Table 8 Evaluation of the Effects of Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) Product in Cynomolgus Monkeys by Inhalation Exposure Histopathology (males)

Organ and tissue		Findings	Group	Control (Albumin)		CHO cell-derived GM-CSF		Yeast-derived GM-CSF		Escherichia coli-derived GM-CSF	
			Dose level	0.5 mg/day		0.5 mg/day		0.5 mg/day		0.5 mg/day	
			\ Animal No.	LQ1M01	LQ1M02	LQ2M01	LQ2M02	LQ3M01	LQ3M02	LQ4M01	LQ4M02
Trachea		Pathological change		-	-	-	-	-	-	-	-
Lung with bronchus	(left of the anterior)	Fibrous thickening, pleura		-	-	-	±	-	-	-	-
	(left of the middle)	Cell infiltration, inflammatory cell, alveolar/bronchiolar		-	-	-	-	-	+	-	-
		Fibrous thickening, pleura		-	-	-	±	-	-	-	-
	(left of the posterior)	Fibrous thickening, pleura		-	-	-	±	-	-	-	-
Lung with bronchus	(right of the anterior)	Cell infiltration, inflammatory cell, alveolar/bronchiolar		-	-	-	±	±	-	-	-
		Cell infiltration, inflammatory cell, subpleura		±	-	-	-	-	-	-	-
	(right of the middle)	Cell infiltration, inflammatory cell, alveolar/bronchiolar		±	+	++	+	-	-	±	-
		Hemorrhage		±	-	±	-	-	-	±	-
		Vacuolated cell, alveolar		-	-	+	-	-	-	-	-
		Retention, eosinophilic substance		±	-	++	±	±	-	±	-
	(right of the posterior)	Cell infiltration, inflammatory cell, alveolar/bronchiolar		-	-	-	-	±	-	-	-
		Granuloma with mineralization		-	-	-	-	-	+	-	-
		Retention, eosinophilic substance		-	-	-	-	±	-	-	-
Hilar lymph node		Pathological change		-	-	-	-	-	-	-	-

-: None/Negative ±: Slight +: Moderate ++: Severe +++: Very severe P: Present

Table 9-1 Evaluation of the Effects of Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) Product in Cynomolgus Monkeys by Inhalation Exposure
Bone marrow examinations - List of abbreviations -

Abbreviation	Expansion
NBMC	Nucleated bone marrow cell counts
PEBL	Proerythroblasts
BAS E	Basophilic erythroblasts
POL E	Polychromatic erythroblasts
ORT E	Orthochromatic erythroblasts
MIT E	Mitotic erythroid cells
MBL	Myeloblasts
PRO	Promyelocytes
N MY	Neutrophilic myelocytes
N META	Neutrophilic metamyelocytes
N BAND	Neutrophilic band cells
N SEG	Neutrophilic segmented cells
EOS	Eosinophils
BASO	Basophils
MIT M	Mitotic myeloid cells
MONO	Monocytes
LYMPH	Lymphocytes
PLASM	Plasma cells
MEGK	Megakaryocytes
RETICU	Reticulum cells
MACRO	Macrophages
MAST	Mast cells
M/E	Myeloid/Erythroid ratio

Table 9-2 Evaluation of the Effects of Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) Product in Cynomolgus Monkeys by Inhalation Exposure
Bone marrow examinations (males)

Group	Dose level	Animal No.	NBMC ($10^4/\mu L$)	Erythroid cells (%)						Myeloid cells (%)									
				PEBL	BAS E	POL E	ORT E	MIT E	Total	MBL	PRO	N MY	N META	N BAND	N SEG	EOS	BASO	MIT M	Total
Control (Albumin)	0.5 mg/day	LQ1M01	144	0.2	5.6	34.8	2.0	2.8	45.4	0.4	2.2	4.0	5.0	5.8	17.0	3.0	0.6	0.2	38.2
		LQ1M02	225	0.2	7.0	33.8	6.0	2.6	49.6	0.4	2.6	3.2	5.8	8.2	16.4	4.0	0.0	0.0	40.6
CHO cell-derived GM-CSF	0.5 mg/day	LQ2M01	225	0.4	5.0	26.8	3.2	0.8	36.2	0.2	2.6	8.6	10.6	9.0	12.8	11.4	1.8	0.2	57.2
		LQ2M02	183	0.6	6.2	23.0	1.0	2.2	33.0	0.4	1.2	7.6	8.2	9.8	20.6	5.8	0.6	0.2	54.4
Yeast-derived GM-CSF	0.5 mg/day	LQ3M01	135	0.2	4.0	26.8	1.4	2.0	34.4	0.8	2.4	5.0	4.8	9.8	22.6	3.8	2.6	0.4	52.2
		LQ3M02	165	0.6	5.4	27.0	4.6	0.6	38.2	0.0	2.8	6.4	6.4	6.8	24.2	3.6	0.4	0.0	50.6
Escherichia coli-derived GM-CSF	0.5 mg/day	LQ4M01	186	0.2	6.2	31.0	3.0	1.6	42.0	0.0	1.6	5.8	5.6	11.4	18.2	4.0	0.6	0.0	47.2
		LQ4M02	231	0.2	6.0	17.6	2.4	1.0	27.2	0.0	1.2	5.2	4.0	11.8	35.0	5.0	0.8	0.6	63.6

