キネレット皮下注 100 mg シリンジ

＜アナキンラ（遺伝子組換え）＞

第 2 部（モジュール 2）
CTD の概要（サマリー）

2.6　非臨床試験の概要文及び概要表

2.6.5　薬物動態試験概要表

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2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験：一覧表

表 2.6.5-1 アナキンラの薬物動態試験の概要

Type of study	Test system	Method of administration	Duration of dosing (number of doses or frequency)	Doses (mg/kg[a])	Testing facility	Study number	eCTD location
Absorption - single dose							
A single-dose, crossover study in male Sprague-Dawley rats to compare the PK of anakinra following i.v. and s.c. administration of anakinra	Sprague-Dawley rat	s.c. bolus, i.v.	NA (single dose)	1, 3, 10, 30 and 100	[redacted] Japan	100421	[4.2.2.2]
A single-dose, crossover study in male New Zealand white rabbits to compare the PK of anakinra following i.v. and s.c. administration of anakinra	New Zealand white rabbit	s.c. bolus, i.v.	NA (single dose)	10 and 100	[redacted] Japan	100422	[4.2.2.2]
A single-dose, crossover study in male cynomolgus monkeys to compare the PK of anakinra following i.v. and s.c. administration of anakinra	Cynomolgus monkey (*Macaca fascicularis*)	s.c. bolus, i.v.	NA (single dose)	10 and 100	[redacted] Japan	100420	[4.2.2.2]

Type of study	Test system	Method of administration	Duration of dosing (number of doses or frequency)	Doses (mg/kg[a])	Testing facility	Study number	eCTD location
Absorption - repeat dose							
A 4-week, toxicity, and TK study of s.c. administered anakinra and orally administered MTX in rats (PK and TK data only reported here; GLP-compliant, toxicity data reported in Module [2.6.6])	Sprague-Dawley rat	s.c. anakinra, p.o. MTX	4 weeks (q.d.)	Anakinra – 0, 1, 10, and 100 MTX – 0, 0.04, and 0.2	[redacted] USA	960048	[4.2.3.2]
A 6-month, toxicity study in rats treated with s.c. anakinra, including 1-month interim and 1-month recovery groups (PK and TK data only reported here; GLP-compliant, toxicity data reported in Module [2.6.6])	Sprague-Dawley rat	s.c.	1 and 6 months (b.i.d.)	0, 2, 20, and 200 mg/kg/day	[redacted] Canada	SY05-T94-04	[4.2.3.2]
The effect of multiple-dose administration of PEG-sTNF-RI on the PK of anakinra in male Sprague-Dawley rats	Sprague-Dawley rat	i.v. anakinra, s.c. PEG-sTNF-RI	4 weeks (anakinra on Days 1 and 27; PEG-sTNF-RI b.i.w. from Day 2)	Anakinra – 100 PEG-sTNF-RI – placebo and 1 and 25	[redacted] USA	100564	[4.2.2.2]
The effect of multiple-dose administration of anakinra on the PK of PEG r-metHu-sTNF-RI in male Sprague-Dawley rats	Sprague-Dawley rat	s.c. anakinra, i.v. PEG-sTNF-RI	21 days (anakinra q.d.; PEG-sTNF-RI on Days 1 and 21)	Anakinra – 0 and 100 PEG-sTNF-RI – 1 and 25	[redacted] USA	100557	[4.2.2.2]

Type of study	Test system	Method of administration	Duration of dosing (number of doses or frequency)	Doses (mg/kg[a])	Testing facility	Study number	eCTD location
A 4-week, toxicity study of anakinra administered by s.c. injection to rhesus monkeys with a 4-week recovery period (PK data only reported here; GLP toxicity data reported in Module [2.6.6] and Module [2.6.7])	Rhesus monkey (*Macaca mulatta*)	s.c.	28 days (q.d.)	0, 10, 100, and 200	[redacted] USA	960040	[4.2.3.2]
A 1-month, toxicity study of anakinra and PEG-sTNF-RI administered s.c. in cynomolgus monkeys with a 1-month recovery period	Cynomolgus monkey (*Macaca fascicularis*)	s.c. anakinra, PEG-sTNF-RI	1 month of dosing (anakinra q.d.; PEG-sTNF-RI q.w.)	Anakinra – 0, 100 PEG-sTNF-RI – 0, 1, 5, and 25	[redacted] Japan	100484	[4.2.3.2]
Distribution							
NA[b]							
Metabolism							
NA							
Excretion							
See Study SY05-T94-04 and Study 960040							
Pharmacokinetic drug interactions							
A 4-week toxicity and toxicokinetics study of s.c. administration of anakinra and p.o. administration of methotrexate in rats	Sprague-Dawley rat	s.c.; Anakinra p.o.; MTX	4 weeks	Anakinra 0, 10, 100 MTX 0, 0.04, 0.2	[redacted] USA	960048	[4.2.3.2]

Type of study	Test system	Method of administration	Duration of dosing (number of doses or frequency)	Doses (mg/kg[a])	Testing facility	Study number	eCTD location
A 4-week study of PEG-sTNF-RI administration on the pharmacokinetics of r-metHuIL-1Ra (anakinra) in male Sprague-Dawley rats	Sprague-Dawley rat	i.v.; Anakinra s.c.; PEG-sTNF-RI	4 weeks	Anakinra 100, on Days 1 and 27. PEG-sTNF-RI 0, 1, 25 (b.i.w.)	[redacted] USA	100564	[4.2.2.2]
The effect of multiple-dose administration of anakinra on the pharmacokinetics of PEG r-metHu-sTNF-RI in male Sprague Dawley rats	Sprague-Dawley rat	s.c.; Anakinra daily i.v.; PEG-sTNF-RI Day 1, Day 21	21 days	Anakinra 0, 100 PEG-sTNF-RI 1, 25	[redacted] USA	100557	[4.2.2.2]
A 1 month, toxicity study of anakinra and sTNF-RI administered subcutaneously in cynomolgus monkeys	Cynomolgus monkey	s.c.; Anakinra daily s.c.; sTNF-RI weekly	1 month	Anakinra 0, 100 sTNF-RI 0, 1, 5, 25	[redacted] Japan	100484	[4.2.3.2]
Other							
NA							

