付録 2.7.6.4
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
腹水	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)	3 (60.0)	0 (0.0)	6 (54.5)	0 (0.0)	6 (30.0)	0 (0.0)
口唇炎	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
便秘	2 (33.3)	0 (0.0)	3 (100.0)	0 (0.0)	5 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (25.0)	0 (0.0)
下痢	6 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	6 (100.0)	1 (16.7)	3 (60.0)	1 (20.0)	9 (81.8)	2 (18.2)	18 (90.0)	2 (10.0)
心窩部不快感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (10.0)	0 (0.0)
変色便	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
胃炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
歯肉出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
歯肉の炎症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
吐血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)
口の感覚鈍麻	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
悪心	2 (33.3)	0 (0.0)	3 (100.0)	0 (0.0)	5 (55.6)	0 (0.0)	3 (50.0)	0 (0.0)	4 (80.0)	0 (0.0)	7 (63.6)	0 (0.0)	12 (60.0)	0 (0.0)
口内炎	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	0 (0.0)
嘔吐	3 (50.0)	0 (0.0)	3 (100.0)	0 (0.0)	6 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	2 (40.0)	0 (0.0)	4 (36.4)	0 (0.0)	10 (50.0)	0 (0.0)
一般・全身障害および投与部位の状態	6 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	6 (100.0)	0 (0.0)	5 (100.0)	1 (20.0)	11 (100.0)	1 (9.1)	20 (100.0)	1 (5.0)
顔面浮腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
疲労	5 (83.3)	0 (0.0)	3 (100.0)	0 (0.0)	8 (88.9)	0 (0.0)	5 (83.3)	0 (0.0)	5 (100.0)	1 (20.0)	10 (90.9)	1 (9.1)	18 (90.0)	1 (5.0)
全身健康状態低下	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (40.0)	1 (20.0)	3 (27.3)	1 (9.1)	3 (15.0)	1 (5.0)
粘膜の炎症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
末梢性浮腫	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (22.2)	0 (0.0)	5 (83.3)	0 (0.0)	1 (20.0)	0 (0.0)	6 (54.5)	0 (0.0)	8 (40.0)	0 (0.0)
発熱	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (36.4)	0 (0.0)	7 (35.0)	0 (0.0)
肝胆道系障害	2 (33.3)	1 (16.7)	2 (66.7)	1 (33.3)	4 (44.4)	2 (22.2)	5 (83.3)	1 (16.7)	4 (80.0)	2 (40.0)	9 (81.8)	3 (27.3)	13 (65.0)	5 (25.0)
肝不全	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.4
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
肝機能異常	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
高ビリルビン血症	2 (33.3)	1 (16.7)	1 (33.3)	0 (0.0)	3 (33.3)	1 (11.1)	5 (83.3)	1 (16.7)	4 (80.0)	2 (40.0)	9 (81.8)	3 (27.3)	12 (60.0)	4 (20.0)
感染症および寄生虫症	3 (50.0)	1 (16.7)	3 (100.0)	2 (66.7)	6 (66.7)	3 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	7 (35.0)	3 (15.0)
胆道感染	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
歯肉炎	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
感染	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
鼻咽頭炎	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
咽頭炎	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
肺炎	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
腎盂腎炎	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
皮下組織膿瘍	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
尿路感染	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
傷害、中毒および処置合併症	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	3 (15.0)	1 (5.0)
転倒	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
手骨折	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
瘢痕ヘルニア	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
処置後出血	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
臨床検査	6 (100.0)	2 (33.3)	2 (66.7)	1 (33.3)	8 (88.9)	3 (33.3)	4 (66.7)	0 (0.0)	4 (80.0)	3 (60.0)	8 (72.7)	3 (27.3)	16 (80.0)	6 (30.0)
アラニンアミノトランスフェラーゼ増加	3 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	1 (5.0)

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付録 2.7.6.4
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
アスパラギン酸アミノトランスフェラーゼ増加	4 (66.7)	1 (16.7)	0 (0.0)	0 (0.0)	4 (44.4)	1 (11.1)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)	3 (27.3)	2 (18.2)	7 (35.0)	3 (15.0)
血中アルカリホスファターゼ増加	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (18.2)	0 (0.0)	5 (25.0)	0 (0.0)
血中ビリルビン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
血中クレアチニン増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
血中乳酸脱水素酵素増加	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	4 (20.0)	0 (0.0)
血中甲状腺刺激ホルモン減少	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
血中甲状腺刺激ホルモン増加	5 (83.3)	0 (0.0)	1 (33.3)	0 (0.0)	6 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	9 (45.0)	0 (0.0)
尿中血陽性	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
Ｃ－反応性蛋白増加	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)	2 (18.2)	0 (0.0)	5 (25.0)	0 (0.0)
γ－グルタミルトランスフェラーゼ増加	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	1 (20.0)	2 (18.2)	1 (9.1)	5 (25.0)	1 (5.0)
ヘモグロビン減少	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
国際標準比増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
好中球数減少	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)

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Eisai

Protocol: Lenvatinib (E7080) Integrated Summary of Safety

付録 2.7.6.4

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Study 202 - Phase I

Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
血小板数減少	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)
遊離サイロキシン減少	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
遊離サイロキシン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
遊離トリヨードチロニン減少	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	4 (20.0)	0 (0.0)
遊離トリヨードチロニン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
体重減少	3 (50.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	3 (50.0)	0 (0.0)	2 (40.0)	0 (0.0)	5 (45.5)	0 (0.0)	9 (45.0)	0 (0.0)
白血球数減少	1 (16.7)	0 (0.0)	1 (33.3)	1 (33.3)	2 (22.2)	1 (11.1)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	1 (5.0)
代謝および栄養障害	6 (100.0)	1 (16.7)	3 (100.0)	2 (66.7)	9 (100.0)	3 (33.3)	5 (83.3)	2 (33.3)	5 (100.0)	2 (40.0)	10 (90.9)	4 (36.4)	19 (95.0)	7 (35.0)
食欲減退	6 (100.0)	1 (16.7)	2 (66.7)	0 (0.0)	8 (88.9)	1 (11.1)	3 (50.0)	0 (0.0)	5 (100.0)	1 (20.0)	8 (72.7)	1 (9.1)	16 (80.0)	2 (10.0)
脱水	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
高アンモニア血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)	2 (40.0)	0 (0.0)	5 (45.5)	0 (0.0)	5 (25.0)	0 (0.0)
高カリウム血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
低アルブミン血症	3 (50.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	1 (16.7)	1 (16.7)	1 (20.0)	0 (0.0)	2 (18.2)	1 (9.1)	6 (30.0)	1 (5.0)
低カルシウム血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (10.0)	0 (0.0)
低クロール血症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
低ナトリウム血症	1 (16.7)	0 (0.0)	2 (66.7)	2 (66.7)	3 (33.3)	2 (22.2)	1 (16.7)	1 (16.7)	1 (20.0)	1 (20.0)	2 (18.2)	2 (18.2)	5 (25.0)	4 (20.0)
筋骨格系および結合組織障害	3 (50.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	0 (0.0)
関節痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
背部痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

Program: T2_7_6_4.sas

09JUN2017 10:03

付録 2.7.6.4
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2						All	
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
骨痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
筋痙縮	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	0 (0.0)
筋骨格系胸痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
筋骨格痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
筋骨格硬直	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	3 (60.0)	1 (20.0)	4 (36.4)	2 (18.2)	4 (20.0)	2 (10.0)
癌疼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (10.0)	0 (0.0)
腫瘍出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (20.0)	1 (20.0)	2 (18.2)	2 (18.2)	2 (10.0)	2 (10.0)
神経系障害	3 (50.0)	0 (0.0)	1 (33.3)	1 (33.3)	4 (44.4)	1 (11.1)	2 (33.3)	0 (0.0)	1 (20.0)	1 (20.0)	3 (27.3)	1 (9.1)	7 (35.0)	2 (10.0)
味覚異常	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
頭痛	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	4 (20.0)	0 (0.0)
肝性脳症	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	1 (16.7)	0 (0.0)	1 (20.0)	1 (20.0)	2 (18.2)	1 (9.1)	3 (15.0)	2 (10.0)
精神障害	1 (16.7)	0 (0.0)	3 (100.0)	1 (33.3)	4 (44.4)	1 (11.1)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	5 (25.0)	1 (5.0)
錯乱状態	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
不眠症	1 (16.7)	0 (0.0)	2 (66.7)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	4 (20.0)	0 (0.0)
腎および尿路障害	2 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (44.4)	1 (11.1)	1 (16.7)	0 (0.0)	2 (40.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	1 (5.0)
蛋白尿	2 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (44.4)	1 (11.1)	1 (16.7)	0 (0.0)	2 (40.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	1 (5.0)
腎機能障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	3 (50.0)	0 (0.0)	2 (66.7)	1 (33.3)	5 (55.6)	1 (11.1)	4 (66.7)	0 (0.0)	4 (80.0)	0 (0.0)	8 (72.7)	0 (0.0)	13 (65.0)	1 (5.0)
咳嗽	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
発声障害	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	5 (45.5)	0 (0.0)	8 (40.0)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

Eisai

Protocol: Lenvatinib (E7080) Integrated Summary of Safety

付録 2.7.6.4
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
鼻出血	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	4 (20.0)	0 (0.0)
しゃっくり	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
低酸素症	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
口腔咽頭痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
胸水	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
皮膚および皮下組織障害	6 (100.0)	1 (16.7)	3 (100.0)	0 (0.0)	9 (100.0)	1 (11.1)	5 (83.3)	0 (0.0)	4 (80.0)	0 (0.0)	9 (81.8)	0 (0.0)	18 (90.0)	1 (5.0)
脱毛症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
褥瘡性潰瘍	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
ざ瘡様皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
爪の障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
手掌・足底発赤知覚不全症候群	5 (83.3)	1 (16.7)	3 (100.0)	0 (0.0)	8 (88.9)	1 (11.1)	3 (50.0)	0 (0.0)	2 (40.0)	0 (0.0)	5 (45.5)	0 (0.0)	13 (65.0)	1 (5.0)
そう痒症	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	0 (0.0)
発疹	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	0 (0.0)
血管障害	5 (83.3)	4 (66.7)	3 (100.0)	2 (66.7)	8 (88.9)	6 (66.7)	3 (50.0)	2 (33.3)	4 (80.0)	2 (40.0)	7 (63.6)	4 (36.4)	15 (75.0)	10 (50.0)
高血圧	5 (83.3)	4 (66.7)	3 (100.0)	2 (66.7)	8 (88.9)	6 (66.7)	3 (50.0)	2 (33.3)	4 (80.0)	2 (40.0)	7 (63.6)	4 (36.4)	15 (75.0)	10 (50.0)
静脈炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

