

Table 5 Composition ratio and radioactivity distribution of P092 and its metabolites in bile at 24 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% in analysis sample	
			(%) <i>of dose</i>)
mBM-1	16.7	Unknown	(8.8 0.1)
mBM-2	20.9	Unknown	(13.7 0.1)
mBM-3	23.4	Unknown	(7.1 0.0)
mBM-4	26.3	Unknown	(8.6 0.1)
mBM-5	30.4	Unknown	(7.5 0.1)
mBM-6	32.5	Unknown	(3.5 0.0)
mBM-7	40.3	Unknown	(5.3 0.0)
mBM-8	41.2	Unknown	(5.7 0.0)
mBM-9	54.1	P092	(5.5 0.0)
Others	--	--	(26.8 0.2)
Unextracted	--	--	(7.6 0.1)
Total radioactivity distribution			(0.68)

Composition ratio = % in analysis sample

Radioactivity distribution = % of dose

--: Not applicable

Table 6 **Composition ratio and radioactivity concentration of P092 and its metabolites in cerebral cortex at 168 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg**

Metabolite No.	Retention time (min)	Component	% in analysis sample (<i>ng eq./mL</i>)
mCOM-1	54.1	P092	27.6 (45.8)
Others	--	--	28.4 (47.1)
Unextracted	--	--	44.0 (73.0)
Total radioactivity concentration			(166.0)

Composition ratio = % in analysis sample

Radioactivity concentration = ng eq./mL

--: Not applicable

Table 7 **Composition ratio and radioactivity concentration of P092 and its metabolites in hypothalamus at 168 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg**

Metabolite No.	Retention time (min)	Component	% in analysis sample (<i>ng eq./mL</i>)
mHTM-1	54.0	P092	38.9 (96.0)
Others	--	--	17.5 (43.2)
Unextracted	--	--	43.6 (107.6)
Total radioactivity concentration			(246.8)

Composition ratio = % in analysis sample

Radioactivity concentration = ng eq./mL

--: Not applicable

Table 8 Comparison of retention times of radioactive components detected in plasma, urine, feces, bile, cerebral cortex, and hypothalamus after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.						t _R (min)	Component
Plasma	Urine	Feces	Bile	Cerebral cortex	Hypo-thalamus		
mPM-1	mUM-1	mFM-1	--	--	--	3.1-3.4	Unknown
--	mUM-2	--	mBM-1	--	--	16.3-16.7	Unknown
--	mUM-3	--	--	--	--	18.9	Unknown
--	--	mFM-2	mBM-2	--	--	20.9-21.0	Unknown
--	mUM-4	--	--	--	--	21.7	Unknown
--	mUM-5	--	mBM-3	--	--	23.2-23.4	Unknown
--	mUM-6	--	mBM-4	--	--	26.1-26.3	Unknown
--	--	mFM-3	--	--	--	29.7	Unknown
--	--	--	mBM-5	--	--	30.4	Unknown
--	mUM-7	--	--	--	--	31.0	Unknown
--	--	mFM-4	--	--	--	31.6	Unknown
--	--	--	mBM-6	--	--	32.5	Unknown
--	mUM-8	--	--	--	--	33.0	Unknown
--	mUM-9	--	--	--	--	33.8	Unknown
--	--	mFM-5	mBM-7	--	--	40.0-40.3	Unknown
--	mUM-10	--	--	--	--	40.9	Unknown
--	--	--	mBM-8	--	--	41.2	Unknown
--	mUM-11	--	--	--	--	41.9	Unknown
mPM-2	--	mFM-6	mBM-9	mCOM-1	mHTM-1	54.0-54.1	P092