Abbreviations: b.i.d., Twice daily; b.i.w., Twice a week; eCTD, Electronic Common Technical Document; GLP, Good Laboratory Practice; i.v., Intravenous(ly); MTX, Methotrexate; NA, Not applicable/available; NOAEL, No-observed-adverse-effect level; PEG r-metHu-sTNF-RI, Polyethylene glycosylated recombinant methinonyl human-soluble tumor necrosis factor-receptor I; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; PK, Pharmacokinetic(s); p.o., Peroral; q.d., Once daily; q.w., Once weekly; s.c., Subcutaneous(ly); TK, Toxicokinetic(s).

[a] Unless otherwise specified, for repeat-dose toxicity studies, the highest NOAEL is underlined.

[b] Distribution results with anakinra from the literature are included in Section [2.6.4.4].

2.6.5.2 分析方法及びバリデーション試験

表 2.6.5-2 分析方法及びバリデーション試験

Analytical methods and validations reports					Test article: Anakinra			
Species/ sample matrix	Analytes	Calibration range (ng/mL)	Type of assay	Method/validation report	Noteworthy findings (precision and accuracy validation)		GLP compliance	Study number
					Stability:			
					Intraday	Interday		
Rat/plasma	Anakinra	0.313 to 20.000 (in 20 % normal goat serum)	ELISA	PK9905IL1ra001/100821 (amendment no. 1)	Standard curve precision (% CV): 3.0 % to 6.8 % QC precision (% CV): 3.6 % to 14.9 % Standard curve accuracy (% AR): 86 % to 113 % QC accuracy (% AR): 99 % to 113 %	Standard curve precision (% CV): 6.7 % to 10.8 % QC precision (% CV): 6.0 % to 12.1 % Standard curve accuracy (% AR): 82 % to 108 % QC accuracy (% AR): 97 % to 108 %	Yes	100421, 960048, SY05-T94-04, 100557, and 100564
					LLOQ: 0.32 ng/mL No interference with rat plasma at dilutions ≥ 1:3 No detection of endogenous anakinra at dilution 1:5 No cross-reactivity or interference observed with other unrelated proteins Stability: 3 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles			
Rabbit/plasma	Anakinra	0.313 to 20.000 (in 20 % normal goat serum)	ELISA	PK9905IL1ra001/100822 (amendment no. 1)	Standard curve precision (% CV): 3.0 % to 6.8 % QC precision (% CV):	Standard curve precision (% CV): 6.7 % to 10.8 % QC precision (% CV):	Yes	100422

Analytical methods and validations reports					Test article: Anakinra			
Species/ sample matrix	**Analytes**	**Calibration range (ng/mL)**	**Type of assay**	**Method/validation report**	**Noteworthy findings (precision and accuracy validation)**		**GLP compliance**	**Study number**
					Stability:			
					Intraday	**Interday**		
					3.6 % to 14.9 % Standard curve accuracy (% AR): 86 % to 113 % QC accuracy (% AR): 99 % to 113 %	6.0 % to 12.1 % Standard curve accuracy (% AR): 82 % to 108 % QC accuracy (% AR): 97 % to 108 %		
					LLOQ: 0.32 ng/mL No interference with rabbit plasma at dilutions ≥ 1:5 Endogenous anakinra was detected at levels slightly over background at dilutions 1:5 and 1:10 No cross-reactivity or interference observed with other unrelated proteins Stability: 3 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles			
Monkey/plasma	Anakinra	0.313 to 20.000 (in 20 % normal goat serum)	ELISA	PK9905IL1ra001/100820 (amendment no. 1)	Standard curve precision (% CV): 3.0 % to 6.8 % QC precision (% CV): 3.6 % to 14.9 % Standard curve accuracy (% AR): 86 % to 113 % QC accuracy (% AR): 99 % to 113 %	Standard curve precision (% CV): 6.7 % to 10.8 % QC precision (% CV): 6.0 % to 12.1 % Standard curve accuracy (% AR): 82 % to 108 % QC accuracy (% AR): 97 % to 108 %	Yes	100420, 100484, and 960040
					LLOQ: 0.32 ng/mL			

Analytical methods and validations reports					Test article: Anakinra			
Species/ sample matrix	**Analytes**	**Calibration range (ng/mL)**	**Type of assay**	**Method/validation report**	**Noteworthy findings (precision and accuracy validation)**		**GLP compliance**	**Study number**
					Stability:			
					Intraday	**Interday**		
					No interference with rat plasma at dilutions ≥ 1:10 No detection of endogenous anakinra at dilution 1:10 No cross-reactivity or interference observed with other unrelated proteins Stability: 3 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles			
					LLOQ: 0.32 ng/mL No interference with human plasma at dilutions ≥ 1:5 No detection of endogenous anakinra at dilution 1:5 No cross-reactivity or interference observed with other unrelated proteins No interference from rheumatoid factor or PEG-sTNF-RI Stability: 3 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles Long-term stability: -70 °C for at least 12 months			
Rat/serum	Anti-anakinra antibodies	NA	ELISA	PK9905IL1ra003/2260.7059	PC[a] precision (% CV): 4.4 % to 14.2 % PC[a] accuracy (% AR): 92 % to 114 %	PC[a] precision[b] (% CV): 1.2 % to 2.4 % PC[a] precision[c] (% CV): 3.0 % to 13.8 % PC[a] accuracy (% AR): 98 % to 104 %	No	SY05-T94-04 and 100557

