
13	Cyclophosphamide	50	20	0.25	6	24

**ADD-ON HIGH DOSE<sup>(b) (4)</sup> ROUP**

1	0.5%CMC-Na	—	20	(b) (4)	6	48
(b) (4)			25	(b)	15	48
3	0.5%CMC-Na	—	20	(b)	6	72
(b) (4)			25	(b) (4)	15	72
5	Cyclophosphamide	50	20	0.25	6	24

\* Specimens were prepared from 5 animals out of 6 or 13 animals to which the drugs were administered, and frequency of micronucleus was examined.

(Sponsor, M4, G2525, p13)

**MICRONUCLEUS TEST (24 HOURS)**

Compound	Number of animals	Frequency of PCE/animal	Frequency of MNPCE [%] (Mean ± S.D.)	Range of MNPCE/PCE (Min - Max)	Ratio of PCE [%] (Mean ± S.D.)
0.5%CMC-Na	5	2000	0.07 ± 0.06	0 - 3	55.2 ± 3.4
(b) (4)	5	2000	0.08 ± 0.09	0 - 5	53.0 ± 6.6
(b) (4)	5	2000	0.06 ± 0.08	0 - 5	51.4 ± 8.5
(b) (4)	5	2000	0.12 ± 0.07	1 - 5	54.4 ± 9.6
Cyclophosphamide 50 mg/kg	5	2000	2.45 ± 1.13 <sup>#</sup>	24 - 88	52.5 ± 5.7

CMC-Na, Carmellose sodium.  
PCE, Polychromatic erythrocytes; MNPCE, Micronucleated polychromatic erythrocytes.  
#: p<0.05 Kastenbaum and Bowman

(Sponsor, M4, G2525, p23)

**MICRONUCLEUS TEST (48 HOURS)**

Compound	Number of animals	Frequency of PCE/animal	Frequency of MNPCE[%] (Mean ± S.D.)	Range of MNPCE/PCE (Min - Max)	Ratio of PCE [%] (Mean ± S.D.)
0.5%CMC-Na	5	2000	0.12 ± 0.09	0 - 5	59.0 ± 4.6
(b) (4)	5	2000	0.07 ± 0.05	0 - 3	51.1 ± 5.1
(b) (4)	5	2000	0.08 ± 0.06	0 - 3	45.7 ± 7.3*

CMC-Na, Carmellose sodium.  
PCE, Polychromatic erythrocytes; MNPCE, Micronucleated polychromatic erythrocytes.  
\*: p<0.05 Student' t-test

(Sponsor, M4, G2525, p24)

**MICRONUCLEUS TEST (72 HOURS)**

Compound	Number of animals	Frequency of PCE/animal	Number of MNPCE[%] (Mean ± S.D.)	Range of MNPCE/PCE (Min - Max)	Ratio of PCE [%] (Mean ± S.D.)
0.5%CMC-Na	5	2000	0.12 ± 0.09	0 - 5	57.0 ± 5.1
(b) (4)	5	2000	0.05 ± 0.04	0 - 2	54.0 ± 2.9
(b) (4)	5	2000	0.07 ± 0.06	0 - 3	56.0 ± 5.8

CMC-Na, Carmellose sodium.  
PCE, Polychromatic erythrocytes; MNPCE, Micronucleated polychromatic erythrocytes.

(Sponsor, M4, G2525, p25)

**4.2.3.7.7 Other**

**RT2002/2502 – Review of the methods used for statistical analysis of toxicological data on NK-104**

This study was a review of statistical methodology, as there was concern that a statistical test (Sheffe's) was used where Dunnett test was recommended by Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. This was found to be the case in eight non-clinical studies, where six studies were found to have altered results.

**STUDIES WHERE A STATISTICAL RETEST REVEILD A PREVIOUSLY UNDETECTED SIGNIFICANT DIFFERENCE IN AT LEAST ONE PARAMETER**

Study	Modification of NOAEL	Correction of overview
One-month repeated oral dose toxicity study of NK-104 in rats	Not needed	Needed
Six-month repeated oral dose toxicity study of NK-104 in rats	Not needed	Not needed
Oral dose study of NK-104 in rats before and early stage of pregnancy	Not needed	Not needed
Oral dose study of NK-104 in pregnant rats during fetal organogenesis	Not needed	Not needed
Oral dose study of NK-104 in pregnant rabbits during fetal organogenesis	Not needed	Not needed
Oral dose study of NK-104 in rats during perinatal and lactation periods	Not needed	Needed

(Sponsor, M4, RT2002/2502, p15)

Studies where a significant difference was detected upon retest were re-reviewed to determine potential changes to conclusions. Regulatory interpretations of studies were re-inspected, but conclusions remained unaltered and further re-review was unnecessary.

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

**Table 2.4.9: NOAELs and Corresponding Exposure Levels in Repeat Dose Toxicity Studies with Pitavastatin: Comparison to Human Exposure**

Study	NOAEL	AUC (ng*h/mL)
Rat: 6-month	1 mg/kg/day	~1000*
Dog: 12-month	0.3 mg/kg/day	384/288**
Monkey: 6-month	3 mg/kg/day	704/459**
Humans	4 mg	153

\*: By extrapolation from another study; \*\*: Male/Female animals

(Sponsor, M2.4, Nonclinical overview, p45)

2.6.7 TOXICOLOGY TABULATED SUMMARY

Single-dose Toxicology – Tabulated Summary

2.6.7.5 Single-Dose Toxicity			Test Article: Pitavastatin				Page 1 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Report Number
Cj:CD-1 mice	Oral (gavage) at 20 or 40 ml/kg (0.5% CMC sodium solution)	0, 125, 250, 500, 1000, 2000	3M, 5F	M: 500 F: 1000	M: 1000 F: 1000 to 2000	<p>0 mg/kg: No noteworthy findings.</p> <p>125 mg/kg: No noteworthy findings.</p> <p>250 mg/kg: Decreased locomotor activity in 1/5F.</p> <p>500 mg/kg: Decreased locomotor activity in 3/5M; decreased locomotor activity, crutching or prone position in 3/5F.</p> <p>1000 mg/kg: 1/5M died on Day 5; hepatic enlargement, ileal invagination and haemorrhage in glandular stomach mucosa observed. Decreased locomotor activity or crutching in all animals. Liver nodule in 1M and forestomach thickening in 2F.</p> <p>2000 mg/kg: 5/5F died by Day 6; 4/5M died by Day 9. Decreased locomotor activity, crutching or prone position in all animals. Closed eyelids and piloerection also seen in some animals. Conjunctival discharge, salivation and clonic convulsion, each seen in one animal only. Reduction in body weight gain from Day 2 through to Day 8 in males with normalisation by Day 15. In females reduction in body weight gain from Day 2 to Day 4 with statistically significant decrease in body weight at Day 4. In male survivor liver nodules, forestomach thickening and splenic atrophy observed. In male decedents macroscopic findings included signs of gastrointestinal disorder, forestomach thickening, splenic atrophy and thymic atrophy. In female decedents macroscopic findings included signs of gastrointestinal disorder and liver discoloration.</p>	IRGE2510 <sup>a</sup>

<sup>a</sup>: A separate toxicokinetics study was conducted with pitavastatin (500 or 1000 mg/kg) administered as a single oral dose to Cj:CD-1 (ICR) mice of both sexes (RI/9945). [2.6.5.5A]. Mean plasma pitavastatin concentrations in mice were 83400 ng/mL (M) and 13700 ng/mL (F) 1 hour after dosing at 500 mg/kg decreasing to 400 ng/mL in both sexes 24 hours after dosing. Mean plasma pitavastatin concentrations in mice were 331100 ng/mL (M) and 12500 ng/mL (F) 1 hour after dosing at 1000 mg/kg decreasing to 400 ng/mL (M) and 800 ng/mL (F), respectively

2.6.7.5 Single-Dose Toxicity (continued)		Test Article: Pitavastatin					Page 2 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Report Number
Slc:Wistar rats	Oral (gavage) at 40 mL/kg (0.5% CMC sodium solution)	M: 0, 500, 1000, 2000; F: 0, 125, 250, 500, 1000, 2000	5M; 5F except for 125 and 250 mg/kg dose groups which comprised 5F only	M: 500; F: 250	M: 500 to 1000; F: 250 to 500	<p>0 mg/kg: No noteworthy findings.</p> <p>125 mg/kg: No noteworthy findings.</p> <p>250 mg/kg: Reduced weight gain.</p> <p>500 mg/kg: 4/5F died by Day 6; no deaths in male animals. Prosis and eye closing in both sexes, decreased spontaneous movement in one male and crouching position, diarrhoea, rhinorrhoea, piloerection, emaciation, nasal bleeding, tiptoe gait, soiled abdomen, prone position and paralytic gait in females. Reduced weight gain in males.</p> <p>1000 and 2000 mg/kg: All animals died by Day 8. Prosis, crouching position, diarrhoea and rhinorrhoea in both sexes, prone position and bradypnoea in females, piloerection, emaciation, tiptoe gait, nasal bleeding, eye closing, lacrimation, hypothermia, cyanosis, dyspnoea, lateral position and paralytic gait in males. Decrease in body weight in both sexes.</p> <p><b>Microscopic Changes:</b> Decedents: stomach distension, gas retention and fluid retention; haemorrhage, thinning and ulceration of forestomach; haemorrhage and ulceration of glandular stomach; haemorrhage of jejunum; and haemorrhage and atrophy of thymus. Fluid retention in caecum and duodenum and liver discoloration observed.</p> <p><b>Histopathological Changes:</b> Slight liver congestion. Hyperkeratosis and ulceration of forestomach, oedema and haemorrhage also seen. Haemorrhage in glandular stomach. No abnormalities in skeletal muscle.</p>	[RG25001]

a: A separate toxicokinetics study was conducted with pitavastatin (30, 100, 250 or 500 mg/kg) administered as a single oral dose to Slc:Wistar rats of both sexes [RF9933]. Plasma concentrations of pitavastatin increased dose-proportionally, however, at doses of 250 mg/kg and above  $C_{max}$  and AUC values indicated saturation of absorption in the digestive tract. AUC values were higher in females as compared to the corresponding male dose group. This was attributed to a sex difference in cytochrome P-450 mediated metabolism leading to higher plasma concentrations in female animals. The plasma concentrations of lactone were <1% of the corresponding pitavastatin plasma concentration. b: Histopathology was conducted on liver and stomach from typical animals showing abnormalities at autopsy and skeletal muscle from animals that exhibited ataxic gait and paralytic gait

2.6.7.5 Single-Dose Toxicity (continued)		Test Article: Pitavastatin					Page 3 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Report Number
Cj: CD (SD) rats	Oral (gavage) at 20 mL/kg (0.5% CMC sodium solution)	100, 200, 400, 600, 800	10M	200 <sup>a</sup>	200 to 400	<p>100 mg/kg: No noteworthy findings</p> <p>200 mg/kg: Transient salivation (Day 1).</p> <p>400 mg/kg: Salivation, paralytic gait, decreased locomotor activity, crouching, decrease in stool volume, decreased in food intake, emaciation and prone position. Body weight gain suppressed on Days 1 to 3; on Day 7 body weight was increased slightly in 8/10 animals. Two animals moribund on Day 7.</p> <p>600 mg/kg: All animals died by Day 7. Decreased locomotor activity, crouching, salivation, decrease in stool volume, decrease in food intake and prone position. Body weight gain suppressed.</p> <p>800 mg/kg: 9/10 animals died by Day 7 and the remaining animal was moribund. Decreased locomotor activity, crouching, loose stool, decrease in stool volume, decrease in food intake, panting and emaciation. Body weight gain suppressed.</p> <p><b>Microscopic changes:</b> Staining (ventral fur, perioral, perinasal) and nasal bleeding. Stomach (distension, watery content, gas retention, drug retention), watery content in duodenum, jejunum and caecum; atrophy in caecum and thymus; liver discoloration.</p>	[RF9808]

a: No deaths occurred by Day 7 (day of necropsy) in the 400 mg/kg dose group, however, two animals were considered moribund because of markedly decreased locomotor activity, prone position and emaciation (marked weight loss)

2.6.7.5 Single-Dose Toxicity (continued)		Test Article: Pitavastatin					Page 4 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Report Number
Wistar Han (WI KH HR) rats	Intravenous (bolus) at 20 mL/kg (0.9% sodium chloride (NaCl))	Preliminary study: 5, 10, 20 <sup>a</sup> ; Main study: 0, 20 <sup>a</sup>	Preliminary study: 2M; 2F; Main study: 5M; 5F	20	> 20	<p><b>Preliminary study:</b> Morbidity/mortality and clinical signs assessed.</p> <p>5 mg/kg: No noteworthy findings.</p> <p>10 mg/kg: No noteworthy findings.</p> <p>20 mg/kg: No noteworthy findings.</p> <p><b>Main study:</b> Morbidity/mortality, clinical signs and body weight assessed and animals subjected to necropsy.</p> <p>0 mg/kg: No noteworthy findings.</p> <p>20 mg/kg: No noteworthy findings.</p>	[387002]

a: Highest dose level achievable in view of the limit of solubility of pitavastatin in the vehicle (1 mg/mL) and maximum volume feasible for the rat by the intravenous route (20 mL/kg)

2.6.7.5 Single-Dose Toxicity (continued)		Test Article: Pitavastatin				Page 5 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Report Number
Beagle dogs	Oral (capsules)	0, 100, 300, 1000	2M	Not applicable	≤ 100	<p><b>Noteworthy Findings</b></p> <p>0 mg/kg: No noteworthy findings.</p> <p>100 mg/kg: One death (Day 4).</p> <p>300 mg/kg: No noteworthy findings.</p> <p>1000 mg/kg: One death (Day 2). Slight increase in pulse rate and increase in urinary volume in decedent.</p> <p><b>Decedents:</b> Vomiting, brown watery stools, tremor, weakness<sup>a</sup>, ataxic gait, abnormality in respiration sound, decreased locomotor activity, lateral position, rigid limbs and decreased food consumption and body weight and slightly increased water intake were observed. Increase in RBC, WBC, Hb, haematocrit and decreased MCH and MCH concentration. Increase in AST, ALT, LDH, CPK, ALP and TC and decreased Na, K and Ca values. Macroscopic changes included rigidity of the heart, congestion of various organs, including liver, kidneys and lungs, and hyperaemia/haemorrhage of various organs including the small and large intestine.</p> <p><b>Histopathological changes</b> included congestion of various organs and tissues, exfoliation of mucosal epithelium, congestion of mucosa, congestion and haemorrhage in the muscular layer of the small and large intestine tract, thickening of the alveolar septum in the lungs and atrophy of hepatocytes.</p> <p><b>Survivors:</b> Vomiting and decreased food consumption and body weight with a slight decrease in water intake. Mild increases in AST, ALT, CPK and ALP which were reversible by Day 14. Changes in electrolyte concentrations and excretion amounts were observed which were reversible by Day 14.</p>

<sup>a</sup>: Described as loss of vigour in report; RBC: Red blood cell count; WBC: White blood cell count; Hb: Haemoglobin; MCH: Mean corpuscular haemoglobin; AST: Aspartate aminotransferase, also known as glutamic oxaloacetic transaminase (SGOT) or aspartate transaminase; ALT: Alanine aminotransferase, also known as glutamic-pyruvic transaminase (SGPT) or alanine transaminase; LDH: Lactate dehydrogenase; CPK: Creatinine phosphokinase; ALP: Alkaline phosphatase; TC: Total cholesterol; Na: Sodium; K: Potassium; Ca: Calcium

2.6.7.5 Single-Dose Toxicity (continued)		Test Article: Pitavastatin				Page 6 of 6
Species / Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Report Number
Cynomolgus monkeys	Oral (gavage) at 5 ml/kg (0.5% carmellose sodium solution)	10, 30, 50	1M; 1F	Not determined	M: > 50 F: > 50	<p><b>Noteworthy Findings</b></p> <p>10 mg/kg: No noteworthy findings.</p> <p><b>Toxicokinetics:</b></p> <p><b>Pitavastatin:</b> T<sub>max</sub> (0.5 hours (M) and 2.0 hours (F)); C<sub>max</sub> (1140 ng/mL (M) and 540 ng/mL (F)); AUC (2890 ng*<sup>h</sup>/mL (M) and 1880 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (4.1 hours (M) and 1.5 hours (F));</p> <p><b>Lactone:</b> T<sub>max</sub> (0.5 hours (M) and 2.0 hours (F)); C<sub>max</sub> (340 ng/mL (M) and 150 ng/mL (F)); AUC (1000 ng*<sup>h</sup>/mL (M) and 670 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (2.4 hours (M) and 1.5 hours (F)).</p> <p>30 mg/kg: No noteworthy findings.</p> <p><b>Toxicokinetics:</b></p> <p><b>Pitavastatin:</b> T<sub>max</sub> (2.0 hours (both sexes)); C<sub>max</sub> (3380 ng/mL (M) and 5430 ng/mL (F)); AUC (16840 ng*<sup>h</sup>/mL (M) and 17310 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (3.0 hours (both sexes));</p> <p><b>Lactone:</b> T<sub>max</sub> (4.0 hours (M) and 2.0 hours (F)); C<sub>max</sub> (450 ng/mL (M) and 980 ng/mL (F)); AUC (3190 ng*<sup>h</sup>/mL (M) and 3450 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (3.9 hours (M) and 1.6 hours (F)).</p> <p>50 mg/kg: No noteworthy findings.</p> <p><b>Toxicokinetics:</b></p> <p><b>Pitavastatin:</b> T<sub>max</sub> (2.0 hours (both sexes)); C<sub>max</sub> (9850 ng/mL (M) and 27700 ng/mL (F)); AUC (33440 ng*<sup>h</sup>/mL (M) and 76330 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (2.9 hours (M) and 2.7 hours (F)).</p> <p><b>Lactone:</b> T<sub>max</sub> (2.0 hours (both sexes)); C<sub>max</sub> (2200 ng/mL (M) and 3850 ng/mL (F)); AUC (8400 ng*<sup>h</sup>/mL (M) and 11680 ng*<sup>h</sup>/mL (F)); t<sub>1/2</sub> (3.1 hours (M) and 2.8 hours (F)).</p>

<sup>a</sup>: Toxicokinetics report; T<sub>max</sub>: The time to reach maximum concentration following drug administration; t<sub>1/2</sub>: Elimination half-life

**Repeat-dose toxicology - Tabulated Summary**

<b>2.6.7.7A Repeat-Dose Toxicity</b>		<b>Test Article: Pitavastatin</b>		Page 1 of 4					
<b>Report Title:</b> NK-104: Sub-acute toxicity to transgenic mice by repeated oral administration for 28 days									
<b>Species/Strain:</b> CD6F1-Tg ras1L2 mice		<b>Duration of Dosing:</b> Once daily for 28 days		<b>Report No.:</b> [SNBL 138.01]					
<b>Initial Age:</b> 10 to 11 weeks		<b>Duration of Post-Dose:</b> NA		<b>Location in CTD:</b> <b>Vol:</b> *					
<b>Study Duration:</b> June to November 2006		<b>Method of Administration:</b> Oral (gavage) at 10 mL/kg		<b>Section:</b> *					
		<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution		<b>GLP Compliance:</b> Yes					
<b>Special Features:</b> None									
<b>No Observed Adverse-Effect Level:</b> Not achieved									
<b>Daily Dose (mg/kg/day)</b>		0 (Control)		70					
				125					
				250					
<b>Toxicokinetics<sup>a</sup></b>									
<b>No. of Animals</b>		M:6	F:6	M:18	F:18	M:18	F:18	M:18	F:18
<b>Plasma concentration (ng/mL)</b>									
Pre-dose on Day 1		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
0.5 hours post-dose on Day 1		BLQ	BLQ	6360	5614	11420	10930	28750	22120
1 hour post-dose on Day 1		BLQ	BLQ	671	865	3976	3162	4432	7512
3 hours post-dose on Day 1		BLQ	BLQ	198	111	459	681	1980	1182
6 hours post-dose on Day 1		BLQ	BLQ	26	32	476	192	1082	1079
24 hours post-dose on Day 1		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
<b>C<sub>max</sub> (ng/mL) on Day 1</b>		NA	NA	6360	5614	11420	10930	28750	22120
<b>T<sub>max</sub> (hours) on Day 1</b>		NA	NA	0.5	0.5	0.5	0.5	0.5	0.5
<b>AUC<sub>0-24</sub> (ng*hr/mL) on Day 1</b>		NA	NA	4790	4500	16820	13140	36230	34730

\*: Not applicable to an electronic submission

a: One mouse/time point/sex/group was bled for control animals. Three mice/time point/sex/group were bled for pitavastatin dosed animals

BLQ: Below the limit of quantification

<b>2.6.7.7A Repeat-Dose Toxicity</b>		<b>Report No. [SNBL 138.01] (continued)</b>		Page 2 of 4					
<b>Daily Dose (mg/kg/day)</b>		0 (Control)		70					
				125					
				250					
<b>Toxicokinetics<sup>a</sup></b>									
<b>No. of Animals</b>		M:6	F:6	M:18	F:18	M:18	F:18	M:18	F:18
<b>Plasma concentration (ng/mL)</b>									
Pre-dose on Day 28		BLQ	BLQ	BLQ	BLQ	4	BLQ	27	111
0.5 hours post-dose on Day 28		BLQ	BLQ	6323	7912	9634	17970	65160	81750
1 hour post-dose on Day 28		56.37 <sup>b</sup>	BLQ	1625	1069	1707	1499	6682	15930
3 hours post-dose on Day 28		BLQ	BLQ	71	104	295	166	1516	1068
6 hours post-dose on Day 28		BLQ	BLQ	19	38	35	158	278	529
24 hours post-dose on Day 28		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	101	86
<b>C<sub>max</sub> (ng/mL) on Day 28</b>		NA	NA	6323	7912	9634	17970	65160	81750
<b>T<sub>max</sub> (hours) on Day 28</b>		NA	NA	0.5	0.5	0.5	0.5	0.5	0.5
<b>AUC<sub>0-24</sub> (ng*hr/mL) on Day 28</b>		NA	NA	5570	5950	8060	12930	48560	69810
<b>Number of Animals<sup>c</sup></b>		M: 10 (6)	F: 10 (6)	M: 10 (20)	F: 10 (20)	M: 10 (20)	F: 10 (20)	M: 10 (23)	F: 10 (23)
<b>Noteworthy Findings</b>									
<b>Died or Sacrificed Moribund</b>		0	0	0	0	0	0	0	0 <sup>d</sup>
<b>Body Weight<sup>e</sup> (g)</b>		26.1	20.1	25.9 (-1)	21.3 (+6)	26.1 (0)	20.6 (+2)	24.7 (-5)	20.7 (+3)
<b>Food Consumption (g)<sup>e</sup></b>		2.7	3.0	3.4 (+26)	3.0 (+0)	3.5 (+30)	3.1 (+3)	3.1 (+37)	3.4 (-13)

a: One mouse/time point/sex/group was bled for control animals. Three mice/time point/sex/group were bled for pitavastatin dosed animals

b: Contaminated control sample

c: Numbers in parentheses represent toxicokinetic group animals

d: One animal died on Day 8 due to a dosing error; the animal was replaced by a corresponding satellite animal to maintain planned group numbers

e: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses

<b>2.6.7.7A Repeat-Dose Toxicity</b>		<b>Report No. [SNBL 138.01] (continued)</b>		Page 3 of 4					
<b>Daily Dose (mg/kg/day)</b>		0 (Control)		70					
				125					
				250					
<b>Number of Animals<sup>a</sup></b>		M: 10 (6)	F: 10 (6)	M: 10 (20)	F: 10 (20)	M: 10 (20)	F: 10 (20)	M: 10 (23)	F: 10 (23)
<b>Noteworthy Findings cont.</b>									
<b>Died or Sacrificed Moribund</b>		0	0	0	0	0	0	0	0 <sup>b</sup>
<b>Clinical Observations<sup>a</sup></b>									
Sedated		-	-	-	-	-	-	2 (-)	-
Hunched posture		-	-	-	-	- (1)	- (1)	5 (5)	3 (7)
Respiration, fast		-	-	-	-	-	-	-	1 (-)
Distended abdomen		-	-	-	-	-	-	- (1)	-
Eye, cloudy		-	-	-	-	- (2)	-	- (1)	- (1)
Eye, discharge, swollen		-	-	-	-	-	-	-	- (1)
Mass, right shoulder		-	-	-	-	-	-	- (1)	-
Swelling, left forelimb		-	-	-	-	-	-	-	- (1)
<b>Number of Animals<sup>a</sup></b>		M: 10 (0)	F: 10 (0)	M: 10 (0)	F: 10 (0)	M: 10 (0)	F: 10 (0)	M: 10 (0)	F: 10 (0)
<b>Ophthalmoscopy (Week 4)</b>									
Haematology <sup>a</sup>									
Erythrocytes (10 <sup>6</sup> /μL)		10.1	9.5	10.3 (+2)	9.9 (+4)	10.1 (0)	9.7 (+2)	9.4 (-7)*	9.0 (-5)
Haemoglobin (g/dL)		14.5	13.9	14.8 (+2)	14.3 (+3)	14.5 (0)	14.1 (+1)	13.3 (-8)*	12.9 (-7)*
Haematocrit (%)		47.8	45.4	49.8 (+4)	46.9 (+3)	48.7 (+2)	47.4 (+4)	45.3 (-5)	43.1 (-5)*
Reticulocytes (10 <sup>6</sup> /μL)		0.221	0.232	0.228 (+5)	0.278 (+20)	0.237 (+7)	0.264 (+14)	0.252 (+14)	0.344 (+48)*
Reticulocytes (%)		2.2	2.5	2.2 (0)	2.8 (+12)	2.4 (+9)	2.7 (+8)	2.7 (+23)	3.8 (+52)*
<b>Urinalysis</b>									
Serum Chemistry <sup>a</sup>									
Total cholesterol		89	74	94 (+6)	76 (+3)	99 (+11)	69 (-7)	68 (-24)	45 (-39)*
Triglycerides (mg/dL)		57	45	57 (0)	51 (+13)	52 (-9)	41 (-9)	33 (-42)*	22 (-51)*
Globulin		1.6	1.6	1.7 (+6)	1.5 (-6)	1.6 (0)	1.5 (-6)	1.5 (-6)*	1.4 (-13)*
Albumin/Globulin ratio		1.7	1.9	1.7 (0)	2.0 (+5)	1.8 (+6)	2.0 (+5)*	1.9 (+12)	2.1 (+11)*

a: Numbers in parentheses represent toxicokinetic group animals; b: One animal died on Day 8 due to a dosing error; the animal was replaced by a corresponding satellite animal to maintain planned group numbers; c: Day 29. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences); \*: p < 0.05; -: No noteworthy findings; ND: Not determined

2.6.7.7A Repeat-Dose Toxicity		Report No. [SNH1.138.01] (continued)						Page 4 of 4	
Daily Dose (mg/kg/day)	0 (Control)		75		125		250		
Noteworthy Findings cont.	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	
Gross Pathology <sup>a</sup>									
Testis: Mild discoloration	-	NA	1	NA	-	NA	1	NA	
Urinary bladder: Red urine, lumen, mild	-	-	-	-	-	-	-	1	
Organ Weights, g <sup>b</sup>									
Liver (absolute)	1.3833	1.1244	1.3906 (+1)	1.1638 (+4)	1.4641 (+6)	1.0998 (-2)	1.5219 (+10)	1.2857 (+14)*	
Liver (relative)	5.1778	5.4610	5.2732 (+2)	5.4785 (0)	5.5379 (+7)	5.3500 (-2)	6.0525 (+17)*	6.2220 (+14)*	
Prostate/seminal vesicles (absolute)	0.4092	NA	0.3996 (-2)	NA	0.4169 (+2)	NA	0.3477 (-15)*	NA	
Histopathology									
Stomach:									
Hyperplasia, nonglandular mucosa (minimal to severe)	0	0	1	2	7	10	10	9	
Moromuclear/polymorphonuclear cell infiltration, submucosa (minimal to moderate)	0	0	1	2	8	9	10	9	

a: Day 29 (of scheduled necropsy)  
 b: Day 29 (at scheduled necropsy). Group means are shown. For treated groups, percent differences from controls are shown in parentheses. A trend towards a decrease in thymus weight (absolute and relative) of males and females in the 250 mg/kg/day group and an increase in adrenal weights (absolute and relative) in males and females of the 125 and 250 mg/kg/day groups was observed although these effects were not statistically significant. Statistical significance is based on actual data (not on the percent differences)  
 \*: p<0.05. Statistical analysis was conducted using Bartlett's test, one-way ANOVA, Dunnett's test, Kruskal-Wallis test, Miller's procedure and Dunn's modification to Steel's test

2.6.7.7B Repeat-Dose Toxicity		Test Article: Pitavastatin						Page 1 of 5	
Report Title: NK-104: Sub-acute toxicity to mice by repeated oral administration for 13 weeks	Duration of Dosing: Once daily for 13 weeks						Report No.: [KOW 14/952398]		
Species/Strain: Crl:CD-1(ICR)BR mice	Duration of Post-Dose: NA						Location in CTD: Vol: *		
Initial Age: 6 weeks	Method of Administration: Oral (gavage) at 10 ml/kg						Section: *		
Study Duration: June to September 1995	Vehicle/Formulation: 0.5% hydroxypropyl methylcellulose solution						GLP Compliance: Yes		
Special Features: None									
No Observed Adverse Effect Level: Not achieved, < 25 mg/kg/day									
Daily Dose (mg/kg/day)	0 (Control)		25		75		225		
Toxicokinetics <sup>a</sup>	M	F	M	F	M	F	M	F	
Sex									
T <sub>max</sub> (hours) Day 1	NA	NA	0.5	0.5	0.5	0.5	0.5	0.5	
Day 90	NA	NA	0.5	0.5	0.5	0.5	0.5	0.5	
C <sub>max</sub> (ng/mL)									
Day 1	NA	NA	417	818	4140	5419	11653	12467	
Day 90	NA	NA	448	699	2062	7348	24060	29306	
C <sub>max</sub> ratio									
Dose level ratio			1	1	3	3	9	9	
Day 1	NA	NA	1	1	9.9	6.6	27.9	13.2	
Day 90	NA	NA	1	1	4.6	10.5	53.7	41.9	
C <sub>24</sub> (ng/mL)									
Day 1	NA	NA	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	
Day 90	NA	NA	BLQ	BLQ	BLQ	BLQ	BLQ	21.1	
AUC <sub>0-24</sub> (ng <sup>h</sup> /mL)									
Day 1	NA	NA	508	963	4210	6860	18671	20066	
Day 90	NA	NA	528	723	2402	5621	22486	23274	

\*: Not applicable to an electronic submission

a: Four mice/sex/group were bled on Days 1 and 90 at 0 (25 mg/kg dose group only on Day 1), 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dosing and on Day 30 at 4 and 24 hours after dosing. The eyes were dissected from animals sampled at 4 and 24 hours after dosing and returned to the Sponsor ([RI:9614]); not submitted as the report is not considered pertinent to the safety of pitavastatin

C<sub>24</sub>: Plasma drug concentration at 24 hours after administration

2.6.7.7B Repeat-Dose Toxicity		Report No. [KOW 14/952398] (continued)						Page 2 of 5	
Daily Dose (mg/kg/day)	0 (Control)		25		75		225		
Toxicokinetics <sup>a</sup>	M	F	M	F	M	F	M	F	
Sex									
AUC <sub>0-24</sub> ratio									
Dose level ratio	NA	NA	1	1	3	3	9	9	
Day 1	NA	NA	1	1	8.3	7.1	36.8	20.8	
Day 90	NA	NA	1	1	4.5	7.8	42.6	32.2	
Accumulation ratio <sup>b</sup>	NA	NA	1.0	0.7	0.6	0.8	1.2	1.2	
Number of Animals <sup>c</sup>	M: 10	F: 10	M: 10 (80)	F: 10 (80)	M: 10 (76)	F: 10 (76)	M: 10 (76)	F: 10 (76)	
Noteworthy Findings									
Died or Sacrificed Moribund <sup>d</sup>	0	0	0 (1 <sup>e</sup> )	1 (1 <sup>e</sup> )	0 (2 <sup>f</sup> )	0 (2 <sup>f</sup> )	0 (2 <sup>f</sup> )	3 (4 <sup>f</sup> )	
Body Weight (g) <sup>g</sup>	40	32	39 (-3)	31 (-3)	39 (-3)	30 (-6)	39 (-3)	31 (-3)	
Food Consumption (g) <sup>h</sup>	46	42	39 (-15)	40 (-5)	37 (-20)	36 (-14)	37 (-20)	38 (-10)	
Efficiency of Food Utilization <sup>i</sup>	57.9	59.3	67.2 (+16)	63.4 (+7)	61.8 (+7)	72.0 (+21)	66.7 (+15)	65.6 (+11)	

a: Four mice/sex/group were bled on Days 1 and 90 at 0 (25 mg/kg dose group only on Day 1), 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dosing and on Day 30 at 4 and 24 hours after dosing. The eyes were dissected from animals sampled at 4 and 24 hours after dosing and returned to the Sponsor ([RI:9614]); not submitted as the report is not considered pertinent to the safety of pitavastatin

b: AUC<sub>0-24</sub>: (Day 90) AUC<sub>0-24</sub>: (Day 1)

c: Numbers in parentheses represent toxicokinetic group animals

d: Sacrificed in Week 4 (Animal No. 154)

e: Deaths occurred in Week 1 (Animal No. 60 (Main Study) and Animal No. 382 (Toxicokinetic Group))

f: Sacrificed in Weeks 6 (Animal No. 210) and 9 (Animal No. 208)

g: Deaths in Weeks 1 (Animal No. 428) and 7 (Animal No. 449)

h: Animal sacrificed in Week 2 (Animal No. 298) and death in Week 11 (Animal No. 303)

i: One animal sacrificed in Week 4 (Animal No. 72) and animals found dead in Weeks 1 (Animal No. 80) and 13 (Animal No. 76)

j: Deaths in Weeks 4 (Animal No. 528) and 6 (Animal No. 510), animal sacrificed in Week 13 (Animal No. 535); no details provided on the 4<sup>th</sup> animal

k: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences). Main study animals only

l: Food conversion ratio = Food consumption/body weight gain. Weeks 1 to 13. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences). Main study animals only

2.6.7.B Repeat-Dose Toxicity	Report No. [KOW 14/952398] (continued)								Page 3 of 5
	0 (Control)		25		75		225		
Daily Dose (mg/kg/day)									
Number of Animals <sup>a</sup>	M: 10	F: 10	M: 10 (80)	F: 10 (80)	M: 10 (76)	F: 10 (76)	M: 10 (76)	F: 10 (76)	
<b>Noteworthy Findings cont.</b>									
<b>Clinical Observations<sup>a</sup></b>									
Lethargy (1 hour after dosing, isolated occurrences in Weeks 2 and 3)	-	-	-	-	-	-	3/10 (4)	- (1)	
<b>Ophthalmoscopy (Week 12)</b>									
Number of Animals <sup>a</sup>	M: 10	F: 10	M: 10	F: 9	M: 10 (34)	F: 10 (34)	M: 10 (34)	F: 8 (33 or 34) <sup>b</sup>	
Corneal opacities	0 (0)	0 (0)	0 (0)	0 (0)	0 (2)	0 (4)	0 (6)	1 (4)	
<b>Haematology</b>	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Urinalysis</b>	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Serum Chemistry<sup>c</sup></b>									
Triglycerides (mg/dL)	111	117	114 (+3)	109 (-7)	134 (+21)	83 (-29)*	93 (-16)	37 (-68)**	
Phospholipid (mg/dL)	305	217	334 (+10)	222 (+2)	290 (-5)	210 (-3)	226 (-26)**	189 (-13)	
<b>Gross Pathology</b>									
Number of Animals <sup>d</sup>	M: 10	F: 10	M: 10	F: 9 (1)	M: 10 (0)	F: 10 (0)	M: 10 (34)	F: 7 (3)	
Forestomach: Thickened	0	0	0	0 (0)	0	0	9	7 (2)	
White	0	0	0	0 (0)	0	0	9	7 (2)	
Roughened	0	0	0	0 (0)	0	0	9	7 (2)	
Invaginated	0	0	0	0 (0)	0	0	3	2 (1)	

a: Numbers in parentheses represent toxicokinetic group animals  
 b: It is not clear from the report when Animal No. 506 died in relation to Week 12 assessments  
 c: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences)  
 d: Main study decedents shown in parentheses  
 ND: Not determined  
 -: No noteworthy findings  
 \*: p ≤ 0.05; \*\*: p ≤ 0.01. Statistical analysis was conducted using Fisher's test, Bartlett's test, Kruskal-Wallis test, Student's t test or William's test

2.6.7.B Repeat-Dose Toxicity	Report No. [KOW 14/952398] (continued)								Page 4 of 5
	0 (Control)		25		75		225		
Daily Dose (mg/kg/day)									
Number of Animals <sup>a</sup>	M: 10	F: 10	M: 10	F: 9 <sup>b</sup> (1)	M: 10	F: 10	M: 10	F: 7 <sup>b</sup> (3)	
<b>Organ Weights<sup>a</sup></b>									
Brain	0.486 g	0.501 g	0.477 (-2)	0.513 (+2)	0.483 (-1)	0.493 (-2)	0.472 (-3)	0.472 (-6)*	
Ovaries	NA	25.0 mg	NA	21.5 (-14)	NA	20.8 (-17)	NA	14.6 (-42)*	
Heart	0.245 g	0.161 g	0.234 (-4)	0.186 (+16)	0.205 (-16)	0.174 (+8)	0.217 (-11)	0.190 (+18)*	
Testes (combined)	0.222 g	NA	0.221 (0)	NA	0.249 (+12)	NA	0.251 (+13)*	NA	
Seminal vesicles	0.356 g	NA	0.346 (-3)	NA	0.316 (-11)	NA	0.284 (-20)	NA	
<b>Histopathology<sup>a</sup></b>									
<b>Liver:</b>									
Centrilobular enlargement of hepatocytes (trace to minimal)	3	0	0	0 (0)	8*	0	10**	2 (0)	
<b>Stomach (non-glandular region):</b>									
Ulceration	0	0	0	0 (0)	1	0	3*	1	
Erosion	0	0	0	0 (0)	0	0	1*	1	
Epithelial hyperplasia and hyperkeratosis (minimal to marked)	0	0	0	3 (0)	7**	9**	10**	7** (2 <sup>b</sup> )	
Submucosal fibrosis, inflammatory cells and/or oedema (minimal to moderate)	0	0	0	0 (0)	0	0	7**	3 (1)	
Papillomatous hyperplasia (moderate)	0	0	0	0 (0)	0	0	4*	1 (1)	

a: Death occurred in Week 1 (Animal No. 60)  
 b: One animal sacrificed in Week 4 (Animal No. 72) and animals found dead in Weeks 1 (Animal No. 80) and 13 (Animal No. 76)  
 c: Decedents shown in parentheses  
 d: At the end of the dosing period (at scheduled necropsy). Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on the percent differences)  
 e: Only epithelial hyperkeratosis was seen in Animal No. 80 and hence is not included in this number  
 \*: p < 0.05; \*\*: p < 0.01. Statistical analysis was conducted using Fisher's test, Bartlett's test, Kruskal-Wallis test, Student's t test or William's test