Program: T2_7_6_4.sas

09JUN2017 10:03

付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any Related TEAEs	6 (100.0)	4 (66.7)	3 (100.0)	3 (100.0)	9 (100.0)	7 (77.8)	6 (100.0)	5 (83.3)	5 (100.0)	5 (100.0)	11 (100.0)	10 (90.9)	20 (100.0)	17 (85.0)
血液およびリンパ系障害	3 (50.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	5 (83.3)	2 (33.3)	2 (40.0)	0 (0.0)	7 (63.6)	2 (18.2)	11 (55.0)	2 (10.0)
貧血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)
白血球減少症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	3 (15.0)	0 (0.0)
リンパ球減少症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
好中球減少症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	1 (16.7)	1 (20.0)	0 (0.0)	4 (36.4)	1 (9.1)	4 (20.0)	1 (5.0)
血小板減少症	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	2 (40.0)	0 (0.0)	3 (27.3)	1 (9.1)	6 (30.0)	1 (5.0)
心臓障害	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
不整脈	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
房室ブロック	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
上室性期外収縮	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
耳および迷路障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
耳鳴	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
内分泌障害	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
甲状腺機能亢進症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
甲状腺機能低下症	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
胃腸障害	6 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	6 (100.0)	1 (16.7)	4 (80.0)	0 (0.0)	10 (90.9)	1 (9.1)	19 (95.0)	1 (5.0)
腹痛	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	3 (50.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (36.4)	0 (0.0)	6 (30.0)	0 (0.0)
肛門そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
腹水	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	3 (15.0)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
口唇炎	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
便秘	2 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (20.0)	0 (0.0)
下痢	5 (83.3)	0 (0.0)	3 (100.0)	0 (0.0)	8 (88.9)	0 (0.0)	4 (66.7)	1 (16.7)	2 (40.0)	0 (0.0)	6 (54.5)	1 (9.1)	14 (70.0)	1 (5.0)
心窩部不快感	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
変色便	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
歯肉出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
歯肉の炎症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
悪心	2 (33.3)	0 (0.0)	3 (100.0)	0 (0.0)	5 (55.6)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	5 (45.5)	0 (0.0)	10 (50.0)	0 (0.0)
口内炎	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)	2 (18.2)	0 (0.0)	4 (20.0)	0 (0.0)
嘔吐	3 (50.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	0 (0.0)
一般・全身障害および投与部位の状態	5 (83.3)	0 (0.0)	3 (100.0)	0 (0.0)	8 (88.9)	0 (0.0)	6 (100.0)	0 (0.0)	4 (80.0)	0 (0.0)	10 (90.9)	0 (0.0)	18 (90.0)	0 (0.0)
顔面浮腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
疲労	4 (66.7)	0 (0.0)	2 (66.7)	0 (0.0)	6 (66.7)	0 (0.0)	5 (83.3)	0 (0.0)	3 (60.0)	0 (0.0)	8 (72.7)	0 (0.0)	14 (70.0)	0 (0.0)
全身健康状態低下	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (10.0)	0 (0.0)
粘膜の炎症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
末梢性浮腫	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (22.2)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	5 (25.0)	0 (0.0)
発熱	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	0 (0.0)
肝胆道系障害	1 (16.7)	0 (0.0)	1 (33.3)	1 (33.3)	2 (22.2)	1 (11.1)	5 (83.3)	1 (16.7)	3 (60.0)	2 (40.0)	8 (72.7)	3 (27.3)	10 (50.0)	4 (20.0)
肝機能異常	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
高ビリルビン血症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	5 (83.3)	1 (16.7)	3 (60.0)	2 (40.0)	8 (72.7)	3 (27.3)	9 (45.0)	3 (15.0)
感染症および寄生虫症	2 (33.3)	1 (16.7)	2 (66.7)	2 (66.7)	4 (44.4)	3 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	5 (25.0)	3 (15.0)

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付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
胆道感染	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
歯肉炎	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
感染	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
咽頭炎	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
肺炎	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
腎盂腎炎	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
皮下組織膿瘍	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
尿路感染	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
臨床検査	6 (100.0)	1 (16.7)	2 (66.7)	1 (33.3)	8 (88.9)	2 (22.2)	3 (50.0)	0 (0.0)	3 (60.0)	2 (40.0)	6 (54.5)	2 (18.2)	14 (70.0)	4 (20.0)
アラニンアミノトランスフェラーゼ増加	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	1 (5.0)
アスパラギン酸アミノトランスフェラーゼ増加	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (9.1)	1 (9.1)	3 (15.0)	1 (5.0)
血中アルカリホスファターゼ増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
血中ビリルビン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
血中クレアチニン増加	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)

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付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
血中乳酸脱水素酵素増加	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	0 (0.0)
血中甲状腺刺激ホルモン減少	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
血中甲状腺刺激ホルモン増加	5 (83.3)	0 (0.0)	1 (33.3)	0 (0.0)	6 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	9 (45.0)	0 (0.0)
尿中血陽性	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
C－反応性蛋白増加	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)	2 (18.2)	0 (0.0)	5 (25.0)	0 (0.0)
γ－グルタミルトランスフェラーゼ増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
国際標準比増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
好中球数減少	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
血小板数減少	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)
遊離サイロキシン減少	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
遊離サイロキシン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
遊離トリヨードチロニン減少	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	4 (20.0)	0 (0.0)

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付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
遊離トリヨードチロニン増加	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
体重減少	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	0 (0.0)
白血球数減少	1 (16.7)	0 (0.0)	1 (33.3)	1 (33.3)	2 (22.2)	1 (11.1)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	1 (5.0)
代謝および栄養障害	5 (83.3)	0 (0.0)	3 (100.0)	2 (66.7)	8 (88.9)	2 (22.2)	4 (66.7)	1 (16.7)	4 (80.0)	0 (0.0)	8 (72.7)	1 (9.1)	16 (80.0)	3 (15.0)
食欲減退	5 (83.3)	0 (0.0)	2 (66.7)	0 (0.0)	7 (77.8)	0 (0.0)	3 (50.0)	0 (0.0)	4 (80.0)	0 (0.0)	7 (63.6)	0 (0.0)	14 (70.0)	0 (0.0)
高アンモニア血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (40.0)	0 (0.0)	4 (36.4)	0 (0.0)	4 (20.0)	0 (0.0)
高カリウム血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
低アルブミン血症	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	1 (20.0)	0 (0.0)	2 (18.2)	1 (9.1)	5 (25.0)	1 (5.0)
低カルシウム血症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
低ナトリウム血症	0 (0.0)	0 (0.0)	2 (66.7)	2 (66.7)	2 (22.2)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	2 (10.0)
筋骨格系および結合組織障害	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
関節痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
筋痙縮	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
神経系障害	2 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)	3 (33.3)	1 (11.1)	2 (33.3)	0 (0.0)	1 (20.0)	1 (20.0)	3 (27.3)	1 (9.1)	6 (30.0)	2 (10.0)
味覚異常	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
頭痛	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	3 (15.0)	0 (0.0)
肝性脳症	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (11.1)	1 (11.1)	1 (16.7)	0 (0.0)	1 (20.0)	1 (20.0)	2 (18.2)	1 (9.1)	3 (15.0)	2 (10.0)
腎および尿路障害	2 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (44.4)	1 (11.1)	1 (16.7)	0 (0.0)	2 (40.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	1 (5.0)
蛋白尿	2 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (44.4)	1 (11.1)	1 (16.7)	0 (0.0)	2 (40.0)	0 (0.0)	3 (27.3)	0 (0.0)	7 (35.0)	1 (5.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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Protocol: Lenvatinib (E7080) Integrated Summary of Safety

付録 2.7.6.5
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase I
Safety Analysis Set