Analytical methods and validations reports					Test article: Anakinra			
Species/ sample matrix	**Analytes**	**Calibration range (ng/mL)**	**Type of assay**	**Method/validation report**	**Noteworthy findings (precision and accuracy validation)**		**GLP compliance**	**Study number**
					Stability:			
					Intraday	**Interday**		
					LLOD/sensitivity: 0.273 µg/mL (13.65 ng/mL before 50-fold dilution) Dilution: 1:50 Stability: 5 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles			
Monkey/serum	Anti-anakinra antibodies	NA	ELISA	PK9905IL1ra003/2260.7060	PC[a] precision (% CV): 1.8 % to 6.7 % PC[a] accuracy (% AR): 92 % to 109 %	PC[a] precision[b] (% CV): 2.2 % to 3.6 % PC[a] precision[c] (% CV): 0.753 % to 6.4 % PC[a] accuracy (% AR): 94 % to 106 %	No	100484 and 960040
					LLOD/sensitivity: 0.547 µg/mL (27.35 ng/mL before 50-fold dilution) Dilution: 1:50 Stability: 5 freeze (-70 °C)/thaw (nominal 37 °C or room temperature) cycles			

Abbreviations: AR, Analytical recovery; CV, Coefficient of variation; ELISA, Enzyme-linked immunosorbent assay; GLP, Good Laboratory Practice; LLOD, Lower limit of detection; LLOQ, Lower limit of quantification; NA, Not applicable; OD, Optical density; PC, Positive control; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; QC, Quality control.

[a] High, medium, and low anti-anakinra antibody PCs (17.5, 4.375, and 1.094 µg/mL, respectively) were diluted in 20 % normal goat serum.

[b] Based on OD values.

[c] Based on concentrations.

2.6.5.3 薬物動態試験：吸収：単回投与

表 2.6.5-3 Sprague-Dawley ラットにアナキンラを単回投与したときの薬物動態（100421 試験）

A single-dose, crossover study in male Sprague-Dawley rats to compare the PK of anakinra following i.v. and s.c administration of anakinra					**Test article:** Anakinra					
					Location in CTD: [4.2.2.2]					
					Study no.: 100421					
Species	Sprague-Dawley rat									
Sex (M/F)/no. of animals	4 M/dose/route									
Feeding condition	Fed									
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5									
Method of administration	i.v. and s.c.									
Dose (mg/kg)	1, 3, 10, 30, and 100									
Sample (whole blood, plasma, serum, etc.)	Plasma									
Analyte	Anakinra									
Assay	ELISA									
PK parameters (mean)	**1 mg/kg**		**3 mg/kg**		**10 mg/kg**		**30 mg/kg**		**100 mg/kg**	
	i.v.	**s.c.**	**i.v.**	**s.c.**	**i.v.**	**s.c.**	**i.v.**	**s.c.**	**i.v.**	**s.c.**
C_{max} (ng/mL)	28700	447	65500	1750	152000	4640	774000	13800	2250000	33700
t_{max} (h)	0.00	1.00	0.00	1.00	0.00	1.50	0.00	1.50	0.00	2.00
$AUC_{0-\infty}$ (ng·h/mL)	3360	1180	8600	4640	23500	13700	94400	44100	283000	137000
Vc (mL/kg)	34.9	NA	45.8	NA	65.8	NA	38.8	NA	44.4	NA
Vd_{ss} (mL/kg)	47.3	NA	71.3	NA	114	NA	53.2	NA	77.4	NA
CL (mL/min/kg)	6.63	NA	7.30	NA	8.33	NA	6.93	NA	7.43	NA
Terminal $t_{1/2}$ (h)	1.07	0.892	0.831	0.778	1.05	0.860	1.03	0.820	1.44	1.10
MRT (h)	0.159	1.89	0.204	1.89	0.267	2.10	0.167	2.22	0.219	2.79
BA (%)	100	47.5	100	68.3	100	68.8	100	61.7	100	61.3
Additional information: Anakinra exhibited linear PK in male Sprague-Dawley rats at a dose that ranged from 1 to 100 mg/kg, as the plasma anakinra CL after i.v. administration and the absolute BA after s.c. administration were dose independent. The mean plasma CL value (7.36 mL/min/kg) was in a range consistent with the glomerular filtration rate in rats. The absolute BA value after s.c. administration was approximately 60 %.										

Source: Study 100421.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; BA, Bioavailability; CL, Clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; i.v., Intravenous; M, Male; MRT, Mean residence time; NA, Not applicable; no., Number; PK,

Pharmacokinetic(s); s.c., Subcutaneous; $t_{1/2}$, Half-time; t_{max}, Time to reach maximum concentration., Vc, Volume of distribution in the central compartment; Vd_{ss}, Volume of distribution at steady state.