Table 9-2 (Continued-1) Evaluation of the Effects of Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) Product in Cynomolgus Monkeys by Inhalation Exposure
Bone marrow examinations (males)

Group	Dose level	Animal No.	MONO (%)	LYMPH (%)	PLASM (%)	MEGK (%)	RETICU (%)	MACRO (%)	MAST (%)	OTHERS (%)	M/E	Erythroid cells ($10^4/\mu L$)					
												PEBL	BAS E	POL E	ORT E	MIT E	Total
Control (Albumin)	0.5 mg/day	LQ1M01	1.6	11.8	2.2	0.2	0.0	0.6	0.0	0.0	0.84	0.3	8.1	50.1	2.9	4.0	65.4
		LQ1M02	2.8	5.0	1.2	0.0	0.0	0.8	0.0	0.0	0.82	0.5	15.8	76.1	13.5	5.9	111.6
CHO cell-derived GM-CSF	0.5 mg/day	LQ2M01	1.8	3.4	1.0	0.0	0.0	0.4	0.0	0.0	1.58	0.9	11.3	60.3	7.2	1.8	81.5
		LQ2M02	3.0	8.0	1.2	0.2	0.0	0.2	0.0	0.0	1.65	1.1	11.3	42.1	1.8	4.0	60.4
Yeast-derived GM-CSF	0.5 mg/day	LQ3M01	2.6	9.6	0.8	0.0	0.0	0.4	0.0	0.0	1.52	0.3	5.4	36.2	1.9	2.7	46.4
		LQ3M02	0.6	9.8	0.4	0.2	0.0	0.2	0.0	0.0	1.32	1.0	8.9	44.6	7.6	1.0	63.0
Escherichia coli-derived GM-CSF	0.5 mg/day	LQ4M01	2.0	8.0	0.4	0.0	0.0	0.4	0.0	0.0	1.12	0.4	11.5	57.7	5.6	3.0	78.1
		LQ4M02	3.4	4.6	1.0	0.0	0.0	0.2	0.0	0.0	2.34	0.5	13.9	40.7	5.5	2.3	62.8

Table 9-2 (Continued-2) Evaluation of the Effects of Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) Product in Cynomolgus Monkeys by Inhalation Exposure
Bone marrow examinations (males)

Group	Dose level	Animal No.	Myeloid cells (10^4/μL)										MONO	LYMPH	PLASM	MEGK	RETICU	MACRO	MAST	OTHERS
			MBL	PRO	N MY	N META	N BAND	N SEG	EOS	BASO	MIT M	Total	(10^4/μL)	(10^4/μL)	(10^4/μL)	(10^4/μL)	(10^4/μL)	(10^4/μL)	(10^4/μL)	(10^4/μL)
Control (Albumin)	0.5 mg/day	LQ1M01	0.6	3.2	5.8	7.2	8.4	24.5	4.3	0.9	0.3	55.0	2.3	17.0	3.2	0.3	0.0	0.9	0.0	0.0
		LQ1M02	0.9	5.9	7.2	13.1	18.5	36.9	9.0	0.0	0.0	91.4	6.3	11.3	2.7	0.0	0.0	1.8	0.0	0.0
CHO cell-derived GM-CSF	0.5 mg/day	LQ2M01	0.5	5.9	19.4	23.9	20.3	28.8	25.7	4.1	0.5	128.7	4.1	7.7	2.3	0.0	0.0	0.9	0.0	0.0
		LQ2M02	0.7	2.2	13.9	15.0	17.9	37.7	10.6	1.1	0.4	99.6	5.5	14.6	2.2	0.4	0.0	0.4	0.0	0.0
Yeast-derived GM-CSF	0.5 mg/day	LQ3M01	1.1	3.2	6.8	6.5	13.2	30.5	5.1	3.5	0.5	70.5	3.5	13.0	1.1	0.0	0.0	0.5	0.0	0.0
		LQ3M02	0.0	4.6	10.6	10.6	11.2	39.9	5.9	0.7	0.0	83.5	1.0	16.2	0.7	0.3	0.0	0.3	0.0	0.0
Escherichia coli-derived GM-CSF	0.5 mg/day	LQ4M01	0.0	3.0	10.8	10.4	21.2	33.9	7.4	1.1	0.0	87.8	3.7	14.9	0.7	0.0	0.0	0.7	0.0	0.0
		LQ4M02	0.0	2.8	12.0	9.2	27.3	80.9	11.6	1.8	1.4	146.9	7.9	10.6	2.3	0.0	0.0	0.5	0.0	0.0