	Group 1						Group 2							
	12 mg (N=6)		16 mg (N=3)		All (N=9)		8 mg (N=6)		12 mg (N=5)		All (N=11)		All (N=20)	
	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3	Any Grade	Grade >= 3
System organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	3 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	5 (55.6)	0 (0.0)	4 (66.7)	0 (0.0)	4 (80.0)	0 (0.0)	8 (72.7)	0 (0.0)	13 (65.0)	0 (0.0)
発声障害	2 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	5 (45.5)	0 (0.0)	8 (40.0)	0 (0.0)
鼻出血	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	4 (20.0)	0 (0.0)
しゃっくり	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
口腔咽頭痛	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
胸水	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
皮膚および皮下組織障害	6 (100.0)	1 (16.7)	3 (100.0)	0 (0.0)	9 (100.0)	1 (11.1)	4 (66.7)	0 (0.0)	4 (80.0)	0 (0.0)	8 (72.7)	0 (0.0)	17 (85.0)	1 (5.0)
脱毛症	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (10.0)	0 (0.0)
褥瘡性潰瘍	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
ざ瘡様皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
爪の障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (5.0)	0 (0.0)
手掌・足底発赤知覚不全症候群	5 (83.3)	1 (16.7)	3 (100.0)	0 (0.0)	8 (88.9)	1 (11.1)	3 (50.0)	0 (0.0)	2 (40.0)	0 (0.0)	5 (45.5)	0 (0.0)	13 (65.0)	1 (5.0)
そう痒症	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
発疹	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	3 (27.3)	0 (0.0)	6 (30.0)	0 (0.0)
血管障害	5 (83.3)	4 (66.7)	3 (100.0)	2 (66.7)	8 (88.9)	6 (66.7)	3 (50.0)	2 (33.3)	4 (80.0)	2 (40.0)	7 (63.6)	4 (36.4)	15 (75.0)	10 (50.0)
高血圧	5 (83.3)	4 (66.7)	3 (100.0)	2 (66.7)	8 (88.9)	6 (66.7)	3 (50.0)	2 (33.3)	4 (80.0)	2 (40.0)	7 (63.6)	4 (36.4)	15 (75.0)	10 (50.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
Subjects with Any TEAEs	46 (100.0)	45 (97.8)
血液およびリンパ系障害	22 (47.8)	13 (28.3)
貧血	2 (4.3)	1 (2.2)
播種性血管内凝固	1 (2.2)	0 (0.0)
白血球減少症	7 (15.2)	0 (0.0)
リンパ球減少症	1 (2.2)	1 (2.2)
好中球減少症	13 (28.3)	2 (4.3)
血小板減少症	16 (34.8)	10 (21.7)
心臓障害	2 (4.3)	2 (4.3)
急性冠動脈症候群	1 (2.2)	0 (0.0)
狭心症	1 (2.2)	1 (2.2)
心不全	1 (2.2)	0 (0.0)
心タンポナーデ	1 (2.2)	1 (2.2)
心膜炎	1 (2.2)	0 (0.0)
先天性、家族性および遺伝性障害	1 (2.2)	0 (0.0)
陰嚢水瘤	1 (2.2)	0 (0.0)
耳および迷路障害	1 (2.2)	0 (0.0)
耳不快感	1 (2.2)	0 (0.0)
内分泌障害	11 (23.9)	0 (0.0)
甲状腺機能低下症	10 (21.7)	0 (0.0)
甲状腺炎	1 (2.2)	0 (0.0)
眼障害	6 (13.0)	0 (0.0)
結膜出血	1 (2.2)	0 (0.0)
眼そう痒症	1 (2.2)	0 (0.0)
眼瞼浮腫	1 (2.2)	0 (0.0)
霧視	3 (6.5)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
胃腸障害	43 (93.5)	7 (15.2)
腹部不快感	1 (2.2)	0 (0.0)
腹部膨満	4 (8.7)	0 (0.0)
腹痛	5 (10.9)	0 (0.0)
下腹部痛	1 (2.2)	0 (0.0)
上腹部痛	3 (6.5)	1 (2.2)
腹水	11 (23.9)	0 (0.0)
口唇炎	1 (2.2)	0 (0.0)
便秘	19 (41.3)	0 (0.0)
齲歯	2 (4.3)	0 (0.0)
下痢	20 (43.5)	6 (13.0)
消化不良	5 (10.9)	0 (0.0)
小腸炎	1 (2.2)	1 (2.2)
腸炎	2 (4.3)	0 (0.0)
心窩部不快感	2 (4.3)	0 (0.0)
胃潰瘍	1 (2.2)	0 (0.0)
胃炎	2 (4.3)	0 (0.0)
萎縮性胃炎	1 (2.2)	0 (0.0)
胃食道逆流性疾患	1 (2.2)	0 (0.0)
歯肉出血	2 (4.3)	0 (0.0)
舌炎	1 (2.2)	0 (0.0)
痔出血	1 (2.2)	0 (0.0)
痔核	2 (4.3)	0 (0.0)
悪心	17 (37.0)	1 (2.2)
食道静脈瘤出血	1 (2.2)	1 (2.2)
歯周病	2 (4.3)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
口内炎	11 (23.9)	0 (0.0)
歯の障害	1 (2.2)	0 (0.0)
食道静脈瘤	5 (10.9)	2 (4.3)
嘔吐	11 (23.9)	1 (2.2)
一般・全身障害および投与部位の状態	34 (73.9)	2 (4.3)
廃用症候群	1 (2.2)	0 (0.0)
顔面浮腫	3 (6.5)	0 (0.0)
疲労	25 (54.3)	0 (0.0)
全身健康状態低下	1 (2.2)	0 (0.0)
インフルエンザ様疾患	1 (2.2)	0 (0.0)
限局性浮腫	1 (2.2)	0 (0.0)
倦怠感	1 (2.2)	1 (2.2)
粘膜の炎症	1 (2.2)	0 (0.0)
末梢性浮腫	16 (34.8)	0 (0.0)
疼痛	2 (4.3)	0 (0.0)
穿刺部位出血	1 (2.2)	0 (0.0)
穿刺部位疼痛	1 (2.2)	1 (2.2)
発熱	10 (21.7)	0 (0.0)
肝胆道系障害	9 (19.6)	2 (4.3)
胆嚢炎	1 (2.2)	0 (0.0)
急性胆嚢炎	1 (2.2)	0 (0.0)
胆石症	1 (2.2)	0 (0.0)
肝機能異常	2 (4.3)	0 (0.0)
高ビリルビン血症	3 (6.5)	1 (2.2)
胆汁うっ滞性黄疸	1 (2.2)	0 (0.0)
門脈血栓症	2 (4.3)	1 (2.2)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
免疫系障害	1 (2.2)	0 (0.0)
過敏症	1 (2.2)	0 (0.0)
感染症および寄生虫症	19 (41.3)	2 (4.3)
肛門膿瘍	1 (2.2)	0 (0.0)
気管支炎	1 (2.2)	0 (0.0)
蓄膿	1 (2.2)	0 (0.0)
胃腸炎	1 (2.2)	0 (0.0)
ウイルス性胃腸炎	1 (2.2)	0 (0.0)
歯肉炎	1 (2.2)	0 (0.0)
麦粒腫	1 (2.2)	0 (0.0)
インフルエンザ	1 (2.2)	0 (0.0)
肺感染	1 (2.2)	1 (2.2)
鼻咽頭炎	13 (28.3)	0 (0.0)
臍炎	1 (2.2)	0 (0.0)
歯周炎	2 (4.3)	0 (0.0)
咽頭炎	1 (2.2)	0 (0.0)
肺炎	1 (2.2)	1 (2.2)
感染性直腸炎	1 (2.2)	0 (0.0)
鼻炎	2 (4.3)	0 (0.0)
敗血症性ショック	1 (2.2)	1 (2.2)
副鼻腔炎	1 (2.2)	0 (0.0)
尿路感染	1 (2.2)	0 (0.0)
傷害、中毒および処置合併症	8 (17.4)	0 (0.0)
節足動物刺傷	2 (4.3)	0 (0.0)
挫傷	1 (2.2)	0 (0.0)
転倒	1 (2.2)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
骨折	1 (2.2)	0 (0.0)
靭帯捻挫	1 (2.2)	0 (0.0)
肋骨骨折	1 (2.2)	0 (0.0)
皮下血腫	1 (2.2)	0 (0.0)
歯牙損傷	1 (2.2)	0 (0.0)
臨床検査	36 (78.3)	14 (30.4)
アラニンアミノトランスフェラーゼ増加	2 (4.3)	0 (0.0)
アスパラギン酸アミノトランスフェラーゼ増加	5 (10.9)	1 (2.2)
血中アルブミン減少	1 (2.2)	0 (0.0)
血中アルカリホスファターゼ増加	2 (4.3)	2 (4.3)
血中カルシウム減少	1 (2.2)	0 (0.0)
血中クレアチニン増加	2 (4.3)	1 (2.2)
血中カリウム増加	1 (2.2)	1 (2.2)
血中甲状腺刺激ホルモン減少	2 (4.3)	0 (0.0)
血中甲状腺刺激ホルモン増加	12 (26.1)	0 (0.0)
血中尿素増加	1 (2.2)	0 (0.0)
尿中血陽性	9 (19.6)	0 (0.0)
Ｃ－反応性蛋白増加	3 (6.5)	0 (0.0)
心電図ＱＴ延長	3 (6.5)	0 (0.0)
γ－グルタミルトランスフェラーゼ増加	4 (8.7)	2 (4.3)
ヘモグロビン減少	2 (4.3)	2 (4.3)
好中球数減少	5 (10.9)	2 (4.3)
便潜血	1 (2.2)	0 (0.0)
血小板数減少	8 (17.4)	6 (13.0)
体重減少	14 (30.4)	2 (4.3)
白血球数減少	5 (10.9)	1 (2.2)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
代謝および栄養障害	36 (78.3)	8 (17.4)
食欲減退	28 (60.9)	1 (2.2)
脱水	4 (8.7)	1 (2.2)
高アンモニア血症	3 (6.5)	0 (0.0)
高コレステロール血症	1 (2.2)	1 (2.2)
高カリウム血症	1 (2.2)	0 (0.0)
高尿酸血症	1 (2.2)	0 (0.0)
低アルブミン血症	7 (15.2)	0 (0.0)
低カルシウム血症	1 (2.2)	0 (0.0)
低血糖症	3 (6.5)	2 (4.3)
低カリウム血症	2 (4.3)	2 (4.3)
低ナトリウム血症	2 (4.3)	2 (4.3)
栄養障害	1 (2.2)	1 (2.2)
筋骨格系および結合組織障害	27 (58.7)	0 (0.0)
関節痛	8 (17.4)	0 (0.0)
関節炎	1 (2.2)	0 (0.0)
背部痛	11 (23.9)	0 (0.0)
側腹部痛	2 (4.3)	0 (0.0)
筋痙縮	2 (4.3)	0 (0.0)
筋骨格系胸痛	2 (4.3)	0 (0.0)
筋骨格痛	5 (10.9)	0 (0.0)
筋肉痛	3 (6.5)	0 (0.0)
頚部痛	2 (4.3)	0 (0.0)
四肢痛	4 (8.7)	0 (0.0)
顎痛	1 (2.2)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	5 (10.9)	3 (6.5)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
癌疼痛	3 (6.5)	2 (4.3)
リンパ腫	1 (2.2)	1 (2.2)
腫瘍熱	1 (2.2)	0 (0.0)
腫瘍破裂	1 (2.2)	1 (2.2)
神経系障害	20 (43.5)	6 (13.0)
浮動性めまい	2 (4.3)	0 (0.0)
味覚異常	2 (4.3)	0 (0.0)
頭痛	9 (19.6)	0 (0.0)
肝性脳症	7 (15.2)	6 (13.0)
感覚鈍麻	1 (2.2)	0 (0.0)
末梢性感覚ニューロパチー	1 (2.2)	0 (0.0)
傾眠	1 (2.2)	0 (0.0)
失神	1 (2.2)	0 (0.0)
緊張性頭痛	1 (2.2)	0 (0.0)
振戦	1 (2.2)	0 (0.0)
精神障害	11 (23.9)	0 (0.0)
不安	1 (2.2)	0 (0.0)
うつ病	2 (4.3)	0 (0.0)
幻覚	1 (2.2)	0 (0.0)
不眠症	10 (21.7)	0 (0.0)
腎および尿路障害	30 (65.2)	10 (21.7)
血尿	1 (2.2)	0 (0.0)
失禁	1 (2.2)	0 (0.0)
頻尿	1 (2.2)	0 (0.0)
蛋白尿	28 (60.9)	9 (19.6)
腎機能障害	5 (10.9)	1 (2.2)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
尿道出血	1 (2.2)	0 (0.0)
生殖系および乳房障害	1 (2.2)	0 (0.0)
性器出血	1 (2.2)	0 (0.0)
呼吸器、胸郭および縦隔障害	27 (58.7)	2 (4.3)
無気肺	1 (2.2)	1 (2.2)
咳嗽	8 (17.4)	0 (0.0)
発声障害	17 (37.0)	0 (0.0)
呼吸困難	2 (4.3)	0 (0.0)
鼻出血	7 (15.2)	0 (0.0)
喀血	1 (2.2)	1 (2.2)
しゃっくり	1 (2.2)	0 (0.0)
口腔咽頭痛	2 (4.3)	0 (0.0)
胸水	4 (8.7)	0 (0.0)
湿性咳嗽	2 (4.3)	0 (0.0)
呼吸不全	1 (2.2)	1 (2.2)
鼻漏	1 (2.2)	0 (0.0)
上気道の炎症	1 (2.2)	0 (0.0)
皮膚および皮下組織障害	41 (89.1)	4 (8.7)
ざ瘡	1 (2.2)	0 (0.0)
脱毛症	3 (6.5)	0 (0.0)
褥瘡性潰瘍	1 (2.2)	0 (0.0)
皮膚嚢腫	1 (2.2)	0 (0.0)
剥脱性皮膚炎	1 (2.2)	0 (0.0)
皮膚乾燥	4 (8.7)	0 (0.0)
湿疹	2 (4.3)	0 (0.0)
紅斑	2 (4.3)	0 (0.0)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.6
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
皮下出血	1 (2.2)	0 (0.0)
過角化	3 (6.5)	0 (0.0)
爪の障害	1 (2.2)	0 (0.0)
手掌・足底発赤知覚不全症候群	30 (65.2)	4 (8.7)
点状出血	1 (2.2)	0 (0.0)
そう痒症	4 (8.7)	0 (0.0)
紫斑	2 (4.3)	0 (0.0)
発疹	14 (30.4)	0 (0.0)
血管障害	35 (76.1)	26 (56.5)
充血	1 (2.2)	0 (0.0)
高血圧	35 (76.1)	25 (54.3)
低血圧	1 (2.2)	1 (2.2)

Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
Subjects with Any Related TEAEs	44 (95.7)	40 (87.0)
血液およびリンパ系障害	21 (45.7)	12 (26.1)
貧血	1 (2.2)	0 (0.0)
白血球減少症	7 (15.2)	0 (0.0)
リンパ球減少症	1 (2.2)	1 (2.2)
好中球減少症	12 (26.1)	2 (4.3)
血小板減少症	16 (34.8)	10 (21.7)
心臓障害	2 (4.3)	1 (2.2)
急性冠動脈症候群	1 (2.2)	0 (0.0)
狭心症	1 (2.2)	1 (2.2)
先天性、家族性および遺伝性障害	1 (2.2)	0 (0.0)
陰嚢水瘤	1 (2.2)	0 (0.0)
耳および迷路障害	1 (2.2)	0 (0.0)
耳不快感	1 (2.2)	0 (0.0)
内分泌障害	11 (23.9)	0 (0.0)
甲状腺機能低下症	10 (21.7)	0 (0.0)
甲状腺炎	1 (2.2)	0 (0.0)
眼障害	4 (8.7)	0 (0.0)
結膜出血	1 (2.2)	0 (0.0)
眼瞼浮腫	1 (2.2)	0 (0.0)
霧視	2 (4.3)	0 (0.0)
胃腸障害	38 (82.6)	4 (8.7)
腹部不快感	1 (2.2)	0 (0.0)
腹部膨満	3 (6.5)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

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付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
腹痛	4 (8.7)	0 (0.0)
下腹部痛	1 (2.2)	0 (0.0)
上腹部痛	3 (6.5)	1 (2.2)
腹水	8 (17.4)	0 (0.0)
口唇炎	1 (2.2)	0 (0.0)
便秘	14 (30.4)	0 (0.0)
下痢	16 (34.8)	4 (8.7)
消化不良	4 (8.7)	0 (0.0)
腸炎	1 (2.2)	0 (0.0)
心窩部不快感	2 (4.3)	0 (0.0)
胃潰瘍	1 (2.2)	0 (0.0)
胃炎	1 (2.2)	0 (0.0)
胃食道逆流性疾患	1 (2.2)	0 (0.0)
歯肉出血	1 (2.2)	0 (0.0)
舌炎	1 (2.2)	0 (0.0)
痔出血	1 (2.2)	0 (0.0)
悪心	15 (32.6)	1 (2.2)
歯周病	1 (2.2)	0 (0.0)
口内炎	11 (23.9)	0 (0.0)
嘔吐	9 (19.6)	1 (2.2)
一般・全身障害および投与部位の状態	31 (67.4)	1 (2.2)
顔面浮腫	3 (6.5)	0 (0.0)
疲労	22 (47.8)	0 (0.0)
限局性浮腫	1 (2.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
倦怠感	1 (2.2)	1 (2.2)
粘膜の炎症	1 (2.2)	0 (0.0)
末梢性浮腫	15 (32.6)	0 (0.0)
発熱	6 (13.0)	0 (0.0)
肝胆道系障害	4 (8.7)	0 (0.0)
胆嚢炎	1 (2.2)	0 (0.0)
急性胆嚢炎	1 (2.2)	0 (0.0)
胆石症	1 (2.2)	0 (0.0)
高ビリルビン血症	2 (4.3)	0 (0.0)
感染症および寄生虫症	6 (13.0)	0 (0.0)
胃腸炎	1 (2.2)	0 (0.0)
歯周炎	2 (4.3)	0 (0.0)
咽頭炎	1 (2.2)	0 (0.0)
感染性直腸炎	1 (2.2)	0 (0.0)
鼻炎	1 (2.2)	0 (0.0)
副鼻腔炎	1 (2.2)	0 (0.0)
傷害、中毒および処置合併症	2 (4.3)	0 (0.0)
挫傷	1 (2.2)	0 (0.0)
転倒	1 (2.2)	0 (0.0)
臨床検査	33 (71.7)	8 (17.4)
アラニンアミノトランスフェラーゼ増加	1 (2.2)	0 (0.0)
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.2)	0 (0.0)
血中アルブミン減少	1 (2.2)	0 (0.0)
血中カルシウム減少	1 (2.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
血中クレアチニン増加	1 (2.2)	0 (0.0)
血中甲状腺刺激ホルモン減少	1 (2.2)	0 (0.0)
血中甲状腺刺激ホルモン増加	12 (26.1)	0 (0.0)
尿中血陽性	9 (19.6)	0 (0.0)
Ｃ－反応性蛋白増加	1 (2.2)	0 (0.0)
心電図ＱＴ延長	3 (6.5)	0 (0.0)
ヘモグロビン減少	2 (4.3)	2 (4.3)
好中球数減少	4 (8.7)	2 (4.3)
血小板数減少	7 (15.2)	5 (10.9)
体重減少	12 (26.1)	1 (2.2)
白血球数減少	4 (8.7)	1 (2.2)
代謝および栄養障害	32 (69.6)	4 (8.7)
食欲減退	26 (56.5)	1 (2.2)
高アンモニア血症	1 (2.2)	0 (0.0)
高コレステロール血症	1 (2.2)	1 (2.2)
低アルブミン血症	6 (13.0)	0 (0.0)
低カルシウム血症	1 (2.2)	0 (0.0)
低カリウム血症	1 (2.2)	1 (2.2)
低ナトリウム血症	1 (2.2)	1 (2.2)
筋骨格系および結合組織障害	11 (23.9)	0 (0.0)
関節痛	4 (8.7)	0 (0.0)
背部痛	2 (4.3)	0 (0.0)
筋痙縮	2 (4.3)	0 (0.0)
筋骨格痛	2 (4.3)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
筋肉痛	2 (4.3)	0 (0.0)
頚部痛	1 (2.2)	0 (0.0)
顎痛	1 (2.2)	0 (0.0)
神経系障害	13 (28.3)	4 (8.7)
浮動性めまい	2 (4.3)	0 (0.0)
味覚異常	2 (4.3)	0 (0.0)
頭痛	4 (8.7)	0 (0.0)
肝性脳症	5 (10.9)	4 (8.7)
失神	1 (2.2)	0 (0.0)
緊張性頭痛	1 (2.2)	0 (0.0)
精神障害	3 (6.5)	0 (0.0)
不安	1 (2.2)	0 (0.0)
うつ病	1 (2.2)	0 (0.0)
不眠症	1 (2.2)	0 (0.0)
腎および尿路障害	29 (63.0)	9 (19.6)
失禁	1 (2.2)	0 (0.0)
頻尿	1 (2.2)	0 (0.0)
蛋白尿	27 (58.7)	9 (19.6)
腎機能障害	4 (8.7)	0 (0.0)
呼吸器、胸郭および縦隔障害	21 (45.7)	1 (2.2)
咳嗽	2 (4.3)	0 (0.0)
発声障害	16 (34.8)	0 (0.0)
鼻出血	7 (15.2)	0 (0.0)
しゃっくり	1 (2.2)	0 (0.0)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
TEAE = Treatment-emergent adverse event.