表 2.6.5-4 New Zealand white ウサギにアナキンラを単回投与したときの薬物動態（100422 試験）

A single-dose, crossover study in male New Zealand white rabbits to compare the PK of anakinra following i.v. and s.c. administration of anakinra			**Test article:** Anakinra	
			Location in CTD: [4.2.2.2]	
			Study no.: 100422	
Species	New Zealand white rabbit			
Sex (M/F)/no. of animals	4 M/dose/route			
Feeding condition	Fed			
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5			
Method of administration	i.v. and s.c.			
Dose (mg/kg)	10 and100			
Sample (whole blood, plasma, serum, etc.)	Plasma			
Analyte	Anakinra			
Assay	ELISA			
PK parameters (mean)	**10 mg/kg**		**100 mg/kg**	
	i.v.	**s.c.**	**i.v.**	**s.c.**
C_{max} (ng/mL)	172000	8060	1370000	40400
t_{max} (h)	0.00	1.54	0.00	2.03
$AUC_{0-\infty}$ (ng·h/mL)	37700	25500	375000	204000
Vc (mL/kg)	58.2	NA	72.9	NA
Vd_{ss} (mL/kg)	85.0	NA	117	NA
CL (mL/min/kg)	5.24	NA	5.05	NA
Terminal $t_{1/2}$ (h)	1.25	0.937	2.27	1.43
MRT (h)	0.321	2.43	0.440	3.64
BA (%)	100	80.8	100	62.3
Additional information: Anakinra exhibited linear PK in New Zealand white rabbits at doses of 10 and 100 mg/kg. The mean plasma CL values (approximately 5 mL/min/kg) were in a range consistent with the glomerular filtration rate for rabbits. The volume of distribution data was consistent with the initial distribution into the physiologic plasma volume followed by subsequent distribution into a steady-state distribution volume similar in magnitude to the extracellular fluid volume. The mean absolute BA values after s.c. administration were 80.8 % and 62.3 % for the 10-mg/kg and 100-mg/kg groups, respectively.				

Source: Study 100422.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinite time; BA, Bioavailability; CL, Clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; i.v., Intravenous; M, Male; MRT, Mean residence time; no., Number; PK, NA, Not applicable; Pharmacokinetic(s); s.c., Subcutaneous; $t_{1/2}$, Half-time; t_{max}, Time to reach maximum concentration; Vc, Volume of distribution in the central compartment; Vd_{ss}, Volume of distribution at steady

state.

表 2.6.5-5 カニクイザルにアナキンラを単回投与したときの薬物動態（100420 試験）

A single-dose, crossover study in male cynomolgus monkeys to compare the PK of anakinra following i.v. and s.c. administration of anakinra			**Test article:** Anakinra	
			Location in CTD: [4.2.2.2]	
			Study no.: 100420	
Species	Cynomolgus monkey			
Sex (M/F)/no. of animals	4M/dose/route			
Feeding condition	Fed			
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5			
Method of administration	i.v. and s.c.			
Dose (mg/kg)	10 and 100			
Sample (whole blood, plasma, serum, etc.)	Plasma			
Analyte	Anakinra			
Assay	ELISA			
PK parameters (mean)	**10 mg/kg**		**100 mg/kg**	
	i.v.	**s.c.**	**i.v.**	**s.c.**
C_{max} (ng/mL)	157000	8480	2220000	34500
t_{max} (h)	0.00	2.00	0.00	4.50
$AUC_{0-\infty}$ (ng·h/mL)	61600	57100	723000	597000
Vc (mL/kg)	65.3	NA	47.1	NA
Vd_{ss} (mL/kg)	176	NA	166	NA
CL (mL/min/kg)	2.75	2.99	2.35	2.83
Terminal $t_{1/2}$ (h)	3.72	2.61	5.55	3.44
MRT (h)	1.07	5.26	1.23	11.4
BA (%)	100	92.4	100	84.3
Additional information: Anakinra exhibited linear elimination kinetics in cynomolgus monkeys at doses of 10 and 100 mg/kg. The mean plasma CL values (2.75 and 2.35 mL/min/kg for the 10 and 100 mg/kg, respectively) were in a range consistent with the glomerular filtration rate in the monkey. The volume of distribution data was consistent with initial distribution into the physiologic plasma volume followed by subsequent distribution into a steady-state distribution volume similar in magnitude to the extracellular fluid volume. The absorption kinetics of anakinra after s.c. administration were nonlinear. As the dose increased to 100 mg/kg, the C_{max} occurred at a later time (4.5 hours), suggesting that the absorption rate decreased at the high dose. The mean absolute BA values after s.c. administration were 92 % and 84 % for doses 10 and 100 mg/kg, respectively.				

Source: Study 100420.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; BA, Bioavailability; CL, Clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; i.v., Intravenous; M, Male; MRT, Mean residence time; NA, Not applicable; no., Number; PK,

Pharmacokinetic(s); s.c., Subcutaneous; $t_{1/2}$, Half-time; t_{max}, Time to reach maximum concentration; Vc, Volume of distribution in the central compartment; Vd_{ss}, Volume of distribution at steady state.

2.6.5.4 薬物動態試験：吸収：反復投与

表 2.6.5-6 Sprague-Dawley ラットにアナキンラとメトトレキサートを併用反復投与したときのアナキンラのトキシコキネティクスに及ぼす影響（960048 試験）

A 4-week, toxicity, and TK study of s.c. administered anakinra and orally administered methotrexate in rats (non-GLP)							**Test article:** Anakinra		
							Location in CTD: [4.2.3.2]		
							Study no.: 960048		
Species	Sprague-Dawley rat								
Sex (M/F)/no. of animals	12 F/group								
Feeding condition	Fed								
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5								
Method of administration	Anakinra, s.c., q.d. for 4 weeks; methotrexate, p.o., q.d. for 4 weeks								
Dose (mg/kg)	Anakinra: 0, 1, 10, and 100; methotrexate: 0, 0.04, and 0.20								
Sample (whole blood, plasma, serum, etc.)	Plasma								
Analyte	Anakinra								
Assay	ELISA								
Plasma TK parameters (mean)	**Anakinra 10 mg/kg**								
	Anakinra alone			**With 0.04 mg/kg methotrexate**			**With 0.20 mg/kg methotrexate**		
	Day 1	**Day 14**	**Day 28**	**Day 1**	**Day 14**	**Day 28**	**Day 1**	**Day 14**	**Day 28**
C_{max} (ng/mL)	3110	7420	20900	3530	12100	19200	3850	4580	14700
t_{max} (h)	1.0	0.5	4.0	2.0	0.5	4.0	1.0	1.0	1.0
AUC_{0-24} (ng·h/mL)	9490	23300	151000	12100	44100	96200	11700	11700	38600
$AUC_{0-\infty}$ (ng·h/mL)	9490	NA	NA	12100	NA	NA	11700	NA	NA
CL/BA (mL/min/kg)	17.6	7.16	1.10	13.8	3.78	1.73	14.2	14.3	4.31
Terminal $t_{1/2}$ (h)	0.625	2.96	1.42	0.651	0.326	2.48	2.34	0.776	1.46
AR	NA	2.45	15.9	NA	3.66	7.97	NA	0.996	3.29
	Anakinra 100 mg/kg								
C_{max} (ng/mL)	32900	56100	210000	58800	80700	167000	28700	33500	136000