2.6.7.7B Repeat-Dose Toxicity		Report No. [KOW 14/92398] (continued)						Page 5 of 5	
Daily Dose (mg/kg/day)	0 (Control)		25		75		225		
Number of Animals <sup>a</sup>	M: 0	F: 0	M: 1 <sup>a</sup>	F: 1 <sup>b</sup>	M: 2 <sup>c</sup>	F: 2 <sup>d</sup>	M: 2 <sup>e</sup>	F: 2 <sup>f</sup>	
<b>Decedents from Toxicokinetic Groups</b>									
<b>Noteworthy Findings cont.</b>									
<b>Gross Pathology</b>									
Fore stomach: Thickened	NA	NA	0	0	2	0	2	3	
White	NA	NA	0	0	0	0	1	2	
Roughened	NA	NA	0	0	0	0	1	1	
Excrescence(s)	NA	NA	0	0	0	0	0	1	
Depressions	NA	NA	0	0	0	0	1	0	
White raised areas (epithelial aspect)	NA	NA	0	0	0	0	0	1	
Number of Animals Examined	M: 0	F: 0	M: 0	F: 0	M: 1 <sup>g</sup>	F: 1 <sup>h</sup>	M: 2 <sup>i</sup>	F: 2 <sup>j</sup>	
<b>Histopathology</b>									
<b>Liver:</b>									
Centrilobular enlargement of hepatocytes (minimal)	NA	NA	NA	NA	0	0	1	0	
<b>Stomach (non-glandular region):</b>									
Ulceration	NA	NA	NA	NA	0	0	1	0	
Erosion	NA	NA	NA	NA	0	0	1	0	
Epithelial hyperplasia and hyperkeratosis (minimal to marked)	NA	NA	NA	NA	1	0	2	1	
Submucosal fibrosis, inflammatory cells and/or oedema (minimal to moderate)	NA	NA	NA	NA	0	0	1	0	
Papillomatous hyperplasia (moderate to marked)	NA	NA	NA	NA	0	0	0	1	

a: Sacrificed in Week 4 (Animal No. 154); b: Death occurred in Week 1 (Animal No. 342)  
c: Sacrificed in Weeks 6 and 9 (Animal Nos. 210 and 208); d: Deaths in Weeks 1 and 7 (Animal Nos. 428 and 449)  
e: Animal sacrificed in Week 2 and death in Week 11 (Animal Nos. 298 and 303)  
f: Deaths in Weeks 4 and 6, animal sacrificed in Week 13 (Animal Nos. 528, 510 and 535); no details provided on the 4<sup>th</sup> animal  
g: Animal No. 208; h: Animal No. 449  
i: Animal Nos. 298 and 303; j: Animal Nos. 528 and 535

2.6.7.7C Repeat-Dose Toxicity		Test Article: Pitavastatin				Page 1 of 5				
Report Title: One-month repeated dose toxicity study of NK-104 by oral administration in rats										
Species/Strain: Sic-Wistar rats	Duration of Dosing: Once daily for 4 weeks (28 days)			Report No.: [RG25002]						
Initial Age: 6 weeks	Duration of Post-Dose: 14 days (M) or 15 days (F)			Location in CTD:		Vot: *				
Study Duration: May to December 1992	Method of Administration: Oral (gavage) at 2 ml/kg			Section: *		GLP Compliance: Yes				
Vehicle/Formulation: 0.5% CMC sodium solution										
Special Features: None										
No Observed Adverse-Effect Level: 2 mg/kg/day										
Daily Dose (mg/kg/day)	0 (Control)		2		10		50		100	
Number of Animals	M: 20	F: 20	M: 12	F: 12	M: 12	F: 12	M: 20	F: 20	M: 20	F: 20
Toxicokinetics	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
<b>Noteworthy Findings</b>										
Died or Sacrificed Moribund	0	0	0	0	0	1/12 <sup>a</sup>	0	0	0	20/20 <sup>b</sup>
Body Weight (g) <sup>c,d</sup>	264	164	254 (-4)	164 (0)	259 (-2)	161 (-2)	257 (-3)	150 (-9)	248 (-6)	104 (-37) (Day 24; n = 1)
Food Consumption (g) <sup>e</sup>	21	15	21 (0)	16 (+7)	21 (0)	16 (+7)	20 (-5)	14 (-7)	19 (-10)	5 (-67) (Day 22; n = 3)

\*: Not applicable to an electronic submission  
a: One female died in the 10 mg/kg/day group due to a dosing accident on Day 24  
b: 19/20 animals died (Day 7 (1), Day 8 (2), Day 9 (2), Day 10 (4), Day 11 (1), Day 12 (2), Day 13 (3), Day 21 (1), Day 23 (1), Day 24 (1), Day 25 (1)) and one animal was sacrificed moribund on Day 15)  
c: Day 28. Group means are shown. For treated groups, percent differences from controls are shown in parentheses  
d: [R12002/2502] detected significant decreases in body weight using Dunnett's test, namely at 100 mg/kg/day in males on Days 10 and 21 and in females at 50 and 100 mg/kg/day on Days 10 and 14. [R12002/2502] also states in 8.3.1 (1) "However, with the old statistical method, similar significant differences in the same dose groups had been detected on other days of measurement,.....". [RG25002] does not include any statistical analysis of body weights  
e: [R12002/2502] detected significant decreases in food consumption using Dunnett's test, namely at 100 mg/kg/day in males on Day 8 and in females at 100 mg/kg/day on Day 15. [R12002/2502] also states in 8.3.1 (2) "However, significant differences had already been detected by the old statistical method on other days of measurement,.....". [RG25002] does not include any statistical analysis of food consumption

2.6.7.7C Repeat-Dose Toxicity	Report No. [RG25002] (continued)										Page 2 of 5	
	0 (Control)		2		10		50		100			
Daily Dose (mg/kg/day)												
Number of Animals	M: 20	F: 20	M: 12	F: 12	M: 12	F: 12 <sup>a</sup>	M: 20	F: 20	M: 20	F: 20 <sup>b</sup>		
<b>Clinical Observations</b>												
Loose stools	-	-	-	-	-	-	Present <sup>c</sup>	Present <sup>d</sup>	Present <sup>e</sup>	-		
Diarrhoea	-	-	-	-	-	-	-	Present <sup>f</sup>	Present <sup>g</sup>	Present <sup>h</sup>		
Soiled abdomen	-	-	-	-	-	-	-	Present <sup>i</sup>	-	-		
Crouching	-	-	-	-	-	-	-	Present <sup>j</sup>	-	Present <sup>k</sup>		
Emaciation	-	-	-	-	-	-	-	Present <sup>l</sup>	-	Present <sup>m</sup>		
Piloerection	-	-	-	-	-	-	-	Present <sup>n</sup>	-	Present <sup>o</sup>		
<b>Urinalysis</b>												
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 5	M: 6	F: 6	M: 6	F: 4		
Chloride (meq/L) <sup>p</sup>	128	152	137 (+7)	217 (+43)	122 (-5)	166 (+9)	124 (-3)	178 (+17)	111 (-13)	52 (-66) <sup>q</sup>		
Protein (no. animals)	1/6 (±)	0/6	1/6 (±)	5/6 (± to +)	0/6	2/5 (± to +)	2/6 (±)	3/6 (±)	0/6	1/4 (++++) <sup>r</sup>		

a: One female died in the 10 mg/kg/day group due to a dosing accident on Day 24; b: 19/20 animals died (Day 7 (1), Day 8 (2), Day 9 (2), Day 10 (4), Day 11 (1), Day 12 (2), Day 13 (3), Day 21 (1), Day 23 (1), Day 24 (1), Day 25 (1)) and one animal was sacrificed moribund on Day 15)  
c: Days 9, 12 to 19, and 22 (between 1 and 5 animals); d: Days 13 to 14, 16 and 19 (1 animal)  
e: Days 9, 12 to 14, 17 to 19 and 22 (between 1 and 3 animals)  
f: Days 14 (1 animal)  
g: Days 15 to 17 (between 1 and 2 animals)  
h: Day 7 (1 animal)  
i: Days 10 to 28 (1 or 2 animals)  
j: Days 27 to 28 (1 animal)  
k: Days 7 to 24 (between 1 and 7 animals)  
l: Day 28 (1 animal)  
m: Days 7 to 15 and Days 20 to 23 (between 1 and 6 animals)  
n: Day 7 and Days 9 to 24 (between 1 and 11 animals)  
o: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on the percent differences): \* p < 0.05  
p: This animal died the following day and the presence of protein was attributed to a moribund change. Histopathologically only congestion was observed in the kidneys  
q: No noteworthy findings; ±/+/++/+++; No definition for the symbols are given in the report. The report states that "++++" denotes a strong positive response

2.6.7.7C: Repeat-Dose Toxicity	Report No. [RG25002] (continued)										Page 3 of 5	
	0 (Control)		2		10		50		100			
Daily Dose (mg/kg/day)												
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 11 <sup>a</sup>	M: 12	F: 12	M: 12	F: 0 <sup>b</sup>		
<b>Haematology<sup>c</sup></b>												
White blood cells (10 <sup>3</sup> /mm <sup>3</sup> )	54	47	55 (+2)	47 (0)	68 (+26)	52 (+11)	68 (+26) <sup>*</sup>	59 (+26)	66 (+22) <sup>*</sup>	NA		
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 11 <sup>a</sup>	M: 12	F: 10	M: 12	F: 0 <sup>b</sup>		
<b>Serum Chemistry<sup>c</sup></b>												
AST (mU/mL)	82	60	79 (-4)	61 (+2)	88 (+7)	64 (+7)	86 (+5)	120 (+100) <sup>**</sup>	84 (+2)	NA		
ALT (mU/mL)	32	18	30 (-6)	22 (+22)	35 (+9)	19 (+6)	35 (+9)	30 (+67) <sup>**</sup>	37 (+16) <sup>*</sup>	NA		
CKMB (mU/mL)	100	714	106 (+6)	707 (-1)	120 (+20)	668 (-6)	136 (+36) <sup>**</sup>	623 (-13)	157 (+57) <sup>**</sup>	NA		
Triglycerides (mg/dL)	84	28	84 (0)	31 (+11)	72 (-14)	26 (-7)	43 (-49) <sup>**</sup>	24 (-14)	29 (-65) <sup>**</sup>	NA		
Total cholesterol (mg/dL)	49	60	49 (0)	60 (0)	49 (0)	59 (-2)	55 (+12) <sup>*</sup>	77 (+28) <sup>**</sup>	60 (+22) <sup>**</sup>	NA		
<b>Ophthalmoscopy</b>												
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12 <sup>a</sup>	M: 12	F: 12	M: 12	F: 20 <sup>b</sup>		
<b>Gross Pathology</b>												
Forestomach: Thickening	0	0	0	0	6	1	11	10	12	19		
Haemorrhage	0	0	0	0	0	0	0	0	0	3		
Haemorrhagic speckles	0	0	0	0	0	0	0	0	0	2		
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 11 <sup>a</sup>	M: 12	F: 12	M: 12	F: 0 <sup>b</sup>		
<b>Organ Weights<sup>c</sup></b>												
Thymus (absolute, mg)	0.35	0.31	0.34 (-3)	0.29 (-6)	0.35 (0)	0.28 (-10)	0.34 (-3)	0.22 (-29) <sup>**</sup>	0.32 (-9)	NA		
Thymus (relative, %)	0.13	0.19	0.13 (0)	0.18 (-5)	0.13 (0)	0.18 (-5)	0.13 (0)	0.14 (-26) <sup>*</sup>	0.13 (0)	NA		
Thyroid (absolute, mg) <sup>d</sup>	15.6	10.8	15.5 (-1)	10.6 (-2)	17.7 (+13)	11.1 (+3)	19.9 (+28) <sup>**</sup>	12.8 (+19)	19.3 (+24) <sup>*</sup>	NA		
Thyroid (relative, %) <sup>d</sup>	5.9	6.6	6.1 (+3)	6.4 (-3)	6.8 (+15)	6.9 (+5)	7.9 (+34) <sup>**</sup>	9.0 (+36) <sup>*</sup>	7.7 (+31) <sup>**</sup>	NA		

a: One female died in the 10 mg/kg/day group due to a dosing accident on Day 24; b: 19/20 animals died (Day 7 (1), Day 8 (2), Day 9 (2), Day 10 (4), Day 11 (1), Day 12 (2), Day 13 (3), Day 21 (1), Day 23 (1), Day 24 (1), Day 25 (1)) and one animal was sacrificed moribund on Day 15)  
c: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on the percent differences)  
d: [R12002/2502] detected significant decreases in organ weights using Dunnett's test rather than Scheffé's test; #: p < 0.05; ##: p < 0.01; ###: p < 0.001  
\*: p < 0.05; \*\*: p < 0.01; Statistical analysis conducted using Dunnett's, Scheffé's or Kruskal-Wallis tests; - No noteworthy findings

2.6.7.7C Repeat-Dose Toxicity	Report No. [RG25002] (continued)										Page 4 of 5	
	0 (Control)		2		10		50		100			
Daily Dose (mg/kg/day)												
Number of Animals	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12 <sup>a</sup>	M: 12	F: 12	M: 12	F: 20 <sup>b</sup>		
<b>Histopathology</b>												
<b>Forestomach:</b>												
Hyperkeratosis (± to +++)	0	0	0	0	12	8	12	12	12	20		
Thickening stratum spinosum (± to +++)	0	0	0	0	12	8	12	12	12	18		
Monocyte infiltration lamina propria mucosa (± to ++)	0	0	0	0	7	3	8	3	6	3		
Oedema in submucosa (± to ++)	0	0	0	0	4	0	7	3	2	3		
Number of Animals	M: 12	F: 12	M: 0	F: 0	M: 0	F: 11 <sup>a</sup>	M: 0	F: 12	M: 12	F: 20 <sup>b</sup>		
<b>Skeletal muscle:</b>												
Vacuolar degeneration of muscular cells (± to ++)	0	0	NA	NA	NA	0	NA	3	0	13		
Atrophy (± to ++)	0	0	NA	NA	NA	0	NA	3	0	8		
Necrosis (± to ++)	0	0	NA	NA	NA	0	NA	3	0	8		
Monocyte infiltration in interstitium (± to ++)	0	0	NA	NA	NA	0	NA	3	0	5		
Fibrosis (± to ++)	0	0	NA	NA	NA	0	NA	2	0	2		

a: One female died in the 10 mg/kg/day group due to a dosing accident on Day 24.  
b: 19/20 animals died (Day 7 (1), Day 8 (2), Day 9 (2), Day 10 (4), Day 11 (1), Day 12 (2), Day 13 (3), Day 21 (1), Day 23 (1), Day 24 (1), Day 25 (1)) and one animal was sacrificed moribund on Day 15.  
Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Severe

2.6.7.7E Repeat-Dose Toxicity		Test Article: Pitavastatin								Page 1 of 3	
Report Title: Six-month consecutive oral toxicity study of NK-104 in rats											
Species/Strain: Slc:Wistar rats		Duration of Dosing: Once daily for 6 months				Report No.: [RFG2506]		Location in CTD:		Vol: *	
Initial Age: 6 weeks		Duration of Post-Dose: 35 days (F) or 37 days (M)				Method of Administration: Oral (gavage) at 2 mL/kg		Vehicle/Formulation: 0.5% CMC sodium solution		GLP Compliance: Yes	
Study Duration: August 1993 to September 1994		Special Features: None				No Observed Adverse-Effect Level: 1 mg/kg/day					
Daily Dose (mg/kg/day)		0 (Control)		0.3		3		10			
Number of Animals		M: 20	F: 20	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 20	F: 20
Toxicokinetics		ND		ND		ND		ND		ND	
Noteworthy Findings											
Died or Sacrificed Moribund		0		0		0		0		0	
Body Weight (g) <sup>a</sup>		412	220	402 (-2)	222 (+1)	392 (-5)	219 (0)	403 (-2)	217 (-1)	402 (-2)	223 (+1)
Food Consumption (g) <sup>a</sup>		19	14	20 (+5)	13 (-7)	19 (0)	13 (-7)	21 (+11)	15 (+7)	20 (+5)	14 (0)
Clinical Observations											
Urinalysis											
Haematology <sup>a</sup>											
Serum Chemistry <sup>a</sup>											
Total cholesterol (mg/dL)		68	95	65 (-4)	96 (+1)	64 (-6)	96 (+1)	64 (-6)	104 (+9)	66 (-3)	113 (+19)***
Ophthalmoscopy											
Number of Animals		M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Gross Pathology											
Forestomach:											
Thickening of wall		0		0		1		2		7	
Organ Weights											

\*: Not applicable to an electronic submission  
 a: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences)  
 -: No noteworthy findings  
 \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001; Statistical analysis conducted using Bartlett's, ANOVA, Dunnett's, Scheffé or Kruskal-Wallis tests

2.6.7.7E Repeat-Dose Toxicity		Report No. [RFG2506] (continued)								Page 2 of 3	
Daily Dose (mg/kg/day)		0 (Control)		0.3		3		10			
Number of Animals		M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12	M: 12	F: 12
Noteworthy Findings cont.											
Histopathology											
Forestomach:											
Hyperkeratosis (± to ++)		0		0		6		6		12	
Acanthosis (± to ++)		0		0		3		3		12	
Vacuolation stratum spinosum (epithelium) (±)		0		0		1		0		0	
Submucosal cellular infiltration (±)		0		0		0		0		1	
Submucosal oedema (±)		0		0		0		1		0	
Cellular infiltration into mucosal lamina propria (± to ++)		0		0		0		1		2	

Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Severe

2.6.7.7E Repeat-Dose Toxicity		Report No. [RFG2506] (continued)								Page 3 of 3	
Daily Dose (mg/kg/day)		0 (Control)		0.3		1		3		10	
Number of Animals		M: 8	F: 8	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 8	F: 8
Toxicokinetics		ND		NA		NA		NA		ND	
Noteworthy Findings cont.											
Died or Sacrificed Moribund		0		NA		NA		NA		0	
Body Weight (g) <sup>a</sup>		440	231	NA	NA	NA	NA	NA	NA	428 (-3)	232 (0)
Food Consumption (g) <sup>a</sup>		19	15	NA	NA	NA	NA	NA	NA	21 (+11)	15 (0)
Clinical Observations											
Urinalysis											
Ophthalmoscopy											
Haematology											
Serum Chemistry <sup>a</sup>											
AST (mU/ml.)		236	106	NA	NA	NA	NA	NA	NA	192 (-19)	164 (+55)**
Gross Pathology											
Organ Weights											
Histopathology											

a: At the end of the treatment free period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 -: No noteworthy findings  
 \*: p<0.05; \*\*: p<0.001; Statistical analysis conducted using Bartlett's, ANOVA, Dunnett's, Scheffé or Kruskal-Wallis tests

2.6.7.F Repeat-Dose Toxicity		Test Article: Pitavastatin						Page 1 of 8	
<b>Report Title:</b> Three-month repeated dose toxicity study of NK-104 by oral administration in dogs									
<b>Species/Strain:</b> Beagle dogs		<b>Duration of Dosing:</b> Once daily for 13 weeks (91 days)			<b>Report No.:</b> [RFG2503], [AG25001] <sup>a</sup>				
<b>Initial Age:</b> ca. 5 months		<b>Duration of Post-Dose:</b> 7 weeks			<b>Location in CTD:</b>		<b>Vol:</b> *		
<b>Study Duration:</b> July 1992 to May 1993		<b>Method of Administration:</b> Oral (capsules)			<b>Section:</b> *				
		<b>Vehicle/Formulation:</b> Lactose			<b>GLP Compliance:</b> Yes				
<b>Special Features:</b> None									
<b>No Observed Adverse-Effect Level:</b> 1 mg/kg/day									
<b>Daily Dose (mg/kg/day)</b>									
		0 (Control)		1		3		10	
<b>Number of Animals</b>		M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5 <sup>b</sup>
<b>Toxicokinetics</b>									
<b>Pitavastatin</b>									
<b>T<sub>max</sub> (hours)</b>									
Day 1 <sup>c</sup>		NA	NA	1.7	1.0	1.0	1.0	1.6	1.2
Day 36 <sup>d</sup>		NA	NA	1.0	1.7	1.7	1.0	1.2	1.0
Day 91 <sup>e</sup>		NA	NA	1.7	1.7	1.0	1.7	1.4	1.3
<b>C<sub>max</sub> (ng/mL)</b>									
Day 1 <sup>c</sup>		NA	NA	246	344	1477	1671	5179	8686
Day 36 <sup>d</sup>		NA	NA	328	359	809	1212	3383	7027
Day 91 <sup>e</sup>		NA	NA	239	302	1346	1058	7637	4931
<b>AUC<sub>0-24</sub> (ng*hr/mL)</b>									
Day 1 <sup>c</sup>		NA	NA	891	1141	3130	4196	14185	18117
<b>t<sub>1/2</sub> (hours)</b>									
Day 1 <sup>c</sup>		NA	NA	3.9	2.7	2.8	3.1	2.3	2.8

<sup>a</sup>: Not applicable to an electronic submission

<sup>b</sup>: Toxicokinetics report

<sup>c</sup>: One female died in the 10 mg/kg/day group on the 7<sup>th</sup> day of dosing accordingly measurements on Day 36 and Day 91 were performed on 4 animals

<sup>d</sup>: Samples taken prior to and 1, 2, 4, 6, 10 and 24 hours after 1<sup>st</sup> dose

<sup>e</sup>: Samples taken prior to and 1, 2, 4, 6 and 10 hours after 36<sup>th</sup> dose

<sup>f</sup>: Samples taken prior to and 1, 2, 4, 6 and 10 hours after 91<sup>st</sup> dose

2.6.7.F Repeat-Dose Toxicity		Report No. [RFG2503], [AG25001] <sup>a</sup> (continued)						Page 2 of 8	
<b>Daily Dose (mg/kg/day)</b>									
		0 (Control)		1		3		10	
<b>Number of Animals</b>		M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5 <sup>b</sup>
<b>Toxicokinetics cont.</b>									
<b>Lactose</b>									
<b>T<sub>max</sub> (hours)</b>									
Day 1 <sup>c</sup>		NA	NA	3.3	1.3	1.7	1.7	2.4	2.2
Day 36 <sup>d</sup>		NA	NA	2.7	2.7	1.7	2.0	3.2	2.5
Day 91 <sup>e</sup>		NA	NA	4.0	2.7	2.0	2.7	3.6	3.0
<b>C<sub>max</sub> (ng/mL)</b>									
Day 1 <sup>c</sup>		NA	NA	38	51	171	208	610	660
Day 36 <sup>d</sup>		NA	NA	60	61	151	224	824	771
Day 91 <sup>e</sup>		NA	NA	38	53	191	219	960	640
<b>AUC<sub>0-24</sub> (ng*hr/mL)</b>									
Day 1 <sup>c</sup>		NA	NA	263	406	922	1330	3515	4360
Day 36 <sup>d</sup>		NA	NA	3.9	4.0	3.2	3.3	3.1	3.6
<b>t<sub>1/2</sub> (hours)</b>									
Day 1 <sup>c</sup>		NA	NA	3.9	4.0	3.2	3.3	3.1	3.6
<b>Noteworthy Findings</b>									
<b>Died or Sacrificed Moribund</b>		0	0	0	0	0	0	0	1 <sup>f</sup>
<b>Body Weight (kg)</b>		10.3	9.3	10.0 (-3)	9.4 (+1)	9.8 (-5)	9.8 (+5)	9.7 (-6)	9.1 (-2)
<b>Food Consumption (g)</b>		257	262	300 (+17)	205 (-22)	300 (+17)	300 (+15)	276 (+7)	248 (-5)
<b>Clinical Observations<sup>g</sup></b>									
Remaining food		2/5 (14)	3/5 (58)	1/3 (1)	2/3 (65)	1/3 (5)	0/3	3/5 (19)	5/5 (133)
Vomiting		3/5 (4)	4/5 (5)	1/3 (1)	2/3 (4)	3/3 (6)	1/3 (5)	5/5 (23)	4/5 (11)
Soft stools		2/5 (6)	2/5 (2)	2/3 (11)	1/3 (24)	3/3 (31)	2/3 (5)	5/5 (106)	4/5 (23)
Diarrhoea		1/5 (1)	0/5	1/3 (1)	2/3 (5)	2/3 (6)	2/3 (4)	3/5 (12)	4/5 (9)
Bloody stool		0/5	0/5	0/5	1/3 (1)	0/5	0/3	2/5 (2)	1/5 (1)
Oestrous bleeding		NA	3/5	NA	1/3	NA	2/3	NA	0/5

<sup>a</sup>: Toxicokinetics report; <sup>b</sup>: One female died in the 10 mg/kg group on the 7<sup>th</sup> day of dosing.

<sup>c</sup>: Samples taken prior to and 1, 2, 4, 6, 10 and 24 hours after 1<sup>st</sup> dose; <sup>d</sup>: Samples taken prior to and 1, 2, 4, 6 and 10 hours after 36<sup>th</sup> dose

<sup>e</sup>: Samples taken prior to and 1, 2, 4, 6 and 10 hours after 91<sup>st</sup> dose; <sup>f</sup>: Week 13 prior to first scheduled necropsy. Group means are shown. For treated groups, percent differences from controls are shown in parentheses; <sup>g</sup>: Total number of observations per group given in parentheses; <sup>h</sup>: One female died in the 10 mg/kg group on the 7<sup>th</sup> day of dosing. This animal did not consume all its food from Day 1, began vomiting on Day 2 and thereafter, on Day 5 ataxia and lack of faeces were noted, by Day 6 the animal exhibited lack of vigour, vomited blood and had diarrhoea and bloody stools

2.6.7.7C Repeat-Dose Toxicity	Report No. [RG25002] (continued)										Page 5 of 5
	After 14- or 15-Day Treatment Free Period										
	0 (Control)		2		10		50		100		
Daily Dose (mg/kg/day)											
Number of Animals	M: 8	F: 8	M: 0	F: 0	M: 0	F: 0	M: 8	F: 8	M: 8	F: 0	
Toxicokinetics	ND	ND	NA	NA	NA	NA	ND	ND	ND	NA	
<b>Noteworthy Findings</b>											
Died or Sacrificed Moribund	0	0	NA	NA	NA	NA	0	0	0	NA	
Body Weight (g) <sup>a</sup>	295	178	NA	NA	NA	NA	298 (+1)	180 (+1)	286 (-3)	NA	
Food Consumption (g) <sup>a</sup>	23	16	NA	NA	NA	NA	23 (0)	16 (0)	22 (-4)	NA	
Clinical Observations <sup>a</sup>	-	-	NA	NA	NA	NA	-	-	-	NA	
Urinalysis	-	-	NA	NA	NA	NA	-	-	-	NA	
Ophthalmoscopy <sup>b</sup>	ND	ND	NA	NA	NA	NA	ND	ND	ND	NA	
<b>Haematology<sup>a</sup></b>											
Haemoglobin (g/dL)	15.9	15.4	NA	NA	NA	NA	15.8 (-1)	15.8 (+3)*	15.6 (-2)	NA	
<b>Serum Chemistry<sup>a</sup></b>											
Triglycerides (mg/dL)	114	46	NA	NA	NA	NA	93 (-18)	39 (-15)	85 (-25)	NA	
Total cholesterol (mg/dL)	53	65	NA	NA	NA	NA	54 (+2)	65 (0)	50 (-6)	NA	
Gross Pathology	-	-	NA	NA	NA	NA	-	-	-	NA	
<b>Organ Weights<sup>a</sup></b>											
Thyroid (absolute; mg)	13.1	12.3	NA	NA	NA	NA	17.1 (+31)*	11.1 (-10)	16.6 (+27)*	NA	
Thyroid (relative; %)	4.5%	6.9%	NA	NA	NA	NA	5.7 (+27)*	6.2 (-10)	5.8 (+29)*	NA	
Number of Animals	M: 8	F: 8	M: 0	F: 0	M: 0	F: 0	M: 0	F: 8	M: 8	F: 0	
<b>Histopathology</b>											

a: At the end of the treatment free period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 b: Not conducted during the treatment free period as no abnormalities were detected during the dosing period.  
 -: No noteworthy findings  
 \*: p<0.05; Statistical analysis conducted using Dunnett's, Scheffé or Kruskal-Wallis tests

2.6.7.7D Repeat-Dose Toxicity	Test Article: Pitavastatin										Page 1 of 4
	Report Title: NK-104: 13-week preliminary study to a rat carcinogenicity study by repeated oral administration										
	Species/Strain: Crl:CD 1(R) rats	Duration of Dosing: Once daily for 13 weeks						Report No.: [KOW 12/942992]	Location in CTD: Vol: *		
Initial Age: 6 weeks	Duration of Post-Dose: NA						Method of Administration: Oral (gavage) at 5 mL/kg		Vehicle/Formulation: 0.5% CMC sodium solution		GLP Compliance: Yes
Study Duration: June to September 1994											
Special Features: None											
No Observed Adverse-Effect Level: Not achieved; < 10 mg/kg/day											
Daily Dose (mg/kg/day)	0 (Control)		10		30		50				
	M	F	M	F	M	F	M	F	M	F	
<b>Toxicokinetics<sup>a</sup></b>											
T <sub>max</sub> (hours)	Day 1		Day 90		Day 1		Day 90		Day 1		
	NA	NA	2.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	
C <sub>max</sub> (ng/mL)	Day 1		Day 90		Day 1		Day 90		Day 1		
	NA	NA	2820	2717	14491	26065	49547	47753	81252	63032	
C <sub>max</sub> ratio	Dose level ratio		Day 1		Day 90		Day 1		Day 90		
	NA	NA	1	1	3	3	5	5	17.6	17.6	
C <sub>24</sub> (ng/mL)	Day 1		Day 90		Day 1		Day 90		Day 1		
	NA	NA	BLQ	BLQ	12	BLQ	BLQ	8	851	16	
AUC <sub>0-24</sub> (ng·h/mL)	Day 1		Day 90		Day 1		Day 90		Day 1		
	NA	NA	10165	10135	53712	63824	154167	136562	155163	118297	

a: Not applicable to an electronic submission  
 a: Maximum of four rats/sex/group were bled on Days 1 and 90 at 0, 0.5, 1, 2, 4, 6, 8 (not from 50 mg/kg dose group), 12 and 24 hours after dosing. All surviving animals from the 50 mg/kg group were sacrificed after sampling on Day 90 with no further investigations. All surviving animals from the 10 and 30 mg/kg dose groups were subjected to detailed necropsy without organ weight measurement and only macroscopic abnormalities preserved.

2.6.7.7D Repeat-Dose Toxicity	Report No. [KOW 12/942992] (continued)										Page 2 of 4
	Daily Dose (mg/kg/day)										
	0 (Control)		10		30		50				
<b>Toxicokinetics<sup>a</sup></b>											
AUC <sub>0-24</sub> ratio	Dose level ratio		Day 1		Day 90		Day 1		Day 90		
	NA	NA	1	1	3	3	5	5	15.2	13.5	
Accumulation ratio <sup>b</sup>	Day 1		Day 90		Day 1		Day 90		Day 1		
	NA	NA	1	1	5.4	7.6	14.7	17.6	1.1	0.9	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	
<b>Noteworthy Findings</b>											
Died or Sacrificed Moribund	0	0	0	0	0	0	5 <sup>d</sup>	4 <sup>d</sup>			
Body Weight (g) <sup>a</sup>	547	313	555 (+1)	319 (+2)	506 (-7)	312 (0)	509 (-7)	311 (-1)			
Food Consumption (g) <sup>g</sup>	251	166	253 (+1)	166 (0)	241 (-4)	170 (+2)	265 (+6)	181 (+9)			
Efficiency of Food Utilization <sup>a</sup>	9.2	14.2	8.9 (-3)	13.9 (-2)	9.8 (+7)	15.1 (+6)	10.0 (+9)	15.3 (+8)			

a: Maximum of four rats/sex/group were bled on Days 1 and 90 at 0, 0.5, 1, 2, 4, 6, 8 (not from 50 mg/kg/day dose group), 12 and 24 hours after dosing. All surviving animals from the 50 mg/kg/day group were sacrificed after sampling on Day 90 with no further investigations. All surviving animals from the 10 and 30 mg/kg/day dose groups were subjected to detailed necropsy without organ weight measurement and only macroscopic abnormalities preserved.  
 b: AUC<sub>0-24</sub> (Day 90)/AUC<sub>0-24</sub> (Day 1)  
 c: One animal found dead in Week 3 (Animal No. 40), animals sacrificed moribund in Weeks 2 (Animal No. 36), 3 (Animal Nos. 34 and 35) and 8 (Animal No. 33)  
 d: Prior to death the majority of animals exhibited poor condition characterised by hunched position, piloerection, lethargy, cold to the touch, emaciation, unsteady gait, walking on toes and half closed eyes.  
 e: One animal found dead in Week 6 (Animal No. 77), animals sacrificed moribund in Weeks 2 (Animal Nos. 76 and 79) and 3 (Animal No. 75)  
 f: At the end of the dosing period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences)  
 g: Food conversion ratio = Food consumption/body weight gain. Weeks 1 to 13. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences).