付録 2.7.6.7
Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Study 202 - Phase II
Safety Analysis Set

System organ Class Preferred Term	12 mg (N=46) Any Grade n (%)	 Grade >= 3 n (%)
口腔咽頭痛	1 (2.2)	0 (0.0)
胸水	1 (2.2)	0 (0.0)
湿性咳嗽	1 (2.2)	0 (0.0)
呼吸不全	1 (2.2)	1 (2.2)
鼻漏	1 (2.2)	0 (0.0)
皮膚および皮下組織障害	39 (84.8)	3 (6.5)
ざ瘡	1 (2.2)	0 (0.0)
脱毛症	3 (6.5)	0 (0.0)
剥脱性皮膚炎	1 (2.2)	0 (0.0)
皮膚乾燥	3 (6.5)	0 (0.0)
湿疹	2 (4.3)	0 (0.0)
紅斑	2 (4.3)	0 (0.0)
皮下出血	1 (2.2)	0 (0.0)
過角化	3 (6.5)	0 (0.0)
爪の障害	1 (2.2)	0 (0.0)
手掌・足底発赤知覚不全症候群	28 (60.9)	3 (6.5)
そう痒症	4 (8.7)	0 (0.0)
紫斑	1 (2.2)	0 (0.0)
発疹	12 (26.1)	0 (0.0)
血管障害	35 (76.1)	25 (54.3)
高血圧	35 (76.1)	25 (54.3)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group.
Subject with two or more TEAEs reported in the same SOC or PT term will be only counted once.
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付録 2.7.6-8　死亡又は重篤な有害事象の被験者ごとの叙述（国際共同 202 試験）

死亡又は死亡以外の重篤な有害事象が認められた被験者に関する叙述を以下に示した。

被験者識別コード	投与群	死亡に至った有害事象	死亡以外の重篤な有害事象
10011002	12 mg QD, Dose-escalation component (Phase 1; Group 1)		X
10021003	12 mg QD, Dose-escalation component (Phase 1; Group 1)		X
10011006	16 mg QD, Dose-escalation component (Phase 1; Group 1)		X
10021006	16 mg QD, Dose-escalation component (Phase 1; Group 1)		X
10022003	8 mg QD, Dose-escalation component (Phase 1; Group 2)		X
10022004	8 mg QD, Dose-escalation component (Phase 1; Group 2)	X	
10022005	8 mg QD, Dose-escalation component (Phase 1; Group 2)		X
10012002	12 mg QD, Dose-escalation component (Phase 1; Group 2)		X
10012004	12 mg QD, Dose-escalation component (Phase 1; Group 2)	X	
10022002	12 mg QD, Dose-escalation component (Phase 1; Group 2)		X
20013005	12 mg QD, Expansion component (Phase 2)		X
20013006	12 mg QD, Expansion component (Phase 2)		X
20023002	12 mg QD, Expansion component (Phase 2)		X
20033002	12 mg QD, Expansion component (Phase 2)	X	X
20033003	12 mg QD, Expansion component (Phase 2)		X
20043001	12 mg QD, Expansion component (Phase 2)		X
20053001	12 mg QD, Expansion component (Phase 2)		X
20053002	12 mg QD, Expansion component (Phase 2)		X
20053003	12 mg QD, Expansion component (Phase 2)		X
20063001	12 mg QD, Expansion component (Phase 2)		X
20063003	12 mg QD, Expansion component (Phase 2)		X
20063004	12 mg QD, Expansion component (Phase 2)		X
20073007	12 mg QD, Expansion component (Phase 2)		X
20083005	12 mg QD, Expansion component (Phase 2)		X
20103003	12 mg QD, Expansion component (Phase 2)		X
20103004	12 mg QD, Expansion component (Phase 2)		X
20113001	12 mg QD, Expansion component (Phase 2)		X
20113003	12 mg QD, Expansion component (Phase 2)	X	
20113005	12 mg QD, Expansion component (Phase 2)		X
20123001	12 mg QD, Expansion component (Phase 2)		X
20123002	12 mg QD, Expansion component (Phase 2)		X
21013002	12 mg QD, Expansion component (Phase 2)		X

死亡に至った有害事象

Narratives for Subjects with Fatal SAEs (4 subjects)

Subject ID:	**10022004**
Age:	47 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	8 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Constipation, diabetes mellitus, gastric ulcer, hepatic cirrhosis, hypertension, lumber disk herniation, varioes oesophageal
Concomitant medications:	Amlodipine besilate, azulene, betamethasone butyrate propionate, candesartan cilexetil, clobetasol propionate, diclofenac sodium, streptococcus faecalis, esomeprazole magnesium hydrate, furosemide, heparinoid, indometacin, ketoprofen, lansoprazole, loperamide hydrochloride, magnesium oxide, omeprazole, seirogan, shakuyakukanzouto, spironolactone, tetracycline hydrochloride, urea, ursodeoxycholic acid, valsartan
Reason for narrative:	
Fatal SAE(s)	Haematemesis
Nonfatal SAE(s)	None
Relationship to study drug:	Not related

AE Description:

Feb 2011	The subject was diagnosed with hepatocellular carcinoma.
11 Jul 2011	The subject started oral study medication, at a dose of 8 mg, frequency once daily.
18 Apr 2012	Study medication was interrupted due to pyrexia.
27 Apr 2012	His pyrexia was recovered and anaemia worsened (Hb value was 7.6 g/dL). Intra-abdominal haemorrhage and varices haemorrhage were suspected. The result of paracentesis for ascites was light yellow. Stool colour was normal. The interruption of the study medication was maintained.
09 May 2012	Hb value was 6.7 g/dL. Study medication was discontinued due to anaemia with the subject having not restarted since interruption on 18 Apr 2012.

14 May 2012 (SAE Start Date)	The subject experienced the event of haematemesis. The subject collapsed at work and was taken to a nearby clinic. A central venous line was inserted through the right jugular vein and fluid administration was initiated along with 6 units of packed red blood cells. Blood pressure was about 60–80/30–50 level. The subject vomited 30 mL of bright red blood on two occasions.
15 May 2012	Urine volume decreased and dopamine hydrochloride was initiated. A gastric tube was inserted. 600 mL of blood was vomited. Blood pressure was about 50–60 level. Agonal respiration (Jaw breathing) was noted. At 15:40 on the same day the subject died.

Investigator's comment:

Anaemia worsened before or after suspension of the study drug; however, as of 27 Apr 2011, no obvious abnormal findings were noted as a result of considering the subjects' condition, the result of paracentesis for ascites, stool colour, etc. Although bleeding may have already occurred, it was reasonable to separate the bleeding from the reported term Haematemesis (a direct cause of death). Haematemesis was likely caused by variceal rupture or gastrointestinal ulceration; however, since his condition was unstable (severe anaemia, decreased blood pressure), endoscopic diagnosis was not made. Considering the lapse of certain period after the discontinuation of the study, haematemesis was determined to be due to bleeding of digestive tract associated with aggravation of hepatic cirrhosis and the underlying disease. The event was not related to the study drug.

Subject ID:	**10012004**
Age:	67 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Ascites, diabetes, gastric varices, hepatitis C virus, hypertension
Concomitant medications:	Amlodipine besilate, sodium azulenesulfonate, dexamethasone, difluprednate, enalapril maleate, furosemide, indometacin, lactulose, loperamide hydrochloride, lormetazepam, loxoprofen sodium hydrate, mitiglinide calcium hydrate, acetaminophen, prochlorperazine, spironolactone, urea, ursodeoxycholic acid
Reason for narrative:	
Fatal SAE(s)	Hepatic failure
Nonfatal SAE(s)	None
Relationship to study drug:	Not related

AE Description:

Around Jul 2009	The subject was diagnosed with hepatocellular carcinoma.
10 Aug 2010	Informed consent was obtained.
20 Aug 2010	The subject started study medication (12 mg).
30 Aug 2010	The study medication was interrupted because his T-Bil value increased to 3.3 mg/dL.
06 Sep 2010	The subject's T-Bil value was 1.5 mg/dL and the study drug was resumed.
22 Sep 2010	The subject's T-Bil value increased to 3.3 mg/dL; therefore, the study drug was interrupted for the second time.
28 Sep 2010	The subject's T-Bil value was 2.0 mg/dL; therefore the study drug was resumed.
29 Sep 2010	The study medication dose was reduced to 8 mg.
27 Oct 2010	The subject had anorexia of Grade 2 and a T-Bil value of 2.6 mg/dL.
28 Oct 2010	The study drug was interrupted for the third time.
11 Nov 2010	Anorexia improved and the subject's T-Bil value was 2.3 mg/dL; therefore the study drug was resumed.
02 Dec 2010	The subject's T-Bil value increased to 3.7 mg/dL; therefore, the study drug was interrupted for the fourth time.
09 Dec 2010	The subject's T-Bil value was 3.5 mg/dL. A CT scan revealed a new lesion, based on which the reporting physician considered that he had PD.

24 Dec 2010	The subject's T-Bil value was 3.9 mg/dL.
06 Jan 2011 (SAE Start Date)	The subject visited the reporting physician's hospital for the final observation more than 30 days after the administration of the study drug. His T-Bil value was 6.8 mg/dL and abdominal bloating worsened which caused his body weight to increase from 73.8 kg to 83 kg. A tumor marker significantly increased. He was admitted to the hospital for hepatic failure due to the aggravation of the underlying disease. It was thought progression of underlying disease brought on the event.
07 Jan 2011	Diuretic drugs were administered; however his body weight remained unchanged (84.0 kg).
08 Jan 2011	The subject's body weight increased to 86.9 kg.
09 Jan 2011	Betamethasone (2 mg) was administered for malaise.
11 Jan 2011	The subject experienced back pain.
12 Jan 2011	Subcutaneous infusion of morphine hydrochloride (Prepenon) was initiated.
13 Jan 2011	Respiratory depression induced by morphine developed and Prepenon was discontinued. The subject responded to be being called during the day; however the subject's heart rate decreased to 40 beats/min (at 21:10 –). After arrest of breathing and dilation of the pupil were confirmed, the subject died (at 21:22).

Investigator's comment:
The subject was withdrawn from the study due to PD on 09 Dec 2010. He was admitted to the hospital due to hepatic failure during observation after the withdrawal on 06 Jan 2011 and he expired on 13 Jan 2011. Tumor markers significantly increased: AFP of 3823 ng/mL on 09 Dec 2010 to 20066 ng/mL on 06 Jan 2011 and PIVKAII of 9347 mAU/mL on 09 Dec 2010 to 29560 mAU/mL on 06 Jan 2011. The major etiology of hepatic failure which led to his hospitalization was most likely the aggravation of the underlying disease.