t_R: Retention time

--: Not applicable

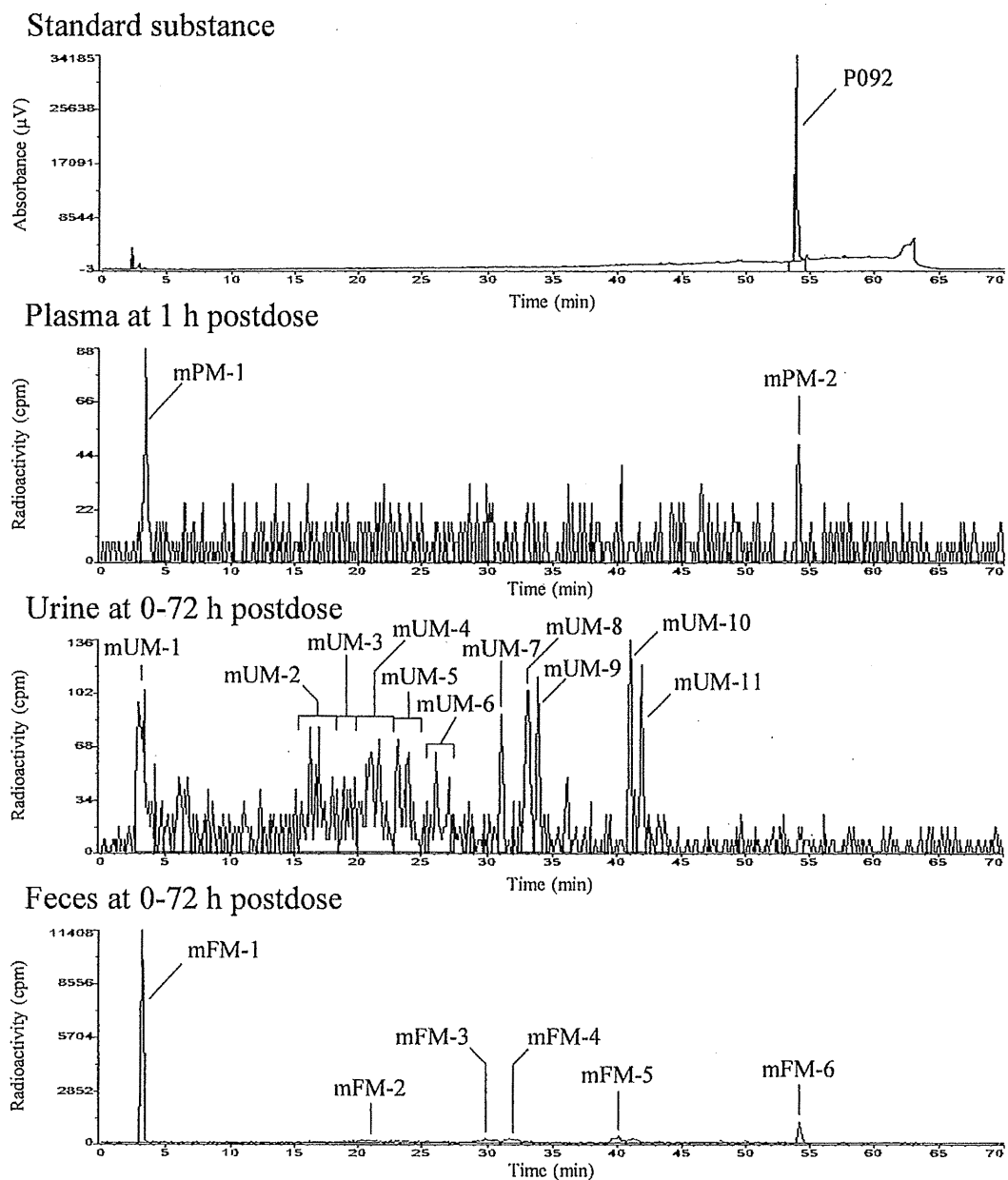


Figure 1 UV chromatogram of P092 maleate standard substance and radiochromatograms of plasma, urine, and feces after single intravenous bolus administration of [14 C]P092 maleate to a male monkey at 1 mg/kg