A 4-week, toxicity, and TK study of s.c. administered anakinra and orally administered methotrexate in rats (non-GLP)							**Test article:** Anakinra		
							Location in CTD: [4.2.3.2]		
							Study no.: 960048		
t_{max} (h)	2.72	1.83	1.17	1.87	1.64	9.75	1.80	1.58	1.03
AUC_{0-24} (ng·h/mL)	122000	310000	1440000	165000	296000	1410000	94000	148000	578000
$AUC_{0-\infty}$ (ng·h/mL)	122000	NA	NA	165000	NA	NA	94000	NA	NA
CL/BA (mL/min/kg)	13.7	5.38	1.16	10.1	5.63	1.18	17.7	11.2	2.89
Terminal $t_{½}$ (h)	2.72	1.83	1.17	1.84	1.64	9.75	1.80	1.58	1.03
AR	NA	2.55	11.8	NA	1.80	8.57	NA	1.58	6.15
Additional information: The female rats in the active treatment groups were exposed to anakinra approximately in proportion to the s.c. administered dose. After multiple doses of anakinra, a significant accumulation of plasma anakinra concentration was observed, which was also observed when anakinra was given alone. The accumulation could be attributed to the decrease in renal glomerular filtration of anakinra secondary to binding to anti-anakinra antibodies or to other proteins. Concomitant oral administration of methotrexate had no apparent effects on the systemic exposure of anakinra to rats. Likewise, anakinra did not influence the systemic exposure of orally administered methotrexate.									

Source: 960048.

Abbreviations: AR, Accumulation ratio; $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; AUC_{0-24}, Area under the curve from time 0 to 24 hours; CL/BA, Apparent clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; GLP, Good Laboratory Practice; M, Male; NA, Not applicable; no., Number; p.o., Peroral; q.d., Once daily; s.c., Subcutaneous(ly); $t_{1/2}$, Half-time; TK, Toxicokinetic(s); t_{max}, Time to reach maximum concentration.

表 2.6.5-7 Sprague-Dawley ラットにアナキンラを反復投与したときのアナキンラの血漿中濃度（SY05-T94-04 試験）

A 6-month, toxicity study in rats treated with s.c.-administered anakinra, including 1-month interim and 1-month recovery groups (non-GLP)					**Test article:** Anakinra	
					Location in CTD: [4.2.3.2]	
					Study no.: SY05-T94-04	
Species	Sprague-Dawley rat					
Sex (M/F)/no. of animals	5/sex/group					
Feeding condition	Fed					
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5					
Method of administration	Anakinra, s.c., b.i.d. for 24 weeks					
Dose (mg/kg)	Anakinra: 1, 10, and 100 (or 2, 20, and 200 mg/kg/day)					
Sample (whole blood, plasma, serum, etc.)	Plasma					
Analyte	Anakinra					
Assay	ELISA					
Dose (mg/kg/day)	**Median plasma concentrations of anakinra (ng/mL) at 2 hours postdose in male rats**					
	Day 4	**Day 8**	**Day 15**	**Week 8**	**Week 13**	**Week 26**
2	191.6	204.2	1329	370.9	285.2	350.0
20	2488	2380	7096	43380	38580	20490
200	20080	20310	39140	273000	187000	210000
	Median plasma concentrations of anakinra (ng/mL) at 2 hours postdose in female rats					
2	175.1	163.6	976.1	471.1	558.7	365.1
20	1895	2878	23370	91600	38 910	12340
200	19560	17140	67080	504000	328000	240000
Additional information: The plasma concentrations of anakinra appeared proportional to the administered dose. No gender difference in disposition was observed. The appearance of anti-anakinra antibodies at Day 15 was correlated in time to the increase in steady-state anakinra concentrations.						

Source: SY05-T94-04.

Abbreviations: b.i.d., Twice a day; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; GLP, Good Laboratory Practice; M, Male; no., Number; s.c., Subcutaneous(ly).