2.6.7.D Repeat-Dose Toxicity	Report No. [KOW 12/942992] (continued)								Page 3 of 4
	0 (Control)		10		30		50		
Daily Dose (mg/kg/day)									
Number of Animals <sup>a</sup>	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 5 (5) <sup>b</sup>	F: 6 (4) <sup>c</sup>	
<b>Noteworthy Findings cont.</b>									
<b>Clinical Observations</b>									
Salivation (Weeks 2 to 13)	-	-	-	-	-	-	Present	Present	
Unsteady gait (Weeks 2 to 4 (both sexes), 6 (F), 7 to 8 (M))	-	-	-	-	-	-	Present	Present	
Walking on toes (Weeks 2 to 5 (both sexes), 7 to 8 (M))	-	-	-	-	-	-	Present	Present	
<b>Ophthalmoscopy</b>	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Haematology</b>	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Urinalysis</b>	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Serum Chemistry<sup>d</sup></b>									
T <sub>3</sub> (ng/dL)	36	48	42 (+17)	44 (-8)	52 (+44)**	42 (-13)	56 (+56)**	50 (+4)	
T <sub>4</sub> (µg/dL)	2.3	2.0	2.4 (+4)	1.9 (-5)	2.5 (+9)	1.7 (-15)*	2.2 (-4)	1.8 (-10)*	
TSH (ng/mL)	2.8	2.3	2.9 (+4)	2.3 (0)	2.9 (+4)	2.3 (0)	2.4 (-14)	2.5 (+9)	
<b>Organ Weights (adjusted)<sup>e</sup></b>									
Brain (g)	2.13	1.97	2.15 (+1)	1.95 (-1)	2.10 (-1)	1.97 (0)	2.04 (-4)*	1.88 (-5)*	
Thyroid (mg)	23.1	16.0	24.1 (+4)	18.3 (+14)	31.5 (+36)**	22.5 (+41)**	31.9 (+38)**	21.9 (+37)**	

a: Decedents shown in parentheses  
 b: One animal found dead in Week 3 (Animal No. 40), animals sacrificed moribund in Weeks 2 (Animal No. 36), 3 (Animal Nos. 34 and 35) and 8 (Animal No. 33)  
 c: One animal found dead in Week 6 (Animal No. 77), animals sacrificed moribund in Weeks 2 (Animal Nos. 76 and 79) and 3 (Animal No. 75)  
 d: At the end of the dosing period (at scheduled necropsy). Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 e: No other assays conducted  
 -: No noteworthy findings  
 ND: Not determined  
 T<sub>3</sub>: Triiodothyroxine; T<sub>4</sub>: Thyroxine; TSH: Thyroid stimulating hormone  
 \*: p ≤ 0.05; \*\*: p ≤ 0.01. Statistical analysis was conducted using Fisher's test, Bartlett's test, Kruskal-Wallis test, Student's t test or William's test. Statistical significance is based on actual data (not on the percent differences)

2.6.7.D Repeat-Dose Toxicity	Report No. [KOW 12/942992] (continued)								Page 4 of 4
	0 (Control)		10		30		50		
Daily Dose (mg/kg/day)									
Number of Animals <sup>a</sup>	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 5 (5) <sup>b</sup>	F: 6 (4) <sup>c</sup>	
<b>Noteworthy Findings cont.</b>									
<b>Gross Pathology</b>									
<b>Forestomach:</b>									
Thickened	0	0	0	0	9	9	5 (4)	6 (3)	
Epithelium sloughing	0	0	0	0	2	4	4 (2)	3 (2)	
Epithelium ridged	0	0	0	0	10	8	5 (0)	6 (0)	
Roughened	0	0	2	3	0	0	0 (1)	0 (2)	
White	0	0	0	0	1	0	0 (5)	0 (3)	
Depression(s) epithelial aspect	0	0	0	0	0	1	0 (3)	0 (1)	
Limiting ridge prominent	0	0	0	0	0	0	0 (2)	0 (0)	
<b>Stomach corpus mucosa:</b>									
Congestion	0	0	0	0	1	0	2 (0)	0 (0)	
<b>Histopathology</b>									
<b>Number of Animals<sup>a</sup></b>									
<b>Thyroid:</b>									
Follicular cell hypertrophy (± to ++)	2	0	2	0	4	0	4*	3*	
<b>Stomach (non-glandular region):</b>									
Epithelial hyperplasia (+ to +++)	0	0	9**	9**	10**	10**	5** (5)	6** (3)	
Epithelial hyperkeratosis (+ to ++)	0	0	9**	8**	10**	10**	5** (5)	6** (3)	
Epithelial erosion	0	0	0	0	0	1	0 (1)	0 (0)	
Epithelial ulceration (+ to ++)	0	0	0	0	0	1	0 (0)	0 (1)	

a: Decedents shown in parentheses  
 b: One animal found dead in Week 3 (Animal No. 40), animals sacrificed moribund in Weeks 2 (Animal No. 36), 3 (Animal Nos. 34 and 35) and 8 (Animal No. 33)  
 c: One animal found dead in Week 6 (Animal No. 77), animals sacrificed moribund in Weeks 2 (Animal Nos. 76 and 79) and 3 (Animal No. 75)  
 d: Sample missing from one animal  
 \*: p < 0.05; \*\*: p < 0.01. Statistical analysis was conducted using Fisher's Exact test  
 Histopathology severity: ±: Trace; +: Minimal; ++: Moderate; +++: Marked

2.6.7.F Repeat-Dose Toxicity		Report No. [RFG2503], [AG25001] (continued)						Page 3 of 8	
Daily Dose (mg/kg/day)	0 (Control)								
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 4 <sup>a</sup>	
<b>Noteworthy Findings cont.</b>									
Water Intake	-	-	-	-	-	-	-	-	
<b>Cardiovascular Examinations<sup>b</sup></b>									
Urinalysis (++)	-	-	-	-	-	-	-	1/4 (Protein) <sup>c</sup>	
<b>Faecal Examination</b>									
<b>Haematology</b>									
<b>Serum Chemistry<sup>d</sup></b>									
AST (mU/ml) Week 4	18.0	21.6	23.7 (+32)*	22.7 (+5)	20.3 (+13)	27.7 (+28)	29.8 (+66)**	38.5 (+78)*	
AST (mU/ml) Week 8	19.6	23.6	24.0 (+22)	23.3 (-1)	24.7 (+26)	27.7 (+17)	30.4 (+55)**	39.3 (+67)*	
AST (mU/ml) Week 12	20.8	24.0	25.0 (+20)*	27.7 (+15)	22.7 (+9)	28.3 (+18)	32.6 (+57)**	40.3 (+168)**	
ALT (mU/ml) Week 4	28.0	34.2	34.7 (+24)	36.7 (+7)	36.3 (+30)	59.3 (+73)	50.4 (+80)**	65.5 (+92)	
ALT (mU/ml) Week 8	28.0	34.0	36.0 (+29)	38.3 (+13)	42.7 (+53)*	60.3 (+77)*	59.2 (+111)**	89.3 (+163)	
ALT (mU/ml) Week 12	30.2	31.4	35.0 (+16)	35.7 (+14)	41.0 (+36)*	59.3 (+89)*	76.6 (+154)**	87.3 (+178)	
ALP (mU/ml) Week 4	218	188	294 (+35)	220 (+17)	219 (+5)	214 (+14)	206 (-6)	259 (+38)	
ALP (mU/ml) Week 8	198	159	260 (+31)	177 (+11)	191 (-4)	165 (+4)	189 (-5)	254 (+60)	
ALP (mU/ml) Week 12	172	147	231 (+34)	172 (+17)	169 (-2)	159 (+8)	163 (-5)	251 (+71)	
Triglycerides (mg/dL) Week 4	44.2	41.4	26.3 (-40)*	43.0 (+4)	27.3 (-38)*	20.0 (-52)**	19.6 (-56)**	24.8 (-40)**	
Triglycerides (mg/dL) Week 8	50.4	38.2	28.0 (-44)*	31.7 (-17)	27.0 (-46)*	24.3 (-36)*	23.2 (-34)**	24.0 (-37)*	
Triglycerides (mg/dL) Week 12	50.4	44.8	25.3 (-30)*	48.7 (+9)	29.0 (-42)*	24.7 (-45)*	24.6 (-51)**	42.5 (-5)	
Total cholesterol (mg/dL) Week 4	166	148	107 (-36)**	128 (-14)	100 (-40)**	86 (-42)**	89 (-46)**	82 (-45)**	
Total cholesterol (mg/dL) Week 8	170	149	107 (-37)**	125 (-16)*	105 (-38)**	86 (-42)**	85 (-51)**	69 (-54)**	
Total cholesterol (mg/dL) Week 12	175	171	111 (-37)**	133 (-22)**	109 (-38)**	91 (-47)**	84 (-51)**	72 (-58)**	
Phospholipid (mg/dL) Week 4	273	258	176 (-36)**	225 (-13)	165 (-40)**	141 (-45)**	141 (-48)**	127 (-51)**	
Phospholipid (mg/dL) Week 8	288	263	182 (-37)**	218 (-17)*	180 (-38)**	147 (-44)**	136 (-53)**	115 (-56)**	
Phospholipid (mg/dL) Week 12	307	313	199 (-35)**	258 (-18)*	200 (-35)**	168 (-46)**	144 (-53)**	146 (-53)**	

a: One female died in the 10 mg/kg/day group on the 7<sup>th</sup> day of dosing; b: Body temperature, pulse rate and respiratory rate; c: Week 4 and Week 12; d: Group means are shown. For treated groups, percent differences from controls are shown in parentheses; Urinalysis: results denoted as -, +, ++, or +++  
 \*: p<0.05; \*\*: p<0.01; t-test or Welch test  
 -: No noteworthy findings; \*: p<0.05; \*\*: p<0.01; t-test or Welch test

2.6.7.F Repeat-Dose Toxicity		Report No. [RFG2503], [AG25001] (continued)						Page 4 of 8	
Daily Dose (mg/kg/day)	0 (Control)								
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 5	F: 4 <sup>a</sup>	
<b>Noteworthy Findings cont.</b>									
<b>Ophthalmoscopy</b>									
Opacity of marginal region Week 8	0	0	0	0	0	0	5/5	4/4	
Opacity of lens Week 12	0	0	0	0	0	0 <sup>b</sup>	5/5	4/4	
<b>ECG</b>									
<b>Hepatic Function Test</b>									
<b>Auditory Examination</b>									
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3 <sup>b</sup>	
<b>Gross Pathology</b>									
Eye: white opacity of lens	0	0	0	0	1/3	1/3	3/3	2/2	
Lungs: milky white net form-structure	0	0	0	0	0	0	3/3	2/2	
Epididymis: atrophy central region (right side)	0	NA	0	NA	0	NA	2/3	NA	
<b>Organ Weights<sup>c</sup></b>									
Lungs (absolute: g)	71.5	68.3	72.3 (+1)	70.5 (+3)	70.2 (-2)	71.1 (+4)	96.8 (+35)*	79.8 (+17)	
Lungs (organ/body weight ratio: %)	0.69	0.72	0.73 (+6)	0.73 (+4)	0.72 (+4)	0.73 (+1)	1.01 (+46)*	0.90 (+25)	

a: Excludes one female that died in the 10 mg/kg/day group on the 7<sup>th</sup> day of dosing.  
 b: Includes the animal that died on Day 7 of dosing  
 c: Week 13. Group means are shown. For treated groups, percent differences from controls are shown in parentheses  
 d: Opacity in the marginal region of the lens in one female after 12 weeks dosing  
 \*: p<0.05; \*\*: p<0.01; t-test or Welch test; -: No noteworthy findings  
 ECG: Electrocardiogram

2.6.7.F Repeat-Dose Toxicity		Report No. [RFG2503], [AG25001] (continued)						Page 5 of 8	
Daily Dose (mg/kg/day)	0 (Control)								
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3 <sup>a</sup>	
<b>Noteworthy Findings cont.</b>									
<b>Histopathology<sup>b</sup></b>									
<b>Lungs:</b> Foci of foam cells with inflammatory cell infiltration (± to +++)	0	0	0	0	1	2	3	2	
Pericardial foci of round cell infiltration (± to +)	1	2	2	0	0	0	0	0	
Lymphatic follicle formation in the parenchyma (+)	1	0	0	0	0	0	0	0	
Focal suppurative pneumonia (+++)	0	0	0	0	0	0	0	1	
Pericardial fresh haemorrhage and oedema (+++)	0	0	0	0	0	0	0	1	
Congestion (+++)	0	0	0	0	0	0	0	1	
<b>Liver:</b> Small granuloma (±)	2	2	1	1	1	0	1	1	
Centrilobular dilatation of sinusoids (± to +)	0	0	0	0	0	0	3	0	
Focal round cell infiltration in sinusoid (± to +)	1	0	0	0	0	0	1	0	
Focal round cell infiltration around central vein (± to +)	0	0	0	0	1	0	0	1	
Congestion (+++)	0	0	0	0	0	0	0	1	
Diffuse dilatation of sinusoid and atrophy of hepatocytes (+++)	0	0	0	0	0	0	0	1	
Fresh haemorrhage in junction of liver and gallbladder (+++)	0	0	0	0	0	0	0	1	
<b>Eye:</b> Degeneration of lens fibre (± to +)	0	0	0	0	1	0	2	1	
Oedema in interstitium with degeneration of the ciliary epidermis (± to +++)	0	0	0	0	0	0	1	1	
Adhesion of ciliary body and lens (±)	0	0	0	0	0	0	1	0	

a: Includes the animal that died on Day 7 of dosing  
 b: Week 13  
 Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Severe

2.6.7.7F Repeat-Dose Toxicity		Report No. [RF02503], [AG25001] (continued)						Page 6 of 8	
Daily Dose (mg/kg/day)		0 (Control)		3		10			
Number of Animals		M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
<b>After 7-Week Treatment Free Period</b>									
<b>Noteworthy Findings</b>									
Died or Sacrificed Moribund	0	0	NA	NA	NA	NA	0	0	
Body Weight (kg) <sup>a</sup>	11.3	9.4	NA	NA	NA	NA	10.1 (-11)	9.8 (+4)	
Food Consumption (g) <sup>a</sup>	280	275	NA	NA	NA	NA	300 (+7)	283 (+3)	
<b>Clinical Observations</b>									
Remaining food	2/2 (24)	1/2 (48)	NA	NA	NA	NA	1/2 (22)	2/2 (90)	
Vomiting	0/2	1/2 (1)	NA	NA	NA	NA	1/2 (1)	0/2	
Soft stool	0/2	0/2	NA	NA	NA	NA	2/2 (4)	0/2	
Bloody stool	0/2	0/2	NA	NA	NA	NA	1/2 (1)	0/2	
Oestrous bleeding	NA	1/2	NA	NA	NA	NA	NA	0/2	
Water Intake	-	-	NA	NA	NA	NA	-	-	
Cardiovascular Examination <sup>b</sup>	-	-	NA	NA	NA	NA	-	-	
Urinalysis	-	-	NA	NA	NA	NA	-	-	
Faecal Examination	-	-	NA	NA	NA	NA	-	-	
Haematology	-	-	NA	NA	NA	NA	-	-	

a: Week 7 of treatment free period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses  
 b: Body temperature, pulse rate and respiratory rate  
 -: No noteworthy findings

2.6.7.7F Repeat-Dose Toxicity		Report No. [RF02503], [AG25001] (continued)						Page 7 of 8	
Daily Dose (mg/kg/day)		0 (Control)		3		10			
Number of Animals		M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
<b>After 7-Week Treatment Free Period</b>									
<b>Noteworthy Findings cont.</b>									
<b>Serum Chemistry<sup>a</sup></b>									
AST (mU/mL) Week 2	20.5	17.0	NA	NA	NA	NA	21.0 (+2)	29.0 (+71)	
AST (mU/mL) Week 4	20.5	24.5	NA	NA	NA	NA	20.0 (-2)	31.5 (+29)	
AST (mU/mL) Week 7	21.0	20.5	NA	NA	NA	NA	21.5 (+2)	23.5 (+15)	
ALT (mU/mL) Week 2	29.0	38.5	NA	NA	NA	NA	35.0 (+21)	46.0 (+19)	
ALT (mU/mL) Week 4	27.5	32.5	NA	NA	NA	NA	25.5 (-7)	37.5 (+15)	
ALT (mU/mL) Week 7	26.0	29.0	NA	NA	NA	NA	32.0 (+23)	39.0 (+34)	
ALP (mU/mL) Week 2	162	147	NA	NA	NA	NA	119 (-27)	210 (+43)	
ALP (mU/mL) Week 4	148	138	NA	NA	NA	NA	116 (-22)	221 (+60)	
ALP (mU/mL) Week 7	146	144	NA	NA	NA	NA	93 (-36)	201 (+40)	
Triglycerides (mg/dL) Week 2	50.5	46.0	NA	NA	NA	NA	39.0 (-23)	41.0 (-11)	
Triglycerides (mg/dL) Week 4	47.0	46.0	NA	NA	NA	NA	38.5 (-18)	51.5 (+12)	
Triglycerides (mg/dL) Week 7	48.5	42.5	NA	NA	NA	NA	37.5 (-23)	44.0 (+4)	
Total cholesterol (mg/dL) Week 2	157	173	NA	NA	NA	NA	162 (+3)	134 (-23)	
Total cholesterol (mg/dL) Week 4	142	180	NA	NA	NA	NA	160 (+13)	147 (-18)	
Total cholesterol (mg/dL) Week 7	152	187	NA	NA	NA	NA	151 (-1)	141 (-25)	
Phospholipid (mg/dL) Week 2	296	312	NA	NA	NA	NA	285 (-4)	246 (-21)	
Phospholipid (mg/dL) Week 4	281	320	NA	NA	NA	NA	283 (+1)	266 (-17)	
Phospholipid (mg/dL) Week 7	308	306	NA	NA	NA	NA	265 (-14)	259 (-15)	
<b>Ophthalmoscopy</b>									
Opacity of lens Week 4	0	0	NA	NA	NA	NA	2/2	2/2	
White opacity of lens Week 7	0	0	NA	NA	NA	NA	2/2	2/2	
ECG	-	-	NA	NA	NA	NA	-	-	

a: Group means are shown. For treated groups, percent differences from controls are shown in parentheses  
 -: No noteworthy findings

2.6.7.7F Repeat-Dose Toxicity		Report No. [RF02503], [AG25001] (continued)						Page 8 of 8	
Daily Dose (mg/kg/day)		0 (Control)		3		10			
Number of Animals		M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2
<b>After 7-Week Treatment Free Period</b>									
<b>Noteworthy Findings cont.</b>									
<b>Hepatic Function Test</b>									
Auditory Examination	-	-	NA	NA	NA	NA	-	-	
<b>Gross Pathology</b>									
Eye: white opacity of lens	0	0	NA	NA	NA	NA	2/2	2/2	
<b>Organ Weights<sup>a</sup></b>									
Lungs (absolute; g)	74.0	65.9	NA	NA	NA	NA	73.2 (-1)	74.7 (+13)	
Lungs (organ/body weight ratio; %)	0.66	0.69	NA	NA	NA	NA	0.72 (+9)	0.77 (+12)	
<b>Histopathology</b>									
Lungs: Pericanal foci of round cell infiltration (± to +)	0	0	NA	NA	NA	NA	1	1	
Dilatation of the subcutaneous lymphatic duct (+)	1	0	NA	NA	NA	NA	0	0	
Foci of foam cells with inflammatory cell infiltration (±)	0	0	NA	NA	NA	NA	0	1	
Liver: Small granuloma (± to +)	1	0	NA	NA	NA	NA	1	1	
Eye: Degeneration of lens fibre (± to +++)	0	0	NA	NA	NA	NA	2	2	
Oedema in interstitium with degeneration of the ciliary epithelium (+ to +++)	0	0	NA	NA	NA	NA	2	2	
Adhesion of ciliary body and lens (+ to +++)	0	0	NA	NA	NA	NA	1	2	
Vacuolation of outer plexiform layer of retina (±)	0	0	NA	NA	NA	NA	2	0	

a: Group means are shown. For treated groups, percent differences from controls are shown in parentheses. The values for male animals are abstracted from table 81 (absolute) and table 82 (organ/body weight ratio; table title incorrectly states "females"); the values for female animals are abstracted from table 83 (absolute; table title incorrectly states "males") and table 84 (organ/body weight ratio)  
 [Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Severe]

2.6.7.7G Repeat-Dose Toxicity		Test Article: Pitavastatin						Page 1 of 7	
Report Title: Twelve-month consecutive oral toxicity study of NK-104 in dogs									
Species/Strain: Beagle dogs	Duration of Dosing: Once daily for 12 months				Report No.: [RFG2504], [AG25004]*				
Initial Age: ca. 6 to 7 months	Duration of Post-Dose: 9 weeks				Location in CTD:   Vol: *				
Study Duration: April 1993 to October 1994	Method of Administration: Oral (capsules)				Section: *				
Special Features: None	Vehicle/Formulation: Lactose				GLP Compliance: Yes				
No Observed Adverse-Effect Level: 0.3 mg/kg									
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
Toxicokinetics									
Pitavastatin									
T <sub>max</sub> (hours)	NA		1.3		1.3		1.3		
Day 1 <sup>b</sup>	NA	NA	1.3	1.0	1.3	1.3	1.0	1.2	
Month 3 <sup>c</sup>	NA	NA	1.3	1.0	1.3	1.3	1.2	1.2	
Month 6 <sup>c</sup>	NA	NA	2.0	2.0	1.3	1.0	1.3	1.3	
Month 9 <sup>c</sup>	NA	NA	2.3	2.0	1.0	1.5	1.3	1.0	
Month 12 <sup>c</sup>	NA	NA	1.5	3.0	1.3	1.5	1.3	1.3	
C <sub>max</sub> (ng/mL)	NA		78		493		2880		
Day 1 <sup>b</sup>	NA	NA	78	113	493	546	2880	2190	
Month 3 <sup>c</sup>	NA	NA	94	76	295	402	1800	1630	
Month 6 <sup>c</sup>	NA	NA	104	76	590	546	3010	1710	
Month 9 <sup>c</sup>	NA	NA	51	44	327	502	1210	1150	
Month 12 <sup>c</sup>	NA	NA	107	60	382	325	2890	1830	
AUC <sub>0-24</sub> (ng*hr/mL)	NA		280		1328		7070		
Day 1 <sup>b</sup>	NA	NA	280	421	1328	1463	7070	5350	
Month 3 <sup>c</sup>	NA	NA	313	249	907	1294	5020	3680	
Month 6 <sup>c</sup>	NA	NA	453	309	2001	1880	9290	4910	
Month 9 <sup>c</sup>	NA	NA	252	195	1143	1477	4120	3600	
Month 12 <sup>c</sup>	NA	NA	384	288	1360	1363	7750	5340	

\*: Not applicable to an electronic submission; a: Toxicokinetics report; b: Samples were taken prior to and 1, 2, 4, 6, 10 and 24 hours after 1<sup>st</sup> dose; c: Samples were taken prior to and 1, 2, 4, 6 and 10 hours after dosing; AUC<sub>0-24</sub>: AUC from zero to the last measurable time

2.6.7.7G Repeat-Dose Toxicity		Report No. [RFG2504], [AG25004]* (continued)						Page 2 of 7	
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
Toxicokinetics cont.									
Lactone									
T <sub>max</sub> (hours)	NA		3.0		2.0		2.0		
Day 1 <sup>b</sup>	NA	NA	3.0	3.5	2.0	2.0	2.0	2.0	
Month 3 <sup>c</sup>	NA	NA	3.5	3.0	2.5	3.0	2.3	1.8	
Month 6 <sup>c</sup>	NA	NA	4.0	4.5	2.8	2.3	2.7	2.5	
Month 9 <sup>c</sup>	NA	NA	3.5	3.5	2.5	3.0	2.0	1.8	
Month 12 <sup>c</sup>	NA	NA	3.0	3.0	3.3	2.5	2.7	2.0	
C <sub>max</sub> (ng/mL)	NA		11		51		250		
Day 1 <sup>b</sup>	NA	NA	11	14	51	54	250	240	
Month 3 <sup>c</sup>	NA	NA	19	11	54	86	340	220	
Month 6 <sup>c</sup>	NA	NA	19	13	86	87	320	200	
Month 9 <sup>c</sup>	NA	NA	13	9	59	78	320	230	
Month 12 <sup>c</sup>	NA	NA	16	11	59	79	310	210	
AUC <sub>0-24</sub> (ng*hr/mL)	NA		78		271		1350		
Day 1 <sup>b</sup>	NA	NA	78	87	271	331	1350	1280	
Month 3 <sup>c</sup>	NA	NA	125	73	318	515	2020	1270	
Month 6 <sup>c</sup>	NA	NA	139	99	558	586	2190	1320	
Month 9 <sup>c</sup>	NA	NA	91	53	381	492	1710	1360	
Month 12 <sup>c</sup>	NA	NA	105	70	341	468	1700	1150	

a: Toxicokinetics report  
 b: Samples were taken prior to and 1, 2, 4, 6, 10 and 24 hours after 1<sup>st</sup> dose  
 c: Samples were taken prior to and 1, 2, 4, 6 and 10 hours after dosing

2.6.7.7G Repeat-Dose Toxicity		Report No. [RFG2504], [AG25004]* (continued)						Page 3 of 7	
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
Toxicokinetics cont.									
Pitavastatin									
Mean concentration in aqueous humour (ng/mL)	NA	NA	Not detected	0.08	Not detected	0.06	0.78	0.64	
Mean concentration in lens (ng/g)	NA	NA	40.4	25.3	150.5	148.9	389.0	291.7	
Mean concentration in vitreous body (ng/mL)	NA	NA	Not detected	Not detected	Not detected	0.12	0.65	2.18	
Lactone									
Mean concentration in aqueous humour (ng/mL)	NA	NA	Not detected						
Mean concentration in lens (ng/g)	NA	NA	Not detected	Not detected	Not detected	0.2	2.4	1.8	
Mean concentration in vitreous body (ng/mL)	NA	NA	Not detected						
Daily Dose (mg/kg)	0 (Control)		0.3		1		3		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
Neurotoxicity Findings									
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	
Body Weight (kg) <sup>a</sup>	10.9	10.5	11.6 (+6)	11.0 (+5)	10.4 (-5)	10.4 (-1)	11.3 (+4)	10.4 (-1)	
Food Consumption (g) <sup>a</sup>	296	271	296 (0)	300 (+11)	300 (+11)	276 (+2)	300 (+1)	233 (-14)	
Water Intake	-	-	-	-	-	-	-	-	
Clinical Observations									
Bloody / soft stool (sporadic)	0/6	0/6	1/4	0/4	0/4	0/4	1/6	0/6	

a: Toxicokinetics report  
 b: Prior to first scheduled necropsy. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences)

2.6.7.7G Repeat-Dose Toxicity	Report No. [RFG2504], [AG25004] (continued)								Page 4 of 7
	0 (Control)		0.3		1		3		
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
<b>Noteworthy Findings cont.</b>									
Cardiovascular Examinations <sup>a</sup>	-	-	-	-	-	-	-	-	
Urinalysis	-	-	-	-	-	-	-	-	
Haematology	-	-	-	-	-	-	-	-	
<b>Serum Chemistry (Month 12)<sup>b</sup></b>									
AST (mU/mL)	19.7	20.3	20.8 (+6)	21.5 (+6)	23.8 (+21)	20.5 (+1)	26.0 (+32)*	23.0 (+13)	
ALT (mU/mL)	23.7	18.7	25.3 (+7)	21.3 (+14)	25.3 (+7)	22.0 (+18)	38.2 (+61)	25.8 (+38)	
Al.P (mU/mL)	101	119	103 (+2)	114 (-4)	135 (+34)	128 (+8)	161 (+59)	110 (-8)	
Triglycerides (mg/dL)	38.8	42.7	37.0 (-5)	31.8 (-26)	22.0 (-43)	31.8 (-26)	22.8 (-41)*	32.5 (-24)	
Total cholesterol (mg/dL)	125	123	112 (-10)	130 (+6)	85 (-32)	101 (-18)	63 (-50)**	99 (-20)	
Phospholipid (mg/dL)	272	281	256 (-6)	294 (+5)	199 (-27)	238 (-15)	158 (-42)**	226 (-20)	
<b>Ophthalmoscopy</b>									
Opacity of the lens (± to ++)	0	0	0	0	1/4	0	2/6	0	
White turbidity of lens	0	0	0	0	0	0	3/6	6/6	
ECC	-	-	-	-	-	-	-	-	
Hepatic Function Test	-	-	-	-	-	-	-	-	
Auditory Function Test	-	-	-	-	-	-	-	-	
Male Sexual Function Test	-	NA	-	NA	-	NA	-	NA	

a: Body temperature, pulse rate and respiratory rate  
 b: Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences)  
 -: No noteworthy findings  
 \*: p<0.05; \*\*: p<0.01; t-test or Welch test  
 Severity: ±: Trace; +: Mild; ++: Moderate

2.6.7.7G Repeat-Dose Toxicity	Report No. [RFG2504], [AG25004] (continued)								Page 5 of 7
	0 (Control)		0.3		1		3		
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	
<b>Noteworthy Findings cont.</b>									
<b>Gross Pathology<sup>a</sup></b>									
<b>Eye:</b>									
White opacity of lens	0	0	0	0	0	0	1/4	1/4	
White opacity and atrophy of lens	0	0	0	0	0	0	2/4	3/4	
Adhesion of lens and vitreous body	0	0	0	0	0	0	0	1/4	
<b>Lung:</b>									
Yellowish white nodules	0	0	0	0	0	0	1/4	-	
<b>Organ Weights<sup>b</sup></b>	-	-	-	-	-	-	-	-	
<b>Histopathology<sup>c</sup></b>									
<b>Lungs:</b>									
Aggregated foci of foam cells (±)	2/4	1/4	1/4	0	0	0	2/4	1/4	
Aggregated foci of foam cells and inflammatory cells (+)	0	0	0	0	0	0	2/4	3/4	
Periductular round cell infiltration foci (+)	0	0	1/4	1/4	0	0	0	0	
<b>Eye:</b>									
Interstitial oedema with degeneration of the ciliary epithelium (± to ++)	0	0	0	1/4	0	0	2/4	1/4	
Degeneration of lens fibre (± to ++)	0	0	0	0	0	0	3/4	4/4	

a: Month 12 (first scheduled necropsy).  
 -: No noteworthy findings  
 Histopathology severity: ±: Trace; +: Mild; ++: Moderate

2.6.7.7G Repeat-Dose Toxicity	Report No. [RFG2504], [AG25004] (continued)								Page 6 of 7
	0 (Control)		0.3		1		3		
Daily Dose (mg/kg/day)	0 (Control)		0.3		1		3		
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2	
<b>After 9-Week Treatment Free Period</b>									
<b>Toxicokinetics</b>									
Mean concentration in aqueous humour (ng/mL)	NA	NA	NA	NA	NA	NA	Not detected	Not detected	
Mean concentration in lens (ng/g)	NA	NA	NA	NA	NA	NA	354.2	134.2	
Mean concentration in vitreous body (ng/mL)	NA	NA	NA	NA	NA	NA	Not detected	Not detected	
<b>As above</b>									
Mean concentration in aqueous humour (ng/mL)	NA	NA	NA	NA	NA	NA	Not detected	Not detected	
Mean concentration in lens (ng/g)	NA	NA	NA	NA	NA	NA	2.3	0.5	
Mean concentration in vitreous body (ng/mL)	NA	NA	NA	NA	NA	NA	Not detected	Not detected	
<b>Noteworthy Findings</b>									
Died or Sacrificed Moribund	0	0	NA	NA	NA	NA	0	0	
Body Weight (kg) <sup>a</sup>	11.1	10.2	NA	NA	NA	NA	10.9 (-2)	10.9 (+7)	
Food Consumption (g) <sup>b</sup>	300	265	NA	NA	NA	NA	300 (0)	300 (+13)	
Water Intake	-	-	NA	NA	NA	NA	-	-	
<b>Clinical Observations</b>									
Cardiovascular Examinations <sup>c</sup>	-	-	NA	NA	NA	NA	-	-	
Urinalysis	-	-	NA	NA	NA	NA	-	-	
Haematology	-	-	NA	NA	NA	NA	-	-	

a: Toxicokinetics report  
 b: At the end of the treatment free period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 c: Body temperature, pulse rate and respiratory rate  
 -: No noteworthy findings

2.6.7.7G Repeat-Dose Toxicity		Report No. [RFG2504], [AG25004] (continued)						Page 7 of 7	
Daily Dose (mg/kg/day)	0 (Control)		0.3		3		3		
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2	
After 9-Week Treatment Free Period									
<b>Noteworthy Findings cont.</b>									
<b>Serum Chemistry*</b>									
AST (mU/mL)	18.5	20.0	NA	NA	NA	NA	21.5 (+16)	17.0 (-15)	
ALT (mU/mL)	16.5	24.0	NA	NA	NA	NA	21.0 (+27)	19.5 (-19)	
ALP (mU/mL)	66	116	NA	NA	NA	NA	138 (+109)	135 (+16)	
Triglycerides (mg/dL)	48.5	59.0	NA	NA	NA	NA	44.5 (-8)	51.5 (-13)	
Total cholesterol (mg/dL)	122	97	NA	NA	NA	NA	136 (+11)	195 (+101)	
Phospholipid (mg/dL)	272	233	NA	NA	NA	NA	321 (+18)	364 (+56)	
<b>Ophthalmoscopy</b>									
Opacity of the lens (± to ++)	0	0	NA	NA	NA	NA	1/2	0	
White turbidity of lens	0	0	NA	NA	NA	NA	1/2	2/2	
<b>EKG</b>									
Heart Rate (b/min)	-	-	NA	NA	NA	NA	-	-	
<b>Reproductive Function Test</b>									
Auditory Function Test	-	-	NA	NA	NA	NA	-	-	
Male Sexual Function Test	-	NA	NA	NA	NA	NA	-	NA	
<b>Gross Pathology</b>									
Eye: White opacity and atrophy of lens	0	0	NA	NA	NA	NA	1/2	2/2	
<b>Organ Weights</b>									
<b>Histopathology</b>									
Lung: Periductal wound cell infiltration foci (+)	0	1/2	NA	NA	NA	NA	0	1/2	
Eye: Interstitial oedema with degeneration of the ciliary epithelium (±)	0	0	NA	NA	NA	NA	1/2	0	
Eye: Degeneration of lens fibre (+ to ++)	0	0	NA	NA	NA	NA	1/2	2/2	

a: At the end of the treatment free period. Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Severity: ± Trace; + Slight; ++ Moderate

2.6.7.7H Repeat-Dose Toxicity		Test Article: Pitavastatin						Page 1 of 6	
Report Title: Four-week consecutive oral toxicity study of NK-104 in cynomolgus monkeys		Duration of Dosing: Once daily dosing for 4 weeks						Report No.: [SBL17-34] <sup>a</sup> , [RF12515] <sup>b</sup>	
Species/Strain: Cynomolgus monkeys		Duration of Post-Dose: N/A						Location in CTD:	
Initial Age: 3 to 5 years		Method of Administration: Oral (gavage) at 5 ml/kg						Vol.: *	
Study Duration: December 1995 to July 1996		Vehicle/Formulation: 0.5% carmellose sodium solution						Section: *	
Special Features: None		GLP Compliance: Yes							
No Observed Adverse-Effect Level: < 3 mg/kg/day									
Daily Dose (mg/kg/day)	0 (Control)		3		8		15		
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	
<b>Toxicokinetics</b>									
<b>Pitavastatin</b>									
T <sub>max</sub> (hours)	Day 1	NA	NA	1.3	1.0	0.8	1.3	3.0	3.0
	Day 28	NA	NA	0.8	0.5	1.3	3.0	2.0	1.5
C <sub>max</sub> (ng/mL)	Day 1	NA	NA	159	139	375	242	888	597
	Day 28	NA	NA	185	121	373	248	755	37693, 302 <sup>c</sup>
AUC <sub>0-24</sub> (ng·h/mL)	Day 1	NA	NA	690	820	1280	1709	4943	3809
	Day 28	NA	NA	552	476	1588	4016	4434	78828, 4071 <sup>c</sup>
t <sub>1/2</sub> (hours)	Day 1	NA	NA	4.2	2.1	2.2	3.6	2.6	2.9
	Day 28	NA	NA	2.9	3.2	2.7	7.5	3.1	1.1, 10.0 <sup>c</sup>

\*: Not applicable to an electronic submission  
a: Following finalisation of [SBL17-34], one of the participating pathologists from Kitasato University reviewed the report and histopathological findings. Although his observations agreed fundamentally with the renal histopathological changes reported, some corrections were suggested. The responsible laboratory (b) (4) report and a revised Table 11.  
b: Toxicokinetics report  
c: Where there is a marked difference between the values of the two individual animals, both values are given.

2.6.7.7H Repeat-Dose Toxicity		Report No. [SBL17-34], [RF12515] <sup>b</sup> (continued)						Page 2 of 6	
Daily Dose (mg/kg/day)	0 (Control)		3		8		15		
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	
<b>Lactone</b>									
T <sub>max</sub> (hours)	Day 1	NA	NA	1.3	1.0	1.0	1.5	3.0	3.0
	Day 28	NA	NA	0.8	0.5	1.3	24.0, 8.0 <sup>b</sup>	2.0	1.5
C <sub>max</sub> (ng/mL)	Day 1	NA	NA	29	45	56	36	283	96
	Day 28	NA	NA	46	25	44	71	280	2904, 21 <sup>b</sup>
AUC <sub>0-24</sub> (ng·h/mL)	Day 1	NA	NA	66	163	236	265	1647	623
	Day 28	NA	NA	120	125	239	935	1606	12818, 315 <sup>b</sup>
t <sub>1/2</sub> (hours)	Day 1	NA	NA	1.5 (n=1)	2.0	1.8	4.1	1.8	2.2
	Day 28	NA	NA	1.4	1.8	3.3	4.6	3.7	3.5

a: Toxicokinetics report  
b: Where there is a marked difference between the values of the two individual animals, both values are given.

2.6.7.H Repeat-Dose Toxicity		Report No. [SBL17-34] (continued)								Page 3 of 6
Daily Dose (mg/kg/day)	0 (Control)		3		8		15			
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2		
<b>Noteworthy Findings cont.</b>										
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	
Body Weight (kg) <sup>a</sup>	4.255	2.870	4.695 (+10)	2.730 (-5)	4.435 (+4)	2.435 (-15)	4.195 (-1)	2.275 (-21)		
Food Consumption (g) <sup>b</sup>	108	108	108 (0)	108 (0)	108 (0)	93.0 (-14)	108 (0)	54.0 (-50) <sup>c</sup>		
<b>Clinical Observations</b>										
Soft stools	-	-	-	-	-	-	-	-	1/2 (Day 6) <sup>f</sup>	
Diarrhoea	-	-	-	-	-	-	-	-	1/2 (Day 7) <sup>f</sup>	
Decreased or loss of appetite	-	-	-	-	-	-	-	-	1/2 (Day 6) <sup>f</sup>	
Decreased spontaneous motor activity	-	-	-	-	-	-	-	-	1/2 (Day 14) <sup>f</sup>	
Emaciation	-	-	-	-	-	-	-	-	1/2 (Day 14) <sup>f</sup>	
Pallid colour of oral cavity mucosa	-	-	-	-	-	-	-	-	1/2 (Day 16) <sup>f</sup>	
Sitting posture	-	-	-	-	-	-	-	-	1/2 (Day 27) <sup>f</sup>	

a: Week 4 prior to first scheduled necropsy. Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 b: 108 g recorded for one animal; no food consumption was recorded for the 2<sup>nd</sup> animal (No. 15).  
 c: Animal No. 15; clinical observation day of onset shown; decreased appetite until Day 12 followed by no appetite.  
 -: No noteworthy findings.