Subject ID:	**20033002**
Age:	53 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Chronic inactive hepatitis B, hemorrhoid, low back pain, periodontitis
Concomitant medications:	Albumin behring, Pabron-S, ambroxol hydrochloride, amigrand, bfluid, bfluid injection, anthrobin P, betamethasone sodium phosphate, Borraza-G, Brotizolam, Solita-T No.3 G, dequalinium chloride, dexmedetomide hydrochloride, dimemorfan phosphate, entecavir hydrate, etodolac, fentanyl citrate, flurbiprofen, furosemide, glucose, haloperidol, hepaflush, purified sodium hyaluronate, scopolamine butylbromide, insulin human, kanamycin monosulfate, ketoprofen, LAC-B granular powder N, lactec, lactulose, levothyroxine sodium hydrate, lidocaine hydrochloride monohydrate, loperamide hydrochloride, loxoprofen sodium hydrate, beaslimin, metoclopramide hydrochloride, midazolam, noradrenaline, olopatadine hydrochloride, omeplazole sodium, SOLDEM 3, PL, polymixin B sulfate, dibasic potassium phosphate, prochlorperazine maleate, proclorperazine maleate, rabeprazole sodium, ramosetron hydrochloride, sennoside A B, sodium chloride, SOLDEM 1, teprenone, terufis, tranexamic acid, torazodone, rikkunshi-to, urea, valsartan
Reason for narrative:	
Fatal SAE(s)	Pneumonia
Nonfatal SAE(s)	Nausea, Vomiting, Septic shock, Respiratory failure
Relationship to study drug:	Not related (Pneumonia, Septic shock), Probably related (Nausea, Vomiting), Possibly related (Respiratory failure)

AE Description:

16 Sep 2010	The subject was diagnosed with postoperative recurrence of hepatocellular carcinoma.
30 Sep 2010	Informed consent was obtained.
08 Oct 2010	The subject started the study medication at a dose of 12 mg/day (Day 1 of Cycle 1).
28 Dec 2010 (SAE Start Date)	Day 1 of Cycle 4 of study medication. The subject experienced nausea and anorexia.
09 Jan 2011	Diarrhoea and epigastric pain appeared.

11 Jan 2011	The subject visited the reporting physician's hospital because of nausea accompanied by vomiting, anorexia and epigastric pain. Regular oral administration of bifidobacterium (LAC-B granular powder N) and metoclopramide was started.
26 Jan 2011	Day 1 of Cycle 5 of study medication. The reporting physician conducted tumor assessment based on the result of a CT scan: Partial response (PR).
10 Feb 2011	Day 15 of Cycle 5 of study medication. Nausea accompanied by vomiting, diarrhoea and anorexia persisted.
17 Feb 2011	The subject was admitted to the department of gastroenterological medicine because nausea accompanied by vomiting did not improve. BFLUID injection (1000 mL/day, peripheral venous nutrition) was given to improve the symptom.
18 Feb 2011	The study medication was interrupted due to diarrhoea, queasy feeling, epigastric pain and anorexia.
20 Feb 2011	The subject's appetite improved and the transfusion was maintained.
21 Feb 2011	The transfusion was completed.
22 Feb 2011	The reporting physician considered that nausea accompanied by vomiting resolved.
25 Feb 2011	Following resolution of the above events (diarrhoea, queasy feeling, epigastric pain and anorexia), the study medication resumed at a reduced dose of 8 mg once daily.
09 Jul 2011	The subject experienced diarrhoea, vomiting and anorexia again with abdominal pain.
14 Jul 2011	Fatigue (malaise) appeared.
24 Oct 2011	Day 15 in Cycle 14. The adverse events persisted and the subject's body weight was decreasing. An intravenous drip infusion of Solita T3 G (maintenance medium) 500 mL was given as per the subject's request before he went home.
05 Nov 2011 (SAE Start Date)	The subject took his last dose of the study medication. He had been drinking water only without having any food since 28 Oct 2011 and his activities of daily living (ADL) decreased. He developed cough and fever, and was taken to the hospital by ambulance. He was later admitted to the gastroenterological medicine ward with a diagnosis of pneumonia.
06 Nov 2011	The subject's respiratory status was unfavorable and he was moved to the intensive care unit (ICU). The study medication was interrupted.
07 Nov 2011	The subject experienced respiratory disorder due to decreased conscious level associated with aggravation of hepatic encephalopathy and he was intubated.
09 Nov 2011	The subject was still under observation in the ICU due to no improvement in his general condition.

10 Nov 2011	The subject's level of consciousness improved and he was able to communicate.
11 Nov 2011	He was extubated.
14 Nov 2011 (SAE Start Date)	Aggravation of pneumonia, decreased oxygenation, and decreased blood pressure were confirmed. He was managed as a case of septic shock and intubated again. His circulatory dynamics was unstable after intubation.
15 Nov 2011	Pyothorax was observed.
17 Nov 2011	Methicillin-resistant Staphylococcus aureus (MRSA) and anaerobes were detected from his sputum and pyothorax, respectively.
18 Nov 2011	A decision was taken not to reintropduce the study medication, which was permanently discontinued. An interruption of over 14 days was expected because of the adverse events.
24 Nov 2011	Treatment with antibiotics and general management was continued for the pneumonia and pyothorax.
25 Nov 2011	After discussion with the subject's family, it was decided that no further aggressive treatment would be given and the subject was transferred to the Department of Gastroenterology.
30 Nov 2011	Pneumonia was beginning to improve after he was transferred to the general ward.
03 Dec 2011	The subject was re-intubated after being extubated by himself; however, oxygenation declined significantly.
05 Dec 2011	His condition worsened and he died of pneumonia. At the time of death, septic shock and respiratory failure were not resolved.

Investigator's comment:

The event (nausea and vomiting) developed after the start of the study drug; therefore, causal relationship with the study drug cannot be ruled out. Although nausea and vomiting pre-existed, the reporting physician considered that he needed hospitalization and treatment on the basis of his wishes. He is in the hospital at the time of the report; however, the event had resolved and the reporting physician completes the report.

Pneumonia occurred coincidentally with extreme dehydration and malnutrition; therefore, the study drug was not related to the event. The pneumonia is determined to be serious because hospitalisation for treatment was required.

The infection which was the primary cause of the septic shock was attributed to extreme dehydration and malnutrition. Thus, the causal relationship between the study drug and the septic shock can be ruled out. As for the unstable respiratory disorder, which was observed during the same period of time, we have never experienced this type of clinical course. In addition, it cannot be explained only by hepatic encephalopathy or aggravation of infection including pneumonia; therefore, an additional adverse event term, "respiratory failure", was reported. It is unknown if the study drug was related to the event since there was no rational evidence to evaluate the causality between the event and the study drug.

Subject ID:	**20113003**
Age:	55 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Expansion component (Phase 2)
Current medical conditions:	Diabetes, hepatitis C virus, hypertension
Concomitant medications:	Candesartan cilexetil, diphenhydramine, fexofenadine hydrochloride, furosemide, glibenclamide, loxoprofen sodium hydrate, magnesium oxide, manidipine hydrochloride, acetaminophen, urea
Reason for narrative:	
Fatal SAE(s)	Tumour rupture
Nonfatal SAE(s)	None
Relationship to study drug:	Not related

AE Description

11 Apr 2008	The subject was diagnosed with hepatocellular carcinoma.
30 Jul 2010	The subject agreed to participate in the study because he had received a diagnosis of progressive hepatocellular carcinoma with multiple metastases to the lung and lymph nodes.
09 Aug 2010	The subject started the study medication. The subject's haemoglobin level was 11.5 g/dL (central measurement).
07 Sep 2010	The subject received his last dose of the study medication.
08 Sep 2010	The study medication was suspended due to proteinuria (4+) on 06 Sep 2010.
13 Sep 2010	The interruption of the study medication was maintained because the uric protein value was +3. A tumor-like mass was found near the liver and the subject complained of pain. The subject therefore started treatment with loxoprofen. A uric protein test was planned for 22 Sep 2010, with the intention that the subject would be withdrawn from the study if the proteinuria did not resolve. Treatment with sorafenib tosilate was due to be started in early October. The subject's haemoglobin was at 11.2 g/dL.

18 Sep 2010 (SAE Start Date)	The subject made an emergency hospital visit because of abdominal fullness and pain in the right hypochondrium. The subject's haemoglobin was 7.4 g/dL (prior to a blood transfusion) and he was found to be anaemic. Marked ascites were observed. The ascitic fluid was red and a ruptured hepatic carcinoma was suspected. A CT angiography of the abdomen revealed aggravated hepatocellular carcinoma and bloody ascites due to a rupture in the carcinoma. Given that the subject had a portal embolus and was at high risk of hepatic failure without active haemorrhage, it was decided that conservative management would be performed and that hepatic artery embolization would be considered depending on the situation. The subject received a blood transfusion of four units of irradiated erythrocyte concentrate, oxygen therapy, pain control and analgesic drugs.
19 Sep 2010	Then subject's CRP value increased to 4.45 mg/dL and it was though possible that he had idiopathic bacterial peritonitis. Antibiotics were therefore started. The subject's haemoglobin level was 8.7 g/dL.
20 Sep 2010	The subject's haemoglobin had dropped to 7.4 g/dL (prior to a blood transfusion). The subject had a sense of abdominal fullness. The subject received a transfusion of four units of irradiated erythrocyte concentrate. It was though there was possible continued bleeding because of the ruptured carcinoma, so the subject underwent another abdominal CT angiogram which confirmed the bleeding.
21 Sep 2010	Pain control was started with fentanyl, ketamine and dexamethasone. Haemoglobin was at 8.2 g/dL. The subject was withdrawn from the study.
22 Sep 2010	The subject's condition worsened, and his haemoglobin was found to be at 5.4 g/dL. Treatment was switched to fentanyl with an oxygen mask because of aggravated pain and respiratory discomfort (SpO_2 in the 80s). The amount of oxygen was eventually increased to 10 L. The subject became lethargic and his blood oxygen level and pulse decreased gradually. The subject was pronounced dead at 15:27.

Investigator's comment

The event was due to aggravation of the underlying disease which had exhibited a worsening trend before the start of the study; therefore the event was not related to the study drug.