表 2.6.5-8 Sprague-Dawley ラットに PEG-sTNF-RI を反復投与したときのアナキンラの薬物動態に及ぼす影響（100564 試験）

The effect of multiple-dose administration of PEG-sTNF-RI on the PK of anakinra in male Sprague-Dawley rats (non-GLP)			**Test article:** Anakinra
			Location in CTD: [4.2.2.2]
			Study no.: 100564
Species	Sprague-Dawley rat		
Sex (M/F)/no. of animals	4 M/route		
Feeding condition	Fed		
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5		
Method of administration	Anakinra, i.v., Days 1 and 27; PEG-sTNF-RI, s.c., twice weekly starting on Day 2 until Day 27 (8 doses)		
Dose (mg/kg)	Anakinra: 100; PEG-sTNF-RI: 0, 1, and 25		
Sample (whole blood, plasma, serum, etc.)	Plasma		
Analyte	Anakinra		
Assay	ELISA		
Plasma PK parameters (mean)	**Anakinra (Day 27)**		
	Placebo PEG-sTNF-RI	1 mg/kg PEG-sTNF-RI	25 mg/kg PEG-sTNF-RI
C_{max} (ng/mL)	135000	154000	172000
$AUC_{0-\infty}$ (ng·h/mL)	82600	109000	120000
Vd_{ss} (mL/kg)	778	671	646
CL (mL/min/kg)	20.4	17.0	15.0
Terminal $t_{1/2}$ (h)	1.12	0.950	2.44
Additional information: There were no significant differences in the anakinra PK parameter values among 3 groups in which anakinra was co-administered with placebo or 1 or 25 mg/kg PEG-sTNF-RI. Therefore, the results suggested that multiple s.c. doses of PEG-sTNF-RI had no effects on the single-dose i.v. PK of anakinra. 2 of 8 rats showed positive seroreactivity to anakinra after a second i.v. dose of 100 mg/kg anakinra; however, the titers were low (1:100). For the 1- and 25-mg/kg PEG-sTNF-RI groups, all rats developed positive seroreactivity to sTNF-RI. The presence of antibodies increased the clearance of PEG-sTNF-RI for the 1-mg/kg group but not for the 25-mg/kg group.			

Source: Study 100564.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; CL, Clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; GLP, Good Laboratory Practice; i.v., Intravenous; M, male; no., Number; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; PK, Pharmacokinetic(s); s.c., Subcutaneous; $t_{1/2}$, Half-time; Vd_{ss}, Volume of distribution at steady state.

表 2.6.5-9 Sprague-Dawley ラットにアナキンラを反復投与したときの PEG-sTNF-RI の薬物動態に及ぼす影響（100557 試験）

The effect of multiple-dose administration of anakinra on the PK of PEG r-metHu-sTNF-RI in male Sprague-Dawley rats (non-GLP)				**Test article:** Anakinra **Location in CTD:** [4.2.2.2] **Study no.:** 100557
Species	Sprague-Dawley rat			
Sex (M/F)/no. of animals	4 M/group			
Feeding condition	Fed			
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5			
Method of administration	s.c. anakinra; i.v. PEG-sTNF-RI			
Dose (mg/kg)	Anakinra: 0 and 100 PEG-sTNF-RI: 1 and 25 mg/kg, i.v. on Days 1 and 21			
Sample (whole blood, plasma, serum, etc.)	Plasma			
Analyte	Anakinra			
Assay	ELISA			
Plasma PK parameters (mean [SD])	**Group 1** **0 mg/kg anakinra** **1 mg/kg PEG-sTNF-RI**	**Group 2** **0 mg/kg anakinra** **25 mg/kg PEG-sTNF-RI**	**Group 3** **100 mg/kg anakinra** **1 mg/kg PEG-sTNF-RI**	**Group 4** **100 mg/kg anakinra** **25 mg/kg PEG-sTNF-RI**
C_{max} (ng/mL)	23400 (3760)	610000 (65300)	21500 (5160)	560000 (46600)
$t_{1/2}$ (h)	14.8 (4.48)	19.7 (8.52)	12.2 (5.49)	23.2 (0.734)
$AUC_{0-\infty}$ (µg·h/mL)	327 (0.0481)	8060 (650)	311 (74.3)	7590 (873)
$AUC_{0-\infty}$/D (ng·h/mL)/(ng/kg)	0.327 (0.0481)	0.323 (0.0260)	0.311 (0.0743)	0.304 (0.034)
CL (mL/h/kg)	3.11 (0.432)	3.12 (0.263)	3.36 (0.814)	3.33 (0.405)
MRT (h)	20.4 (2.94)	22.9 (3.17)	17.8 (1.33)	23.2 (2.42)
Vd_{ss} (mL/kg)	62.6 (7.38)	71.1 (9.38)	59.3 (11.3)	76.6 (3.5)
Additional information: There were no significant differences in the PK parameters between groups given the same dose of PEG-sTNF-RI in the presence or absence of anakinra. On Day 21, 13 of 16 rats showed seroreactivity to sTNF-RI, but only 5 of 16 were seropositive to PEG-sTNF-RI. CL was significantly increased in seropositive animals; 3 of 16 rats were seropositive to anakinra (all had received 100 mg/kg), but no effect on the CL of PEG-sTNF-RI was observed.				

Source: Study 100557.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; CL, Clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; D, Dose (amount); EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; GLP, Good Laboratory Practice; i.v., Intravenous; M, Male; MRT, Mean residence time; no., Number; PEG r-metHu-sTNF-RI, Polyethylene glycosylated recombinant methinonyl human-soluble tumor necrosis factor-receptor I; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; PK, Pharmacokinetic(s); s.c., Subcutaneous; SD, Standard deviation; $t_{1/2}$, Half-time; Vd_{ss}, Volume of distribution at steady state.