2.6.7.H Repeat-Dose Toxicity		Report No. [SBL17-34] (continued)								Page 4 of 6
Daily Dose (mg/kg/day)	0 (Control)		3		8		15			
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2		
<b>Noteworthy Findings cont.</b>										
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	
ECC	-	-	-	-	-	-	-	-	-	
Urinalysis	-	-	-	-	-	-	-	-	+ <sup>a</sup>	
<b>Haematology<sup>b</sup></b>										
Platelets (10 <sup>9</sup> /mm <sup>3</sup> )	52.50 (40.8, 64.2)	32.75 (17.6, 47.9)	-22 (40.3, 41.6)	+42 (45.1, 47.9)	-28 (30.5, 44.6)	+58 (33.9, 69.4)	-23 (36.6, 44.3)	+103 (50.6, 82.4) <sup>c</sup>		
<b>Serum Chemistry<sup>b</sup></b>										
AST (IU/L)	31.0 (25, 37)	26.5 (20, 33)	+2 (31, 32)	+15 (23, 38)	-31 (21, 22)	+358 (78, 165)	+15 (33, 38)	+909 (38, 497) <sup>c</sup>		
ALT (IU/L)	32.5 (27, 38)	34.5 (31, 38)	+22 (36, 43)	+30 (30, 60)	-34 (19, 24)	+345 (121, 186)	+54 (39, 61)	+72 <sup>c</sup> (47, 72) <sup>c</sup>		
LDH (IU/L)	586 (578, 594)	561.0 (505, 617)	+55 (810, 1001)	-5 (495, 570)	-11 (384, 656)	+74 (832, 1118)	+434 (676, 728)	+5357 (726, 5260) <sup>c</sup>		
CPK (IU/L)	213.5 (149, 278)	233.0 (115, 351)	+47 (252, 377)	-51 (70, 160)	-52 (76, 130)	+39 (196, 452)	+44 (230, 383)	+5357 (284, 25147) <sup>c</sup>		
Total cholesterol (mg/dL)	89.5 (89, 90)	87.0 (85, 89)	-23 (61, 76)	+22 (105, 108)	+33 (85, 153)	+4 (85, 96)	+8 (74, 120)	-1 (74, 99)		
BUN (mg/dL)	17.70 (17.4, 18.0)	19.75 (18.9, 20.6)	-9 (13.9, 18.3)	-15 (15.7, 17.7)	-4 (16.6, 17.4)	+21 (17.6, 30.2)	-11 (15.6, 15.8)	+77 (24.7, 45.4) <sup>c</sup>		
Creatinine (mg/dL)	1.120 (0.86, 1.38)	0.900 (0.77, 1.03)	-20 (0.88, 0.91)	-7 (0.83, 0.85)	-24 (0.75, 0.96)	+27 (0.86, 1.42)	+3 (1.11, 1.19)	+36 (1.06, 1.39)		

a: Animal No. 15. Urinary occult blood observed at Weeks 2 and 4. At Week 4 ketones were elevated (80 mg/dL) with decreased Na and Cl. Erythrocytes and leukocytes present in urinary sediment at Week 4. Decreased blood values of Na, K, and Cl were also seen.  
 b: Week 4 prior to first scheduled necropsy. For controls, group means are shown. For treated groups, percent differences from controls are shown. Values for individual animals are given in parentheses.  
 c: Animal No. 15; BUN: Blood urea nitrogen  
 -: No noteworthy findings

2.6.7.H Repeat-Dose Toxicity		Report No. [SBL17-34] (continued)								Page 5 of 6
Daily Dose (mg/kg/day)	0 (Control)		3		8		15			
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2		
<b>Noteworthy Findings cont.</b>										
<b>Organ Weights (%)<sup>a</sup></b>										
Thymus (absolute; g)	1.75 (1.7, 1.8)	1.55 (1.4, 1.7)	+57 (2.2, 3.3)	+48 (1.9, 2.7)	+69 (2.8, 3.1)	-16 (0.3, 2.3)	-34 (0.7, 1.6)	-68 (0.3 <sup>b</sup> , 0.7)		
Thymus (relative; g/kg)	0.415 (0.40, 0.43)	0.560 (0.47, 0.65)	+48 (0.43, 0.80)	+34 (0.69, 1.03)	+61 (0.59, 0.75)	-13 (0.15, 0.83)	-29 (0.15, 0.44)	-63 (0.16 <sup>b</sup> , 0.26)		
Kidneys (bilateral) (absolute; g)	16.45 (15.4, 17.5)	12.20 (11.1, 13.3)	+14 (18.7, 18.8)	+16 (13.5, 14.7)	+33 (21.0, 22.9)	-1 (11.8, 12.4)	+30 (16.3, 26.4)	+28 (18.3 <sup>b</sup> , 12.9)		
Kidneys (bilateral) (relative; g/kg)	3.940 (3.72, 4.16)	4.350 (4.24, 4.46)	+4 (3.69, 4.52)	+20 (5.13, 5.31)	+26 (4.44, 5.52)	+19 (4.46, 5.87)	+29 (4.47, 5.67)	+69 (4.74, 10.00) <sup>c</sup>		
<b>Gross Pathology</b>										
Emaciation (+)	-	-	-	-	-	-	-	1/2 <sup>b</sup>		
Thymus: atrophy (++)	-	-	-	-	-	1/2	-	1/2 <sup>b</sup>		
<b>Histopathology</b>										
<b>Spleen:</b>										
Brown pigment, macrophages (+)	0	0	0	0	1	0	0	0		
Hyaline material in follicle (± to +)	2	2	1	1	1	1	1	0		
Atrophy of white pulp (++)	0	0	0	0	0	1	0	1 <sup>a</sup>		
<b>Tonsil:</b>										
Atrophy (± to ++)	0	0	0	0	0	1	0	1 <sup>a</sup>		
<b>Submandibular lymph node:</b>										
Atrophy (+ to ++)	0	0	0	0	0	1	0	1 <sup>a</sup>		

a: Week 4 prior to first scheduled necropsy. For controls, group means are shown. For treated groups, percent differences from controls are shown. Values for individual animals are given in parentheses  
 b: Animal No. 15  
 -: No noteworthy findings  
 Severity: +: Mild; ++: Moderate

2.6.7.7H Repeat-Dose Toxicity		Report No. [SBI.17-34] (continued)								Page 6 of 6
Daily Dose (mg/kg/day)	0 (Control)		1		2		4		15	
Number of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
<b>Noteworthy Findings cont.</b>										
<b>Histopathology cont.</b>										
<b>Kidney:</b>										
Hyaline cast (± to ++)	0	0	0	0	0	1	0	2 <sup>a</sup>		
Dilatation of tubule (+)	0	0	0	0	0	1	0	1 <sup>a</sup>		
Necrosis proximal tubular epithelium (± to ++)	0	0	2	1	2	2	2	2 <sup>a</sup>		
Swelling proximal tubular epithelium (± to ++)	0	0	0	0	0	1	1	2 <sup>a</sup>		
Regeneration proximal tubular epithelium (± to +++)	0	0	2	2	2	2	2	2 <sup>a</sup>		
Interstitial mononuclear cell infiltration (± to +)	2	1	2	1	2	2	1	2 <sup>a</sup>		
Brown pigment in tubular epithelium (±)	1	0	2	0	1	0	0	0		
Desquamation of tubular epithelium (± to ++)	0	0	0	0	2	1	2	2 <sup>a</sup>		
Ilyaline droplet in tubular epithelium (±)	0	0	0	0	0	0	0	1 <sup>a</sup>		
<b>Pancreas:</b>										
Atrophy of acinar cell (± to ++)	0	0	0	0	0	1	0	2 <sup>a</sup>		
<b>Adrenal gland:</b>										
Cortical hyperplasia (±)	0	0	0	0	0	1	0	1 <sup>a</sup>		
Decrease in fat droplets in cortex (± to +)	0	0	0	0	0	1	0	1 <sup>a</sup>		
<b>Thymus:</b>										
Atrophy (++ to +++)	0	0	0	0	0	0	1	1 <sup>a</sup>		
Cyst (±)	0	1	0	1	0	0	0	0		
<b>Stomach:</b>										
Dilatation of crypt (±)	0	0	1	0	0	0	0	0		
Lymphocyte hyperplasia <sup>b</sup> (+)	0	0	0	0	0	0	1	1		
Erosion in pyloric part (±)	0	0	0	0	0	0	0	1 <sup>a</sup>		
<b>Skeletal muscle:</b>										
Atrophy of muscle fibre	0	0	0	0	0	0	0	1 <sup>a</sup>		

a: Animal No. 15 / includes Animal No. 15

b: Lamina propria of pyloric part; Histopathology severity: ±: Very slight; +: Slight; ++: Moderate; +++: Marked

2.6.7.7I Repeat-Dose Toxicity		Test Article: Pitavastatin								Page 1 of 6	
Report Title: A 26-week consecutive oral toxicity study of NK-104 in cynomolgus monkeys, followed by an 8-week recovery period											
Species/Strain: Cynomolgus monkeys	Duration of Dosing: Once daily dosing for 26 weeks	Report No.: [SBI.17-35] <sup>a</sup> , [RI-G2515] <sup>b</sup> , [Peer Review] <sup>c</sup>									
Initial Age: 3 to 5 years	Duration of Post-Dose: 8 weeks	Location in CTD:									
Study Duration: March 1996 to May 1997	Method of Administration: Oral (gavage) at 5 mL/kg	Vol.: * Section: *									
	Vehicle/Formulation: 0.5% carmellose sodium solution	GLP Compliance: Yes									
Special Features: None											
No Observed Adverse-Effect Level: 3 mg/kg/day											
Daily Dose (mg/kg/day)	0 (Control)		0.5		1		2		6		
Number of Animals	M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6	
<b>Toxicokinetics:</b>											
Pitavastatin											
<b>T<sub>max</sub> (hours)</b>	Day 1 <sup>d</sup>	NA	NA	1.1	1.4	0.6	0.9	0.8	1.0	0.8	1.2
	Day 28 <sup>e</sup>	NA	NA	0.9	1.5	2.9	1.6	2.4	1.4	0.7	1.5
	Day 91 <sup>f</sup>	NA	NA	0.6	1.3	0.9	2.8	1.4	1.3	0.9	1.5
	Day 182 <sup>g</sup>	NA	NA	1.9	0.6	2.5	0.8	1.1	0.6	1.3	1.4
<b>C<sub>max</sub> (ng/mL)</b>	Day 1 <sup>d</sup>	NA	NA	12	7	33	29	114	68	512	459
	Day 28 <sup>e</sup>	NA	NA	9	4	20	11	165	116	322	196
	Day 91 <sup>f</sup>	NA	NA	11	6	23	19	93	57	187	139
	Day 182 <sup>g</sup>	NA	NA	8	7	35	43	110	66	240	217
<b>AUC<sub>0-24</sub> (ng·h/mL)</b>	Day 1 <sup>d</sup>	NA	NA	98	51	232	142	796	341	1383	1291
	Day 28 <sup>e</sup>	NA	NA	60	19	233	73	1313	489	1573	1275
	Day 91 <sup>f</sup>	NA	NA	70	46	164	114	542	336	932	893
	Day 182 <sup>g</sup>	NA	NA	89	51	492	382	704	459	1468	1320

\*: Not applicable to an electronic submission

a: Following finalisation of [SBI.17-35], one of the participating pathologists from Kitasato University reviewed the report and histopathological findings. Although his observations agreed fundamentally with the renal histopathological changes reported, some corrections were suggested. The responsible laboratory

(b) (4) was requested to conduct an additional microscopic examination and an amendment to the report was issued. This report includes the Amendment to the Final report and a revised Table 13; b: Toxicokinetics report; c: A Pathology Working Group of 3<sup>rd</sup> party pathologists (licensed by the Japanese Society of Toxicologic Pathology) was established by the Sponsor and a peer review of renal slides from the 26 week administration / 8 week treatment-free period was conducted; d: Day 1 0.5, 1, 2, 4, 8 and 24 hours after 1<sup>st</sup> dose; e: Day 28 0.5, 1, 2, 4, 8 and 24 hours after 28<sup>th</sup> dose; f: Day 91 0.5, 1, 2, 4, 8 and 24 hours after 91<sup>st</sup> dose; g: Day 182 0.5, 1, 2, 4, 8 and 24 hours after 182<sup>nd</sup> dose

2.6.7.7i Repeat-Dose Toxicity		Report Nos. [SBI.17-35], [RFG2515]. [Peer Review] (continued)										Page 2 of 6	
Daily Dose (mg/kg/day)		0 (Control)		0.5		1		3		6		6	
Number of Animals		M: 6	F: 6	M: 4	F: 4	M: 6	F: 6						
Toxicokinetics cont.		Pitavastatin cont.											
t <sub>1/2</sub> (hours)	Day 1 <sup>b</sup>	NA	NA	5.2	16.1	7.3	6.7	5.0	6.4	2.6	2.3		
	Day 28 <sup>e</sup>	NA	NA	7.6	5.8	7.7	5.0	4.9	3.1	5.5	4.4		
	Day 91 <sup>d</sup>	NA	NA	6.2	6.7	6.7	6.4	6.1	7.9	3.8	4.1		
	Day 182 <sup>f</sup>	NA	NA	8.4	16.4	7.3	7.2	2.9	3.3	3.0	4.7		
T <sub>max</sub> (hours)	Day 1 <sup>f</sup>	NA	NA	1.3	1.8	0.6	1.1	1.1	1.8	1.0	1.3		
	Day 28 <sup>e</sup>	NA	NA	0.6	2.3	0.8	1.0	2.5	1.4	0.9	1.9		
	Day 91 <sup>d</sup>	NA	NA	1.0	1.8	0.9	1.1	1.3	1.8	1.1	1.3		
	Day 182 <sup>f</sup>	NA	NA	2.6	1.0	1.8	1.0	1.3	1.0	1.4	2.1		
C <sub>max</sub> (ng/mL)	Day 1 <sup>f</sup>	NA	NA	2	3	11	10	27	17	112	94		
	Day 28 <sup>e</sup>	NA	NA	1	1	5	1	23	15	39	35		
	Day 91 <sup>d</sup>	NA	NA	2	2	3	5	18	9	36	24		
	Day 182 <sup>f</sup>	NA	NA	2	3	7	6	21	14	43	43		
AUC <sub>0-24</sub> (ng*h/mL)	Day 1 <sup>f</sup>	NA	NA	12	22	55	41	225	110	473	397		
	Day 28 <sup>e</sup>	NA	NA	10	4	45	9	213	94	208	241		
	Day 91 <sup>d</sup>	NA	NA	9	11	22	19	143	43	205	183		
	Day 182 <sup>f</sup>	NA	NA	20	17	71	28	194	96	282	275		
t <sub>1/2</sub> (hours)	Day 1 <sup>f</sup>	NA	NA	3.0	2.8	3.3	3.8	4.3	3.8	2.7	2.1		
	Day 28 <sup>e</sup>	NA	NA	10.1	1.9	5.9	6.1	5.2	3.8	5.3	5.1		
	Day 91 <sup>d</sup>	NA	NA	3.3	6.7	7.9	2.9	6.9	3.8	3.7	5.0		
	Day 182 <sup>f</sup>	NA	NA	11.0	6.4	5.3	4.2	3.5	4.2	7.0	6.9		

a: Toxicokinetics report; b: Day-1 0.5, 1, 2, 4, 8 and 24 hours after 1<sup>st</sup> dose; c: Day 28 0.5, 1, 2, 4, 8 and 24 hours after 28<sup>th</sup> dose; d: Day 91 0.5, 1, 2, 4, 8 and 24 hours after 91<sup>st</sup> dose; e: Day 182 0.5, 1, 2, 4, 8 and 24 hours after 182<sup>nd</sup> dose  
 f: Day 1 0.5, 1, 2, 4, 8 and 24 hours after 1<sup>st</sup> dose  
 g: Day 28 0.5, 1, 2, 4, 8 and 24 hours after 28<sup>th</sup> dose; h: Day 91 0.5, 1, 2, 4, 8 and 24 hours after 91<sup>st</sup> dose  
 i: Day 182 0.5, 1, 2, 4, 8 and 24 hours after 182<sup>nd</sup> dose

2.6.7.7i Repeat-Dose Toxicity		Report Nos. [SBI.17-35], [RFG2515]. [Peer Review] (continued)										Page 3 of 6	
Daily Dose (mg/kg/day)		0 (Control)		0.5		1		3		6		6	
Number of Animals		M: 6	F: 6	M: 4	F: 4	M: 6	F: 6						
Noteworthy Findings													
Died or Sacrificed Moribund		0	0	0	0	0	0	0	0	0	0	0	0
Body Weight (kg) <sup>a</sup>		4.318	2.980	4.418 (+2)	3.175 (+7)	4.278 (-1)	3.133 (+5)	4.510 (+4)	2.940 (-1)	3.923 (-9)	3.150 (+6)		
Food Consumption (g) <sup>a</sup>		108	99	108 (0)	108 (+9)	108 (0)	91.5 (-8)	108 (0)	108 (+9)	108 (0)	92 (-7)		
Water Intake		-	-	-	-	-	-	-	-	-	-	-	-
Clinical Observations		-	-	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy		-	-	-	-	-	-	-	-	-	-	-	-
ECG <sup>b</sup>		-	-	-	-	-	-	-	-	-	-	-	-
Haematology		-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis		-	-	-	-	-	-	-	-	-	-	-	-
Renal Function Test <sup>c</sup>		-	-	-	-	-	-	-	-	-	-	-	-

a: At week 26 prior to first scheduled necropsy. Group means are shown. For treated groups, percent differences from controls are shown in parentheses  
 b: Heart rate, P-R, QRS, QT and QTc  
 c: Pre-test and at weeks 8, 16 and 23 of the dosing period and week 6 of the recovery period, phenolsulphonephthalein (PSP, 6 mg/mL) was administered intravenously (0.5 mL/kg) and blood collected 15 and 45 minutes later. The absorbance of serum was determined at 560 nm and the PSP concentration calculated.  
 - No noteworthy findings

2.6.7.7i Repeat-Dose Toxicity		Report Nos. [SBI.17-35], [RFG2515]. [Peer Review] (continued)										Page 4 of 6	
Daily Dose (mg/kg/day)		0 (Control)		0.5		1		3		6		6	
Number of Animals		M: 6	F: 6	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 6	F: 6
Noteworthy Findings cont.													
Serum Chemistry													
Total cholesterol (mg/dL) Week 4		112.5	129.7	114.0 (+1)	130.3 (0)	100.0 (-11)	119.5 (-8)	96.5 (-14)	88.8 (-32)**	106.2 (-6)	90.2 (-30)**		
Total cholesterol (mg/dL) Week 13		116.0	135.7	107.5 (-7)	143.8 (+6)	96.0 (-17)	127.0 (-6)	94.5 (-19)	98.3 (-28)*	103.2 (-11)	87.8 (-35)**		
Total cholesterol (mg/dL) Week 26		110.5	130.2	101.8 (-8)	137.3 (+5)	93.8 (-15)	117.0 (-10)	89.5 (-19)	96.8 (-26)	99.3 (-10)	95.8 (-26)*		
Triglycerides (mg/dL) Week 4		49.8	48.5	38.5 (-23)	38.3 (-21)	33.5 (-33)	34.3 (-29)	25.3 (-49)**	31.0 (-36)	30.7 (-38)*	31.7 (-35)		
Triglycerides (mg/dL) Week 13		44.8	34.2	29.8 (-33)**	30.5 (-11)	27.3 (-39)**	38.5 (+13)	24.5 (-45)**	27.0 (-21)	27.3 (-39)**	32.2 (-6)		
Triglycerides (mg/dL) Week 26		49.0	35.3	35.8 (-27)	32.5 (-8)	39.0 (-20)	29.8 (-16)	24.0 (-51)**	38.3 (+8)	27.3 (-44)**	34.8 (-1)		
Bone Marrow Smears		ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
Number of Animals		M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Organ Weights <sup>a</sup>													
Kidneys (R and L; absolute, g)		16.38	10.05	17.13 (+5)	12.80 (+27)	19.83 (+21)**	14.78 (+47)*	20.50 (+25)**	14.25 (+42)*	18.35 (+12)	15.70 (+56)**		
Kidneys (R and L; relative, g/kg)		3.583	3.753	3.908 (+9)	4.140 (+10)	4.658 (+30)**	4.850 (+29)**	4.580 (+28)**	4.963 (+32)**	4.810 (+34)**	4.995 (+33)**		
Gross Pathology													
Histopathology													
Kidney:													
Glomerulosclerosis (±)		0	0	1	0	0	0	0	0	1	0		
Hyaline cast (±)		1	0	1	0	0	0	0	0	1	0		
Mineralisation renal papilla (±)		2	1	1	0	2	1	0	0	1	0		
Mineralisation in cortex (±)		0	0	0	0	1	0	0	0	0	0		
Interstitial mononuclear cell infiltration (±)		4	3	4	3	4	4	3	4	4	4		
Swelling of proximal tubular epithelium (±)		0	0	0	0	0	0	0	0	3	4		

a: Group means are shown. For treated groups, percent differences from controls are shown in parentheses. Statistical significance is based on actual data (not on percent differences); - No noteworthy findings; \*: p<0.05; \*\*: p<0.01; Dunnett's, Kruskal-Wallis or Fisher test; Histopathology severity: ±: Very slight

2.6.7.7f Repeat-Dose Toxicity		Report Nos. [SBI.17-35], [RFG2515], [Peer Review] (continued)								Page 5 of 6	
After 8-Week Treatment Free Period											
Daily Dose (mg/kg/day)	0 (Control)		0.5		1		3		6		
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2	
Toxicokinetics	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Noteworthy Findings</b>											
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	0	
Bdy Weight (kg) <sup>a</sup>	3.970	3.295	N/A	N/A	N/A	N/A	N/A	N/A	4.490 (+13)	3.110 (-6)	
Food Consumption (g) <sup>a</sup>	108	93	N/A	N/A	N/A	N/A	N/A	N/A	108 (0)	99 (+6)	
Water Intake	-	-	-	-	-	-	-	-	-	-	
Clinical Observations	-	-	-	-	-	-	-	-	-	-	
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-	
EKG <sup>b</sup>	-	-	-	-	-	-	-	-	-	-	
Haematology	-	-	-	-	-	-	-	-	-	-	
Urinalysis	-	-	-	-	-	-	-	-	-	-	
Renal Function Test <sup>c</sup>	-	-	-	-	-	-	-	-	-	-	
Serum Chemistry <sup>d</sup>											
Total cholesterol (mg/dL) Week 4	118.0	130.5	NA	NA	NA	NA	NA	NA	136.5 (+16)	150.5 (+15)	
Total cholesterol (mg/dL) Week 8	117.0	139.0	NA	NA	NA	NA	NA	NA	122.5 (+3)	132.0 (-5)	
Triglycerides (mg/dL) Week 4	34.0	40.5	NA	NA	NA	NA	NA	NA	34.0 (0)	23.5 (-42)	
Triglycerides (mg/dL) Week 8	54.0	41.5	NA	NA	NA	NA	NA	NA	35.0 (-35)	20.5 (-51)	
Gross Pathology	-	-	-	-	-	-	-	-	-	-	

a: Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 b: Heart rate, P-R, QRS, QT and QTc  
 c: Pre-test and at Weeks 8, 16 and 23 of the dosing period and Week 6 of the recovery period, phenolsulphonethalein (PSP, 6 mg/mL) was administered intravenously (0.5 mL/kg) and blood collected 15 and 45 minutes later. The absorbance of serum was determined at 560 nm and the PSP concentration calculated.  
 d: Week 4 of the treatment free period  
 - No noteworthy findings

2.6.7.7f Repeat-Dose Toxicity		Report Nos. [SBI.17-35], [RFG2515], [Peer Review] (continued)								Page 6 of 6	
After 8-Week Treatment Free Period											
Daily Dose (mg/kg/day)	0 (Control)		0.5		1		3		6		
Number of Animals	M: 2	F: 2	M: 0	F: 0	M: 0	F: 0	M: 0	F: 0	M: 2	F: 2	
<b>Noteworthy Findings cont.</b>											
Organ Weights <sup>a</sup>											
Kidneys (R and L; absolute; g)	19.50	13.55	NA	NA	NA	NA	NA	NA	17.65 (-9)	13.65 (+1)	
Kidneys (R and L; relative; µ/kg)	4.940	4.230	NA	NA	NA	NA	NA	NA	3.930 (-20)	4.465 (+6)	
<b>Histopathology</b>											
Kidney:											
Mineralisation renal papilla (±)	1	1	NA	NA	NA	NA	NA	NA	1	1	
Interstitial mononuclear cell infiltration (±)	1	2	NA	NA	NA	NA	NA	NA	2	2	

a: Group means are shown. For treated groups, percent differences from controls are shown in parentheses.  
 Histopathology severity: ±: Very slight

### Genetic Toxicology – Tabulated Summary

2.6.7.8A Genotoxicity: <i>In Vitro</i>		Test Article: Pitavastatin				Page 1 of 4	
<b>Report Title:</b> Mutagenicity testing of NK-104 in bacterial reverse mutation assays							
<b>Test for Induction of:</b> Reverse mutation in bacterial cells				<b>No. of Independent Assays:</b> 2		<b>Report No.:</b> [3140]	
<b>Strains:</b> <i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537) and <i>Escherichia coli</i> (WP2 <i>uvrA</i> )				<b>No. of Replicate Cultures:</b> 1 or 3		<b>Location in CTD:</b>	
<b>Metabolising System:</b> Phenobarbital and 5,6-benzoflavone induced male rat liver S9				<b>No. of Cells Assayed/Culture:</b> NA		<b>Vol.:</b> * <b>Section:</b> *	
<b>Vehicles:</b> For Test Article: DMSO For Positive Controls: DMSO or water				<b>GLP Compliance:</b> Yes			
<b>Treatment:</b> Pre-incubation in the absence of S9 and with S9				<b>Date of Treatment:</b> May to July 1992			
<b>Cytotoxic Effects:</b> Limited, 313 µg/plate and above; no precipitate							
<b>Genotoxic Effects:</b> None							
Metabolic Activation	Test Article	Dose Level (µg/plate)	Preliminary Test 1 Revertant Colony Counts (1 replicate only)				
			Base Pair Substitution Type			Frameshift Type	
Without Activation (-S9)	DMSO	0	TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537
		1.2	136	13	18	23	10
		4.9	103	17	27	18	9
		20	131	12	19	30	11
		78	122	12	15	18	10
		313 <sup>a</sup>	126	15	14	23	9
		1250 <sup>a</sup>	131	16	18	16	11
		5000 <sup>a</sup>	106	12	24	22	4
			77	17	23	12	2
		AF-2	0.01	832	NA	201	NA
	AF-2	0.1	NA	NA	NA	455	NA
	Sodium azide	0.5	NA	378	NA	NA	NA
ICR-191	1.0	NA	NA	NA	NA	1525	

\*: Not applicable to an electronic submission  
 a: Growth inhibition observed  
**ICR-191:** Acridine mutagen (6-Chloro-9-[3-(2-chloroethylamino)propylamino]-2-methoxyacridine dihydrochloride)  
**AF-2:** 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide

2.6.7.8A Genotoxicity: <i>In Vitro</i>		Report No.: [3140] (continued)					Page 2 of 4	
Metabolic Activation	Test Article	Dose Level (µg/plate)	Preliminary Test 1 Revertant Colony Counts (1 replicate only)					
			Base Pair Substitution Type			Frameshift Type		
			TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537	
With Activation (+S9)	DMSO	0	121	15	33	28	14	
	Pitavastatin	1.2	134	14	33	29	18	
		4.9	116	7	34	22	20	
		20	124	14	38	33	22	
		78	128	17	36	23	13	
		313	129	10	22	41	21	
		1250	145	20	29	32	19	
		5000	92	10	26	27	13 <sup>a</sup>	
	2-aminoanthracene	2.0	NA	181	NA	NA	NA	
	2-aminoanthracene	10.0	NA	NA	436	NA	NA	
Benzo[a]pyrene	5.0	760	NA	NA	175	85		

a: Growth inhibition observed

2.6.7.8A Genotoxicity: <i>In Vitro</i>		Report No.: [3140] (continued)					Page 3 of 4	
Metabolic Activation	Test Article	Dose Level (µg/plate)	Assay 1 Revertant Colony Counts (Mean)					
			Base Pair Substitution Type			Frameshift Type		
			TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537	
Without Activation (-S9)	DMSO	0	132 ± 23	16 ± 4	31 ± 1	19 ± 7	8 ± 1	
	Pitavastatin	10	125 ± 4	14 ± 3	33 ± 7	26 ± 1	8 ± 2	
		20	113 ± 23	17 ± 4	26 ± 4	23 ± 2	7 ± 2	
		39	117 ± 15	15 ± 5	29 ± 3	25 ± 6	7 ± 3	
		78	119 ± 16	17 ± 2	36 ± 2	27 ± 3	10 ± 2	
		156	137 ± 15	15 ± 3	32 ± 6	24 ± 3	12 ± 2	
		313 <sup>a</sup>	117 ± 16	15 ± 2	25 ± 5	25 ± 4	11 ± 4	
		0.01	895 ± 25	NA	198 ± 16	NA	NA	
	AF-2	0.1	NA	NA	NA	458 ± 49	NA	
	Sodium azide	0.5	NA	364 ± 20	NA	NA	NA	
ICR-191	1.0	NA	NA	NA	NA	1492 ± 51		
With Activation (+S9)	DMSO	0	120 ± 9	14 ± 3	33 ± 5	36 ± 5	19 ± 2	
	Pitavastatin	156	NT	20 ± 4	NT	34 ± 10	15 ± 8	
		313	113 ± 5	16 ± 4	39 ± 10	38 ± 5	16 ± 5	
		625	116 ± 13	18 ± 4	36 ± 1	35 ± 5	15 ± 2	
		1250	119 ± 17	11 ± 4	39 ± 4	37 ± 8	14 ± 4	
		2500	110 ± 19	14 ± 1	38 ± 5	29 ± 3	15 ± 2 <sup>a</sup>	
		5000	85 ± 1	13 ± 3	30 ± 5	25 ± 7	9 ± 1 <sup>a</sup>	
		2-aminoanthracene	2.0	NA	231 ± 13	NA	NA	NA
	2-aminoanthracene	10.0	NA	NA	462 ± 44	NA	NA	
	Benzo[a]pyrene	5.0	814 ± 55	NA	NA	178 ± 10	89 ± 5	

a: Growth inhibition observed

2.6.7.8A Genotoxicity: <i>In Vitro</i>		Report No.: [3140] (continued)					Page 4 of 4	
Metabolic Activation	Test Article	Dose Level (µg/plate)	Assay 2 Revertant Colony Counts (Mean)					
			Base Pair Substitution Type			Frameshift Type		
			TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA1537	
Without Activation (-S9)	DMSO	0	150 ± 10	17 ± 5	31 ± 3	19 ± 2	12 ± 8	
	Pitavastatin	10	148 ± 9	17 ± 1	31 ± 5	22 ± 6	12 ± 2	
		20	151 ± 15	15 ± 3	28 ± 5	20 ± 1	10 ± 5	
		39	146 ± 19	11 ± 4	21 ± 6	18 ± 1	12 ± 3	
		78	148 ± 15	12 ± 2	28 ± 5	22 ± 2	13 ± 3	
		156	142 ± 24	11 ± 0	25 ± 8	22 ± 1	14 ± 4	
		313 <sup>a</sup>	138 ± 13	11 ± 2	23 ± 2	24 ± 5	14 ± 5	
		0.01	859 ± 14	NA	168 ± 8	NA	NA	
	AF-2	0.1	NA	NA	NA	427 ± 15	NA	
	Sodium azide	0.5	NA	390 ± 4	NA	NA	NA	
ICR-191	1.0	NA	NA	NA	NA	1293 ± 142		
With Activation (+S9)	DMSO	0	149 ± 15	18 ± 4	20 ± 3	32 ± 9	19 ± 4	
	Pitavastatin	156	NT	19 ± 1	NT	34 ± 5	25 ± 4	
		313	149 ± 9	19 ± 5	22 ± 4	35 ± 8	22 ± 3	
		625	146 ± 15	15 ± 7	22 ± 5	39 ± 10	18 ± 5	
		1250	147 ± 10	14 ± 1	21 ± 3	31 ± 11	22 ± 6	
		2500	147 ± 14	14 ± 6	19 ± 4	27 ± 2	21 ± 4 <sup>a</sup>	
		5000	100 ± 14	12 ± 1	21 ± 7	22 ± 10	12 ± 5 <sup>a</sup>	
		2-aminoanthracene	2.0	NA	204 ± 16	NA	NA	NA
	2-aminoanthracene	10.0	NA	NA	386 ± 44	NA	NA	
	Benzo[a]pyrene	5.0	815 ± 38	NA	NA	181 ± 21	107 ± 22	

a: Growth inhibition observed

<b>2.6.7.BB Genotoxicity: In Vitro</b>		<b>Test Article:</b> Pitavastatin		Page 1 of 3			
<b>Report Title:</b> Chromosomal aberration test in cultured mammalian cells on NK-104							
<b>Test for Induction of:</b> Chromosome aberrations		<b>No. of Independent Assays:</b> 1 or 4		<b>Report No.:</b> [3141]			
<b>Strains:</b> Chinese hamster lung cells		<b>No. of Replicate Cultures:</b> 2		<b>Location in CTD:</b>			
<b>Metabolizing System:</b> Phenobarbital and 5, 6-benzoflavone induced male rat liver S9		<b>No. of Cells Analyzed/Culture:</b> 1(X)		<b>Vol.:</b> * <b>Section:</b> *			
<b>Vehicles:</b> For Test Article: DMSO or 1% CMC sodium solution For Positive Controls: Saline				<b>GLP Compliance:</b> Yes			
<b>Treatment:</b> Direct method: 24 or 48 hours treatment without S9 and with no recovery period.				<b>Date of Treatment:</b> May to December 1992			
<b>Metabolic Activation Method:</b> 6 hours treatment with and without S9 followed by 18 hour recovery period.							
<b>Cytotoxic Effects:</b> DMSO as solvent: no cytotoxicity up to 3900 µg/mL (limit of solubility). 1% CMC sodium solution as solvent: cytotoxicity at 1250 and 2500 µg/mL with and without S9 and also at 938 µg/mL in the presence of S9 in an additional assay.							
<b>Genotoxic Effects:</b> DMSO as solvent: no genotoxicity up to 3900 µg/mL (limit of solubility). 1% CMC sodium solution as solvent: Positive in the presence of S9 at 625 µg/mL for the induction of structural chromosome aberrations (2 assays; 13.5 and 18.9% incidences); significantly different from control at 938 µg/mL without S9 (7.0% incidence) and at 468.5 µg/mL with S9 (6.5% incidence).							
<b>Direct Method</b>							
Test Article	Dose Level (µg/mL)	24-Hour Treatment (no recovery period)			48-Hour Treatment (no recovery period)		
		Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome
No treatment	-	0.0	0.5	Negative	0.5	0.5	Negative
DMSO	0	0.0	2.0	Negative	0.5	0.5	Negative
Pitavastatin	0.8	0.0	1.0	Negative	0.5	1.0	Negative
	1.6	0.0	0.0	Negative	0.0	0.0	Negative
	3.1	0.0	0.5	Negative	0.0	0.0	Negative
	6.2	0.0	0.5	Negative	0.0	0.5	Negative
MMC	0.05	0.5	57.0	Positive	0.0	65.5	Positive

\*: Not applicable to an electronic submission

a: Preliminary tests suggested that 50% cell growth inhibition dose was approximately 3.1 µg/mL in the Direct Method and 520 µg/mL (DMSO) and 270 µg/mL (1% CMC sodium solution) and 950 µg/mL (DMSO) and 625 µg/mL (1% CMC sodium solution) in the Metabolic Activation Methods, respectively.

MMC: Mitomycin C

<b>2.6.7.BB Genotoxicity: In Vitro</b>		<b>Report No.:</b> [3141] (continued)		Page 2 of 3			
<b>Metabolic Activation Method Assay 1</b>							
Test Article	Dose Level (µg/mL)	Absence of S9			With S9		
		6-Hour Treatment; 18-Hour Recovery Period			6-Hour Treatment; 18-Hour Recovery Period		
		Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome
No treatment	-	0.0	0.5	Negative	0.0	0.5	Negative
DMSO	0	0.0	0.0	Negative	0.5	1.5	Negative
Pitavastatin	16	0.0	0.5	Negative	0.5	1.0	Negative
	33	0.5	0.5	Negative	0.5	1.0	Negative
	65	0.0	0.5	Negative	0.5	0.0	Negative
	130	0.5	0.0	Negative	0.0	0.0	Negative
	260	0.0	0.0	Negative	0.0	0.5	Negative
	520	1.0	0.0	Negative	1.0	0.0	Negative
	1040	1.0	1.0	Negative	0.0	3.5	Negative
DMN	400	1.0	0.5	Negative	0.0	52.5	Positive
<b>Metabolic Activation Method Assay 2</b>							
Test Article	Dose Level (µg/mL)	Absence of S9			With S9		
		6-Hour Treatment; 18-Hour Recovery Period			6-Hour Treatment; 18-Hour Recovery Period		
		Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome
No treatment	-	0.0	0.0	Negative	0.0	2.0	Negative
DMSO	0	0.0	0.0	Negative	0.0	0.5	Negative
Pitavastatin	520	0.0	1.0	Negative	1.0	1.0	Negative
	1040	1.0	1.0	Negative	2.0	1.0	Negative
	2080	1.0	1.0	Negative	0.0	2.5	Negative
	3900 <sup>a</sup>	0.5	1.0	Negative	0.5	3.0	Negative
	400	0.0	1.0	Negative	0.0	40.0	Positive

a: Limit of solubility in DMSO; DMN: Dimethylnitrosamine

2.6.7.8B Genotoxicity: <i>In Vitro</i>		Report No.: 13141 (continued)						Page 3 of 3
Test Article	Dose Level (µg/mL)	Metabolic Activation Method Assay 3						
		Absence of S9			With S9			
		6-Hour Treatment; 18-Hour Recovery Period			6-Hour Treatment; 18-Hour Recovery Period			
		Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	
No treatment	-	0.0	0.5	Negative	0.0	1.0	Negative	
1% CMC sodium soln.	0	0.0	0.5	Negative	0.0	1.0	Negative	
Pitavastatin	313	0.0	0.0	Negative	0.0	1.5	Negative	
	625	1.0	2.5	Negative	0.5	13.5	Positive*	
	1250			Tox			Tox	
	2500			Tox			Tox	
DMN	400	0.5	0.5	Negative	0.0	55.0	Positive	

2.6.7.8C Genotoxicity: <i>In Vitro</i>		Report No.: 13141 (continued)						Page 3 of 3
Test Article	Dose Level (µg/mL)	Metabolic Activation Method Additional Assay						
		Absence of S9			With S9			
		6-Hour Treatment; 18-Hour Recovery Period			6-Hour Treatment; 18-Hour Recovery Period			
		Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	Incidence of polyploidy cells (%)	Incidence of cells with chromosomal aberrations (%)	Outcome	
No treatment	-	0.5	0.0	Negative	0.5	1.0	Negative	
1% CMC sodium soln.	0	0.5	0.0	Negative	0.0	0.5	Negative	
Pitavastatin	468.5	0.0	0.5	Negative	0.5	6.5	Suspicious**	
	625	1.0	0.5	Negative	1.9	18.9	Positive**	
	938	2.0	7.0	Suspicious*			Tox	
	400	0.0	1.0	Negative	0.0	71.5	Positive	

Tox: Metaphase cells were observed in less than 50 cells per culture due to cytotoxicity

\*: Significantly different from control (p<0.05) using  $\chi^2$  squares

\*\* : Significantly different from control (p<0.001) using  $\chi^2$  squares

2.6.7.8C Genotoxicity: <i>In Vitro</i>		Test Article: Pitavastatin				Page 1 of 1
Report Title: <i>In vivo/in vitro</i> unscheduled DNA synthesis (UDS) test of NK-104 with rat hepatocyte						
Test for Induction of: Unscheduled DNA synthesis		No. of Independent Assays: 1		Report No.: 13638 (1-4-014)		
Strains: Crj: CD (SD) male rats		No. of Replicate Cultures: 3		Location in CTD:		
Metabolism System: Rat liver primary cell cultures		No. of Cells Analysed/Culture: 150		Vol.: * Section: *		
Vehicles: For Test Article: 0.5% CMC sodium solution		For Positive Controls: Water for Injection (DMN) or corn oil (2AFF)		GLP Compliance: No		
Treatment: 2 or 16 hours						Date of Treatment: November 1997
Cytotoxic Effects: None						
Genotoxic Effects: None						
Test Article	Dose Level (mg/kg)	Nuclear Grain Count (Mean ± SD)	Cytoplasmic Grain Count (Mean ± SD)	Net Nuclear Grains (Mean ± SD)	Incidence of Repaired Cells (%; Mean ± SD)*	Outcome
<b>2-Hour Post-Treatment (3 animals per group)</b>						
0.5% CMC sodium solution	0	6.3 ± 0.3	7.9 ± 1.0	-1.6 ± 0.7	2.2 ± 0.4	Negative
Pitavastatin	100	7.9 ± 0.3	9.1 ± 0.9	-1.3 ± 0.7	5.1 ± 1.9	Negative
	200	7.3 ± 0.8	7.6 ± 0.6	-0.4 ± 0.6	5.8 ± 1.7	Negative
DMN	5	36.7 ± 2.5	6.3 ± 0.3	30.4 ± 2.5	100.0 ± 0.0	Positive
<b>16-Hour Post-Treatment (3 animals per group)</b>						
0.5% CMC sodium solution	0	7.8 ± 0.5	8.4 ± 1.0	-0.7 ± 0.7	1.6 ± 0.4	Negative
Pitavastatin	100	9.0 ± 1.1	9.2 ± 0.7	-0.2 ± 1.0	5.3 ± 2.3	Negative
	200	8.2 ± 0.3	8.3 ± 0.9	0.0 ± 0.7	6.4 ± 0.8	Negative
2AFF	100	37.9 ± 0.5	8.0 ± 0.4	29.8 ± 0.2	100.0 ± 0.0	Positive

\*: Not applicable to an electronic submission

2AFF: 2-acetylaminofluorene

a: Unscheduled DNA synthesis positive cells (percentage of cells having ≥ 5 net nuclear grains)

2.6.7.9A Genotoxicity: <i>In Vivo</i>		Test Article: Pitavastatin		Page 1 of 2
Report Title: Micronucleus test of NK-104 by single oral administration in mice				
Test for Induction of: Bone-marrow micronuclei		Treatment Schedule: Single dose		Report No.: 18G25003
Species/Strain: Crj:CD-1 (ICR) mice		Sampling Time: Preliminary study: 24, 48 or 72 hours after dosing; Main study: 24 hours after dosing		Location in CTD:
Age: 6 to 8 weeks		Method of Administration: Oral (gavage) (10, 20 or 40 mL/kg depending on dose level)		Vol.: * Section: *
Cells Evaluated: Erythrocytes				
No. of Cells Analysed/Animal: 2000		Vehicle/Formulation: 0.5% CMC sodium solution; distilled water for CP		GLP Compliance: Yes
Special Features: None				
Date of Dosing: May to November 1992				
Toxic/Cytotoxic Effects:				
Toxicity study (n = 3M and 3F per group): One death at 1000 mg/kg; clinical signs included decreased spontaneous motor activity, piloerection, hypothermia, crouching and prone position. At 2000 mg/kg 2/3M and 2/3F died; clinical signs included decreased spontaneous motor activity, crouching, piloerection, prone position, eye closing and hypothermia; decreased body weight gain.				
Preliminary micronucleus test (n = 5M and 5F per group per time point): 3/15F died at 1000 mg/kg; clinical signs included decreased spontaneous motor activity, piloerection, prone position, eye closing, hypothermia and crouching.				
Main micronucleus test: Clinical signs at 1000 mg/kg included decreased spontaneous motor activity, piloerection, hypothermia and crouching.				
Genotoxic Effects: None				
Evidence of Exposure: Yes, based on clinical signs observed. Supportive toxicokinetics (pitavastatin concentrations determined in plasma and bone marrow 1, 2, 6 and 24 hours after dosing) provided by a separate study conducted independently with a single oral dose of 500 or 1000 mg/kg [RF9945]. With the exception of the 1000 mg/kg group at 6 hours, the bone marrow concentrations of pitavastatin in male animals exceeded the pitavastatin concentrations in the plasma and up to and including the 6-hour time point pitavastatin concentrations in both the plasma and bone marrow were higher in the animals administered 1000 mg/kg. In females, there were no clear differences in pitavastatin concentrations between the dose groups for both plasma and bone marrow and up to and including the 6-hour time point. Pitavastatin concentrations were significantly lower than that determined in the parallel group of male animals.				