死亡以外の重篤な有害事象

Narratives for Subjects with Nonfatal SAEs (28 subjects)

Subject ID:	**10011002**
Age:	52 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Dose-escalation component (Phase 1; Group 1)
Current medical conditions:	Abdominal pain, alveolar pyorrhea, hepatitis C virus, hypertension, pruritus, rash
Concomitant medications:	Albumin tannate, amlodipine besilate, amoxicillin hydrate, sodium azulenesulfonate, bifidobacterium, candesartan cilexetil, dexamethasone, difluprednate, famotidine, flurbiprofen axetil, loperamide hydrochloride, lormetazepam, loxoprofen sodium hydrate, magnesium oxide, oseltamivir phosphate, oxycodone hydrochloride, povidone-iodine, sultamicillin tosilate hydrate
Reason for narrative:	
Nonfatal SAE(s)	Hyperbilirubinaemia
Relationship to study drug:	Not related

AE Description:

2009	The subject was diagnosed with hepatocellular carcinoma.
27 Aug 2009	Informed consent was obtained.
09 Sep 2009	The subject enrolled into the clinical study.
10 Sep 2009	The subject started the study medication (12 mg/body).
25 Feb 2010	A CT scan showed progressive disease (PD). The subject took his final dose of the study medication.
18 Mar 2010 (SAE Start Date)	The subject's T-Bil increased to 3.6 mg/dL during the observation period, so a CT scan was conducted, although it was not stated in the protocol. The results of the CT scan confirmed that the subject's mass had further enlarged, leading to hepatic failure.
23 Mar 2010	The subject's T-Bil went up to 7.9 mg/dL. Jaundice was visually confirmed and it was explained to the subject that hospitalization might be required in the future.
26 Mar 2010	The subject's T-Bil increased to 10.9 mg/dL and he was hospitalized as biliary obstruction was observed. Percutaneous transhepatic biliary drainage (PTBD) was performed.
29 Mar 2010	The subject had a stent inserted. Because an arterial injury was found at the time of treatment the subject underwent astriction with a catheter.

03 Apr 2010	The subject experienced bleeding again from the PTCD insertion site for which hemostasis with TAE conducted.
12 Apr 2010	No bleeding was observed and biliary outflow was favorable. Total bilirubin (T-Bil) value improved to 3.6 mg/dL.
14 Apr 2010	The subject experienced ascites with the underlying disease and received puncture of ascites.
16 Apr 2010	The subject received puncture of ascites.
23 Apr 2010	The subject received puncture of ascites.
26 Apr 2010	The subject was transferred to the palliative care of another hospital.
20 May 2010	The subject died from the aggravation of the underlying disease.

Investigator's comment:
Hyperbilirubinaemia developed owing to the aggravation of cancer and was not related to the study drug. Although jaundice had been named as the event term, the term was changed to hyperbilirubinaemia because an influence caused by hepatic failure was also presumable.

Subject ID:	**10021003**
Age:	74 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	12 mg QD, Dose-escalation component (Phase 1; Group 1)
Current medical conditions:	Pain-shoulder, bile duct obstruction, cataract, chapped fingers, chronic hepatitis C, dry skin, gout, insomnia
Concomitant medications:	Amlodipine besilate, candesartan cilexetil, Oronine R H ointment, diphenhydramine, etizolam, flubiprofen, indometacin, levofloxacin hydrate, loxoprofen sodium hydrate, oseltamivir phosphate, acetaminophen, sodium gualenate hydrate, urea
Reason for narrative:	
Nonfatal SAE(s)	Biliary tract infection
Relationship to study drug:	Possibly related

AE Description:

06 Oct 2009	The subject was diagnosed with hepatocellular carcinoma.
05 Nov 2009	The subject started the study medication (12 mg QD).
19 Nov 2009	The subject experienced elevated γ-GTP level (Grade 3) and pyrexia (37.6 °C), for which he was considered to have cholangitis (Grade 2). The administration of Cravit (levofloxacin) was initiated (7 days).
20 Nov 2009	The subject discontinued the study medication.
24 Nov 2009	Cholangitis resolved and the subject restarted the study medication (12 mg QD).
27 Nov 2009	The subject was discharged from hospital.
04 Dec 2009	The subject visited the hospital for the first time since his discharge on 27 Nov 2009. His γ-GTP and CRP level had increased. Cravit was administered for prophylaxis.
06 Dec 2009 (SAE Start Date)	The subject started experiencing pyrexia.
07 Dec 2009	The subject revisited the hospital. The CRP level had further increased and the T-Bil tended to rise. The recurrence of cholangitis was suspected, so a CT scan was performed and revealed a biliary dilatation. The subject was hospitalized and the administration of an antibiotic agent [Sulperazon (sulbactam sodium)] was initiated.
08 Dec 2009	The subject underwent a PTCD. Although the subject did not have pyrexia his CRP levels were high. Therefore, the administration of the antibiotic agent was continued.
14 Dec 2009	Since the insertion of the PTCD, the tube had been leaking, therefore it was changed.

16 Dec 2009	The subject's WBC count and biliary enzyme levels declined. The inflammation was subsiding and the administration of the antibiotic drug was completed.
17 Dec 2009	The subject was dehydrated due to diarrhea and drainage from the PTCD. Fluid replacement was initiated.
18 Dec 2009	After he took an antihypertensive drug, he felt sick.
19 Dec 2009	The administration of the antihypertensive drug was discontinued.
20 Dec 2009	The fluid replacement was complete.
21 Dec 2009	The subject's physical condition improved and the dose of the study medication was reduced to 8 mg and was initiated orally.
25 Dec 2009	After the administration of the study drug the subject's blood pressure increased and so the antihypertensive were resumed.
28 Dec 2009	The subject had pyrexia of 38 °C. Cholangitis was suspected as the cause of the fever and the subject's hospitalizations course was prolonged. Soldem 3A was started.
29 Dec 2009	The study medication was interrupted due to the subject experiencing pyrexia and diarrhea. His condition seemed poor.
30 Dec 2009	A blood test revealed no abnormalities and the subject was discharged from hospital. The antihypertensive drug was discontinued.
02 Jan 2010	The subject developed pyrexia at home.
06 Jan 2010	The subject repeatedly experienced pyrexia. The reoccurrence of cholangitis was suspected and administration of antibiotics was started. Because the underlying disease was aggravated the subject was withdrawn from the study.
07 Jan 2010	The tube of the PTCD was replaced.
11 Jan 2010	The antibiotic administration was discontinued and the cholangitis was considered to be resolved.
15 Jan 2010	The subject was discharged from hospital.

Investigator's comment:
This case was about a subject with bile duct stenosis induced by his underlying disease. Several stents were placed in him. There was no doubt that the obstruction of the stents was mainly responsible for the cholangitis. However, it could not be completely ruled out that the administration of the study drug might have increased some risk factors of cholangitis. Therefore, a causal relationship between the study drug and the event could not be excluded. In the case of obstruction of the stents, if left untreated, it would progress to a life threatening condition, leading to a serious clinical state. In this case, since PTCD was performed swiftly, his clinical condition improved. As for the criteria of seriousness, hospitalisation was considered to be appropriate. In addition, the recurrence of cholangitis in early Jan 2010 was a sequence of the event on 06 Dec 2009, so it was assessed as the same event.

Subject ID:	**10011006**
Age:	62 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	16 mg QD, Dose-escalation component (Phase 1; Group 1)
Current medical conditions:	Gastritis, cancer pain, cough, hepatitis B virus
Concomitant medications:	Albumin tannate, amlodipine besilate, bifidobacterium, candesartan cilexetil, codeine phosphate hydrate, mentholatum AD, famotidine, loxoprofen sodium hydrate, magnesium oxide, morphine hydrochloride hydrate, oxycodone hydrochloride, prochlorperazine, rebamipide, trichlormethiazide
Reason for narrative:	
Nonfatal SAE(s)	Pneumonia
Relationship to study drug:	Possibly related

AE Description:

2003	Subject was diagnosed with hepatocellular carcinoma.
01 Mar 2010	The subject was enrolled in the study.
02 Mar 2010	The subject started study medication (16 mg/body).
27 Apr 2010	Cycle 3 of the study medication was initiated.
01 May 2010 (SAE Start Date)	The subject was admitted to hospital with pneumonia.
11 May 2010	The pneumonia began to improve.
14 May 2010	The study medication was reintroduced at a reduced dosage of 12 mg/day.
18 May 2010	The subject was discharged from hospital.
25 May 2010	The subject had an X-ray which showed improved pneumonia (Day 1 of Cycle 4). The administration of the study drug was discontinued because subject had a high level of CRP and febricula.
27 May 2010	The subject had reported having pyrexia with a temperature of 39°C and he was instructed to visit the hospital. The subject was admitted to hospital and administration of Zosyn (tazobactam) was started.
30 May 2010	The antibiotic agent was changed to Tienam (imipenem and cilastatin sodium).
01 Jun 2010	The subject's temperature remained over 37°C. The fever was declining slowly.
02 Jun 2010	A CT scan revealed a lesion with cavitation necrosis at the internal right lobe and a lung abscess was suspected.
08 Jun 2010	The subject's antibiotics were discontinued.

10 Jun 2010	The subject's underlying disease was confirmed to have worsened; the study medication was withdrawn and it was decided its administration should be terminated.
11 Jun 2010	The subject's temperature had stayed around 37°C and his general condition was favorable. The subject was discharged from hospital.
17 Jun 2010	The subject visited the hospital for scheduled follow-up. A mild fever persisted and a CT scan showed that the lung abscess was unchanged. Levofloxacin was prescribed and the subject was instructed to rest at home.
24 Jun 2010	The subject's condition started to stabilize, although he continued to experience occasional mild fevers.
06 Jul 2010	He was transferred to the care of another hospital.