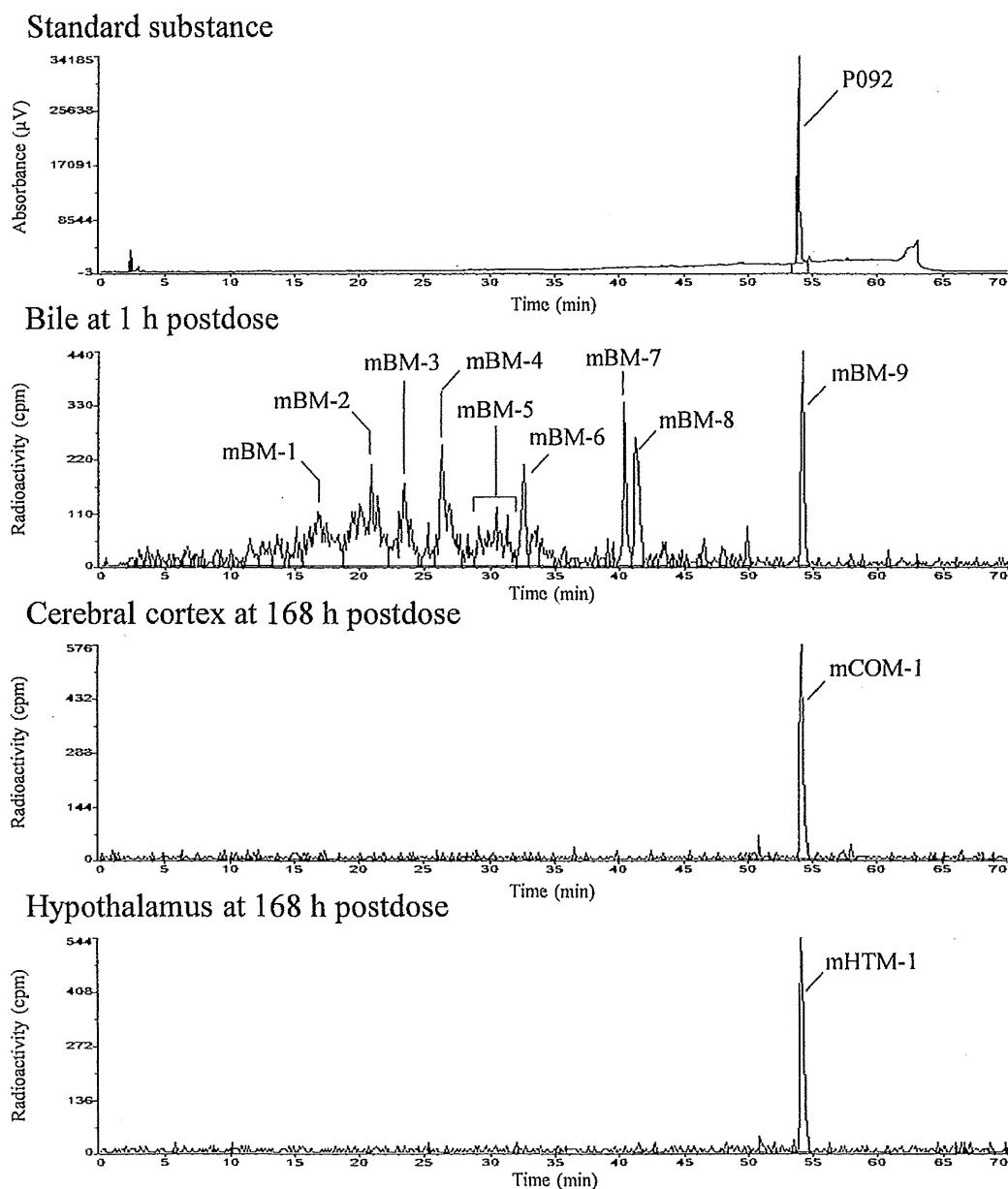


Figure 2 UV chromatogram of P092 maleate standard substance and radiochromatograms of bile, cerebral cortex, and hypothalamus after single intravenous bolus administration of [^{14}C]P092 maleate to a male monkey at 1 mg/kg

Appendix 1 Peak area percentage and composition ratio of P092 and its metabolites in plasma at 1 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks	
			[% in analysis sample]
mPM-1	3.4	Unknown		7.8
			[5.4]
mPM-2	54.0	P092		3.7
			[2.5]
Others	--	--		88.5
			[60.9]
Recovery of radioactivity in sample pretreatment*				68.8