\*: Not applicable to an electronic submission

CP: Cyclophosphamide

2.6.7.9A Genotoxicity: In Vivo		Report No.: [R625003] (continued)		Preliminary Micronucleus Test				Page 2 of 2
Test Article	Dose (mg/kg)	No. of Animals	Number of Reticulocytes/Total Number of Erythrocytes Observed (%; Mean ± SD)		Number of Micronucleated Polychromatic Erythrocytes/Total Number of Polychromatic Erythrocytes Observed (%; Mean ± SD)			
<b>24-Hour Harvest</b>								
			<b>Males</b>	<b>Females</b>	<b>Males</b>	<b>Females</b>		
0.5% CMC sodium soln.	0	MS; F5	57.5 ± 5.2	60.3 ± 4.4	0.13 ± 0.08	0.10 ± 0.06		
Pitavastatin	500	MS; F5	60.6 ± 5.3	61.7 ± 4.7	0.13 ± 0.07	0.14 ± 0.09		
	1000 <sup>a</sup>	MS; F5	52.7 ± 6.2	58.9 ± 5.7	0.16 ± 0.10	0.12 ± 0.09		
CP	50	MS; F5	55.5 ± 5.9	58.3 ± 6.8	2.30 ± 0.84 <sup>b</sup>	2.14 ± 0.48 <sup>b</sup>		
<b>48-Hour Harvest</b>								
			<b>Males</b>	<b>Females</b>	<b>Males</b>	<b>Females</b>		
Pitavastatin	500	MS; F5	56.8 ± 2.8	61.2 ± 4.0	0.10 ± 0.12	0.08 ± 0.06		
	1000	MS; F5	50.2 ± 6.7	58.6 ± 2.1	0.15 ± 0.08	0.10 ± 0.09		
<b>72-Hour Harvest</b>								
			<b>Males</b>	<b>Females</b>	<b>Males</b>	<b>Females</b>		
Pitavastatin	500	MS; F5	61.1 ± 8.1	63.3 ± 5.0	0.06 ± 0.07	0.10 ± 0.14		
	1000 <sup>c</sup>	MS; F5	55.4 ± 4.5	60.0 ± 5.3	0.07 ± 0.04	0.06 ± 0.05		
<b>Main Micronucleus Test</b>								
Test Article	Dose (mg/kg)	No. of Animals	Number of Reticulocytes/Total Number of Erythrocytes Observed (%; Mean ± SD)		Number of Micronucleated Polychromatic Erythrocytes/Total Number of Polychromatic Erythrocytes Observed (%; Mean ± SD)			
<b>24-Hour Harvest</b>								
			<b>Males</b>	<b>Females</b>	<b>Males</b>	<b>Females</b>		
0.5% CMC sodium soln.	0	MG; F6	55.8 ± 4.2	64.7 ± 5.1	0.09 ± 0.07	0.08 ± 0.04		
Pitavastatin	250	MG; F6	54.3 ± 9.6	64.4 ± 4.3	0.15 ± 0.07	0.14 ± 0.10		
	500	MS <sup>d</sup> ; F6	54.4 ± 3.3	64.0 ± 4.8	0.14 ± 0.07	0.13 ± 0.14		
	1000	MG; F6	51.3 ± 1.7 <sup>d</sup>	59.3 ± 11.8	0.15 ± 0.07	0.12 ± 0.03		
CP	50	MG; F6	52.5 ± 11.3	62.1 ± 5.8	2.83 ± 0.51 <sup>b</sup>	1.90 ± 0.64 <sup>b</sup>		

a: A replacement animal was included in this group as one animal died because of a dosing error  
 b: Significant at p < 0.05 in Kasitenbaum and Bowman's table; c: Two replacement animals were included in this group as three animals died because of a dosing error  
 d: Significant at p < 0.05 using Student's t-test; SD: Standard Deviation

2.6.7.9B Genotoxicity: In Vivo		Test Article: Pitavastatin		Page 1 of 2
Report Title: Single cell gel (SCG) assay of NK-104 with mice (COMET assay)				
Test for Induction of: DNA damage		Treatment Schedule: Single daily dose for 2 days (21 hour interval between doses); the positive control was given as a single dose		Report No.: [A819 (144-121)]
Species/Strain: Male Sle:ICR mice	Sampling Time: 3 hours after the second dose		Location in CTD:	
Age: 8 weeks	Method of Administration: Oral (gavage) at 10 mL/kg body weight		Vol.:	Section: *
Cells Evaluated: Liver, lungs, spleen and thymus				
No. of Cells Analyzed/Organ/Animal: 150	No. of Animals:	Five animals per dose		GLP Compliance: Yes
Special Features: None	Vehicle/Formulation: 0.5% CMC sodium solution; water for injection		Date of Dosing: November 2007	
for ethyl methanesulphonate (EMS)				
Toxic Effects: None; no clinical signs of toxicity or treatment-related effects on body weight.				
Genotoxic Effects: None; pitavastatin did not induce DNA damage in the mouse liver, lung, spleen or thymus in this study.				
Evidence of Exposure: Supportive toxicokinetics in male mice after a single oral dose of 225 mg/kg; C <sub>max</sub> and AUC <sub>0-24</sub> values were 11653 ng/ml, and 18671 ng*hr/ml. [KOW 14952398]. Pitavastatin concentrations were also determined in plasma 1, 2, 6 and 24 hours after a single oral dose of 500 mg/kg to mice; plasma pitavastatin concentrations in male mice were 83400 ng/mL at 1 hour after dosing decreasing to 400 ng/mL at 24 hours after dosing [R19945].				
*: Not applicable to an electronic submission				

2.6.7.9B Genotoxicity: In Vivo		Report No.: [A819 (144-121)] (continued)		Page 2 of 2
Single Cell Gel Electrophoresis (SCG) Assay with Liver Cells Obtained from Pitavastatin Treated Male Mice				
Test Article	Dose (mg/kg)	Olive Tail Moment (Mean ± SD)	Percentage Tail DNA (Mean ± SD)	
Vehicle	0	0.406 ± 0.101	3.126 ± 0.720	
Pitavastatin	125	0.458 ± 0.148	3.344 ± 1.043	
	250	0.601 ± 0.083 <sup>a</sup>	4.028 ± 0.638	
	500	0.471 ± 0.066	3.698 ± 0.442	
EMS	300	4.009 ± 0.699 <sup>b</sup>	18.367 ± 2.349 <sup>b</sup>	
Single Cell Gel Electrophoresis (SCG) Assay with Lung Cells Obtained from Pitavastatin Treated Male Mice				
Test Article	Dose (mg/kg)	Olive Tail Moment (Mean ± SD)	Percentage Tail DNA (Mean ± SD)	
Vehicle	0	0.884 ± 0.151	5.365 ± 0.817	
Pitavastatin	125	0.958 ± 0.169	5.826 ± 0.549	
	250	0.872 ± 0.044	5.742 ± 0.207	
	500	0.791 ± 0.158	5.350 ± 0.807	
EMS	300	4.153 ± 0.714 <sup>a</sup>	21.149 ± 2.037 <sup>a</sup>	
Single Cell Gel Electrophoresis (SCG) Assay with Spleen Cells Obtained from Pitavastatin Treated Male Mice				
Test Article	Dose (mg/kg)	Olive Tail Moment (Mean ± SD)	Percentage Tail DNA (Mean ± SD)	
Vehicle	0	0.558 ± 0.055	5.565 ± 0.452	
Pitavastatin	125	0.516 ± 0.065	5.171 ± 0.340	
	250	0.531 ± 0.109	5.280 ± 0.735	
	500	0.514 ± 0.036	5.243 ± 0.296	
EMS	300	2.604 ± 0.603 <sup>a</sup>	13.821 ± 2.277 <sup>a</sup>	
Single Cell Gel Electrophoresis (SCG) Assay with Thymus Cells Obtained from Pitavastatin Treated Male Mice				
Test Article	Dose (mg/kg)	Olive Tail Moment (Mean ± SD)	Percentage Tail DNA (Mean ± SD)	
Vehicle	0	0.408 ± 0.040	4.005 ± 0.465	
Pitavastatin	125	0.437 ± 0.088	4.253 ± 0.577	
	250	0.417 ± 0.071	4.017 ± 0.731	
	500	0.500 ± 0.029	4.788 ± 0.170	
EMS	300	2.087 ± 0.240 <sup>a</sup>	14.128 ± 1.442 <sup>a</sup>	

\*: p ≤ 0.05 vs. vehicle using Dunnett's test; #: p ≤ 0.025 vs. vehicle using Aspin-Welch t test

<b>2.6.7.9C Genotoxicity: In Vivo</b>		<b>Test Article:</b> Pitavastatin		Page 1 of 1	
<b>Report Title:</b> Micronucleus test of NK-104 repeated oral administration in rats					
<b>Test for induction of:</b> Bone-marrow micronuclei		<b>Treatment Schedule:</b> Repeated doses (animals were dosed consecutively for 93 days) <sup>a</sup>		<b>Report No.:</b> [KW92117]	
<b>Species/Strain:</b> Not stated <sup>a</sup>		<b>Sampling Time:</b> Bone marrow smears were prepared at autopsy 24 hours after the last dose and stored for 19 to 20 weeks before examination for micronucleated polychromatic erythrocytes (5 specimens per animal).			
<b>Age:</b> Not stated		<b>Method of Administration:</b> Oral (gavage)		<b>Location in CTD:</b>	
<b>Cells Evaluated:</b> Erythrocytes		<b>No. of Cells Analyzed/Animal:</b> 1000		<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution	
				<b>Vol.:</b> * <b>Section:</b> *	
<b>Special Features:</b> The animals were dosed in a separate study (see footnote), bone marrows prepared at autopsy and specimen staining and examination were conducted 19 to 20 weeks later. It was therefore not possible to utilise a positive control.				<b>GLP Compliance:</b> Not stated	
				<b>Date of Dosing:</b> December 1992 to February 1993	
<b>Toxic/Cytotoxic Effects:</b> Clinical signs observed in these animals are described in [KW92083].					
<b>Genotoxic Effects:</b> None					
<b>Evidence of Exposure:</b> Evidence of exposure is indicated by clinical signs as described in [KW92083]. Supportive toxicokinetics (pitavastatin and lactone concentrations determined in plasma up to 24 hours after dosing) are provided by a separate study conducted independently with a single oral dose of 30, 100, 250 or 500 mg/kg to Slc:Wistar and Crj:CD (SD) rats [RF9933]. Plasma concentrations of pitavastatin increased dose-proportionally, however, at doses of 250 mg/kg and above C <sub>max</sub> and AUC values indicated saturation of absorption in the digestive tract. AUC values were higher in females as compared to the corresponding male dose group and this occurred in both rat strains. This was attributed to a sex difference in cytochrome P-450 mediated metabolism leading to higher plasma concentrations in female animals. There were no differences in pharmacokinetics between rat strains. The plasma concentrations of lactone were <1% of the corresponding pitavastatin plasma concentration.					
<b>Test Article</b>	<b>Dose (mg/kg/day)</b>	<b>No. of Animals</b>	<b>No. of Micronucleated Polychromatic Erythrocytes (Mean)</b>	<b>No. of Micronucleated Polychromatic Erythrocytes/Total No. of Polychromatic Erythrocytes Observed (%; Mean ± SD)</b>	<b>No. of Polychromatic Erythrocytes/Total No. of Erythrocytes Observed (%; Mean ± SD)</b>
0.5% CMC-Na soln.	0	M6	5	0.08 ± 0.08	26.42 ± 1.69
Pitavastatin	2	M6	4	0.07 ± 0.08	26.98 ± 1.21
	10	M6	6	0.10 ± 0.09	27.20 ± 1.98
	30 (50) <sup>b</sup>	M6	7	0.12 ± 0.12	26.40 ± 1.38
* : Not applicable to an electronic submission; a: This study used male animals from the "Reproductive and developmental toxicity study of NK-104 in rats administered orally prior to and in the early stages of pregnancy (Seg. I)" [KW92083] in which Crj:CD (SD) rats were dosed orally for 93 days consecutively.					
b: The dose was 50 mg/kg on Days 1 to 35 and then the dose was reduced to 30 mg/kg on Day 36 for the remaining administration period.					

**Carcinogenicity – Tabulated Summary**

<b>2.6.7.10A Carcinogenicity</b>		<b>Test Article:</b> Pitavastatin		Page 1 of 10	
<b>Report Title:</b> NK-104 potential tumourigenic effects in repeated oral gavage administration to mice					
<b>Species/Strain:</b> Crj:CD-1 (ICR) BR mice		<b>Duration of Dosing:</b> Once daily for 92 weeks		<b>Report No.:</b> [KOW 16/982522] <sup>a</sup>	
<b>Initial Age:</b> 6 weeks		<b>Method of Administration:</b> Oral (gavage) at 10 mL/kg		<b>Location in CTD:</b>	
<b>Date of First Dose:</b> 14 May 1996		<b>Vehicle/Formulation:</b> 0.5% hydroxypropylmethyl cellulose suspension		<b>Vol.:</b> * <b>Section:</b> *	
		<b>Treatment of Controls:</b> 0.5% hydroxypropylmethyl cellulose suspension		<b>GLP Compliance:</b> Yes	
<b>Basis for High-Dose Selection:</b> In the 13 week preliminary study [KOW 14/952398] dose levels of 25, 75 and 225 mg/kg were utilised. 225 mg/kg/day was considered too high as the maximum tolerated dose due to histopathological changes observed in the forestomach. Whereas although 75 mg/kg elicited histopathological changes in the forestomach this dose was selected in the absence of other changes on bodyweight or other parameters.					
<b>Special Features:</b> None					
<b>Daily Dose (mg/kg/day)</b>	0 (Control)		12		75
<b>Toxicokinetics</b>					
<b>Number of Animals<sup>a</sup></b>	M:0	F:0	M:5	F:5	M:5
<b>Plasma Concentrations (ng/mL)</b>					
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	1283
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	498
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	1458
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	2763
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	11144
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	8328
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	40
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	52
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	173
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	214
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	380
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	667
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	810
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	538
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	1756
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	2371
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	20208
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	15275
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	21
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	21
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	86
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	365
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	345
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	338
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	647
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	518
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	2288
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	10895
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	12174
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	27762
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	48
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	37
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	111
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	329
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	713
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	287
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	748
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	637
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	2246
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	8513
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	11475
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	18269
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	25
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	51
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	266
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	193
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	327
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	630
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	359
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	300
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	588
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	2099
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	3161
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	8361
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	17
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	51
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	42
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	337
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	283
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	636
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	520
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	438
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	1690
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	2459
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	3407
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	8039
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	50
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	109
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	52
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	135
Week 13 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	241
Week 13 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	378
Week 26 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	440
Week 26 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	840
Week 39 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	1644
Week 39 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	2267
Week 52 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	976
Week 52 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	22318
Week 65 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	44
Week 65 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	41
Week 78 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	97
Week 78 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	240
Week 91 0.5 hours (T <sub>min</sub> )	ND	ND	ND	ND	350
Week 91 3.0 hours (T <sub>min</sub> )	ND	ND	ND	ND	396
* : Not applicable to an electronic submission					
a: Two further statistical analyses ([5483 (1444048)] and [KOW016]) of the tumours and non neoplastic findings and a PWG peer review [I:PI 668-001/002] were carried out; b: 5 animals/sex/group per time point; T <sub>min</sub> : The time to reach minimum concentration following drug administration					

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)														Page 2 of 10					
Toxicokinetics cont.: 5 animals/sex/group per time point																					
Dose Level (mg/kg/day)	Dose Level Ratio	Week 13		Week 26		Week 39		Week 52		Week 65		Week 78		Week 91							
		C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio	C <sub>max</sub> Ratio						
		M	F	M	F	M	F	M	F	M	F	M	F	M	F						
12	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1						
30	2.5	1.1	5.6	2.2	4.4	3.5	21.0	3.0	13.4	1.6	7.0	3.3	5.6	3.7	2.7						
75	6.3	8.7	16.7	25.0	28.4	18.8	53.6	15.4	28.7	8.8	27.9	6.6	18.4	22.2	26.6						
Daily Dose (mg/kg/day)		0 (Control)														12	30	75			
Number of Animals and Gender		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60	
At Start		60		60		60		60		60		60		60		60		60		60	
Died or Sacrificed Moribund		31		24		27		32		25		30		31		32		32		38	
Terminal Sacrifice		29		36		33		28		35		30		29		28		28		22	
Survival (%)		48		60		55		47		58		50		48		47		47		37	
Body Weight Gain (g) <sup>a</sup>		15.5		12.1		+3		+8		-5		-1		-5		-2		-6		-15*	
Body Weight Gain (g) <sup>b</sup>		15.1		12.7		-10		+4		-9		+7		-9		-5		-13		-8	
Food Consumption (g) <sup>c</sup>		3738		3639		+3		+2		+4		0		+1		-2		+3		0	
Efficiency of Food Utilization (Weeks 1 to 13)		-		-		-		-		-		-		-		-		-		-	
Clinical Observations		-		-		-		-		-		-		-		-		-		-	
Ophthalmoscopy		-		-		-		-		-		-		-		-		-		-	
Haematology		-		-		-		-		-		-		-		-		-		-	

a: Weeks 0 to 52. For controls, group means are shown. For treated groups, percent differences from controls are shown  
b: Weeks 1 to 92. For controls, group means are shown. For treated groups, percent differences from controls are shown  
c: No noteworthy findings  
\*: p < 0.05; Statistical analysis conducted using Fisher's, Mantel's, Bartlett's, one-way ANOVA, William's, Student's, Shirley's or Kruskal-Wallis tests

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)										Page 3 of 10						
Daily Dose (mg/kg/day)		0 (Control)										12	30	75				
Number of Animals and Gender		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60		
Noteworthy Findings																		
Gross Pathology																		
Forestomach: Excrescence(s)		0	1	0	0	2	1	0	2	5	5							
Raised area(s) epithelium		0	0	0	1	0	1	0	1	1	1							
Nodule epithelium		0	0	0	0	0	0	0	0	0	1	1						
Depression(s)		2	0	2	0	1	0	1	0	2	2							
Thickened		0	2	0	0	0	1	0	3	1	3							
Roughened mucosa		1	2	0	2	0	1	1	0	4	6							
Mass(es)		0	0	0	0	0	0	0	0	1	0							
White		0	1	0	0	0	2	0	1	0	2							
Limiting ridge prominent		0	0	0	0	0	0	0	0	0	1							

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)										Page 4 of 10									
Daily Dose (mg/kg/day)		0 (Control)										12	30	75							
Number of Animals and Gender		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60		M: 60		F: 60					
Noteworthy Findings cont.																					
Histopathology - Non-Neoplastic																					
Stomach:																					
Epithelial hyperkeratosis (± to +++) <sup>a</sup>		21	33	21	35	29	36	38 <sup>***</sup>	47 <sup>***</sup>	36 <sup>***</sup>	48 <sup>***</sup>										
Epithelial hyperplasia (± to +++) <sup>b</sup>		1	3	2	4	4	10 <sup>**</sup>	3	9 <sup>**</sup>	10 <sup>**</sup>	17 <sup>**</sup>										
Epithelial papillomatous hyperplasia (+ to +++) <sup>c</sup>		0	0	0	0	0	0	0	2 <sup>§</sup>	2 <sup>§</sup>											
Number of Animals and Gender		M: 8		F: 8		M: 6		F: 4		M: 4		F: 16		M: 8		F: 13		M: 19		F: 14	
Squamous cell hyperplasia <sup>d</sup>		4	3	5	3	1	9 <sup>**</sup>	6	9 <sup>**</sup>	17 <sup>**</sup>	13 <sup>**</sup>										

a: [KOW/016]: In both sexes, the trend test was statistically significant when all groups were included in the analysis (p < 0.001). When the 75 mg/kg dose group was excluded, the trend test was still statistically significant (p < 0.001). Upon exclusion of the 30 mg/kg dose group, the trend test was no longer statistically significant. The pairwise comparisons for the 30 and 75 mg/kg dose groups with the control group were statistically significant (p < 0.001). #: p < 0.05; ##: p < 0.01; ###: p < 0.001 using pairwise tests; §: p < 0.05; §§: p < 0.01; §§§: p < 0.001 using trend tests.

b: [KOW/016]: In both sexes, the trend test was statistically significant when all groups were included in the analysis (p < 0.001). When the 75 mg/kg dose group was excluded, the trend test was still statistically significant in females (p = 0.007) but was no longer statistically significant in males. In females, upon exclusion of the 30 mg/kg dose group, the trend test was still statistically significant (p=0.004). The pairwise comparison in males between the 75 mg/kg dose group and control group was statistically significant (p = 0.003). The pairwise comparison in females between the 12, 30 and 75 mg/kg dose groups and control group were statistically significant (p = 0.013, p = 0.019 and p < 0.001, respectively). #: p < 0.05; ##: p < 0.01; ###: p < 0.001 using pairwise tests; §: p < 0.05; §§: p < 0.01; §§§: p < 0.001 using trend tests.

c: [KOW/016]: In both sexes, the trend test was statistically significant when all groups were included in the analysis (p = 0.032 and p = 0.022 in males and females, respectively). The 75 mg/kg dose groups were the only groups with this finding and the pairwise comparison with the control group were not statistically significant. §: p < 0.05 using trend tests.

d: Summary of results from the Pathology Working Group as included in [EPL 668-001/002]. [KOW/016]: In both sexes, the trend test was statistically significant when all groups were included in the analysis (p < 0.001). When the 75 mg/kg dose group was excluded, the trend test was still statistically significant in females (p = 0.008) but was no longer statistically significant in males. In females, upon exclusion of the 30 mg/kg dose group, the trend test was still statistically significant (p = 0.009). The pairwise comparison in males between the 75 mg/kg dose group and control group was statistically significant (p = 0.001). The pairwise comparison in females between the 12, 30 and 75 mg/kg dose groups and control group were statistically significant (p = 0.047, p = 0.039 and p = 0.002, respectively). #: p < 0.05; ##: p < 0.01; ###: p < 0.001 using pairwise tests; §: p < 0.05; §§: p < 0.01; §§§: p < 0.001 using trend tests.

[KOW 16/982522]: #: p < 0.05; \*\*: p < 0.01 using Fisher's Exact test; Histopathology severity: ±: Trace; +: Minimal; ++: Moderate; +++: Marked

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 5 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals and Gender		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Noteworthy Findings cont.</b>											
<b>Histopathology – Non-Neoplastic cont.</b>											
<b>Liver:</b>											
Hypertrophy centrilobular hepatocytes (± to ++) <sup>a</sup>	7	1	10	2	15 <sup>a†</sup>	2	22 <sup>***†††††</sup>	2	20 <sup>***†††††</sup>	2	
<b>Skeletal muscle:</b>											
Atrophy of myofibres (± to ++)	19	18	21	30 <sup>*</sup>	32 <sup>*</sup>	34 <sup>**</sup>	30 <sup>*</sup>	26	28	29 <sup>*</sup>	
<b>Lungs:</b>											
Vascular congestion (± to +++) <sup>b</sup>	22	17	25	14	31	21	35 <sup>**</sup>	21	33 <sup>*</sup>	35 <sup>**†††</sup>	
<b>Number of Animals and Gender</b>											
M: 60	F: 60	M: 57	F: 59	M: 60	F: 58	M: 60	F: 60	M: 59	F: 60	M: 59	F: 60
<b>Mesenteric lymph nodes:</b>											
Sinus histiocytosis (± to +++)	6	0	5	1	11	9 <sup>**</sup>	8	7 <sup>**</sup>	14 <sup>*</sup>	17 <sup>**</sup>	
<b>Number of Animals and Gender</b>											
M: 57	F: 60	M: 59	F: 58	M: 58	F: 59	M: 58	F: 56	M: 60	F: 58		
<b>Cervical lymph nodes:</b>											
Sinus histiocytosis (± to +++)	0	2	4	1	4	5	3	4	9 <sup>**</sup>	14 <sup>**</sup>	
<b>Overall Tumour Incidence (% of animals affected)</b>											
	55	58	52	52	38	48	42	55	53	28	
<b>Total No. Animals with Tumours<sup>c</sup></b>											
	33	35	31	31	23	29	25	33	32	17 <sup>††</sup>	
<b>Total No. Animals with Single Tumours<sup>c</sup></b>											
	26	28	20	25	14 <sup>†</sup>	21	17	27	26	8 <sup>††</sup>	
<b>Total No. Animals with Multiple Tumours</b>											
	7	7	11	6	9	8	8	6	6	9	

a: [KOW/016]: In males, the trend test was statistically significant when all groups were included in the analysis (p<0.001). When the 75 mg/kg dose group was excluded, the trend test was still statistically significant (p<0.001). Upon exclusion of the 30 mg/kg dose group, the trend test was still statistically significant (p=0.047). The pairwise comparisons for the 30 and 75 mg/kg dose groups with the control group were statistically significant (p<0.001 and p=0.001, respectively). ###: p < 0.01; ####: p < 0.001 using pairwise tests; §: p < 0.05; §§§: p < 0.001 using trend tests.

b: [KOW/016]: In females, the trend test was statistically significant when all groups were included in the analysis (p=0.001). When the 75 mg/kg dose group was excluded, the trend test was no longer statistically significant. The pairwise comparison between the 75 mg/kg dose group and control group was statistically significant (p=0.021). #: p < 0.05 using pairwise tests; §§: p < 0.01 using trend tests.

c: [S483 (144-048)]: §: p ≤ 0.05 using Fisher's test; §§: p ≤ 0.01 using Fisher's test; [KOW 16/982522]: \*: p < 0.05. \*\*: p < 0.01 using Fisher's Exact test

Histopathology severity: ±: Trace; +: Minimal; ++: Moderate; +++: Marked; ++++: Severe

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 6 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals and Gender		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Noteworthy Findings cont.</b>											
<b>Total No. Animals with Benign Tumours</b>											
	20	19	21	14	18	19	22	13	28	12	
<b>Total No. Benign Tumours<sup>b</sup></b>											
	26	22	29	15	24	24	27	15	32	16	
<b>Total No. Benign Tumours<sup>c</sup></b>											
	26	23	29	15	25	25	27	16	35	19	
<b>Total No. Animals with Malignant Tumours<sup>b</sup></b>											
	17	21	14	22	9	14	6 <sup>†</sup>	24	7 <sup>†</sup>	10 <sup>†</sup>	
<b>Total No. Malignant Tumours<sup>c</sup></b>											
	17	24	14	23	9	15	6 <sup>†</sup>	26	8	10	
<b>Total No. of Tumours<sup>b</sup></b>											
	43	46	43	38	33	39	33	41	40	26	
<b>Total No. of Animals with Metastasis</b>											
	1	2	1	3	0	2	0	2	0	1	
<b>Number of Animals</b>											
M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Neoplastic Lesions – Number of Animals</b>											
<b>Lungs:<sup>a</sup></b>											
Bronchiolo-alveolar adenoma	5	7	10	3	8	7	14 <sup>*</sup>	6	10	3	
Bronchiolo-alveolar carcinoma (malignant)	3	5	5	1	1	1	1	1	3	0	
<b>Spleen:</b>											
Haemangioma	0	0	1	0	1	0	1	0	1	0	
Haemangiosarcoma (malignant)	0	0	0	1	0	0	0	0	0	0	
<b>Liver:</b>											
Hepatocellular adenoma	8	0	7	0	8	0	6	0	8	0	
Hepatocellular carcinoma (malignant)	3	0	1	0	4	0	2	1	2	0	
Haemangioma	0	1	0	0	0	1	0	0	1	0	

a: [S483 (144-048)]: §: p ≤ 0.05 using Fisher's test

b: These values do not include the squamous cell papillomas identified in [EPL 668-001/002]

c: These values include the squamous cell papillomas identified in [EPL 668-001/002]

d: [KOW/016]: In males, the pairwise comparison between the 30 mg/kg/day group and the control group was statistically significant (p = 0.017). No significant result was found for the trend test. #: p < 0.05 using pairwise tests.

[KOW 16/982522]: \*: p < 0.05 using Fisher's Exact test

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 7 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Neoplastic Lesions – Number of Animals cont.</b>											
<b>Testis:</b>											
Interstitial cell adenoma	3	NA	0	NA	2	NA	2	NA	1	NA	
Haemangioma	0	NA	0	NA	1	NA	0	NA	0	NA	
<b>Ovary:</b>											
Cystadenoma	NA	1	NA	0	NA	0	NA	1	NA	1	
Granulosa cell tumour	NA	0	NA	1	NA	0	NA	0	NA	0	
Luteoma	NA	1	NA	1	NA	1	NA	2	NA	0	
<b>Thyroid:</b>											
Follicular cell adenoma	1	1	0	0	0	0	0	0	0	0	
<b>Stomach:</b>											
Squamous cell papilloma <sup>a</sup>	0	1	1	0	2	2	0	1	2	3 <sup>†</sup>	
Squamous cell papilloma <sup>b</sup>	0	1	0	0	1	1	0	1	3	3 <sup>†</sup>	
<b>Harderian gland:</b>											
Adenoma <sup>c</sup>	3	1	6	4	1	6 <sup>†</sup>	4	0	3	2	
Adenocarcinoma (malignant)	0	0	1	0	0	0	0	0	0	0	

a: [KOW/016]: In females, the trend test was statistically significant when all groups were included in the analysis (p=0.032). When the 75 mg/kg dose group was excluded, the trend test was not statistically significant. The pairwise comparisons with the control group were non-significant. §: p < 0.05 using trend tests.

b: Summary of results from the Pathology Working Group as included in [EPL 668-001/002]. [KOW/016]: In females, the trend test was statistically significant when all groups were included in the analysis (p<0.020). When the 75 mg/kg dose group was excluded, the trend test was no longer statistically significant. The pairwise comparisons with the control were not statistically significant. §: p < 0.05 using trend tests.

c: [KOW/016]: In females, the pairwise comparison between the 12 mg/kg group and the control group was statistically (p = 0.043). No significant result was found for the trend test. #: p < 0.05 using pairwise tests.

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 8 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Neoplastic Lesions – Number of Animals cont.</b>											
<b>Lymphoid system</b>											
Plasmocytic lymphoma (malignant)	4	1	0	6	3	2	1	5	0	4	
Lymphoblastic/lymphocytic lymphoma (malignant)	5	8	4	3	0	5	0	3	1	1	
Immunoblastic lymphoma (malignant)	0	0	1	0	0	0	0	0	0	0	
Myeloid leukaemia (malignant)	1	0	0	0	0	1	0	0	1	0	
Histiocytic sarcoma (malignant)	0	3	0	4	1	4	0	6	0	3	
<b>Pancreas</b>											
Islet cell adenoma	1	0	0	0	0	0	0	0	0	0	
<b>Kidney</b>											
Tubular cell adenoma	0	0	1	0	0	0	0	0	0	0	
<b>Epididymis</b>											
Interstitial cell tumour	0	NA	0	NA	1	NA	0	NA	0	NA	
<b>Seminal vesicle</b>											
Adenoma	1	NA	0	NA	0	NA	0	NA	0	NA	
<b>Adrenal</b>											
Cortical adenoma	3	0	3	0	0	0	0	0	5	0	
Cortical carcinoma (malignant)	1	0	0	0	0	0	0	0	0	0	
<b>Subcutaneous tissue</b>											
Fibrosarcoma (malignant)	0	1	1	1	0	0	1	1	1	0	
Rhabdomyosarcoma (malignant)	0	0	1	0	0	0	0	0	0	0	
Haemangioma	1	0	0	0	0	0	0	0	0	0	
Basophilic squamous cell carcinoma (malignant)	0	3	0	0	0	0	0	0	0	0	

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 9 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Neoplastic Lesions – Number of Animals cont.</b>											
<b>Uterus</b>											
Endometrial polyp <sup>a</sup>	NA	5	NA	1	NA	1	NA	1	NA	5 <sup>§</sup>	
Endometrial polyp and stromal cell sarcoma (malignant) <sup>a</sup>	NA	0	NA	0	NA	0	NA	1	NA	0	
Leiomyoma	NA	1	NA	2	NA	2	NA	3	NA	2	
Leiomyosarcoma (malignant)	NA	0	NA	0	NA	1	NA	1	NA	0	
Haemangioma	NA	1	NA	1	NA	0	NA	1	NA	0	
Haemangiosarcoma (malignant)	NA	0	NA	0	NA	0	NA	1	NA	0	
Granular cell tumour-cervix	NA	0	NA	0	NA	1	NA	0	NA	0	
<b>Cervix</b>											
Leiomyoma	NA	2	NA	0	NA	0	NA	0	NA	0	
Granular cell tumour	NA	0	NA	0	NA	1	NA	0	NA	0	
Cervical polyp	NA	0	NA	1	NA	0	NA	0	NA	0	
<b>Vagina</b>											
Granular cell tumour-cervix	NA	0	NA	0	NA	1	NA	0	NA	0	
<b>Brain</b>											
Mixed glioma (malignant)	0	0	0	1	0	0	0	0	0	0	
Meningeal sarcoma (malignant)	0	0	0	0	0	0	1	0	0	1	
<b>Femur/Joint</b>											
Synovium	0	0	0	0	0	0	0	0	1	0	

a: [KOW/016]: For benign endometrial polyp the trend test was statistically significant when all groups were included in the analysis (p = 0.032). When the 75 mg/kg dose group was excluded, the trend test was not statistically significant. The pairwise comparisons with the control group were non significant. For benign endometrial polyp and malignant endometrial stromal cell sarcoma combined, the trend test was statistically significant when all groups were included in the analysis (p = 0.028). When the 75 mg/kg dose group was excluded, the trend test was not statistically significant. The pairwise comparisons with the control group were non significant. §: p < 0.05 using trend tests

2.6.7.10A Carcinogenicity		Report No. [KOW 16/982522] (continued)								Page 10 of 10	
Daily Dose (mg/kg/day)		0 (Control)		12		30		75			
Number of Animals		M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60	M: 60	F: 60
<b>Neoplastic Lesions – Number of Animals cont.</b>											
<b>Pituitary</b>											
Adenoma	0	0	0	0	0	1	0	0	0	0	
<b>oesophagus</b>											
Adenoma	0	0	0	1	0	0	0	0	0	0	
Undifferentiated sarcoma (malignant)	0	0	0	1	0	0	0	0	0	0	
<b>Skeletal muscle</b>											
Rhabdomyosarcoma (malignant)	0	1	0	0	0	0	0	0	0	0	
<b>Skin</b>											
Fibrosarcoma (malignant)	0	0	0	2	0	0	0	0	0	0	
<b>Mammary gland</b>											
Adenocarcinoma (malignant)	0	2	0	3	0	1	0	5	0	0	
<b>Sternum/bone marrow</b>											
Osteosarcoma (malignant)	0	0	0	0	0	0	0	0	0	1	
<b>Head/leg</b>											
Haemangiosarcoma (malignant)	0	0	0	0	0	0	0	1	0	0	
<b>Total No. clinically observed masses<sup>a</sup></b>	43	46	43	38	33	39	33	41	40	26	

a: Benign and malignant

2.6.7.10B Carcinogenicity		Test Article: Pitavastatin				Page 1 of 3					
<b>Report Title:</b> A 26-week oral dose carcinogenicity and toxicokinetic study of NK-104 in CB6F1-Tg rasH2 mice											
<b>Species/Strain:</b> CB6F1-Tg rasH2 mice		<b>Duration of Dosing:</b> Once daily for 26 weeks				<b>Report No.:</b> [SNBL138.03]					
<b>Initial Age:</b> 9 to 10 weeks at start of dosing		<b>Method of Administration:</b> Oral (gavage) at 10 mL/kg				<b>Location in CTD:</b>					
<b>Date of First Dose:</b> 4 April 2007		<b>Vehicle/Formulation:</b> 0.5% w/v CMC sodium solution in sterile water for injection, USP (0.5% CMC sodium solution)				<b>Vol.:</b> *		<b>Section:</b> *			
<b>Treatment of Controls:</b> Negative Controls		0.5% CMC sodium solution;				<b>GLP Compliance:</b> Yes					
Positive Controls		N-Methyl-N-nitrosourea (MNU) in 0.9% Saline for Injection, USP; single intraperitoneal (i.p.) dose given on Day 1 (10 mL/kg)									
<b>Basis for High-Dose Selection:</b> In the 4 week preliminary study [SNBL138.01] dose levels of 70, 125 and 250 mg/kg were utilised. The high dose, 250 mg/kg/day, was associated with clinical signs of toxicity and histopathological changes observed in the stomach.											
<b>Special Features:</b> None											
<b>Daily Dose (mg/kg)</b>		0 (Control)		75 MNU		30		75		150	
<b>Toxicokinetics<sup>a</sup></b>											
<b>C<sub>max</sub> (ng/mL) on Day 1</b>		-		ND		1457		1094		7705	
<b>T<sub>max</sub> (hours) on Day 1</b>		-		ND		0.5		0.5		0.5	
<b>AUC<sub>0-24</sub> (ng<sup>h</sup>/mL) on Day 1</b>		-		ND		996		1006		5562	
<b>C<sub>max</sub> (ng/mL) in Week 26</b>		-		ND		1033		1196		5871	
<b>T<sub>max</sub> (hours) in Week 26</b>		-		ND		0.5		0.5		0.5	
<b>AUC<sub>0-24</sub> (ng<sup>h</sup>/mL) in Week 26</b>		-		ND		1076		1326		4904	
<b>No. of Animals and Gender for Main Groups</b>		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25	
<b>No. of Animals and Gender for Toxicokinetics and Replacement</b>		6		6		0		0		23	
<b>At Start</b>		31		31		25		25		48	
<b>Died or Sacrificed Moribund</b>		5		2		20		15		2	

a: Not applicable to an electronic submission  
 a: Three animals /sex/group/time point; blood samples were collected six times on Day 1 and Day 182 (Week 26). For the control group samples were taken 0.5 hours post-dose on both days; for pitavastatin treated animals blood samples were taken pre-dose and 0.5, 1, 3, 6 and 24 hours after dosing  
 b: Plasma concentrations for the three individual animals at 0.5 hours were 5533, 32190 and 134200 ng/mL.; the plasma concentration for animal C403 at this time point was extremely high