表 2.6.5-10 アカゲザルにアナキンラを反復投与したときのトキシコキネティクス（960040 試験）

A 4-week, toxicity study of anakinra administered by s.c. injection to rhesus monkeys, with a 4-week recovery period		**Test article:** Anakinra	
		Location in CTD: [4.2.3.2]	
		Study no.: 960040	
Species		Rhesus monkey	
Sex (M/F)/no. of animals		3 M and 3 F for Groups 2 and 3; 5 M and 5 F for Groups 1 and 4	
Feeding condition		Fed	
Vehicle/formulation		10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5	
Method of administration		s.c. bolus injection, q.d. for 28 consecutive days	
Dose (mg/kg)		0 (control), 10, 100, and 200	
Sample (whole blood, plasma, serum, etc.)		Plasma	
Analyte		Anakinra	
Assay		ELISA	
Plasma TK parameters (mean [SD])	**10 mg/kg**	**100 mg/kg**	**200 mg/kg**
	Day 1		
n	6	6	10
C_{max} (ng/mL)	5841 (430)	40660 (20110)	59580 (9660)
t_{max} (h)	1.7 (0.5)	2.5 (1.2)	3.8 (1.8)
$t_{1/2}$ (h)	1.96 (0.13)	2.14 (0.84)	2.81 (0.73)
AUC_{0-24} (ng·h/mL)	32490 (1870)	344800 (81900)	670700 (114700)
$AUC_{0-\infty}$ (ng·h/mL)	32510 (1870)	347100 (85700)	677000 (114600)
CL/BA (mL/min/kg)	5.142 (0.316)	5.045 (1.198)	5.048 (0.826)
	Day 28		
n	6	5	10
C_{max} (ng/mL)	7849 (4250)	38390 (8850)	56040 (14070)
t_{max} (h)	2.0 (1.1)	2.0 (1.2)	2.7 (1.2)
$t_{1/2}$ (h)	2.72 (0.69)	3.36 (0.88)	4.74 (1.30)
AUC_{0-24} (ng·h/mL)	57150 (36760)	375600 (156500)	606400 (138700)
CL/BA (mL/min/kg)	3.908 (1.963)	4.921 (1.495)	5.769 (1.353)

A 4-week, toxicity study of anakinra administered by s.c. injection to rhesus monkeys, with a 4-week recovery period		**Test article:** Anakinra	
		Location in CTD: [4.2.3.2]	
		Study no.: 960040	
AR	1.74 (1.07)	1.07 (0.34)	0.92 (0.27)
Additional information: The rhesus monkeys in the active treatment groups were exposed to anakinra approximately in proportion to the administered dose, as plasma clearance (CL/BA) was dose independent (approximately 5 mL/min/kg). No sex difference in the TK of anakinra was observed (p-values > 0.3). No accumulation of mean plasma concentration was noted after multiple doses of anakinra for 4 weeks in the 100-and 200-mg/kg groups. An accumulation (74 %) of mean plasma concentration on Day 28 was observed for the 10-mg/kg group, although the variability was high. The accumulation could be attributed to a decrease in the systemic clearance of anakinra in the presence of anti-anakinra antibodies. A 2-hour urinary recovery period of anakinra expressed as a percentage of the daily dose ranged from 0.026 % to 3.2 %.			

Source: Study 960040.

Abbreviations: AR, Accumulation ratio; AUC_{0-24}, Area under the curve from time 0 to 24 hours; $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; CL/BA, Apparent clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; M, Male; n, Number of animals; no., Number; q.d., Once a day; s.c., Subcutaneous; SD, Standard deviation; $t_{1/2}$, Half-life; TK, Toxicokinetic(s); t_{max}, Time to reach maximum concentration.

表 2.6.5-11 カニクイザルにアナキンラを反復投与したときのトキシコキネティクス（100484 試験）

A 1-month, toxicity study of anakinra and PEG-sTNF-RI administered s.c. in cynomolgus monkeys with a 1-month recovery period (GLP)				**Test article:** Anakinra **Location in CTD:** [4.2.3.2] **Study no.:** 100484
Species	Cynomolgus monkey			
Sex (M/F)/no. of animals	3 to 4/sex/group			
Feeding condition	Fed			
Vehicle/formulation	10 mmol/L citrate, 140 mmol/L sodium chloride, 0.5 mmol/L EDTA, 0.1 % Tween 80 at pH 6.5			
Method of administration	Anakinra, s.c., q.d.; PEG-sTNF-RI, s.c., once weekly for 4 weeks			
Dose (mg/kg)	Anakinra: 0, 100; PEG-sTNF-RI: 0, 1, 5, and 25			
Sample (whole blood, plasma, serum, etc.)	Plasma			
Analyte	Anakinra			
Assay	ELISA			
	Anakinra 100 mg/kg			
	Anakinra alone	**With 1 mg/kg PEG-sTNF-RI**	**With 5 mg/kg PEG-sTNF-RI**	**With 25 mg/kg PEG-sTNF-RI**
Plasma TK parameters (mean)	**Day 0**			
C_{max} (ng/mL)	44900	50600	37900	35500
t_{max} (h)	2.67	2.08	2.33	2.50
$AUC_{0-\infty}$ (ng·h/mL)	442000	490000	376000	403000
CL/BA (mL/min/kg)	3.85	3.42	4.55	4.20
Terminal $t_{1/2}$ (h)	5.04	3.90	3.79	4.25
MRT (h)	8.50	7.48	7.61	8.21
	Day 13			
C_{max} (ng/mL)	46700	42500	36800	31600
t_{max} (h)	1.75	2.00	2.00	2.50
$AUC_{0-\infty}$ (ng·h/mL)	425000	371000	311000	292000
CL/BA (mL/min/kg)	4.35	4.53	5.65	6.00
	Day 27			

A 1-month, toxicity study of anakinra and PEG-sTNF-RI administered s.c. in cynomolgus monkeys with a 1-month recovery period (GLP)			**Test article:** Anakinra	
			Location in CTD: [4.2.3.2]	
			Study no.: 100484	
C_{max} (ng/mL)	46000	38900	36000	39900
t_{max} (h)	2.67	2.08	1.75	2.25
$AUC_{0-\infty}$ (ng·h/mL)	462000	369000	330000	372000
CL/BA (mL/min/kg)	3.98	4.57	5.22	5.28
Additional information: Monkeys in the active treatment groups were exposed to anakinra. On Day 0, there were no significant differences (p-value > 0.05) in anakinra TK parameters between the animals receiving anakinra alone and animals receiving anakinra concomitantly with PEG-sTNF-RI. Thus, single-dose administration of PEG-sTNF-RI in the dose range of 1 to 25 mg/kg did not alter the single-dose (100 mg/kg) s.c. TK of anakinra. On Days 13 and 27, there was a trend of increased CL of anakinra with increasing dose of PEG-sTNF-RI, but it was not significant. In conclusion, multiple s.c. doses of PEG-sTNF-RI had no apparent effects on the multiple-dose s.c. TK of anakinra.				