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

Appendix 2 Peak area percentage and composition ratio of P092 and its metabolites in urine at 0-72 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks	
			[% in analysis sample]
mUM-1	3.3	Unknown	[9.0 8.6]
mUM-2	16.3	Unknown	[10.2 9.8]
mUM-3	18.9	Unknown	[3.8 3.6]
mUM-4	21.7	Unknown	[10.7 10.3]
mUM-5	23.2	Unknown	[7.6 7.3]
mUM-6	26.1	Unknown	[5.3 5.1]
mUM-7	31.0	Unknown	[2.8 2.7]
mUM-8	33.0	Unknown	[6.0 5.8]
mUM-9	33.8	Unknown	[3.2 3.1]
mUM-10	40.9	Unknown	[4.9 4.7]
mUM-11	41.9	Unknown	[4.2 4.0]
Others	--	--	[32.3 31.0]
Recovery of radioactivity in sample pretreatment*				95.9

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

Appendix 3 Peak area percentage and composition ratio of P092 and its metabolites in feces at 0-72 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks	
			[% in analysis sample]
mFM-1	3.1	Unknown		46.5
			[35.5]
mFM-2	21.0	Unknown		6.4
			[4.9]
mFM-3	29.7	Unknown		5.6
			[4.3]
mFM-4	31.6	Unknown		4.6
			[3.5]
mFM-5	40.0	Unknown		4.9
			[3.7]
mFM-6	54.1	P092		5.4
			[4.1]
Others	--	--		26.6
			[20.3]
Recovery of radioactivity in sample pretreatment*				76.3

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

Appendix 4 Peak area percentage and composition ratio of P092 and its metabolites in bile at 24 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks	
			[% in analysis sample]
mBM-1	16.7	Unknown		9.5
			[8.8]
mBM-2	20.9	Unknown		14.8
			[13.7]
mBM-3	23.4	Unknown		7.7
			[7.1]
mBM-4	26.3	Unknown		9.3
			[8.6]
mBM-5	30.4	Unknown		8.1
			[7.5]
mBM-6	32.5	Unknown		3.8
			[3.5]
mBM-7	40.3	Unknown		5.7
			[5.3]
mBM-8	41.2	Unknown		6.2
			[5.7]
mBM-9	54.1	P092		5.9
			[5.5]
Others	--	--		29.0
			[26.8]
Recovery of radioactivity in sample pretreatment*				92.4

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

Appendix 5 Peak area percentage and composition ratio of P092 and its metabolites in cerebral cortex at 168 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks	
			[% in analysis sample]
mCOM-1	54.1	P092		49.3
			[27.6]
Others	--	--		50.7
			[28.4]
Recovery of radioactivity in sample pretreatment*				56.0

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

Appendix 6 Peak area percentage and composition ratio of P092 and its metabolites in hypothalamus at 168 h after single intravenous bolus administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg

Metabolite No.	Retention time (min)	Component	% Peaks [% in analysis sample]	
mHTM-1	54.0	P092	68.9	
				38.9
Others	--	--	31.1	
				17.5
Recovery of radioactivity in sample pretreatment*			56.4	

Peak area percentage = % Peaks

Composition ratio = % in analysis sample

--: Not applicable

* Recovery of radioactivity from analysis sample to HPLC sample

15. $[^{14}\text{C}]$ P092 マレイン酸塩を
ラットに単回静脈内投与したときの
放射能の血中濃度、排泄及び分布

本写しは原本と相違ありません
㈱LSIメディエンス 鹿島研究所
2015年 3月18日
試験責任者 中井弘司

最終報告書

[¹⁴C]P092・マレイン酸塩をラットに単回静脈内投与したときの
放射能の血中濃度、排泄及び分布

(試験番号：B130898)

株式会社LSIメディエンス

1. 陳述書

表題： [^{14}C]P092・マレイン酸塩をラットに単回静脈内投与したときの放射能の血中濃度，
排泄及び分布

試験番号：B130898

本試験は下記の基準に従い実施したものである。

「申請資料の信頼性の基準」

(医薬品，医療機器等の品質，有効性及び安全性の確保等に関する法律施行規則 第43条)

試験責任者：

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