2.6.7.10B Carcinogenicity		Report No. [SNBL138.03] (continued)								Page 2 of 3	
Daily Dose (mg/kg)		0 (Control)		75 MNU		30		75		150	
<b>No. of Animals and Gender</b>		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25		M: 25 F: 25	
<b>Died or Sacrificed Moribund</b>		3		1		20		15		1	
<b>Noteworthy Findings</b>											
<b>Survival (%)</b>		88		96		20		40		96	
<b>No. of Animals and Gender</b>		22		24		5		10		24	
<b>Body Weight (%)</b>		27.2 g		22.4 g		-3		0		+4	
<b>Food Consumption (%)<sup>a</sup></b>		3.9 g		3.8 g		-10		+5		+5	
<b>Clinical Observations</b>		-		-		-		-		-	
<b>Haematology</b>		-		-		-		-		-	
<b>Mass(es)</b>		-		-		-		-		-	
<b>Number Animals Examined</b>		31		31		25		25		48	
<b>No. of Animals with Mass(es)</b>		0		1 (ear) <sup>d</sup>		9 <sup>e</sup>		22 <sup>e</sup>		6 (all ear) <sup>d</sup>	
<b>No. of Animals with ≥1 Mass</b>		0		0		5		21		0	
<b>Organ Weights (adjusted)<sup>f</sup></b>		-		-		-		-		-	
<b>Gross Pathology</b>		-		-		-		-		-	

a: At the end of the dosing period (at scheduled necropsy). Group means are shown. For treated groups, percent differences from controls are shown.  
 b: Increased incidences of hunched posture, rapid and slow respiration, limb splay and gasping which typically preceded moribund euthanasia or death.  
 c: Variable increases in neutrophils and/or lymphocytes.  
 d: These masses, which were observed most frequently in the ear, tail, vaginal opening and ventral neck region, were considered to have an incidence consistent with background levels for transgenic rasH2 mice and therefore were unrelated to test article administration.  
 e: A statistically significant increase in the incidence of masses was observed; these masses were primarily located on the ears, lips, mouths, tails, eyelids and the anal, anogenital and vaginal openings of the mice.  
 f: Three animals with masses on the ear; two animals with masses on the tail; and one animal with a mass on the vaginal opening  
 g: Animal 325 had two masses in the ear and mass on the tail; Animal 333 had a mass on the ventral neck  
 h: Increased thymus, spleen, liver, and thyroid/parathyroid gland organ weights and decreased salivary gland and uterus organ weights in females; increased thymus, lung and spleen organ weights in males. Increased group organ weights were attributed to tumours in each specific organ in at least one individual animal.  
 i: Gross enlargement of thymus, spleen, and/or stomach masses were observed in several animals at the scheduled necropsy and were considered related to MNU treatment.  
 -: No noteworthy findings

2.6.7.10B Carcinogenicity	Report No. [SNB1.138.03] (continued)										Page 3 of 3
	0 (Control)		75 MNU		30		75		150		
Daily Dose (mg/kg)	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	
No. of Animals and Gender	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	
Noteworthy Findings cont.											
Histopathology - Non-Neoplastic											
Number Animals Examined	25	25	24	25	25	25	25	26 <sup>a</sup>	25	25	
Stomach:											
Mono-nuclear/polymorphonuclear cell infiltration, submucosa (± to ++)	1	0	3	4	0	0	0	0	1	0	
Thickening and hyperkeratosis, mucosa (± to ++)	2	7	0	1	2	7	18	19	19	24	
Histopathology - Neoplastic <sup>a</sup>											
Number Animals Examined	25	25	23	25	24	24	25	26 <sup>a</sup>	25	25	
Lungs:											
Alveolar/bronchiolar adenoma	0	1	0	0	0	0	0	2	2	0	
Alveolar/bronchiolar carcinoma	0	0	1	1	0	1	0	0	0	0	
Spleen:											
Haemangiosarcoma	2	1	1	2	1	1	0	2	2	0	
Stomach:											
Forestomach squamous cell carcinoma	0	0	6	8	0	0	0	0	1	0	
Forestomach papilloma	0	0	14	15	0	0	0	0	0	0	
Haemangiosarcoma	0	0	0	0	1	0	0	0	0	0	
Duodenum: Haemangiosarcoma	0	0	0	0	0	0	0	0	0	1	
Mesentery: Haemangiosarcoma (n/no. of animals examined)	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	
All Tissues Combined: Lymphosarcoma	0	0	200	90	0	0	0	0	0	0	
Total Number of Tumours	3	2	226	128	2	2	0	4	5	1	

a: One additional spare animal included for histopathological evaluation; b: With the exception of lymphosarcoma (all tissues combined) and forestomach papillomas which are commonly expressed in this mouse strain by MNU dosing, only neoplastic lesions observed in control and/or pitavastatin treated animals are presented; no pitavastatin treatment-related neoplasms were observed; c: Neoplasms were observed in MNU treated animals (males and/or females) in the brain, pituitary, optic nerves, tongue, submandibular and/or sublingual glands, trachea, oesophagus, thyroid and/or parathyroids, skin mammary, thymus, mandibular lymph nodes, heart, aorta, liver, gallbladder, adrenals, kidneys, pancreas, mesenteric lymph nodes, duodenum, caecum, jejunum, urinary bladder, seminal vesicles, prostate, ovaries, uterus, vagina, skeletal muscle, sciatic nerve, bone (sternum and femur), bone marrow, reticuloendothelium, Zymbal's gland, lymph nodes, skin perineum, hepatic lymph nodes and skin; Histopathology severity: ±: Minimal; +: Mild; ++: Moderate

2.6.7.10C Carcinogenicity	Test Article: Pitavastatin				Page 1 of 4
Report Title: Two-stage lung carcinogenicity study of NK-104 in Tg-rasH2 mice	Duration of Dosing: Once daily for 26 weeks				Report No.: [G2536]
Species/Strain: Jic: C57BL/6J-rasH2/rl mice	Method of Administration: Oral (gavage) at 10 mL/kg				Location in CTD:
Initial Age: 8 weeks at start of dosing	Vehicle/Formulation: 0.5% w/v CMC sodium solution				Vol.: * Section: *
Date of First Dose: May 2007 <sup>a</sup>	Urethane was selected as the initiator for this study and was given as a single i.p. dose at 250 mg/kg (10 mL/kg) on Day 1. On Day 15 dosing commenced with 0.5% CMC sodium solution (negative and positive control groups) or pitavastatin by the oral (gavage) route.				GLP Compliance: Yes
Study Design:	Urethane was selected as the initiator for this study and was given as a single i.p. dose at 250 mg/kg (10 mL/kg) on Day 1. On Day 15 dosing commenced with 0.5% CMC sodium solution (negative and positive control groups) or pitavastatin by the oral (gavage) route.				
Treatment of Controls:	Negative Controls: 0.5% CMC sodium solution from Day 15 with an i.p. injection of physiological saline solution at 10 mL/kg on Day 1. Positive Controls: 0.5% CMC sodium solution from Day 15 with an i.p. injection of urethane in physiological saline at 250 mg/kg at 10 mL/kg on Day 1.				
Daily Dose (mg/kg/day)	Control: 0 (Day 15 onwards) (physiological saline i.p. on Day 1)	Control: 0 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)	150 (Day 15 onwards) (physiological saline i.p. on Day 1)	150 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)	
Toxicokinetics	ND	ND	ND	ND	ND
Number of Animals and Gender	M: 9	F: 9	M: 15	F: 15	M: 12
Noteworthy Findings					
Died or Sacrificed Moribund	1	0	3	3	0
Clinical Observations					
Decrease in locomotor activity (no. of animals)	-	-	1/15	2/12	4/12
Body Weight (g) <sup>b</sup>	27.0	24.9	28.9 (+7) <sup>ab</sup>	24.8 (0)	27.9 (+3)
Food Consumption (g) <sup>c</sup>	3.0	2.9	3.3 (+10) <sup>a</sup>	3.1 (+7)	3.4 (+13) <sup>***</sup>
Water Consumption (mL) <sup>d</sup>	4.1	4.8	4.7 (+15) <sup>a</sup>	5.2 (+8)	4.5 (+10)

\*: Not applicable to an electronic submission; a: Start of initiator administration was May 8 2007 (males) and May 10 2007 (females); start of test article or control administration was May 22 2007 (males) and May 24 2007 (females); b: Death attributed to haemorrhage from a spleen haematoma which was not considered treatment related; c: Day 197. Group means are shown. For treated groups, percent differences from controls are shown in parenthesis. The comparisons were as follows: Positive Control vs. Negative Control; Pitavastatin alone vs. Negative Control; Pitavastatin and Urethane vs. Positive Control. Statistical significance is based on actual data (not on the percent differences); d: Two deaths were attributed to the concomitant administration of urethane; one animal was sacrificed moribund following an accidental caging injury; - No noteworthy findings; \*: p<0.05; \*\*\*: p<0.001; Statistical analysis was conducted using Student's t test; #: p<0.05; ##: p<0.01; ###: p<0.001; Statistical analysis was conducted using Aspin-Welch's test

2.6.7.10C Carcinogenicity Daily Dose (mg/kg/day)	Report No. (t2536) (continued)								Page 2 of 4
	Control: 0 (Day 15 onwards) (physiological saline i.p. on Day 1)		Control: 0 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		150 (Day 15 onwards) (physiological saline i.p. on Day 1)		150 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		
Number of Animals and Gender	M: 9	F: 9	M: 15	F: 15	M: 12	F: 12	M: 15	F: 15	
<b>Cross Pathology<sup>a</sup></b>									
<b>Number Animals Examined<sup>b</sup> (Decedents)</b>	8 (1)	9 (0)	12 (3)	12 (3)	12 (0)	11 (1)	14 (1)	12 (3)	
Retention of blood, fluid and/or pleural effusion (abdominal or thoracic cavity)	0 (1)	0 (0)	0 (3)	1 (2)	0 (0)	0 (1)	0 (1)	1 (2)	
Haematoma (in tissues other than lung and spleen)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	
Mass(es) (in tissues other than lung and spleen)	0 (0)	0 (0)	0 (1)	0 (0)	0 (0)	1 (0)	0 (0)	0 (1)	
Nodule(s) (in tissues other than lung and spleen)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
<b>Lung:</b>									
Spot(s) and/or Mottle(s)	0 (0)	1 (0)	1 (1)	1 (1)	0 (0)	0 (0)	3 (0)	1 (0)	
Congestion	0 (1)	0 (0)	0 (1)	0 (1)	0 (0)	0 (1)	0 (0)	0 (3)	
Nodule(s)	2 (0)	2 (0)	7 (1)	8 (0)	2 (0)	1 (0)	8 (1)	7 (1)	
Mass(es)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
<b>Spleen:</b>									
Spot(s), Mottle(s) and/or Area(s)	0 (0)	3 (0)	1 (0)	2 (0)	4 (0)	1 (0)	3 (0)	2 (0)	
Hypertrophy	0 (1)	0 (0)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Nodule(s)	1 (0)	0 (0)	7 (1)	3 (0)	0 (0)	0 (0)	4 (0)	5 (0)	
Haematoma	0 (0)	0 (0)	0 (2)	0 (1)	1 (0)	0 (1)	0 (0)	0 (0)	
Mass(es)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	
<b>Forestomach:</b>									
Elevated area	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (1)	
Thickening	0 (0)	0 (0)	0 (0)	0 (0)	10 (0)	11 (1)	14 (1)	12 (2)	

a: Number of animals with finding  
b: At the end of the dosing period (at scheduled necropsy).

2.6.7.10C Carcinogenicity Daily Dose (mg/kg/day)	Report No. (t2536) (continued)								Page 3 of 4
	Control: 0 (Day 15 onwards) (physiological saline i.p. on Day 1)		Control: 0 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		150 (Day 15 onwards) (physiological saline i.p. on Day 1)		150 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		
Number of Animals and Gender	M: 9	F: 9	M: 15	F: 15	M: 12	F: 12	M: 15	F: 15	
<b>Organ Weights<sup>a</sup></b>									
Spleen (relative: %)	0.25	0.33	0.33 (+32)	0.42 (+27) <sup>*</sup>	0.25 (0)	0.36 (+9)	0.31 (-6)	0.49 (+17)	
<b>Histopathology – Non-Neoplastic</b>									
<b>Number Animals Examined</b>	8	9	12	12	12	11	14	12	
<b>Forestomach:</b>									
Hyperkeratosis (± to +)	0	0	0	0	12	11	14	12	
Hyperplasia (± to ++)	0	0	0	0	12	11	14	12	
Erosion (±)	0	0	0	0	2	2	1	3	
Inflammation (±)	0	0	0	0	5	7	7	9	
<b>Lung (with bronchus):</b>									
Alveolar/bronchiolar adenoma (P)	2	1	7	6	3	1	8	10	
Alveolar/bronchiolar carcinoma (P)	0	1	4	4	0	1	4	1	
Alveolar/bronchiolar hyperplasia (±)	4	2	3	3	5	2	7	4	
Granulation (±)	1	0	0	1	1	0	3	1	
Haemorrhage (±)	0	0	1	0	0	0	0	0	
Inflammation (±)	1	0	1	6	1	2	6	6	
<b>Spleen:</b>									
Haemangiosarcoma (P)	0	0	8	6	1	0	7	5	
Fibrosis (± to +)	4	0	2	0	3	0	2	1	
Angiectasis (±)	0	0	0	0	1	0	0	0	
Deposit, haemosiderin (±)	0	3	0	0	3	1	1	1	

a: At the end of the dosing period (at scheduled necropsy). Group means are shown. For treated groups, percent differences from controls are shown in parentheses. The comparisons are as follows: Positive Control vs. Negative Control; Pitavastatin alone vs. Negative Control; Pitavastatin and Urethane vs. Positive Control. Statistical significance is based on actual data (not on the percent differences); - No noteworthy findings; #: p≤0.05; Statistical analysis was conducted using Aspin-Welch's test; I Histopathology severity: P: Non-graded change; ±: Minimal; +: Mild; ++: Moderate

2.6.7.10C Carcinogenicity Daily Dose (mg/kg/day)	Report No. (t2536) (continued)								Page 4 of 4
	Control: 0 (Day 15 onwards) (physiological saline i.p. on Day 1)		Control: 0 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		150 (Day 15 onwards) (physiological saline i.p. on Day 1)		150 (Day 15 onwards) (urethane 250 mg i.p. on Day 1)		
Number of Animals and Gender	M: 9	F: 9	M: 15	F: 15	M: 12	F: 12	M: 15	F: 15	
<b>Histopathology – Neoplastic</b>									
<b>Number Animals Examined</b>	8	9	12	12	12	11	14	12	
<b>Lung:</b>									
Hyperplasia incidence (%)	50.0	22.2	25.0	25.0	41.7	18.2	50.0	33.3	
Adenoma incidence (%)	25.0	11.1	58.3	50.0	25.0	9.1	57.1	83.3	
Carcinoma incidence (%)	0.0	11.1	33.3	33.3	0.0	9.1	28.6	8.3	
Adenoma and/or carcinoma incidence (%)	25.0	22.2	75.0 <sup>*</sup>	75.0 <sup>*</sup>	25.0	18.2	78.6	91.7	
Adenoma multiplicity <sup>a</sup>	0.25 ± 0.46	0.11 ± 0.33	0.83 ± 0.94	1.00 ± 1.54	0.42 ± 0.79	0.09 ± 0.30	0.93 ± 1.07	1.25 ± 0.87	
Carcinoma multiplicity <sup>a</sup>	0.00 ± 0.00	0.11 ± 0.33	0.42 ± 0.67	0.33 ± 0.49	0.00 ± 0.00	0.09 ± 0.30	0.57 ± 1.16	0.08 ± 0.29	
Adenoma and/or carcinoma multiplicity <sup>a</sup>	0.25 ± 0.46	0.22 ± 0.44	1.25 ± 1.14 <sup>*</sup>	1.33 ± 1.44 <sup>*</sup>	0.42 ± 0.79	0.18 ± 0.40	1.50 ± 1.22	1.33 ± 0.78	
<b>No. Animals with Lung Tumour Lesions</b>	2	1	7	6	3	1	8	10	
Adenoma area (mm <sup>2</sup> /cm <sup>2</sup> ; mean ± SD)	1.51 ± 1.06	0.24 ± 0.00	0.82 ± 0.69	0.93 ± 0.72	1.12 ± 0.83	1.21 ± 0.00	0.77 ± 0.52	0.53 ± 0.37	
<b>No. Animals with Lung Tumour Lesions</b>	0	1	4	4	0	1	4	1	
Carcinoma area (mm <sup>2</sup> /cm <sup>2</sup> ; mean ± SD)	NA	6.49 ± 0.00	3.56 ± 3.59	5.29 ± 6.63	NA	0.90 ± 0.00	3.70 ± 3.86	2.00 ± 0.00	
<b>No. Animals with Lung Tumour Lesions</b>	2	2	9	9	3	2	11	11	
Adenoma and/or carcinoma area (mm <sup>2</sup> /cm <sup>2</sup> ; mean ± SD)	1.51 ± 1.06	3.37 ± 4.42	2.22 ± 2.66	2.97 ± 4.66	1.12 ± 0.83	1.06 ± 0.22	1.90 ± 2.59	0.66 ± 0.57	

a: Multiplicity: Number of tumours/animal  
Statistical significance is based on comparison with the Negative Control group.  
\*: p ≤ 0.05; Statistical analysis was conducted using Fisher's exact probability test  
#: p ≤ 0.05; Statistical analysis was conducted using Aspin-Welch test

2.6.7.10D Carcinogenicity		Test Article: Pitavastatin				Page 1 of 9			
Report Title: NK-104: Potential tumorigenic effects in repeated oral gavage administration to rats									
Species/Strain: CrI: CD BR rats		Duration of Dosing: Once daily for 104 weeks (M) or 92 weeks (F)				Report No.: [KOW 13/971903]			
Initial Age: 5 to 6 weeks		Method of Administration: Oral (gavage) at 5 mL/kg				Location in CTD:			
Date of First Dose: 28 December 1994		Vehicle/Formulation: 0.5% CMC sodium solution				Vol: *		Section: *	
		Treatment of Controls: 0.5% CMC sodium solution				GLP Compliance: Yes			
Basis for High-Dose Selection: In the 13-week preliminary study [KOW 12/942992] dose levels of 10, 30 and 50 mg/kg were utilised. 50 mg/kg/day was considered too high as the maximum tolerated dose due to deaths early in the study and histopathological changes observed in the forestomach, liver, kidney, thyroid and skeletal muscle whereas although doses of 10 or 30 mg/kg elicited histopathological changes in the forestomach this was in the absence of other changes in bodyweight or food intake. A dose of 25 mg/kg/day selected as the highest dose level.									
Special Features: None									
Daily Dose (mg/kg/day)		0 (Control)		1		5		25	
Toxicokinetics: Number of Animals <sup>a</sup>		M: 0 F: 0		M: 6 F: 6		M: 6 F: 6		M: 6 F: 6	
Plasma Concentrations (ng/mL)									
Month 3	0.5 hours (T <sub>max</sub> )	ND	ND	94	124	1908	2424	19971	20505
Month 3	6.0 hours (T <sub>min</sub> )	ND	ND	29	6	129	44	1646	877
Month 6	0.5 hours (T <sub>max</sub> )	ND	ND	122	193	2502	2239	32395	29594
Month 6	6.0 hours (T <sub>min</sub> )	ND	ND	39	11	181	63	1361	1697
Month 9	0.5 hours (T <sub>max</sub> )	ND	ND	211	199	2184	2214	21449	29571
Month 9	6.0 hours (T <sub>min</sub> )	ND	ND	23	12	167	139	2062	1585
Month 12	0.5 hours (T <sub>max</sub> )	ND	ND	201	270	2895	4560	26466	38756
Month 12	6.0 hours (T <sub>min</sub> )	ND	ND	23	18	122	75	978	2051
Month 15	0.5 hours (T <sub>max</sub> )	ND	ND	196	250	4459	3673	26450	51708
Month 15	6.0 hours (T <sub>min</sub> )	ND	ND	19	17	165	127	1000	1300
Month 18	0.5 hours (T <sub>max</sub> )	ND	ND	394	133	3049	3688	35746	31269
Month 18	6.0 hours (T <sub>min</sub> )	ND	ND	183	12	147	86	1178	1583
Month 21	0.5 hours (T <sub>max</sub> )	ND	ND	504	137 <sup>a</sup>	2678	2716 <sup>a</sup>	37433	31024
Month 21	6.0 hours (T <sub>min</sub> )	ND	ND	36	28 <sup>a</sup>	189	45 <sup>a</sup>	1571	1904
Month 24	0.5 hours (T <sub>max</sub> )	ND	ND	235	NS	3077	NS	37471	NS
Month 24	6.0 hours (T <sub>min</sub> )	ND	ND	21	NS	81	NS	767	NS

\*: Not applicable to an electronic submission; a: Only one animal; all other animals died; NS: No sample

2.6.7.10D Carcinogenicity		Report No. [KOW 13/971903] <sup>b</sup> (continued)				Page 2 of 9			
Daily Dose (mg/kg/day)		0 (Control)		1		5		25	
Toxicokinetics cont.									
Dose Level Ratio		NA		1		5		25	
Number of Animals		M: 0 F: 0		M: 6 F: 6		M: 6 F: 6		M: 6 F: 6	
Time		C <sub>max</sub> Ratio	C <sub>min</sub> Ratio	C <sub>max</sub> Ratio	C <sub>min</sub> Ratio	C <sub>max</sub> Ratio	C <sub>min</sub> Ratio	C <sub>max</sub> Ratio	C <sub>min</sub> Ratio
Month 3		ND	ND	ND	ND	1	1	20.4	4.4
Month 6		ND	ND	ND	ND	1	1	10.3	7.2
Month 9		ND	ND	ND	ND	1	1	14.4	5.2
Month 12		ND	ND	ND	ND	1	1	22.8	8.7
Month 15		ND	ND	ND	ND	1	1	7.7	0.8
Month 18		ND	ND	ND	ND	1	1	5.3	5.2
Month 21		ND	ND	ND	ND	1	1	13.1	3.9
Month 24		ND	ND	ND	ND	1	1	ND	ND
Daily Dose (mg/kg)		0 (Control)		1		5		25	
Number of Animals and Gender		M: 55 F: 55		M: 55 F: 55		M: 55 F: 55		M: 55 F: 55	
Number of Animals									
At Start		55		55		55		55	
Died or Sacrificed Moribund		36		39		34		21	
Terminal Sacrifice		19		16		21		31	
Survival (%)		35		29		38		60	

C<sub>max</sub>: Plasma concentration at 0.5 hours after dosing

C<sub>min</sub>: Plasma concentration at 6 hours after dosing

a: Two further statistical analyses (5483 (144-048)) and (RF2001/37) of the tumours and non neoplastic findings and a PWG peer review (EPL 668-001/002) were carried out

b: Value obtained from one animal only

2.6.7.10D Carcinogenicity	Report No. [KOW 13/971903] (continued)							Page 3 of 9	
	0 (Control)		5		25		25		
Daily Dose (mg/kg/day)	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
Number of Animals and Gender									
Body Weight Gain (g) <sup>a</sup>	744	365	+1	+1	+3	+14	-6	+5	
Food Consumption (g) <sup>a</sup>	24485	15755	+1	+2	+2	+3	-5*	0	
Efficiency of Food Utilisation (Weeks 1-26)	-	-	-	-	-	-	-	-	
Clinical Observations	-	-	-	-	-	-	-	-	
Ophthalmoscopy									
Cataracts	-	-	-	-	-	-	2/55	3/55	
Haematology	-	-	-	-	-	-	-	-	
Serum Chemistry	-	-	-	-	-	-	-	-	
Noteworthy Findings									
Gross Pathology									
Liver:									
Pale areas	6	2	7	4	3	9	6	19	
Spleen:									
Enlarged	19	5	20	10	18	6	14	14	
Forestomach:									
Mass	0	0	0	0	0	0	4	0	
Excrescence(s)	0	0	0	0	0	0	2	0	
Roughened	0	0	0	1	25	5	44	29	
Sloughing	0	0	0	0	5	0	5	14	
Thickened	2	1	3	3	31	15	52	40	
White discoloration	0	1	1	0	11	2	39	16	
Pituitary:									
Enlarged	13	36	16	31	10	37	22	21	

-: No noteworthy findings

a: Weeks 0 to 92 for females and Weeks 0 to 104 for males. For controls, group means are shown. For treated groups, percent differences from controls are shown

\*: p < 0.05; Statistical analysis conducted using Fisher's, Mantel's, Bartlett's, one-way ANOVA, William's, Student's, Shirley's or Kruskal-Wallis tests

2.6.7.10D Carcinogenicity	Report No. [KOW 13/971903] (continued)							Page 4 of 9	
	0 (Control)		5		25		25		
Daily Dose (mg/kg/day)	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
Number of Animals and Gender									
Noteworthy Findings cont.									
Gross Pathology									
Lungs:									
Pale focus	7	5	12	6	13	8	21	10	
Petechiae	7	6	6	3	5	11	8	13	
Mammary glands:									
Thickened	1	22	1	15	0	26	0	7	
Histopathology - Non-Neoplastic									
Thyroids:									
Follicular cystic hyperplasia (± to ++)	4	0	2	0	1	1	5	6*	
Liver:									
Basophilic hepatocyte foci (± to ++)	4	19	1	12	2	25	11	43**	
Vacuolated/clear cell hepatocyte foci (± to ++)	2	1	4	0	7	0	15**	3	
Focal hepatocyte necrosis (+ to ++)	2	0	4	2	1	5*	1	5*	
Skeletal muscle:									
Myofibre atrophy (± to +++)	7	0	6	0	8	1	19**	0	
Stomach:									
Epithelial hyperplasia (± to ++++)	6	3	7	6	40**	34**	49**	53**	
Epithelial papillomatous hyperplasia (± to +++)	1	1	0	0	2	3	7*	0	
Epithelial hyperkeratosis (+ to +++)	0	1	0	1	14**	5	43**	47**	
Epithelial erosion (± to ++++)	1	0	0	0	4	1	6	1	
Epithelial ulceration (± to +++)	2	0	2	3	4	3	3	0	

\*: p < 0.05; \*\*: p < 0.01 using Fisher's exact test

Histopathology severity: ±: Trace; +: Minimal; ++: Moderate; +++: Marked; ++++: Severe

2.6.7.10D Carcinogenicity	Report No. [KOW 13/971903] (continued)							Page 5 of 9	
	0 (Control)		5		25		25		
Daily Dose (mg/kg/day)	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
Number of Animals and Gender									
Overall Tumour Incidence (% of animals affected)	84	93	76	91	82	89	84	80	
Total No. Animals with Tumours	46	51	42	50	45	49	46	44	
Total No. Animals with Single Tumours	22	22	24	26	26	16	16	21	
Total No. Animals with Multiple Tumours <sup>a</sup>	24	29	18	24	19	33	30	23	
Total No. Animals with Benign Tumours	39	46	36	47	37	48	45	43	
Total No. Benign Tumours <sup>b</sup>	67	75	61	73	57	86	77	73	
Total No. Benign Tumours <sup>c</sup>	67	75	61	73	58	86	84	73	
Total No. Animals with Malignant Tumours	10	13	9	11	14	11	13	6	
Total No. Malignant Tumours	14	14	9	12	16	11	14	6	
Total No. of Tumours	81	89	70	85	73	97	91	79	
Total No. of Animals with Metastasis	1	2	1	1	1	0	1	0	
Number of Animals and Gender	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
Neoplastic Lesions - Number of Animals									
Lungs:									
Bronchiolo-alveolar adenoma	0	0	1	0	0	0	0	0	
Bronchiolo-alveolar carcinoma (malignant)	0	0	0	0	0	1	0	0	
Thymus:									
Squamous cell carcinoma (malignant)	0	0	0	0	0	0	1	0	
Liver:									
Hepatocellular adenoma	0	0	0	2	2	2	2	1	
Hepatocellular carcinoma (malignant)	0	0	1	0	0	0	0	0	

a: [5483 (144-048)]; ∅: p ≤ 0.05 using Fisher's test

b: These values do not include the squamous cell papillomas identified in [EPL 668-001/002]

c: These values include the squamous cell papillomas and carcinomas identified in [EPL 668-001/002]

2.6.7.10D Carcinogenicity	Report No. [KOW 13/971903] (continued)								Page 6 of 9
	Daily Dose (mg/kg/day)	0 (Control)		1		5		25	
Number of Animals	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
<b>Neoplastic Lesions - Number of Animals cont.</b>									
<b>Pancreas:</b>									
Islet cell adenoma	4	0	1	0	4	1	3	0	
Islet cell carcinoma (malignant)	1	0	1	0	2	0	1	0	
Acinar cell adenoma	0	0	1	0	0	1	1	0	
<b>Kidneys:</b>									
Mesenchymal tumour (malignant)	0	0	0	0	0	0	1	0	
Nephroblastoma (malignant)	0	1	0	0	0	0	0	0	
<b>Testis:</b>									
Interstitial cell adenoma	0	NA	2	NA	1	NA	2	NA	
<b>Prostate:</b>									
Adenocarcinoma (malignant)	0	NA	1	NA	0	NA	0	NA	
<b>Ovary:</b>									
Cystadenoma	NA	0	NA	0	NA	0	NA	1	
Granulosa cell tumor	NA	0	NA	0	NA	1	NA	0	
<b>Thyroid:</b>									
Follicular cell adenoma	3	0	1	0	0	1	7	0	
Follicular cell carcinoma (malignant)	0	0	0	0	0	0	4**	1	
Total no. neoplastic lesions in thyroid	3	0	1	0	0	1	11***	1	
C-cell adenoma	2	2	7	5	5	2	4	1	
C-cell carcinoma (malignant)	1	0	2	1	1	0	1	2	
<b>Adrenals:</b>									
Cortical adenoma	2	0	0	0	1	0	0	0	
Pheochromocytoma	5	0	4	0	2	1	1	1	
Pheochromocytoma (malignant)	2	0	1	0	1	0	0	0	

\*\* p<0.01 (p = 0.006); \*\*\* p<0.001 (using Fisher's) with time to tumour analysis test (Peto's test)

2.6.7.10D Carcinogenicity	Report No. [KOW 13/971903] (continued)								Page 7 of 9
	Daily Dose (mg/kg/day)	0 (Control)		1		5		25	
Number of Animals	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	
<b>Neoplastic Lesions - Number of Animals cont.</b>									
<b>Pituitary:</b>									
Adenoma <i>pars distalis</i>	30	36	22	28	12	33	32	27	
Adenocarcinoma <i>pars distalis</i> (malignant)	0	3	1	1	1	3	0	1	
Adenoma <i>pars intermedia</i>	0	0	0	0	0	0	1	0	
<b>Mammary gland:</b>									
Fibroadenoma	0	29	1	27	3	33	1	28	
Fibroadenoma with atypia	0	1	0	0	0	0	0	0	
Fibroma	0	0	0	2	1	1	1	4	
Adenoma	0	5	0	5	0	2	0	3	
Adenoma with atypia	0	0	0	0	0	1	0	0	
Adenocarcinoma (malignant)	0	6	0	5	2	6	0	0	
<b>Lymphoid system:</b>									
Pleomorphic lymphoma (malignant)	0	0	0	1	0	0	1	0	
Lymphoblastic/lymphocytic lymphoma (malignant)	1	0	0	0	1	0	0	1	
Malignant lymphoma (malignant)	0	0	0	0	1	0	0	0	
Histiocytic sarcoma (malignant)	2	1	0	1	1	0	1	0	
Lymphoid leukaemia (malignant)	2	0	1	0	1	0	2	0	
Fibrous histiocytic sarcoma (malignant)	1	0	0	0	0	0	0	1	
<b>Lymph node - mesenteric:</b>									
Haemangioma	0	0	0	0	2	0	0	0	
<b>Lymph node - mediastinal:</b>									
Haemangioma	0	0	0	1	0	0	0	0	
<b>Parathyroid:</b>									
Adenoma	0	0	1	0	0	0	0	0	
<b>Skeletal muscle:</b>									
Fibroma	0	0	0	0	0	0	1	0	

2.6.7.10D Carcinogenicity	Report No. [KOW 13071903] (continued)						Page 8 of 9	
	0 (Control)		1		5		25	
Daily Dose (mg/kg/day)								
Number of Animals	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55
<b>Neoplastic Lesions - Number of Animals cont.</b>								
<b>Skin:</b>								
Keratinocanthoma	3	0	0	0	0	0	0	0
Squamous cell papilloma	0	0	2	0	1	0	0	0
Squamous cell carcinoma (malignant)	0	0	0	1	0	0	0	0
Fibroma	6	0	7	1	5	0	8	1
Basophilic squamous cell carcinoma (malignant)	0	0	0	0	1	0	0	0
Basal cell carcinoma (malignant)	0	1	0	0	0	0	0	0
<b>Subcutaneous tissue:</b>								
Fibroma	9	1	9	2	15	3	9	5
Fibrosarcoma (malignant)	1	0	0	0	1	0	1	0
Lipoma	2	0	1	0	2	2	4	0
Rhabdomyosarcoma (malignant)	0	1	1	0	0	0	0	0
Osteosarcoma (malignant)	0	0	0	1	0	0	0	0
<b>Brain:</b>								
Astrocytoma (malignant)	1	0	0	0	1	0	0	0
Mixed glioma	0	0	0	0	0	1	0	0
<b>Head:</b>								
Zymbal gland - squamous cell carcinoma (malignant)	0	0	0	0	0	0	1	0
Osteosarcoma (malignant)	0	0	0	0	1	0	0	0
Pinna of ear - fibrosarcoma (malignant)	1	0	0	0	0	0	0	0
<b>Bone:</b>								
Osteoma	0	0	0	0	1	0	0	0
<b>Tail:</b>								
Squamous cell papilloma	0	0	1	0	0	0	0	0
Myxoma	1	0	0	0	0	0	0	0

2.6.7.10D Carcinogenicity	Report No. [KOW 13071903] (continued)						Page 9 of 9	
	0 (Control)		1		5		25	
Daily Dose (mg/kg/day)								
Number of Animals	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55	M: 55	F: 55
<b>Neoplastic Lesions - Number of Animals cont.</b>								
<b>Paws</b>								
Fibrosarcoma (malignant)	0	0	0	0	1	0	0	0
<b>Larynx</b>								
Rhabdomyosarcoma (malignant)	0	0	0	0	0	1	0	0
<b>Cervix</b>								
Fibroma	NA	0	NA	0	NA	1	NA	0
<b>Vagina</b>								
Squamous cell papilloma	NA	1	NA	0	NA	0	NA	1
Squamous cell carcinoma (malignant)	NA	0	NA	1	NA	0	NA	0
<b>Abdominal cavity</b>								
Fibrosarcoma (malignant)	0	1	0	0	0	0	0	0
<b>Spinal cord</b>								
Astrocytoma (malignant)	1	0	0	0	0	0	0	0
<b>Stomach<sup>a</sup></b>								
Squamous cell papilloma <sup>b</sup>	0	0	0	0	1	0	5 <sup>##</sup>	0
Squamous cell carcinoma <sup>b</sup>	0	0	0	0	0	0	2	0
Total (squamous cell papilloma and squamous cell carcinoma) <sup>b</sup>	0	0	0	0	1	0	7 <sup>###</sup>	0
<b>Total no. clinically observed masses<sup>c</sup></b>	<b>81</b>	<b>89</b>	<b>70</b>	<b>85</b>	<b>73</b>	<b>97</b>	<b>91</b>	<b>79</b>

a: Summary of results from the Pathology Working Group as included in [EPL 668-001A]02]

b: [RF2001/037] (additional statistical analysis using Peto's test on dose dependency and Fisher's test on the comparison between the control group and each pitavastatin group): ##: p<0.01; ###: p<0.001; using Peto's test; \*: p<0.05 using Fisher's test

c: Benign and malignant

2.6.7.10E Carcinogenicity		Test Article: Pitavastatin		Page 1 of 3	
<b>Report Title:</b> Study on the promoting effect of NK-104 on development of thyroid tumours in rats pre-treated with N-bis (2-hydroxypropyl) nitrosamine					
<b>Species/Strain:</b> C57BL/6J male rats		<b>Duration of Dosing:</b> Once daily for 15 weeks (105 days)		<b>Report No.:</b> [G2523]	
<b>Initial Age:</b> 6 weeks		<b>Method of Administration:</b> Oral (gavage) at 5 mL/kg		<b>Location in CTD:</b>	
<b>Date of First Dose:</b> 21 October 1998		<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution		<b>Vol.:</b> * <b>Section:</b> *	
<b>Treatment of Controls:</b> Negative Controls		0.5% sodium carboxymethyl cellulose solution;		<b>GLP Compliance:</b> Yes	
Positive Controls		Phenobarbital			
<b>Study Design:</b> The rats (6 weeks old at study start) were given N-bis (2-hydroxypropyl) nitrosamine (DHPN) i.p. once weekly for 5 weeks (initiation phase). Seven days after the last dose of DHPN administration with pitavastatin was initiated (rats aged 11 weeks; promotion phase). The study design is summarised below.					
<b>Study Design</b>					
<b>Dose Group</b>	<b>Dose mg/kg</b>	<b>DHPN Initiator (700 mg/kg i.p.: 10 mL/kg)</b>	<b>L-thyroxine (0.3 mL/rat; subcutaneous; 7.5 or 15 µg/rat)</b>		
Control	0	Yes	No		
Pitavastatin	1	Yes	No		
Pitavastatin	5	Yes	No		
Pitavastatin	25	Yes	No		
Pitavastatin	25	Yes	Yes (7.5 µg/rat)		
Pitavastatin	25	Yes	Yes (15 µg/rat)		
Pitavastatin	25	No (saline)	No		
Phenobarbital	80	Yes	No		