Investigator's comment:

The subject was hospitalized from 01 May 2010 to 18 May 2010 due to pneumonia and subsequently an image showed that the pneumonia was improving on 25 May 2010. However, he was re-admitted to the hospital on 27 May 2010 because he experienced fever. At first, the fever and the pneumonia were considered to be an individual adverse event, but a CT scan on 02 Jun 2010 confirmed a lung abscess and so the adverse event term was changed to "recurrence of pneumonia/lung abscess". Judging from his overall clinical progression, a chest X-ray on 25 May 2010 revealed that his pneumonia once subsided, although his fever and CRP levels stayed high. The symptoms of the pneumonia worsened again, leading to the lung abscess. Accordingly, the "fever" and the "recurrence of pneumonia/lung abscess" were considered to have been associated with the "pneumonia" which developed on 01 May 2010; therefore these events were evaluated as one ongoing event. As a result it was concluded that the adverse event term "pneumonia" should be reported in this case. As for the causal relationship between the event and the study drug, the event appeared while the study drug was being administered. In addition, the event recurred when the study drug was resumed. Thus a causal relationship between the event and the study drug cannot be ruled out, which is the same evaluation as the previous report. This case had been followed up; however, he was transferred to another hospital on 06 Jul 2010. Consequently, the outcome of the event was assessed as "recovering" as of 06 Jul 2010. Further investigation seemed difficult and his follow-up was closed.

Subject ID:	**10021006**
Age:	69 years
Sex:	Female
Race:	Asian (Japanese)
Treatment Group:	16 mg QD, Dose-escalation component (Phase 1; Group 1)
Current medical conditions:	Arrhythmia, esophageal varices, gastritis, hepatitis C, portal thrombosis, tumor pain
Concomitant medications:	Human serum albumin, aminoleban, amlodipine besilate, lac-B, cefdinir, dextrome thorphan hy-drobromide hydrate, soldem 1, levact, furosemide, lactulose, loperamid hydrochloraide, loperamide hydrochloride, magnesium oxide, metoclopramide, omeprazole, acetaminophen, plaunotol, prochlorperazine, sennoside, spironolactone-A, urea, zolpidem tartrate
Reason for narrative:	
Nonfatal SAE(s)	Hepatic encephalopathy (2 events)
Relationship to study drug:	Probably related (2 events)

AE Description:

Dec 2004	Subject was diagnosed with hepatocellular carcinoma.
15 Mar 2010	The subject started study medication (16 mg).
22 Mar 2010	Disorientation was observed while the subject was talking with a nurse; however, it was not seen during the physician's examination. No flapping tremors were observed.
23 Mar 2010	Her blood was collected. The results of the test showed that her AST/ALT, T-Bil and ammonia (NH_3) levels had increased, but the results did not meet the criteria for withdrawal from the clinical study or dose reduction.
25 Mar 2010	She started taking lactulose in consideration of hepatic dysfunction or hyperammonemia.
27 Mar 2010	Study drug was interrupted by the subject's physician. Her hepatic function tended to worsen. Although it did not meet the criteria for drug withdrawal stated in the protocol, the physician decided to interrupt the administration of the study drug.
29 Mar 2010	The hepatic dysfunction and hyperammonemia improved. In addition, there was a tendency towards improvement in her general condition. Lactulose was suspended temporarily due to persistent diarrhea.
01 Apr 2010	Study medication was resumed at a dose of 16 mg.
02 Apr 2010	Although she defecated twice on the previous day, she requested a prescription for laxatives. Lactulose was re-administered.

07 Apr 2010	The subject's hands were sometimes flickering, which did not appear during examinations. An intestinal regulator and antidiarrheal agent were initiated for watery stools.
09 Apr 2010 (SAE Start Date)	Grade 2 anorexia and Grade 3 hepatic dysfunction (with flapping tremors) were confirmed. Lactulose was resumed.
10 Apr 2010	Study medication was interrupted. She was unable to communicate with people.
12 Apr 2010	Grade 3 hepatic dysfunction was diagnosed on the basis of clinical examination. The scheduled administration of the second Cycle was cancelled.
13 Apr 2010	The subject had a urine leukocyte of 3+ and inflammation reaction did not increase. The subject had a specimen taken for urine bacterial culture.
14 Apr 2010	Urine culture showed gram negative bacilli and urinary tract infection was diagnosed.
15 Apr 2010	Cefdinir was administered (scheduled one week). A CT examination showed SD of multiple lung metastases; LNSD (slightly reduced with internal necrosis) of mediastinum; the incidence of ascites; increasing portal abscess plugging or thrombus, which was assessed as SD. The reporting physician explained the above mentioned results to the subject and the subject's husband. The subject wanted to continue the study. The study medication would be reduced and be resumed after the subject recovered.
19 Apr 2010	The subject recovered from the event and had a good appetite and a clear sensorium.
24 Apr 2010	The study medication was resumed at a dose of 12 mg.
26 Apr 2010	A blood test performed indicated a hepatic function increase.
27 Apr 2010	No flapping tremor was noted, the subject became less expressive.
28 Apr 2010	The subject ate 30% of the meal provided for dinner and vomited food residues shortly after she took the oral medication prescribed for the evening.
30 Apr 2010 (SAE Start Date)	The subject showed mask like faces, mild consciousness disturbance and flapping tremor occurred. PS3. The administration of the study drug was interrupted. Therapy with aminoleban and soldem 1 was initiated.
01 May 2010	The subject developed lethargy, but experienced no disorientation or flapping tremor. The subject was able to ingest food and fluid at a certain level.
03 May 2010	The subject experienced poor oral intake. No flapping tremor or constipation was noted. The subject slightly choked when swallowing meals, but no rale was heard on the chest auscultation. A mild cough and sputum occurred without progression.
04 May 2010	The subject's general condition improved.

06 May 2010	Because of the interruption of the study drug, the subject's general condition and hepatic function disorder improved. A tumor assessment with a tumor marker and imaging was performed.
07 May 2010	The subject was consulted and she did not wish to continue treatment with the study drug due to the severe hepatotoxicity that occurred even after a dose reduction. The subject's primary doctor agreed that discontinuation of the study drug was appropriate and therefore the study medication was not restarted.
10 May 2010	The subject recovered from the event.

Investigator's comment:

The subject's liver reserve improved gradually and the ammonia value decreased after the study drug was interrupted on 10 Apr 2010. The subject became awake and alert on 19 Apr 2010, and the reporting physician considered that the subject recovered from hepatic encephalopathy although the ammonia value was still slightly high. Based on the course, the subject's impaired liver function and hepatic encephalopathy were related to the study drug.

Event occurred while the subject was hospitalized for medication. Thus event was not matched to definition of severe adverse reaction. However event was evaluated as serious because principally it was classified as serious event that required hospitalization. Medically important was thought to be appropriate for seriousness for this event. The subject experienced the same event before study medication was reduced. The causal relationship was assessed as probable because repeatability of event was considered.

Subject ID:	**10022003**
Age:	61 years
Sex:	Male
Race:	Asian (Japanese)
Treatment Group:	8 mg QD, Dose-escalation component (Phase 1; Group 2)
Current medical conditions:	Ascites, atrioventricular block first degree, constipation, diabetes mellitus, diarrhoea, dry skin, gastritis, hepatic cirrhosis, insomnia, pain, varices oesophageal
Concomitant medications:	Celecoxib, dexamethasone, streptococcus faecalis, livact, furosemide, scopolamine butylbromide, indometacin, insulin aspart, insulin glargine, insulin human, lactulose, lansoprazole, loxoprophen sodium hydrate, magnesium oxide, metoclopramide, soldem, oxycodone hydrochloride hydrate, prochlorparazine maleate, sennoside A B, shakuyakukanzouto, sodium gualenate hydrate, spironolactone, tizanidine hydrochloride, urea, zolpidem tartrate
Reason for narrative:	
Nonfatal SAE(s)	Hyperbilirubinaemia (2 events)
Relationship to study drug:	Probably related (2 events)

AE Description:

Jul 2010	The subject was diagnosed with hepatocellular carcinoma.
12 Jul 2011	Study medication was started (8 mg/day). Before the study medication was started the subject's T-Bil was 1.7 mg/dL (Grade 1).
19 Jul 2011 (SAE Start Date)	The subject experienced hyperbilirubinaemia. Laboratory data showed a high level of T-Bil (in hospital: 2.6 mg/dL, central laboratory: 2.5 mg/dL, Grade 2).
02 Aug 2011	Laboratory data showed that T-Bil had further increased (in-hospital 3.8 mg/dL, central laboratory: 3.7 mg/dL, Grade 3). No jaundice was confirmed.
06 Aug 2011	Administration of study medication was suspended due to other adverse events (nausea and vomiting).
09 Aug 2011	Laboratory data showed that T-Bil had further increased (in-hospital: 5.2 mg/dL, central laboratory: 5.0 mg/dL, Grade 3). He was urgently hospitalized for observation. Yellow staining of the eye balls was observed.
10 Aug 2011	A CT showed no findings of suspected bile duct obstruction. Neither nausea nor vomiting was observed after hospitalization.
16 Aug 2011	A blood test showed an improved T-Bil (in hospital: 1.7 mg/dL, central laboratory: 1.7 mg/dL, Grade 1).
18 Aug 2011	Study medication was re-initiated at the lower dose of 4 mg/day.

23 Aug 2011	A blood test showed a slight increase in T-Bil (in-hospital: 1.9 mg/dL, central laboratory: 1.8 mg/dL, Grade 1); however ongoing administration of the study drug was possible.
25 Aug 2011	The subject was discharged from the hospital. The subject received his last dose of study medication on 29 Aug 2011.
30 Aug 2011 (SAE Start Date)	The subject visited the outpatient department as scheduled. Hyperbilirubinaemia recurred after a blood test showed an increased T-Bil (in hospital: 4.0 mg/dL, central laboratory: 4.0 mg/dL) and she was hospitalized for observation. The study medication was skipped. The subject had anorexia and fluid infusion was started.
01 Sep 2011	A blood test was performed in the hospital which showed that t-Bil level slightly improved at 3.6 mg/dL.
06 Sep 2011	Blood tests showed improved in T-Bil (in hospital: 1.9 mg/dL, central laboratory: 1.8 mg/dL, Grade 1). Images confirmed progressive disease (PD). The subject was withdrawn from the study.
07 Sep 2011	The subject was discharged from the hospital.

Investigator's comment:
The subject's T-Bil levels were within normal limits during the screening phase and increased after administration of the study drug was initiated. After temporary suspension of the study medication, the event improved; thus, study medication was resumed at a lower dose. Thus the causal relationship between the event and the study drug could not be ruled out. The event subsided after the administration of the study drug was interrupted, but resumption of the study drug was considered difficult. In addition, the image confirmed that the lesion had extended. The subject withdrawal from the clinical study was determined.