Source: Study 100484.

Abbreviations: $AUC_{0-\infty}$, Area under the curve from time 0 to infinity; CL/BA, Apparent clearance; C_{max}, Maximum concentration; CTD, Common Technical Document; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked immunosorbent assay; F, Female; GLP, Good Laboratory Practice; i.v., Intravenous; M, Male; MRT, Mean residence time; no., Number; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; q.d., Once daily; s.c., Subcutaneous(ly); $t_{1/2}$, Half-life; TK, Toxicokinetic(s); t_{max}, Time to reach maximum concentration.

2.6.5.5 薬物動態試験：分布

アナキンラの分布試験は実施しなかった（文献で報告されている結果は、[2.6.4.4]項参照）。

2.6.5.6 薬物動態試験：タンパク結合

アナキンラのタンパク結合試験は実施しなかった。

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

アナキンラの妊娠又は授乳動物における試験は実施しなかった。

2.6.5.8 薬物動態試験：その他の分布試験

アナキンラのその他の分布試験は実施しなかった。

2.6.5.9 薬物動態試験：代謝：*In Vivo*

アナキンラの *in vivo* 代謝試験は実施しなかった。

2.6.5.10 薬物動態試験：代謝：*In Vitro*

アナキンラの *in vitro* 代謝試験は実施しなかった。

2.6.5.11 薬物動態試験：推定代謝経路

アナキンラの代謝経路の推定は実施しなかった。

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導／阻害

アナキンラの薬物代謝酵素の誘導又は阻害試験は実施しなかった。

2.6.5.13 薬物動態試験：排泄

［2.6.4.6］項参照

2.6.5.14　薬物動態試験：排泄：胆汁中

アナキンラの胆汁中排泄試験は実施しなかった。

2.6.5.15 薬物動態試験：薬物相互作用

表 2.6.5-12 薬物相互作用

Pharmacokinetic drug-drug interactions					**Test article:** Anakinra	
Type of study	**Species/strain**	**Method of administration**	**Doses (mg/kg)**	**Sex/ no. per group**	**Noteworthy findings**	**Study no.**
A 4-week toxicity and toxicokinetics study of s.c. administration of anakinra and p.o. administration of methotrexate in rats	Rat/ Sprague-Dawley	s.c.; Anakinra p.o.; MTX	Anakinra 0, 10, 100 MTX 0, 0.04, 0.2	F/12	Concomitant oral administration of methotrexate had no apparent effects on the systemic exposure of anakinra to rats. Likewise, anakinra did not influence the systemic exposure of orally administered methotrexate.	960048
A 4-week study of PEG-sTNF-RI administration on the pharmacokinetics of r-metHuIL-1Ra (anakinra) in male Sprague-Dawley rats	Rat/ Sprague-Dawley	i.v.; Anakinra s.c.; PEG-sTNF-RI	Anakinra 100, on Days 1 and 27. PEG-sTNF-RI 0, 1, 25 (b.i.w.)	M/4	There were no significant differences in the anakinra pharmacokinetic parameters when anakinra was co-administered with placebo, 1, or 25 mg/kg PEG-sTNF-RI. Therefore, the results suggested that multiple s.c. doses of PEG-sTNF-RI had no effects on the single-dose i.v. pharmacokinetics of anakinra.	100564
The effect of multiple-dose administration of anakinra on the pharmacokinetics of PEG r-metHu-sTNF-RI in male Sprague Dawley rats	Rat/ Sprague-Dawley	s.c.; Anakinra daily i.v.; PEG-sTNF-RI Day 1, Day 21	Anakinra 0, 100 PEG-sTNF-RI 1, 25	M/4	There were no significant differences in the PK parameters between groups given the same dose of PEG-sTNF-RI in the presence or absence of anakinra. Anakinra at serum levels of approximately 20000 ng/mL for 1 week and 10600 to 290000 ng/mL for 1 month did not alter the kinetics of the i.v. dose of PEG-sTNF-RI.	100557
A 1 month, toxicity study of anakinra and sTNF-RI administered subcutaneously in cynomolgus monkeys	Monkeys/ cynomolgus	s.c.; Anakinra daily s.c.; sTNF-RI weekly	Anakinra 0, 100 sTNF-RI 0, 1, 5, 25	M/2 F/2	Single-dose administration of PEG-sTNF-RI in the dose range of 1 to 25 mg/kg did not alter the single-dose (100 mg/kg) s.c. PK of anakinra. On Days 13 and 27, there was a trend of increased CL of anakinra with increasing dose of PEG-sTNF-RI, but it was not statistically significant.	100484

Abbreviations: b.i.w., Twice a week; CL, Clearance; F, Female; GLP, Good Laboratory Practice; i.v., Intravenous; M, Male; MTX, Methotrexate; no., Number; PEG-sTNF-RI, Polyethylene glycosylated soluble tumor necrosis factor-receptor I; PK, Pharmacokinetic(s); p.o., Peroral; PEG r-metHu-sTNF-RI, Polyethylene glycosylated recombinant methinonyl human-soluble tumor

necrosis factor-receptor I; s.c., Subcutaneous.

2.6.5.16　薬物動態試験：その他

アナキンラのその他の薬物動態試験は実施しなかった。