\*: Not applicable to an electronic submission

2.6.7.10E Carcinogenicity		Report No. [G2523] (continued)							Page 2 of 3
Daily Dose (mg/kg)	Q (Control)	1	5	25	25 (7.5 µg/rat L-thyroxine)	25 (15 µg/rat L-thyroxine)	25 (no DHPN initiation)	80 Phenobarbital	
Number of Animals and Gender	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	
Toxicokinetics	ND	ND	ND	ND	ND	ND	ND	ND	
<b>Noteworthy Findings</b>									
Died or Sacrificed Moribund	0	1 (Day 101)	0	1 (Day 129)	0	0	0	1 (Day 141)	
Body Weight (g) <sup>a</sup>	658	-1	-7	-7	-9*	-10**	-6	-6	
Clinical Observations <sup>b</sup>	-	-	-	-	-	-	-	-	
Organ Weights (adjusted) <sup>c</sup>									
Thyroid (mg)	42	+2	+5	+29**	-12	-29**	+17	+67***	
Liver (g)	23	0	-5	-13*	-13*	-15*	-8	+24*	
<b>Gross Pathology (No. of animals with finding)</b>									
Thyroid Nodule	2	2	2	4	2	0	0	5	
Liver Swelling	0	0	1	1	0	0	0	6	

a: At the end of the dosing period (at scheduled necropsy). For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).  
 b: Clinical signs only observed in animals that subsequently died; emaciation, decrease in locomotor activity, abnormal gait, weakness, inability to stand, prone position (lateral recumbency), hyperthermia, swelling of the forelimb, staining around perineum and hematuria observed in one or more rats  
 \*: p≤0.05; \*\*: p≤0.01; \*\*\*: p≤0.001. Statistical analysis was conducted using Dunnett's test  
 -: No noteworthy findings

2.6.7.10E Carcinogenicity		Report No. [G2523] (continued)							Page 3 of 3
Daily Dose (mg/kg)	Q (Control)	1	5	25	25 (7.5 µg/rat L-thyroxine)	25 (15 µg/rat L-thyroxine)	25 (no DHPN initiation)	80 Phenobarbital	
Number of Animals and Gender	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	M: 20	
<b>Noteworthy Findings cont.</b>									
<b>Histopathology</b>									
Number Animals Examined	20	19	20	19	20	20	20	20	
<b>Thyroid</b>									
Cyst	5	7	6	10	3	0*	0*	12*	
Hypertrophy, follicle, diffuse	0	0	0	5*	0	0	5*	9**	
Dilated follicle, diffuse	0	0	0	0	4	15**	0	0	
Follicular cell hyperplasia	12	12	14	18*	4*	0**	0**	19**	
Follicular cell adenoma	6	3	7	6	1*	0*	0*	12	
Follicular cell carcinoma (malignant)	1	0	2	1	2	0	0	6*	
Number Animals Examined	20	19	20	19	19	20	20	19	
<b>Liver</b>									
Hepatocytes, centrilobular swelling (++)	0	0	0	0	0	0	0	19	
Hepatocytes, ground glass appearance (++)	0	0	0	0	0	0	0	19	
Invasion of mononuclear tumour cells (+++)	0	0	0	0	1	0	0	1	

\*: p≤0.05; \*\*: p≤0.01. Statistical analysis was conducted using Dunnett's test  
 Histopathology severity: ++: Moderate; +++: Marked

## Reproductive Toxicology – Tabulated Summary

### Segment I

2.6.7.12A Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation		Test Article: Pitavastatin				Page 1 of 5			
<b>Report Title:</b> Reproductive and developmental toxicity study of NK-104 in rats administered orally prior to and in the early stages of pregnancy (Seg. 1)									
<b>Design similar to ICH 4.1.1? Yes</b>		<b>Duration of Dosing:</b> Males: daily for 70 days prior to mating, throughout the mating period and until the day before necropsy (97 or 98 days); Females: daily for 14 days prior to mating, throughout the mating period and until GD7.				<b>Report Nos.:</b> [KW92083] and [2000KW100]*			
<b>Species/Strain:</b> Crj:CD(SD) rats		<b>Day of Mating:</b> GD0				<b>Location in CTD:</b>			
<b>Initial Age:</b> ca. 10 weeks (F) and ca. 6 weeks (M) at start of treatment.		<b>Day of C-Section:</b> GD20				<b>Vol.:</b> *			
<b>Date of First Dose:</b> 22 September 1992 (M); 17 November 1992 (F)		<b>Method of Administration:</b> Oral (gavage) at 2 mL/kg				<b>Section:</b> *			
<b>Special Features:</b> None		<b>Vehicle/Formulation:</b> 0.5% CMC solution				<b>GLP Compliance:</b> Yes			
<b>No Observed Adverse-Effect Level:</b> F <sub>0</sub> Males: 10 mg/kg/day; F <sub>0</sub> Females: 10 mg/kg/day; F <sub>1</sub> Litters: 30 mg/kg									
<b>Daily Dose (mg/kg/day)</b>		0		2		10		30 <sup>b</sup>	
<b>No. of Animals and Gender</b>		M: 24 F: 24		M: 24 F: 24		M: 24 F: 24		M: 24 F: 24	
<b>Toxicokinetics</b>		ND		ND		ND		ND	
<b>Treated Males:</b>									
<b>No. Animals Evaluated</b>		24		24		24		24	
<b>No. Died or Sacrificed Moribund</b>		0		0		0		3 <sup>c</sup>	
<b>Body Weight (g)<sup>d</sup></b>		567		-3		-2		-6	
<b>Food Consumption (g)<sup>e</sup></b>		30.8		-4		-4		-8	

\*: Not applicable to an electronic submission; a: A histopathological examination of the testis and epididymis from the treated male rats was conducted and reported separately. The results are incorporated into the tabulated format; b: Male animals were dosed at 50 mg/kg on Days 1 to 35 of administration and at 30 mg/kg thereafter; the dose was reduced due to mortality; c: Deaths occurred on Days 14, 21 and 23 of administration whilst the animals were receiving daily doses at 50 mg/kg; d: Day 92 of the dosing period. For controls, group mean is shown. For treated groups, percent differences from controls are shown. In the high dose group (50 mg/kg on Days 1 to 35 and 30 mg/kg thereafter) body weight was significantly decreased as compared to the control group on Days 8, 15, 22, 29, 36, 43 and 50. [RT2002/2502] also detected significant decreases in body weight using Dunnett's test in the high dose group on Days 57 and 71; e: Days 64 to 71 of the dosing period. For controls, group mean is shown. For treated groups, percent differences from controls are shown. In the high dose group (50 mg/kg on Days 1 to 35 and 30 mg/kg thereafter) food consumption was significantly decreased as compared to the control group for dosing periods 1 to 8, 8 to 15, 15 to 22, 22 to 29, 29 to 36 and 57 to 64

2.6.7.12A Reproductive and Developmental Toxicity cont. - Fertility and Early Embryonic Development to Implantation		Report Nos.: [KW920R3] and [2000KW100] <sup>a</sup> (continued)			Page 2 of 5			
Daily Dose (mg/kg/day)	0 (Control)				2	10	30 <sup>b</sup>	
<b>Treated Males cont.:</b>								
No. Animals Evaluated	24				24	24	24	
No. Died or Sacrificed Moribund	0				0	0	3 <sup>c</sup>	
<b>Clinical Observations (Survivors)</b>								
Loss of hair on neck or around the nose	2				0	1	2	
Crust formation on neck or around the nose	2				0	1	1	
Flushing of the auricles, extremities and tail	1				0	0	0	
Salivation	0				0	0	1	
<b>Clinical Observations (Decedents)</b>								
Decreased locomotor activity	NA				NA	NA	3	
Soiling of hair and/or around eyes	NA				NA	NA	3	
Red soiling around eyes	NA				NA	NA	1	
Piloerection	NA				NA	NA	1	
Decreased faeces	NA				NA	NA	2	
<b>Necropsy Findings (Scheduled)</b>								
Stomach	Forestomach - white discoloration				0	0	0	11
	Forestomach - thickening				0	0	0	11

a: A histopathological examination of the testis and epididymis from the treated male rats was conducted and reported separately. The results are incorporated into the tabulated format  
 b: Male animals were dosed at 50 mg/kg on Days 1 to 35 of administration and at 30 mg/kg thereafter; the dose was reduced due to mortality.  
 c: Deaths occurred on Days 14, 21 and 23 of administration whilst the animals were receiving daily doses at 50 mg/kg

2.6.7.12A Reproductive and Developmental Toxicity cont. - Fertility and Early Embryonic Development to Implantation		Report Nos.: [KW920R3] and [2000KW100] <sup>a</sup> (continued)			Page 3 of 5			
Daily Dose (mg/kg/day)	0 (Control)				2	10	30 <sup>b</sup>	
<b>Treated Males cont.:</b>								
No. Animals Evaluated (No. Died or Sacrificed Moribund)	24 (0)				24 (0)	24 (0)	24 (3)	
<b>Necropsy Findings (Decedents)</b>								
	Brain	Subdural bleeding			NA	NA	NA	1
	Lungs	Congestion			NA	NA	NA	1
	Stomach	Forestomach - white discoloured area			NA	NA	NA	2
		Forestomach - erosions			NA	NA	NA	1
		Forestomach - bleeding			NA	NA	NA	1
<b>Organ Weights</b>								
		ND			ND	ND	ND	ND
<b>Histopathology (Survivors only)<sup>c</sup></b>								
	Testis	-			-	-	-	-
	Epididymis	Granulomatous lesions in serosa (+)			1	0	0	0
		Cellular infiltration in serosa, mainly lymphocytes local (+)			1	0	0	0
		Cellular infiltration in interstitium, lymphocytes			0	1	0	0
No. Animals Evaluated	24				24	24	21	
<b>Sperm Analysis<sup>d</sup></b>								
	Stage I-II	-			-	-	-	-
	Stage VII-VIII	-			-	-	-	-
	Stage IX-XI <sup>e</sup>	Spermatids (elongated)			123	116	110	112**
	Repeat Stage IX-XI <sup>e</sup> assessment	Spermatids (elongated)			114	ND	ND	113
	Stage XII <sup>f</sup>	Spermatids (elongated)			138	129	120	125*

a: A histopathological examination of the testis and epididymis from the treated male rats was conducted and reported separately. The results are incorporated into the tabulated format  
 b: Male animals were dosed at 50 mg/kg on Days 1 to 35 of administration and at 30 mg/kg thereafter; the dose was reduced due to mortality  
 c: Mean number of cells  
 \*: p<0.05; \*\*: p<0.01 using Bartlett's, Dunnett's or Welch's t-test in which Bonferroni's arrangement was performed was used  
 -: No noteworthy findings; Histopathology severity: +: Slight

2.6.7.12A Reproductive and Developmental Toxicity cont. - Fertility and Early Embryonic Development to Implantation		Report Nos.: [KW920R3] and [2000KW100] <sup>a</sup> (continued)			Page 4 of 5		
Daily Dose (mg/kg/day)	0 (Control)				2	10	30 <sup>b</sup>
<b>Treated Females:</b>							
No. Evaluated	24				24	24	24
No. Died or Sacrificed Moribund	0				0	0	0
<b>Clinical Observations</b>							
	-				-	-	-
<b>Necropsy Observations</b>							
	-				-	-	-
Premating Body Weight (g) <sup>c</sup>	251				+1	+1	0
Gestation Body Weight (g) <sup>d</sup>	402				+1	+1	-1
Premating Food Consumption (g) <sup>e</sup>	21.1				+1	+1	-2
Gestation Food Consumption (g) <sup>f</sup>	26.9				+4	0	+1
<b>Reproductive Function of Treated Males:</b>							
No. Animals Evaluated	24				24	24	24
No. Died or Sacrificed Moribund	0				0	0	3 <sup>g</sup>
No. Males Paired	24				24	24	21
No. of Males that Mated (1 <sup>st</sup> mating and 2 <sup>nd</sup> mating periods combined)	23				24	24	21
Copulation Index (%)	95.8				100	100	100
No. of Fertile Males (1 <sup>st</sup> mating and 2 <sup>nd</sup> mating periods combined)	23				23	23	21
Male Fertility Index (%)	100				95.8	95.8	100

a: A histopathological examination of the testis and epididymis from the treated male rats was conducted and reported separately. The results are incorporated into the tabulated format  
 b: Male animals were dosed at 50 mg/kg on Days 1 to 35 of administration and at 30 mg/kg thereafter; the dose was reduced due to mortality.  
 c: Day 15 of dosing period prior to mating. For controls, group mean is shown. For treated groups, percent differences from controls are shown.  
 d: Day 20 of gestation. For controls, group mean is shown. For treated groups, percent differences from controls are shown  
 e: Days 11 to 15 of dosing period. For controls, group mean is shown. For treated groups, percent differences from controls are shown  
 f: Days 17 to 20 of gestation. For controls, group mean is shown. For treated groups, percent differences from controls are shown  
 g: Deaths occurred on Days 14, 21 and 23 of administration whilst the animals were receiving daily doses at 50 mg/kg  
 -: No noteworthy findings

2.6.7.12A Reproductive and Developmental Toxicity cont. - Fertility and Early Embryonic Development to Implantation		Report No.: [K W92083] and [2000KW100] (continued)				Page 5 of 5
Daily Dose (mg/kg/day)	0 (Control)	2	10	30		
<b>Reproductive Function of Treated Females:</b>						
No. Evaluated	24	24	24	24		
No. Died or Sacrificed Moribund	0	0	0	0		
No. of Females Inseminated (1 <sup>st</sup> mating and 2 <sup>nd</sup> mating periods combined)	24	24	24	24		
Mean No. Oestrous Cycles	3.1	3.1	3.2	3.0		
Copulation Index (%)	100	100	100	100		
Mean No. of Days Prior to Mating	Not stated	Not stated	Not stated	Not stated		
No. of Pregnant Females	24	23	23	24		
Female Fertility Index (%)	100	95.8	95.8	100		
No. Aborted or with Total Resorption of Litter	0	0	0	0		
Mean No. Corpora Lutea	18.3	18.0	18.5	17.3		
Mean No. Implantations	16.7	16.5	17.3	15.8		
Implantation Rate (%)	91.3	92.0	93.9	91.8		
Mean % Pre-implantation Loss	8.7	8.0	6.1	8.2		
Mean No. Live Conceptuses	15.4	15.5	16.3	14.7		
Sex Ratio (% male)	49.3	53.9	49.3	53.0		
Total No. Post-implantation Loss (dead foetuses)	31	24	24	27		
Mean % Post-implantation Loss	7.8	6.3	6.0	7.1		
Foetal Body Weight (g) <sup>b</sup>	3.49	+1	+1	-1		
No. Live Foetuses with External Anomalies	1 <sup>c</sup>	2 <sup>d</sup>	0	0		
No. Abnormal Placentae	0	0	0	0		

- a: A histopathological examination of the testis and epididymis from the treated male rats was conducted and reported separately. The results are incorporated into the tabulated format
- b: For controls, group means are shown. For treated groups, percent differences from controls are shown.
- c: Vestigial tail
- d: One foetus with micrognathia and open eyelids and a 2<sup>nd</sup> foetus with general oedema

2.6.7.12B Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation		Test Article: Pitavastatin	Page 1 of 6
<b>Report Title:</b> Study on effects of oral administration of NK-104 on fertility and early embryonic development to implantation in rabbits			
<b>Design similar to ICH 4.1.1? Yes</b>	<b>Duration of Dosing:</b> Daily for 28 days prior to mating; throughout the mating period (up to 14 days) and until GD6 (M: total of 42 days dosing; F: a total of 37 days dosing for animals that mated or 42 days for animals that did not mate)		<b>Report No.:</b> [160320]
	<b>Day of Mating:</b> GDO		<b>Location in CTD:</b>
<b>Species/Strain:</b> Kbl:JW rabbits	<b>Day of C-Section:</b> GD28		<b>Vol.:</b> *
<b>Initial Age:</b> ca. 12 weeks (virgin females) and ca. 15 weeks (virgin males) at start of treatment.	<b>Method of Administration:</b> Oral (gavage) at 2 mL/kg		<b>Section:</b> *
<b>Date of First Dose:</b> 9 July 2001	<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution		<b>GLP Compliance:</b> Yes
<b>Special Features:</b> None			
<b>No Observed Adverse-Effect Level:</b> F <sub>0</sub> Males: 0.5 mg/kg/day; F <sub>0</sub> Females: 0.5 mg/kg/day; F <sub>1</sub> Litters: 2.0 mg/kg			
<b>Daily Dose (mg/kg/day)</b>	0		0.5
<b>Toxicokinetics</b>	M: 16	F: 16	M: 16
<b>C<sub>max</sub> (ng/mL) Day 1 of dosing</b>	NA	NA	392
<b>C<sub>max</sub> (ng/mL) after repeated dosing<sup>a</sup></b>	NA	NA	457
<b>AUC (ng*hr/mL) Day 1 of dosing</b>	NA	NA	2255
<b>AUC (ng*hr/mL) after repeated dosing<sup>a</sup></b>	NA	NA	2023
			2648
			4758
			4478
			8443
			7585
<b>Treated Males:</b>			
No. Animals Evaluated	16	16	16
No. Died or Sacrificed Moribund	0	0	3 <sup>b</sup>
Body Weight (kg) <sup>c</sup>	3.44	-1	-1
			+6

- \*: Not applicable to an electronic submission
- a: Males on Day 42 of administration (end of mating period) and in females on Day 28 of administration prior to mating period
- b: Deaths occurred on Days 19, 20 and 22 of administration.
- c: Deaths occurred on Days 16, 19 (two animals), 23 (two animals), 27, 39; two animals sacrificed moribund on Days 20 and 23 of administration.
- d: Scheduled necropsy (Day 43). For controls, group mean is shown. For treated groups, percent differences from controls are shown.

2.6.7.12B Reproductive and Developmental Toxicity cont. – Fertility and Early Embryonic Development to Implantation		Report No.: [100320] (continued)			Page 2 of 6
Daily Dose (mg/kg/day)		0 (Control)	0.5	1.0	2.0
<b>Treated Males cont.:</b>					
No. Animals Evaluated		16	16	16	16
No. Died or Sacrificed Moribund		0	0	3 <sup>b</sup>	9 <sup>c</sup>
Food Consumption Day 16 of Dosing (g) <sup>d</sup>		153	-7	-22*	-31*
Food Consumption Day 23 of Dosing (g) <sup>d</sup>		156	-4	-5	-8
Clinical Observations (Decedents/Moribund Animals only)					
Decreased locomotor activity		-	-	Present	Present
Prone position		-	-	Present	Present
Hypothermia		-	-	Present	Present
Bradypnoea		-	-	Present	Present
Serum Chemistry <sup>d</sup>					
Total cholesterol (mg/dL)	Day 15 of dosing	27.6	-20	-18	-13*
Total cholesterol (mg/dL)	Day 28 of dosing	25.6	-18	-20	-33*
No. Animals Examined		16	16	13	7
Necropsy Findings (Scheduled)					
No. Animals Examined		0	0	3	9
Necropsy Findings (Decedents)					
Stomach	Dark red spot on mucosa	NA	NA	0	1
Kidney	White in colour	NA	NA	3	9

a: For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on percent differences)

b: Deaths occurred on Days 19, 20 and 22 of administration.

c: Deaths occurred on Days 16, 19 (two animals), 23 (two animals), 27, 39; two animals sacrificed moribund on Days 20 and 23 of administration.

d: For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on percent differences)

-: No noteworthy findings

\*: p<0.05 using Bartlett's or Dunnett's tests

2.6.7.12B Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation		Report No.: [100320] (continued)			Page 3 of 6
Daily Dose (mg/kg/day)		0 (Control)	0.5	1.0	2.0
<b>Treated Males cont.:</b>					
No. Animals Examined		16	16	13	7
Organ Weights (Scheduled Necropsy)					
Histopathology (Scheduled Necropsy)					
Testis (seminiferous tubule)	Multinucleated giant cell formation (± to ++)	6	6	3	2
	Degeneration (± to +)	9	4	1	0
	Atrophy (± to +++)	3	5	4	2
Epididymis	Desquamated cell debris in lumen (± to ++)	14	14	8	6
Prostate	Cellular infiltration, lymphoid cell (+)	1	0	0	0
	Hyperplasia, epithelium (± to +)	2	3	4	0
Sperm Analysis					
		-	-	-	-
<b>Treated Females:</b>					
No. Evaluated		16	16	16	16
No. Died or Sacrificed Moribund		0	0	1*	6 <sup>c</sup>
Clinical Observations (Decedents/Moribund Animals only)					
Decreased locomotor activity		-	-	Present	Present
Prone position		-	-	Present	Present
Hypothermia		-	-	Present	Present
Bradypnoea		-	-	-	Present
Prenatal Body Weight (kg) <sup>e</sup>		3.22	-2	-2	-1
Gestation Body Weight (kg) <sup>f</sup>		3.66	0	0	-1

a: Death on Day 28 of administration

b: Deaths on Days 20, 22 and 23 of administration; animals sacrificed moribund on Days 23, 25, and 28 of administration

c: Day 29 (prior to mating). For controls, group mean is shown. For treated groups, percent differences from controls are shown

d: GD28. For controls, group mean is shown. For treated groups, percent differences from controls are shown

-: No noteworthy findings

Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Marked

2.6.7.12B Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation		Report No.: [100320] (continued)			Page 4 of 6
Daily Dose (mg/kg/day)		0 (Control)	0.5	1.0	2.0
<b>Treated Females cont.:</b>					
No. Evaluated		16	16	16	16
Prenatal Food Consumption (g) <sup>d</sup>		187	-10*	-13*	-13
Gestation Food Consumption (g) <sup>e</sup>		128	+6	-9	-18
Serum Chemistry <sup>d</sup>					
Total cholesterol (mg/dL)	Day 15 of dosing	46.4	-20**	-26**	-31**
Total cholesterol (mg/dL)	Day 28 of dosing	50.8	-26**	-34**	-21**
No. Animals Examined		16	16	15	10
Necropsy Findings (Scheduled)					
No. Animals Examined		0	0	1	6
Necropsy Findings (Decedents)					
Liver	White spot	NA	NA	0	1
Kidney	White in colour	NA	NA	1	5
Organ Weights (Scheduled Necropsy)					
		-	-	-	-

a: Day 26 (prior to mating). For controls, group mean is shown. For treated groups, percent differences from controls are shown. Food consumption significantly decreased on Days 9 and 12 for 1.0 mg/kg group and on Days 9, 12 and 16 for the 2 mg/kg dose group

b: GD28. For controls, group mean is shown. For treated groups, percent differences from controls are shown

c: For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on percent differences)

-: No noteworthy findings

\*: p<0.05; \*\*: p<0.01 using Bartlett's or Dunnett's tests

2.6.7.12B Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation		Report No.: [100320] (continued)			Page 5 of 6
Daily Dose (mg/kg/day)	0 (Control)	0.5	1.0	2.0	
<b>Reproductive Function of Treated Males:</b>					
No. Animals Evaluated	16	16	16	16	
No. Died or Sacrificed Moribund	0	0	3 <sup>a</sup>	9 <sup>b</sup>	
No. of Males that Mated	16	16	12	7 <sup>c</sup>	
1 <sup>st</sup> mating	NA	NA	1 <sup>d</sup>	1 <sup>d</sup>	
2 <sup>nd</sup> mating	NA	NA	1 <sup>d</sup>	1 <sup>d</sup>	
Copulation Index (%)	100	100	100	100	
No. of Fertile Males	14	15	11 (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	7 (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	
Male Fertility Index (%)	87.5	93.8	84.6	87.5	
<b>Reproductive Function of Treated Females:</b>					
No. Evaluated	16	16	16	16	
No. Died or Sacrificed Moribund	0	0	1 <sup>e</sup>	6 <sup>e</sup>	
No. of Females Inseminated	16	16	12	7	
1 <sup>st</sup> mating	NA	NA	2	3	
2 <sup>nd</sup> mating	NA	NA	2	3	
Mean No. Oestrous Cycles	Not stated	Not stated	Not stated	Not stated	
Copulation Index (%)	100	100	93.3	100	
Mean No. of Days Prior to Mating	1.1	1.1	1.2	1.1	
No. of Pregnant Females	14	15 <sup>a</sup>	12 <sup>b</sup> (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	9 (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	
Female Fertility Index (%)	87.5	93.8	85.7	90.0	

a: Deaths occurred on Days 19, 20 and 22 of administration.  
 b: Deaths occurred on Days 16, 19 (two animals), 23 (two animals), 27, 39; two animals sacrificed moribund on Days 20 and 23 of administration.  
 c: One animal died on Day 39 during the mating period  
 d: Mated with non-treated female  
 e: Death on Day 28 of administration  
 f: Deaths on Days 20, 22 and 23 of administration; animals sacrificed moribund on Days 23, 25, and 28 of administration; g: Excludes one dam as only implantation scars were noted

2.6.7.12B Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation		Report No.: [100320] (continued)			Page 6 of 6
Daily Dose (mg/kg/day)	0 (Control)	0.5	1.0	2.0	
<b>Reproductive Function of Treated Females cont.:</b>					
No. of Pregnant Females	14	15 <sup>a</sup>	12 <sup>b</sup> (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	9 (1 <sup>st</sup> and 2 <sup>nd</sup> mating)	
No. Aborted or with Total Resorption of Litter	0	1 <sup>b</sup>	1 <sup>b</sup>	0	
Mean No. Corpora Lutea	9.7	9.8	9.8	9.1	
Mean No. Implantations	8.8	8.1	8.4	7.3	
Implantation Rate (%)	88.3	80.9	84.2	79.0	
Mean % Preimplantation Loss	11.7	19.2	15.8	21.0	
Mean No. Live Conceptuses	8.1	7.6	7.9	7.1	
Sex Ratio (% male)	48	57	42	40	
Mean No. Postimplantation Loss	0.6	0.4	0.5	0.2	
Mean % Postimplantation Loss	7.2	4.7	4.8	2.4	
Foetal Body Weight (g) - Males	36	0	+4	+4	
Foetal Body Weight (g) - Females	36	+2	+1	-1	
No. Foetus with External Anomalies	0	0	0	0	
No. Abnormal Placentae	0	0	0	0	

a: Excludes one dam as only implantation scars were noted  
 b: Dams excluded from analysis as only implantation scars were noted  
 c: For controls, group mean is shown. For treated groups, percent differences from controls are shown.

### Segment II

2.6.7.13A Reproductive and Developmental Toxicity - Effects on Embryo-fetal Development		Test Article: Pitavastatin			Page 1 of 5
<b>Report Title:</b> Study by oral administration of NK-104 during period of fetal organogenesis in rats (Segment II)					
<b>Design similar to ICH 4.1.3? Yes</b>		<b>Duration of Dosing:</b> GD7 to GD17		<b>Report No.:</b> [R102508]	
<b>Species/Strain:</b> Crj:CD(SD) rats		<b>Day of Mating:</b> GD0		<b>Location in CTD:</b>	
<b>Initial Age:</b> 11 (F) or 12 (M) weeks when mated		<b>Day of C-Section:</b> GD20		<b>Section:</b> *	
<b>Study Duration:</b> February to November 1994		<b>Method of Administration:</b> Oral (gavage) at 2 mL/kg		<b>Vol. *</b>	
<b>Special Features:</b> The dose groups were designed for 25 dams to undergo C-section on GD20 and 15 dams to spontaneously deliver. Pups were culled to 4/sex/litter on LD4 and subsequently culled to 2/sex/litter on LD21.		<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution		<b>GLP Compliance:</b> Yes	
<b>No Observed Adverse-Effect Level:</b> F <sub>0</sub> Females: 10 mg/kg/day F <sub>1</sub> Litters: 30 mg/kg/day					
<b>Daily Dose (mg/kg):</b>	0 (Control)	3	10	30	
<b>Pregnant Pairs/Dose C-section (Delivery):</b>	F:25 (15)	F:25 (15)	F:25 (15)	F:25 (15)	
Toxicokinetics <sup>a</sup>	ND	ND	ND	ND	
No. Died or Sacrificed Moribund	0	0	0	0	
No. Pregnant at GD20	22	23	23	23	
No. Delivered Spontaneously	13	14	14	15	
Clinical Observations	-	-	-	-	
Gestation Body Weight (g) <sup>b</sup>	418	0	-1	-3	
Gestation Body Weight Gain (GD0 to GD20; g) <sup>b</sup>	153	-1	-3	-10**	
Gestation Food Consumption (g) <sup>c</sup>	28	-4	-4	-4	
Lactation Body Weight (g) <sup>d</sup>	326	-2	-2	-3	
Lactation Food Consumption (g) <sup>d</sup>	80	-6	-6	-4	

\*: Not applicable to an electronic submission  
 a: Supportive toxicokinetics in rats orally dosed with pitavastatin at 1, 3 and 10 mg/kg from GD7 to GD17 presented in [R19932]. C<sub>max</sub> (ng/mL) and AUC (ng\*hr/mL) for 1 mg/kg/day on GD17 were 110 and 1250; for 3 mg/kg/day on GD17 530 and 3330 and for 10 mg/kg 1780 and 12620, respectively. Lactone was not detected in plasma.  
 b: At GD20. For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). Pregnant animals only. \*\*: p<0.01 using Scheffé's d-test; c: Statistically significant decrease (p<0.05 using Scheffé's d-test) in food consumption in the 30 mg/kg dose group on GD9 and GD14 and on GD13 using Dunnett's test [R12002/2502]  
 d: At L.D21. For controls, group mean is shown. For treated groups, percent differences from controls are shown.  
 -: No noteworthy findings.

2.6.7.13A Reproductive and Developmental Toxicity – Effects on Embryo-fetal Development	Report No.: [RF(2508)] (continued)				Page 2 of 5
Daily Dose (mg/kg/day):	0 (Control)	3	10	30	
Planned Dams/Dues C-section (Delivery):	F:25 (15)	F:25 (15)	F:25 (15)	F:25 (15)	
No. Pregnant at GD20	22	23	23	23	
Necropsy Observations (GD20)	-	-	-	-	
Necropsy Observations (LD21)	-	-	-	-	
Histopathology	ND	ND	ND	ND	
Mean No. Corpora Lutea	18.2	18.0	17.3	17.3	
Mean No. Implantations	16.5	16.3	16.1	14.9	
Total No. Dead Foetuses	16	16	23	10	
Implantation Site	0	0	0	0	
Early Resorption	14	15	23	9	
Late Resorption	2	1	0	1	
Dead Foetuses	0	0	0	0	
Mean No. Live Foetuses per Litter	15.8	15.7	15.1	14.4	
Pup Sex Ratios (% males)	52	48.9	49	48.5	
Body Weight (g) - Males <sup>a</sup>	3.36	+1	+5	+4	
Body Weight (g) - Females <sup>a</sup>	3.22	0	+3	+3	
No. Foetuses with External Anomalies	0	0	1 <sup>b</sup>	2 <sup>c</sup>	
No. Foetuses with Visceral Anomalies (%)	18 (10.7)	12 (6.9)	23 (13.6)	17 (10.6)	
No. Foetuses Examined	169	173	169	161	
Thymic remnant in neck (%)	15 (8.9)	10 (5.8)	18 (10.7)	13 (8.1)	
Dilatation of renal pelvis (%)	4 (2.4)	3 (1.7)	2 (1.2)	4 (2.5)	
Persistent left umbilical cord (%)	0	0	2 (1.2)	0	

a: For controls, group mean is shown. For treated groups, percent differences from controls are shown  
 b: Agnathia  
 c: Exencephaly and open eyelids; anal atresia and anury

2.6.7.13A Reproductive and Developmental Toxicity – Effects on Embryo-fetal Development	Report No.: [RF(2508)] (continued)				Page 3 of 5
Daily Dose (mg/kg/day):	0 (Control)	3	10	30	
Planned Dams/Dues C-section (Delivery):	F:25 (15)	F:25 (15)	F:25 (15)	F:25 (15)	
No. Foetuses with Skeletal Anomalies (%)	1 (0.6)	0	2 (1.1)	1 (0.6)	
No. Foetuses Examined	179	187	178	171	
No. Foetuses with Variations (%)	8 (4.5)	3 (1.6)	11 (6.2)	5 (2.9)	
Cervical rib (%)	0	1 (0.5)	3 (1.7)	2 (1.2)	
14 <sup>th</sup> rib (%)	1 (0.6)	2 (1.1)	1 (0.6)	0	
25 <sup>th</sup> presacral vertebrae (%)	4 (2.2)	0	1 (0.6)	1 (0.6)	
Splitting of vertebral bodies (%)	2 (1.1)	0	5 (2.8)	2 (1.2)	
No. Delivered Spontaneously	13	14	14	15	
No. of Dams with Live Newborns	13	14	14	15	
Gestation Index (%)	100	100	100	100	
Gestation Period (days)	22.1	22.0	22.0	22.0	
Mean No. Implantations per Litter	16.2	16.3	16.2	15.3	
Mean No. Live Newborns per Litter	13.6	14.8	14.7	13.3	
Mean No. Dead Newborns per Litter	1.6	0.4	0.4	0.7	
Birth Index (%)	85.4	91.6	90.7	86.8	
Live Foetal Sex Ratios (% males)	42.9	59.4	48.1	46.7	
Mean Foetal Body Weight: Males <sup>a</sup>	6.3 g	0	-3	-2	
Mean Foetal Body Weight: Females <sup>a</sup>	5.9 g	0	-2	-2	
No. Live Newborns with External Anomalies (%)	1 (0.5) <sup>b</sup>	1 (0.5) <sup>c</sup>	0	1 (0.5) <sup>b</sup>	
% Survival to LD4	87.8	98.7	91.3	89.9	
% Survival to LD21	100	100	100	100	

a: For controls, group means are shown. For treated groups, percent differences from controls are shown.  
 b: Anal atresia and anury  
 c: Short tail

2.6.7.13A Reproductive and Developmental Toxicity – Effects on Embryo-fetal Development	Report No.: [RF(2508)] (continued)				Page 4 of 5
Daily Dose (mg/kg/day):	0 (Control)	3	10	30	
Planned Dams/Dues C-section (Delivery):	F:25 (15)	F:25 (15)	F:25 (15)	F:25 (15)	
F <sub>1</sub> Generation:					
No. Litters Evaluated Postweaning	12	14	14	14	
Pup Physical Development <sup>a</sup>	-	-	-	-	
Pup Functional Development <sup>b</sup>	-	-	-	-	
Pup Behavioural Observations <sup>c</sup>	-	-	-	-	
Pup Skeletal Observations (LD21)	-	-	-	-	
No. Offspring Examined	48	56	52	56	
No. Offspring with Anomalies	0	0	0	0	
No. Offspring with Variations (%)	5 (10.4)	3 (5.4)	7 (13.3)	5 (8.9)	
Accessory sternbrae (%)	3 (6.3)	2 (3.6)	5 (9.6)	4 (7.1)	
Shortened 13 <sup>th</sup> rib (%)	0	1 (1.8)	0	0	
25 presacral vertebrae (%)	1 (2.1)	1 (1.8)	1 (1.9)	0	
Lumbarisation of 1st sacral vertebra (%)	1 (2.1)	1 (1.8)	0	0	
Irregular alignment of caudal vertebrae (%)	0	0	1 (1.9)	2 (3.6)	
No. Litters Evaluated Postweaning	12	14	14	14	
Pup Body Weights LD21 preculcating (g) - Males <sup>d</sup>	57	+2	-4	0	
Pup Body Weights LD21 preculcating (g) - Females <sup>d</sup>	56	-2	-1*	-4	
Pup Body Weights LD56 postculcating (g) - Males <sup>d</sup>	331	+5	+1	+7	
Pup Body Weights LD56 postculcating (g) - Females <sup>d</sup>	222	-3	+1	-2	
Pup Necropsy Observations (LD56)	-	-	-	-	
Organ Weights LD56 (total no. of pups)	-(24)	-(28)	-(27)	-(27)	
Histopathology	ND	ND	ND	ND	

a: Separation of auricular, appearance of hair, eruption of incisors, separation of eyelids, descent of testis, opening of vagina  
 b: Gait, corneal reflex, pain response, righting reflex, air righting reflex, prey reflex  
 c: Open field behaviour, rotarod performance, water maze  
 d: For controls, group mean is shown. For treated groups, percent differences from controls are shown. \*: p<0.05 using Scheffé's rank-test  
 -: No noteworthy findings

2.6.7.13A Reproductive and Developmental Toxicity – Effects on Embryo-foetal Development		Report No.: [RF/G2508] (continued)			Page 5 of 5
Daily Dose (mg/kg/day):	0 (Control)	3	10	30	
<b>F<sub>1</sub> Generation cont:</b>					
No. of Mated Animals Males/Females	12/12	14/14	13/13	14/14	
No. of Animals Successfully Mating (% Males/Females)	100/100	92.9/92.9	92.3/92.3	92.9/92.9	
No. of Males Successfully Impregnating Females (%)	100	100	83.3	100	
No. Pregnant Females	12	13	10	13	
Time of Copulation after Mating (days)	4.1	3.8	2.5	3.5	
Gestation Body Weight Gain (g) <sup>a</sup>	146	+3	+2	+5	
<b>F<sub>1</sub> Litters:</b>					
No. of Dams	11	12	10	13	
Mean No. Corpora Lutea per Litter	19.7	16.8	19.3	17.6	
Mean No. of Implantations per Litter	17.4	15.1	15.6	15.9	
Total No. Dead Foetuses (%)	16 (8.2)	8 (3.7)	13 (8.8)	18 (8.8)	
Implantation Site (%)	0	0	0	0	
Early Resorption (%)	15 (7.7)	8 (3.7)	12 (7.4)	16 (7.8)	
Late Resorption (%)	1 (0.6)	0	1 (1.4)	2 (1.0)	
Dead Foetuses (%)	0	0	0	0	
Mean No. Live Foetuses per Litter	15.9	14.4	14.3	14.5	
Pup Sex Ratios (% males)	50.3	54.3	45.5	47.6	
Body Weight (g) - Males <sup>b</sup>	3.26	+9	-5	+6	
Body Weight (g) - Females <sup>b</sup>	3.11	+9	-5	+6	
No. Foetuses with External Anomalies (%)	0	1 (0.6) <sup>d</sup>	0	1 (0.5) <sup>d</sup>	

a: GD0 to GD21. For controls, group mean is shown. For treated groups, percent differences from controls are shown. Pregnant animals only.  
b: For controls, group means are shown. For treated groups, percent differences from controls are shown.  
c: Epigastrius  
d: Exencephaly and myeloschisis

2.6.7.13B Reproductive and Developmental Toxicity – Effects on Embryo-foetal Development		Test Article: Pitavastatin		Page 1 of 4
<b>Report Title:</b> Study by oral administration of NK-104 during fetal organogenesis in rabbits (Segment II)				
<b>Design similar to ICH 4.1.3? Yes</b>	<b>Duration of Dosing:</b> GD6 to GD18		<b>Report No.:</b> [RF/G2507]	
	<b>Day of Mating:</b> GD0			
<b>Species/Strain:</b> Kbl:JW rabbits	<b>Day of C-Section:</b> GD29		<b>Location in CFB:</b>	
<b>Initial Age:</b> 16 weeks on arrival	<b>Method of Administration:</b> Oral (gavage) at 1 mL/kg		<b>Vol. *</b>	<b>Section: *</b>
<b>Study Duration:</b> September 1993 to May 1994	<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution		<b>GLP Compliance:</b> Yes	
<b>Special Features:</b> None				
<b>No Observed Adverse-Effect Level:</b> F <sub>1</sub> Females: 0.1 mg/kg/day F <sub>1</sub> Litters: 1.0 mg/kg/day (threshold)				
Daily Dose (mg/kg/day):	0 (Control)	0.1	0.3	1
Dams/Dose:	F:16	F:16	F:16	F:16
Toxicokinetics <sup>a</sup>	ND	ND	ND	ND
No. Died or Sacrificed Moribund	1 <sup>b</sup>	0	1 <sup>c</sup>	3 <sup>d</sup>
No. Not Pregnant	1	1	2	2
No. Pregnant	15	15	14	14
No. Pregnant at GD29 Necropsy	14	15	11 <sup>e</sup>	9 <sup>f</sup>
<b>Clinical Observations (no. of animals and day of obs.)</b>				
Decreased faeces	1 (G19-G21)	1 (G19-G22)	4 (G14-G26)	8 (G14-G29)
Vaginal bleeding	-	-	1 (G26)	1 (G26)
Weakness (no. animals)	-	-	-	1 (G23)
Body Weight (kg) <sup>g</sup>	4.17	-3	+3	-1
Food Consumption (g) <sup>g</sup>	133	-6	-3	-14

\*: Not applicable to an electronic submission  
a: Supportive toxicokinetics in rabbits orally dosed with pitavastatin at 0.1, 0.3 and 1 mg/kg from GD6 to GD18 presented in [G2526]. C<sub>max</sub> (ng/mL) and AUC (ng\*h/mL) for 0.1 mg/kg/day on GD18 were 81 and 607; for 0.3 mg/kg/day on GD18 295 and 2045 and for 1 mg/kg 1484 and 22538, respectively. For lactone the C<sub>max</sub> (ng/mL) and AUC (ng\*h/mL) for 0.1 mg/kg/day on GD18 were 2 and 12; for 0.3 mg/kg/day on GD18 6 and 60 and for 1 mg/kg 33 and 630.  
b: Dosing error GD15; c: Animal found dead on GD27; d: Deaths occurred on GD22, GD24 and GD28  
e: Two animals aborted (G1923 and G1927); f: Two animals aborted (G1921 and G1927)  
g: At GD29. For controls, group mean is shown. For treated groups, percent differences from controls are shown. Pregnant animals only  
-: No noteworthy findings

2.6.7.13B Reproductive and Developmental Toxicity – Effects on Embryo-foetal Development	Report No.: [RF(2507)] (continued)				Page 2 of 4
Daily Dose (mg/kg/day):	0 (Control)	0.1	0.3	1	
Dams/Dogs:	F:16	F:16	F:16	F:16	
No. Died or Sacrificed Moribund	1 <sup>a</sup>	0	1 <sup>b</sup>	3 <sup>c</sup>	
No. Not Pregnant	1	1	2	2	
No. Pregnant at (H)29 Necropsy	14	15	11 <sup>d</sup>	9 <sup>e</sup>	
Necropsy Observations	Scheduled Necropsy (Number of aborted or dead dams with abnormal findings)				
Kidneys: pale coloured	0	0	(2)	2 (5 <sup>f</sup> )	
Liver: pale coloured	1	1	0	2 (5 <sup>f</sup> )	
diffuse white areas	0	0	(1)	0	
accentuated lobular pattern	0	0	0	(4 <sup>g</sup> )	
Gallbladder: appearance of white material	0	0	(1)	1 (3 <sup>g</sup> )	
Lung: haemorrhage	(1)	0	0	0	
Trachea: haemorrhage	(1)	0	(1)	0	
Thoracic cavity: bloody hydrothorax	(1)	0	0	0	
Thymus: haemorrhage	0	0	0	(1)	
Colon: haemorrhage	0	0	(1)	0	
Stomach: haemorrhage glandular stomach	0	0	(1)	0	
petechia glandular stomach	0	0	0	(1)	
Mean No. Corpora Lutea	8.9	10.4	10.5	9.7	
Mean No. Implantations	6.7	8.5	8.8	8.3	
Mean % Pre-implantation Loss	0	0	0	0	

- a: Dosing error GD15
- b: Animal found dead on GD27
- c: Deaths occurred on (H)22, (H)24 and (H)28
- d: Two animals aborted (GD23 and GD27)
- e: Two animals aborted (G21 and G27)
- f: Includes one animal that aborted
- g: Includes the two animals that aborted

2.6.7.13B Reproductive and Developmental Toxicity – Effects on Embryo-foetal Development	Report No.: [RF(2507)] (continued)				Page 3 of 4
Daily Dose (mg/kg/day):	0 (Control)	0.1	0.3	1.0	
Histopathology					
Number of Animals Examined <sup>a</sup>	1	1	1	7	
Liver: Fatty deposition (large and fine droplets; + to +++)	0	1	1	7	
Fatty deposition (diffuse fine droplets; +++)	1	0	0	0	
Degeneration and/or necrosis (+ to +++)	0	0	1	4	
Calcification (± to +)	0	0	1	3	
Gallbladder: Necrosis of epithelial cells (+++)	0	0	1	4	
haemorrhagic necrosis epithelium (++)	0	0	0	1	
Number of Animals Examined <sup>a</sup>	0	0	2	7	
Kidney: Necrosis renal tubular epithelium (+++)	NA	NA	1	3	
Cast in renal tubules (+ to ++)	NA	NA	1	4	
Dilatation proximal tubules and flatness (± to +++)	NA	NA	1	5	
Calcification renal tubules (± to +++)	NA	NA	1	4	
Congestion (++)	NA	NA	0	1	
Perivascular cell infiltration (± to ++)	NA	NA	2	3	

- a: Only animals with necropsy findings were examined for histopathology
- Histopathology severity: ±: Slight; +: Mild; ++: Moderate; +++: Severe

2.6.7.13B Reproductive and Developmental Toxicity – Effects on Embryo-foetal Development	Report No.: [RF(2507)] (continued)				Page 4 of 4
Daily Dose (mg/kg/day):	0 (Control)	0.1	0.3	1.0	
Litters:					
No. Litters Evaluated	14	15	11	9	
No. Dead Foetuses	8	9	8	7	
No. Live Foetuses	86	118	89	68	
Mean No. Resorptions - Early	6	3	6	4	
Mean No. Resorptions - Late	2	6	2	3	
Mean % Postimplantation Loss	0	0	0	0	
Mean Foetal Body Weight (g): Males <sup>a</sup>	50.63	-15	-5	-10	
Mean Foetal Body Weight (g): Females <sup>a</sup>	47.63	-7	0	-10	
Live Foetal Sex Ratios (% males)	51	43	53	59	
Foetal Anomalies:					
Foetuses with any anomaly observed (external, visceral or skeletal)	1	2	2	0	
Total Number Foetuses Examined (Litters)	86 (14)	118 (15)	89 (11)	68 (9)	
Number with Gross External Anomalies (Litters)	0 (0)	0 (0)	0 (0)	0 (0)	
Total Number Foetuses Examined (Litters)	34 (14)	46 (15)	34 (11)	25 (9)	
Number with Soft Tissue Anomalies (Litters) <sup>b</sup>	0 (0)	2 (2)	2 (2)	0 (0)	
Total Number Foetuses Examined (Litters)	52 (13)	72 (15)	55 (11)	43 (9)	
Number with Skeletal Anomalies <sup>c</sup> (Litters)	1 (1)	0 (0)	0 (0)	0 (0)	
Number with Skeletal Variations <sup>c</sup> (Litters)	18 (8)	36 (13)	28 (9)	19 (7)	
13 <sup>th</sup> rib	17	35	27	17	
27 pre-sacral vertebrae	4	9	5	7	
Lumbarisation of 1 <sup>st</sup> sacral vertebrae	0	1	0	0	
Splitting of sternbrae	1	0	0	0	

- a: For controls, group mean is shown. For treated groups, percent differences from controls are shown.
- b: Thymic remnant in neck
- c: Absence of cervical vertebral arch

**Segment III**

<b>2.6.7.14A Reproductive and Developmental Toxicity – Effects on Pre- and Postnatal Development, Including Maternal Function</b>		<b>Test Article:</b> Pitavastatin			<b>Page 1 of 5</b>	
<b>Report Title:</b> Study by oral administration of NK-104 in rats during the perinatal and lactation periods (Segment III)						
<b>Design similar to ICH 4.1.27 Yes</b>		<b>Duration of Dosing:</b> GD17 to LD21			<b>Report No.:</b> [RF(2511)]	
		<b>Day of Mating:</b> GD0			<b>Location in CTD:</b>	
<b>Species/Strain:</b> Crj:CD(SD) rats		<b>Method of Administration:</b> Oral (gavage) at 2 ml/kg			<b>Vol.:</b> "	
<b>Initial Age:</b> 11 (F) to 12 (M) weeks		<b>Vehicle/Formulation:</b> 0.5% CMC sodium solution			<b>Section:</b> "	
<b>Study Duration:</b> January 1995 to March 1996		<b>Litters Culled/Not Culled:</b> Culled to 4/sex/litter on LD4; culled to 2/sex/litter on LD21			<b>GLP Compliance:</b> Yes	
<b>Special Features:</b> None						
<b>No Observed Adverse-Effect Level:</b> F <sub>0</sub> Females: < 1 mg/kg F <sub>1</sub> Offspring: < 1 mg/kg						
<b>Daily Dose (mg/kg/day)</b>						
	0 (Control)	1	3	10	30	
<b>F<sub>0</sub> Females</b>						
<b>Toxicokinetics*</b>						
No. Pregnant (No. successful copulations per group)	ND	ND	ND	ND	ND	
No. Pregnant (No. successful copulations per group)	24 (25)	24 (25)	24 (25)	23 (25)	15 (16)	
No. Died or Sacrificed Moribund	0	1 <sup>b</sup>	0	5 <sup>c</sup>	14 <sup>d</sup>	
No. Aborted or with Total Resorption of Litter	0	0	0	0	0	
<b>Clinical Observations (no. of animals with obs.)</b>						
Decreased spontaneous motor activity	-	-	-	1	6	
Emaciation	-	-	-	1	-	
Soiling around anus or eyelid	-	-	-	1	1	
Weakness (debility)	-	-	-	-	1	
Piloerection	-	-	-	-	2	

\*: Not applicable to an electronic submission

a: Supportive toxicokinetics in rats orally dosed with pitavastatin at 1, 3 and 10 mg/kg from GD17 to GD21 presented in [RI-9932]. C<sub>max</sub> (ng/mL) and AUC (ng\*h/mL) for 1 mg/kg on GDE21 were 70 and 610, for 10 mg/kg on GD21 70 and 4100 and for 30 mg/kg 4150 and 16690, respectively. Lactone was not detected in plasma. No supportive toxicokinetics for pitavastatin administered during lactation.

b: Death occurred on GD23

c: Deaths occurred on GD22 (1), GD23 (2), LD2 (1) and LD4 (1)

d: Deaths occurred on GD22 (5), GD23 (3), LD2 (2), LD3 (1) and LD4 (3)

-: No noteworthy findings

<b>2.6.7.14A Reproductive and Developmental Toxicity cont.</b>		<b>Report No.:</b> [RF(2511)] (continued)				<b>Page 2 of 5</b>
<b>Daily Dose (mg/kg/day)</b>						
	0 (Control)	1	3	10	30	
<b>F<sub>0</sub> Females cont.</b>						
No. Pregnant (No. successful copulations per group)	24 (25)	24 (25)	24 (25)	23 (25)	15 (16)	
<b>Necropsy Observations During Gestation</b>						
<b>Number of Animals Died or Sacrificed</b>						
Liver Discolouration	0	1	0	3	8	
Kidneys Discolouration	NA	0	NA	1	6	
Stomach Discolouration	NA	0	NA	2	5	
Stomach Petechia	NA	0	NA	1	7	
Stomach Haemorrhage	NA	0	NA	1	1	
Ileum Haemorrhage	NA	0	NA	0	1	
Vagina Bleeding or discharge	NA	0	NA	2	3	
Uterus Haemorrhage	NA	0	NA	0	1	
Foetal remains	NA	1	NA	0	1	
<b>Necropsy Observations During Lactation</b>						
<b>Number of Animals (including unscheduled)</b>						
Liver Discolouration	24 (0)	23 (0)	24 (0)	20 (2)	1 (6)	
Kidneys Discolouration	-	-	-	1 (1)	-(3)	
Stomach Discolouration	-	-	-	-(1)	-(3)	
Stomach Forestomach thickening	-	-	-	2 (-)	-(3)	
Vagina Discharge or bleeding	-	-	-	-(2)	-(3)	
Thymus Atrophy	-	-	-	-(3)	-(2)	
Ileum Haemorrhage	-	-	-	-(3)	-(1)	
Uterus Haemorrhage	-	-	-	-(3)	-(1)	
Foetal remains	-	-	-	-(3)	-(1)	
Adrenal Congestion	-	-	-	-(3)	-(1)	
Anus Staining	-	-	-	-(3)	-(1)	

2.6.7.14A Reproductive and Developmental Toxicity cont.		Report No.: [RFG2511] (continued)				Page 3 of 5
Daily Dose (mg/kg/day)	0 (Control)	1	3	10	30	
<b>F. Females cont.</b>						
Gestation Body Weight Gain (g) <sup>a</sup>	49	-12	0	-10	-51***	
Lactation Body Weight Day 0 (g) <sup>b</sup>	300	0	-4	-2	-4	
Lactation Body Weight Day 21 (g) <sup>b</sup>	332	+2	-3	-2	NA	
Gestation Food Consumption Day 21 (g) <sup>b</sup>	18	-11	0	-17	-39*	
Lactation Food Consumption Day 21 (g) <sup>b</sup>	80	+1	0	-8	NA	
No. Pregnant (No. successful copulations per group)	24 (25)	24 (25)	24 (25)	23 (25)	15 (16)	
No. of Dams with Liveborn Pups	24	23	24	20	7	
Mean Duration of Gestation (days)	22.3	22.3	22.4	22.4	22.4	
Abnormal Parturition	-	-	-	-	-	
Nursing Failures	0	6 (LD 1, 2 and 3)	5 (LD 5)	4 (LD 1, 2 and 7)	1 (LD 2)	
Gestation Index (%)	100	95.8	100	87	46.7^^^	
<b>F. Litters:</b>						
No. Litters Evaluated	24	24	24	23	15	
Mean No. Implantations	16.3	17.0	16.2	16.6	15.7	
Mean No. Stillborn Pups/Litter	0.5	2.6	2.1	2.0	3.6	
Mean No. Liveborn Pups/Litter	14.4	12.8	12.6	13.0	10.7	
No. of Newborns with External Anomalies	0	0	0	0	0	
Birth Index (%)	88.4	76.3	78.9	78.9	68.9	
No. of Litters with Stillborn Pups	10	14	12	11	5	
No. of Litters with all Stillborn Pups	0	0	0	0	0	
Postnatal Survival to Day 4 (%)	97.3 <sup>†</sup>	70.5 <sup>‡</sup>	78.9	68.6 <sup>§</sup>	0.0 <sup>¶</sup>	

a: GD17 to GD21. For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). Pregnant animals only; b: For controls, group mean is shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). Pregnant animals only  
 c: A significant decrease in food consumption at 10 mg/kg on LD0 and LD4 [RT2002/2502]  
 †: p < 0.05; ‡: p < 0.001 using Scheffé's d-test; §: p < 0.001 using  $\chi^2$  test  
 ¶: p < 0.05; #: p < 0.01; ##: p < 0.001 using Wilcoxon's rank test  
 -: No noteworthy findings

2.6.7.14A Reproductive and Developmental Toxicity cont.		Report No.: [RFG2511] (continued)				Page 4 of 5
Daily Dose (mg/kg/day)	0 (Control)	1	3	10	30	
<b>F. Litters cont.:</b>						
Postnatal Survival to Weaning (%)	100	100	100	92	NA	
No. of Total Litter Losses	0	6	5	4	1	
Newborn Body Weights LD0 preculling (g) - Males <sup>a</sup>	6.3	-2	+2	-3	-6	
Newborn Body Weights LD0 preculling (g) - Females <sup>a</sup>	6.0	-2	0	-3	-7	
<b>F. Generation:</b>						
Pup Body Weights LD21 preculling - Males <sup>a</sup>	60 g	0	0	-3**	NA	
Pup Body Weights LD21 preculling - Females <sup>a</sup>	57 g	0	+2	-4 <sup>†</sup>	NA	
Pup Body Weights LD56 preculling - Males <sup>a</sup>	352 g	0	+1	-2	NA	
Pup Body Weights LD56 preculling - Females <sup>a</sup>	234 g	-1	-4	-3	NA	
Pup Sex Ratios (% males)	52.3	49.8	51.2	53.3	54.7	
Pup Clinical Signs	Not stated	Not stated	Not stated	Not stated	Not stated	
Toxicokinetics	ND	ND	ND	ND	ND	
<b>Pup Physical Development</b>						
Separation of auricular % (total no. of pups)	90.1 (338)	95.4 (232)	91.3 (263)	73.0 (193)	0 <sup>¶</sup> (35)	
Appearance of hair (total no. of pups)	- (192)	- (133)	- (152)	- (108)	NA	
Eruption of incisors % (total no. of pups)	96.4 (192)	93.4 (133)	97.4 (152)	88.4 <sup>†</sup> (108)	NA	
Separation of eyelids % (total no. of pups)	95.3 (192)	93.4 (133)	97.4 (152)	83.0 (108)	NA	
Descent of testis (total no. of pups)	- (98)	- (66)	- (78)	- (55)	NA	
Opening of vagina (total no. of pups)	- (48)	- (32)	- (38)	- (27)	NA	
<b>Pup Functional Development<sup>b</sup></b>						
	- (48)	- (33)	- (38)	- (28)	NA	
<b>Pup Behavioural Observations<sup>c</sup></b>						
	- (48)	- (33)	- (38)	- (28)	NA	

a: For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)  
 b: Gait, corneal reflex, pain response, righting reflex, air righting reflex, prey reflex  
 c: Open field behaviour, rotarod performance, water maze  
 †: p < 0.05; ‡: p < 0.01 using Wilcoxon's rank test; §: p < 0.05 using Dunnett's test; ¶: p < 0.01 using Scheffé's rank test  
 -: No noteworthy findings

2.6.7.1.4A Reproductive and Developmental Toxicity cont.		Report No.: [RFG2511] (continued)				Page 5 of 5
Daily Dose (mg/kg/day)	0 (Control)	1	3	10		30
<b>F, Generation cont.:</b>						
Pup Skeletal Observations (LD21)						
No. of offspring with 25 presacral vertebrae (total no. of pups)	1 (96)	5 <sup>a</sup> (67)	0 (76)	0 (53)		NA
No. of offspring with lumbarisation of 1 <sup>st</sup> sacral vertebra (total no. of pups)	0 (96)	4 <sup>a</sup> (67)	0 (76)	0 (53)		NA
Pup Necropsy Observations (LD56)	-	-	-	-		NA
Organ Weights LD56 (total no. of pups)	-(47)	-(32)	-(38)	-(27)		NA
Histopathology	ND	ND	ND	ND		NA
No. of Mated Animals Males/Females	24/24	16/16	18/18	14/14		NA
No. of Animals Successfully Mating % Males/Females	95.8/95.8	100/100	88.9/88.9	85.7/85.7		NA
No. of Males Successfully Impregnating Females %	91.3	100	100	91.7		NA
No. Pregnant Females	21/24	16/16	16/18	11/14		NA
Time of Copulation after Mating (days)	3.0	4.9	2.9	2.8		NA
Gestation Body Weight Gain Mean from (D0) to (D20) (g) <sup>a</sup>	145	+12	+6	+6		NA
<b>F, Litters:</b>						
No. of Dams	20	16	15	11		0
Mean No. Corpora Lutea per Litter	19.2	19.6	19.8	18.0		NA
Mean No. of Implantations per Litter	16.1	17.2	16.2	16.1		NA
Total No. Dead Foetuses	40	13 <sup>##</sup>	13	6 <sup>##</sup>		NA
Implantation Site	0	0	0	0		NA
Early Resorption	36	11 <sup>##</sup>	13	6 <sup>##</sup>		NA
Late Resorption	4	0	0	0		NA
Dead Foetuses	0	2	0	0		NA
Mean No. Live Foetuses per Litter	14.1	16.4	15.3	15.5		NA
Pup Sex Ratios (% males)	53.3	51.8	52.1	52.3		NA
Body Weight (g) - Males <sup>a</sup>	3.36	-1	-2	-1		NA
Body Weight (g) - Females <sup>a</sup>	3.20	-1	-1	0		NA
No. Foetuses with External Anomalies	0	0	2 <sup>a</sup>	0		NA
a: For controls, group mean is shown. For treated groups, percent differences from controls are shown; b: Exencephaly (1) and micrognathia (1) #: p < 0.05; ##: p < 0.01 using Wilcoxon's rank test; -: No noteworthy findings						
2.6.7.1.4B Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function		Test Article: Pitavastatin			Page 1 of 2	
Report Title: Study by oral administration of NK-104 in rats during the perinatal and lactation periods (Additional study)						
Design similar to ICH 4.1.2? Yes		Duration of Dosing: GD17 to LD21			Report No.: [RFG2512]	
		Day of Mating: GDO			Location in CTD:	
Species/Strain: Crj:CD(SD) rats		Method of Administration: Oral (gavage) at 2 mL/kg			Vol: *	
Initial Age: 11 (F) to 12 (M) weeks		Vehicle/Formulation: 0.5% CMC sodium solution			Section: *	
Study Duration: September to December 1995		Litters Culled/Not Culled: Culled to 4/sex/litter on LD4; culled to 1/sex/litter on LD21			GLP Compliance: Yes	
Special Features: None						
No Observed Adverse-Effect Level: F <sub>0</sub> Females: 0.3 mg/kg/occasion F <sub>1</sub> Offspring: 0.3 mg/kg/occasion						
Daily Dose (mg/kg/day)	0 (Control)	0.1	0.3			
<b>F<sub>0</sub> Females</b>						
Toxicokinetics	ND	ND	ND			
No. Pregnant (No. successful copulations per group)	25 (25)	23 (25)	22 (25)			
No. Died or Sacrificed Moribund	0	0	0			
No. Aborted or with Total Resorption of Litter	0	0	0			
Nursing Failures	1 (I,12)	3 (I,12, I,12, I,12)	2 (I,12 and I,12 respectively)			
Clinical Observations	-	-	-			
Necropsy Observations	-	-	-			
Gestation Body Weight Day 21 (g) <sup>a</sup>	443	-2	-2			
Lactation Body Weight Day 21 (g) <sup>a</sup>	338	0	0			
Gestation Food Consumption Day 21 (g) <sup>a</sup>	22	-18	-14			
Lactation Food Consumption Day 21 (g) <sup>a</sup>	90	-4	0			
No. Pregnant Dams	25	23	22			
No. of Dams with Liveborn Pups	25	22	22			
*: Not applicable to an electronic submission a: For controls, group mean is shown. For treated groups, percent differences from controls are shown. Pregnant animals only. -: No noteworthy findings						

2.6.7.14B Reproductive and Developmental Toxicity cont.		Report No.: [RFG2512] (continued)		Page 2 of 2
Daily Dose (mg/kg/day)		0 (Control)	0.1	0.3
<b>F. Females cont.:</b>				
Gestation Index (%)		100	95.7	100
Mean Duration of Gestation (days)		22.2	22.2	22.1
Abnormal Parturition		-	-	-
<b>F. Litters:</b>				
No. Litters Evaluated		25	23	22
Mean No. Implantations per Litter		16.3	17.1	16.5
Mean No. Stillborn Pups/Litter		0.9	1.7	1.0
Mean No. Liveborn Pups/Litter		14.2	14.3	14.1
Birth Index (%)		87.3	84.7	85.4
Pup Sex Ratios (% males)		49.0	48.6	55.2
Newborn Body Weights LD0 preculling (g) - Males <sup>a</sup>		6.5	-2	-3
Newborn Body Weights LD0 preculling (g) - Females <sup>a</sup>		6.2	-2	-3
No. of Newborns with External Anomalies		0	0	0
Postnatal Survival to Day 4 (%)		94.5	82.0	90.3
Postnatal Survival to Weaning (%)		100	100	100
<b>F. Generation:</b>				
Pup Body Weights I.D21 preculling (g) - Males <sup>a</sup>		59	+2	0
Pup Body Weights I.D21 preculling (g) - Females <sup>a</sup>		57	0	0
Pup Clinical Signs		Not stated	Not stated	Not stated
Toxicokinetics		ND	ND	ND
Pup Physical Development <sup>b</sup>		-	-	-
Pup Functional Development <sup>c</sup>		-	-	-
Neecropsy				
Kidney Dilatation of pelvis		2M, 5F	1M, 5F	4M, 2F

a: For controls, group means are shown. For treated groups, percent differences from controls are shown.  
b: Separation of auricular, appearance of hair, eruption of incisors, separation of eyelids  
c: Gait, corneal reflex, pain response, righting reflex, air righting reflex, preyer reflex  
-: No noteworthy findings

**Toxicokinetics – Tabulated Summary**

2.6.7.3 Toxicokinetics		Overview of Toxicokinetics Data				Test Article: Pitavastatin				Page 1 of 4	
Species and Strain	Dose (mg/kg /day)	Duration of Dosing	Pharmacokinetic Parameter Representing Systemic Exposure								Report Number
			C <sub>max</sub> (ng/mL)				AUC <sub>0-24</sub> (ng•h/mL)				
			Male		Female		Male		Female		
		Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>		
Human	4 mg/day	Day 1	47	NA	47 <sup>b</sup>	NA	102	NA	102 <sup>b</sup>	NA	[PKI]/[NKN98389N]/ NK-104.1.01]
	4 mg/day	Day 14	55	NA	55 <sup>b</sup>	NA	153	NA	153 <sup>b</sup>	NA	
CB6F1-Tg rasH2 mice	70	Day 1	6360	135	5614	119	4790	47	4500	44	[SNBL.138.01]
	125	Day 1	11420	243	10930	233	16820	165	13140	129	
	250	Day 1	28750	612	22120	471	36230	355	34730	340	
	70	Week 4	6323	115	7912	144	5570	36	3950	39	
	125	Week 4	9634	175	17970	327	8060	53	12930	85	
CB6F1-Tg rasH2 mice	250	Week 4	65160	1185	81750	1486	48560	317	69810	456	[SNBL.138.03]
	30	Day 1	1457	31	1094	23	996	10	1006	10	
	75	Day 1	7705	164	7459	159	5562	55	6080	60	
	150	Day 1	12960	276	12790	272	14010	137	15350	150	
	30	Week 26	1035	19	1196	22	1076	7	1326	9	
Cr:CD-1(ICR)HR mice	75	Week 26	5871	107	4618	84	4904	32	4787	31	[KOW 14/95279R]
	150	Week 26	13420	244	57310	1042	15840	104	43480	284	
	25	Day 1	417	9	818	17	508	5	963	9	
	75	Day 1	4140	88	5419	115	4210	41	6860	67	
	225	Day 1	11653	248	12467	265	18671	183	20066	197	
Cr:CD-1(ICR)HR mice	25	Week 13	448	8	699	13	528	3	723	5	[KOW 14/95279R]
	75	Week 13	2062	37	7348	134	2402	16	5621	37	
	225	Week 13	24060	437	29306	533	22486	147	23274	152	

a: Ratio represents extent of systemic exposure in animal species at steady state to that in humans  
b: Values determined in male healthy subjects  
Note: Data presented are mean values for male and female animals on the last day when toxicokinetic sampling occurred and thus are considered to be at steady state after repeat oral administration  
AUC<sub>0-24</sub>: AUC from zero to 24 hours post-dose

2.6.7.3 Toxicokinetics		Overview of Toxicokinetics Data (continued)						Test Article: Pitavastatin				Page 2 of 4
Species and Strain	Dose (mg/kg/day)	Duration of Dosing	Pharmacokinetic Parameter Representing Systemic Exposure								Report Number	
			C <sub>max</sub> (ng/mL)				AUC <sub>0-24</sub> (ng <sup>2</sup> /h/mL)					
			Male		Female		Male		Female			
Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>			
Human	4 mg/day	Day 1	47	NA	47 <sup>b</sup>	NA	102	NA	102 <sup>b</sup>	NA	[PKH/NKN98389N/ NK-104.1.01]	
	4 mg/day	Day 14	55	NA	55 <sup>b</sup>	NA	153	NA	153 <sup>b</sup>	NA		
CrI:CD-1(ICR)BR mice	12	Week 9I	440	8	840	15	Not detected	NA	Not detected	NA	[KOW 16/982522]	
	30	Week 9I	1644	30	2267	41	Not detected	NA	Not detected	NA		
	75	Week 9I	9776	178	22318	406	Not detected	NA	Not detected	NA		
CrI:CD BR rats	10	Day 1	2820	60	2717	58	10165	100	10135	99	[KOW 12/942092]	
	30	Day 1	14491	308	26065	555	53712	527	63824	626		
	50	Day 1	49547	1054	47753	1016	154167	1511	136562	1339		
	10	Week 13	4652	85	5366	98	10527	69	6740	44		
	30	Week 13	29352	534	37470	681	57289	374	50924	333		
	50	Week 13	81252	1477	65032	1182	155163	1014	118297	773		
CrI:CD BR rats	1	Week 92 (F)	235	4	137 (n=1)	2	Not detected	NA	Not detected	NA	[KOW 13/971903]	
	5	Week 104 (M)	3077	56	2716 (n=1)	49	Not detected	NA	Not detected	NA		
	25	Week 4 (F)	37471	681	31024	564	Not detected	NA	Not detected	NA		
Kbl:JW rabbits	0.5	Week 4 (F)	457	8	368	7	2023	13	2648	17	[100320]	
	1	Week 6 (M)	1021	19	937	17	4758	31	4478	29		
	2		2369	43	2130	39	8443	55	7585	50		

a: Ratio represents extent of systemic exposure in animal species at steady state to that in humans

b: Values determined in male healthy subjects

Note: Data presented are mean values for male and female animals on the last day when toxicokinetic sampling occurred and thus are considered to be at steady state after repeat oral administration

2.6.7.3 Toxicokinetics		Overview of Toxicokinetics Data (continued)						Test Article: Pitavastatin				Page 3 of 4
Species and Strain	Dose (mg/kg/day)	Duration of Dosing	Pharmacokinetic Parameter Representing Systemic Exposure								Report Number	
			C <sub>max</sub> (ng/mL)				AUC <sub>0-24</sub> (ng <sup>2</sup> /h/mL)					
			Male		Female		Male		Female			
Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>			
Human	4 mg/day	Day 1	47	NA	47 <sup>b</sup>	NA	102	NA	102 <sup>b</sup>	NA	[PKH/NKN98389N/ NK-104.1.01]	
	4 mg/day	Day 14	55	NA	55 <sup>b</sup>	NA	153	NA	153 <sup>b</sup>	NA		
Beagle dog	5	Day 1	2890	61	3310	70	Not detected	NA	Not detected	NA	[A92005]	
	15	Day 1	11880	253	16160	344	Not detected	NA	Not detected	NA		
	50	Day 1	59000	1255	101000	2149	Not detected	NA	Not detected	NA		
	5	Day 9	2520	46	3950	72	Not detected	NA	Not detected	NA		
	15	Day 9	7250	132	16080	292	Not detected	NA	Not detected	NA		
	50	Day 9	Not detected	NC	Not detected	NC	Not detected	NA	Not detected	NA		
Beagle dog	1	Day 1	246	5	344	7	891 <sup>d</sup>	9	1141 <sup>d</sup>	11	[AG25001]	
	3	Day 1	1477	31	1671	36	3130 <sup>d</sup>	31	4196 <sup>d</sup>	41		
	10	Day 1	5179	110	8686	185	14185 <sup>d</sup>	139	18117 <sup>d</sup>	178		
	1	Week 13	239	4	302	5	NC	NA	NC	NA		
	3	Week 13	1346	24	1058	19	NC	NA	NC	NA		
	10	Week 13	7637	139	4931	90	NC	NA	NC	NA		
Beagle dog	0.3	Day 1	78	2	113	2	280	3	421	4	[AG25004]	
	1	Day 1	493	10	546	12	1328	13	1463	14		
	3	Day 1	2880	61	2190	47	7070	69	5350	52		
	0.3	Week 52	107	2	60	1	384	2	288	2		
	1	Week 52	382	7	325	6	1360	9	1363	9		
	3	Week 52	2890	53	1830	33	7750	51	5340	35		

a: Ratio represents extent of systemic exposure in animal species at steady state to that in humans

b: Values determined in male healthy subjects

c: Mean of 2 animals

d: AUC<sub>0-∞</sub> (AUC from zero to infinity)

Note: Data presented are mean values for male and female animals on the last day when toxicokinetic sampling occurred and thus are considered to be at steady state after repeat oral administration; NC: Not calculable

2.6.7.3 Toxicokinetics		Overview of Toxicokinetics Data (continued)								Test Article: Pitavastatin		Page 4 of 4
Species and Strain	Dose (mg/kg /day)	Duration of Dosing	Pharmacokinetic Parameter Representing Systemic Exposure								Report Number	
			C <sub>max</sub> (ng/mL)				AUC <sub>0-24</sub> (ng·h/mL)					
			Male		Female		Male		Female			
		Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>	Value	Ratio <sup>a</sup>			
Human	4 mg/dav	Day 1	47	NA	47 <sup>b</sup>	NA	102	NA	102 <sup>b</sup>	NA	[PK11/NK/N98389N/ NK-104.1.01]	
	4 mg/dav	Day 14	55	NA	55 <sup>b</sup>	NA	153	NA	153 <sup>b</sup>	NA		
Cynomolgus monkey	10	Day 1	1140	24	340	11	2890	28	1880	18	[RFG2513] <sup>f</sup>	
	30	Day 1	3380	72	5430	116	16840	165	17310	170		
	50	Day 1	9850	210	27700	589	33440	328	76330	748		
Cynomolgus monkey	3	Day 1	159	3	139	3	690	7	820	8	[RFG2514] <sup>d</sup>	
	8	Day 1	375	8	242	5	1280	13	1709	17		
	15	Day 1	888	19	597	13	4943	48	3809	37		
	3	Day 28	185	3	121	2	552	4	476	3		
	8	Day 28	373	7	248	5	1588	10	4016	26		
	15	Day 28	755	14	37693, 302 <sup>e</sup>	685, 5 <sup>e</sup>	4434	29	78828, 4071 <sup>e</sup>	515, 27 <sup>e</sup>		
Cynomolgus monkey	0.5	Day 1	12	0.3	7	0.2	98	1	51	0.5	[RFG2513]	
	1	Day 1	33	0.7	29	0.6	232	2	142	1		
	3	Day 1	114	2	68	1	796	8	341	3		
	6	Day 1	512	11	459	10	1383	14	1291	13		
	0.5	Week 26	8	0.1	7	0.1	89	0.6	51	0.3		
	1	Week 26	35	0.6	43	0.8	492	3	382	2		
	3	Week 26	110	2	66	1	704	5	459	3		
	6	Week 26	240	4	217	4	1468	10	1320	9		

a: Ratio represents extent of systemic exposure in animal species at steady state to that in humans  
b: Values determined in male healthy subjects; c: 1/sex/group  
d: Mean of 2 animals  
e: Where there is a marked difference between the values of the two individual animals, both values are given  
Note: Data presented are mean values for male and female animals on the last day when toxicokinetic sampling occurred and thus are considered to be at steady state after repeat oral administration

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

**Conclusions:**

**Table 2.4.3: Pharmacokinetic Parameters of Pitavastatin after Oral Administration**

Species	Dose (mg/kg)	T <sub>max</sub> (hours)	C <sub>max</sub> (ng/mL)	AUC (ng·h/mL)	t <sub>1/2</sub> (hours)	F* (%)
Rat	0.3	0.7	22 ± 2	140 ± 10	7.7	31
	1.0	0.9	231 ± 35	1170 ± 220	6.7	80
	3.0	0.5	911 ± 210	3950 ± 650	6.5	91
Rabbit	0.1	6.0	69 ± 5	1030 ± 70	4.2	64
	0.3	4.5	314 ± 33	4340 ± 190	4.7	89
	1.0	1.5	1184 ± 154	15670 ± 1550	3.9	97
Dog	0.1	1.9	29 ± 9	170 ± 30	4.0	58
	0.3	2.5	93 ± 24	630 ± 130	4.3	71
	1.0	0.6	724 ± 131	2570 ± 270	4.3	88
Monkey	0.3	2.7	17 ± 5	160 ± 60	4.5	31
	1.0	3.2	61 ± 11	310 ± 70	4.5	18
	3.0	2.2	165 ± 43	850 ± 160	3.7	17

\* F: Bioavailability; AUC: Area under the concentration-time curve; Results are expressed as mean ± SE

(Sponsor, M2.4, Nonclinical overview, p18)

Human Pharmacokinetics at Clinical Doses						
Species	Dose (mg)	T <sub>max</sub> (hours)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·h/mL)	T <sub>1/2</sub> (hours)	F* (%)
Human	1	1.6	13 ± 4	24 ± 13	1.4	ND
	2	1.5	20 ± 8	56 ± 31	8.2	ND
	4	1.1	55 ± 22	153 ± 46	8.9	ND

Values were determined after 21 days repeat oral daily administration to healthy adult Caucasian males