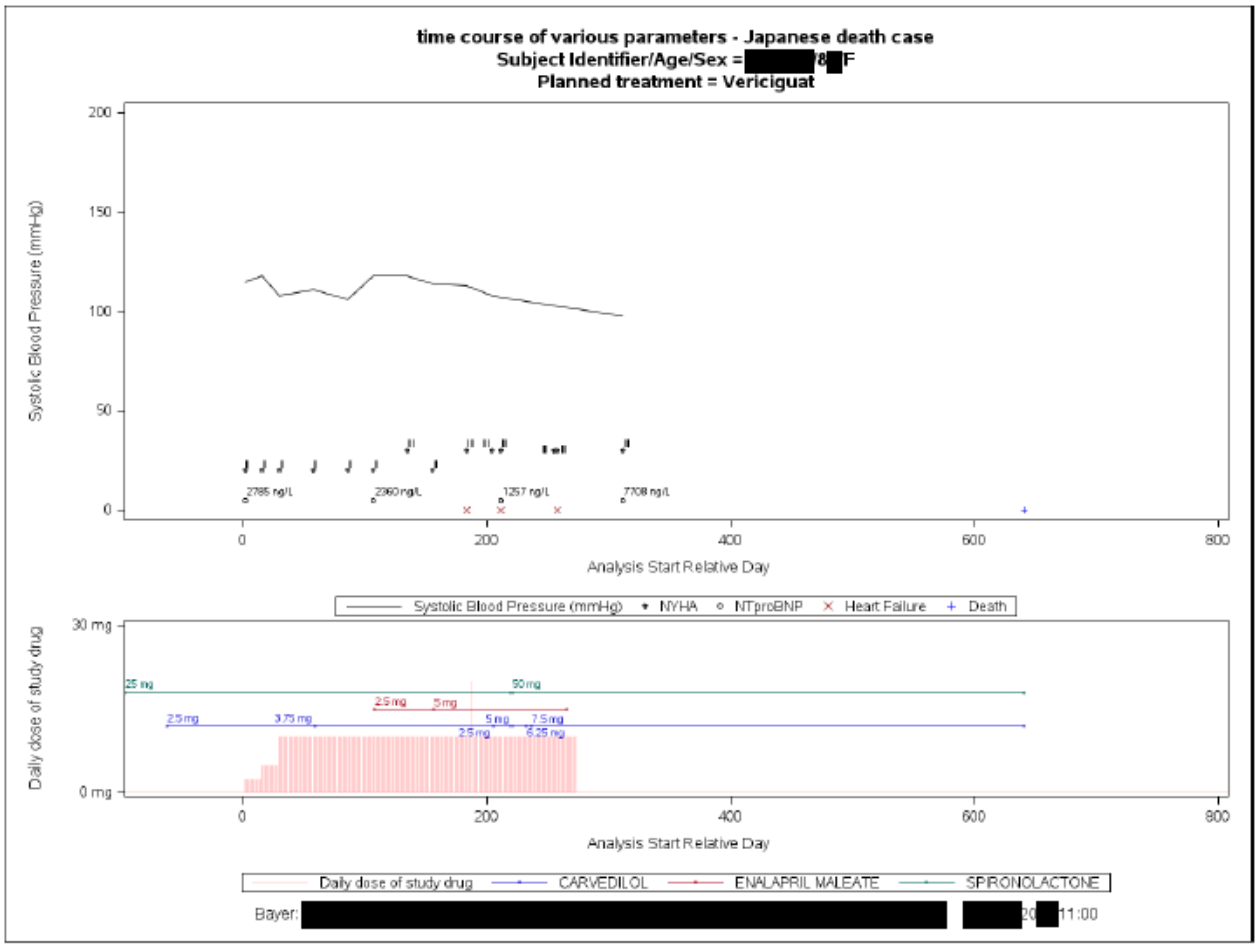

time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8[redacted]F
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
2785 ng/L
2360 ng/L
1257 ng/L
7708 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
0 mg
25 mg
50 mg
2.5 mg
3.75 mg
5 mg
7.5 mg
6.25 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
ENALAPRIL MALEATE
SPIRONOLACTONE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure acute	急性心不全		Day 69
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 11

Age	Sex	Race	Ethnicity	Country
6[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 3 months, 9 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Diabetes mellitus; Hyperlipidaemia; Hypertension; Epilepsy; Hyperkalaemia; Cerebrovascular accident; Chronic kidney disease; Extremity contracture; Thermal burn; Hyperuricaemia; Coronary artery disease
History of Medical/ Surgical Procedures	None

Concomitant Medications at Randomization	carvedilol, febuxostat, valproate sodium, acetylsalicylic acid, sulfadiazine silver, tolvaptan, sitagliptin phosphate monohydrate, furosemide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-17	3155 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-29	19 %		
1		NYHA CLASS II	28.4 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 12 年 1 ヵ月前から脳血管発作があった。

第 11 日に被験者は虚血性脳卒中のため他院へ入院した。脳の核 MRI 検査で左後頭葉に梗塞が認められた。アルテプラーゼ及びアセチルサリチル酸が投与された。治験責任（分担）医師の判断により治験薬の投与は中止され、最終投与日は第 11 日であった。第 15 日に急性腎障害（非重篤な有害事象）が発現し、第 21 日まで持続的血液透析が行われた。第 69 日に被験者は急性心不全のため死亡した（目撃者ありと報告

された）。治験責任（分担）医師は、「情報がほとんどないため、因果関係は不明である」とし、因果関係は否定できないと判断した。剖検に関する情報は報告されなかった。死亡時に、急性腎障害の転帰は不明と報告された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	10	placebo	0	1
11	11	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-15	108	65	67	
1	103	64	71	7[redacted]3
1	104	62	69	

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	8(L)	16	7.353	57

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-15	167.076(H)
1	203.32(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

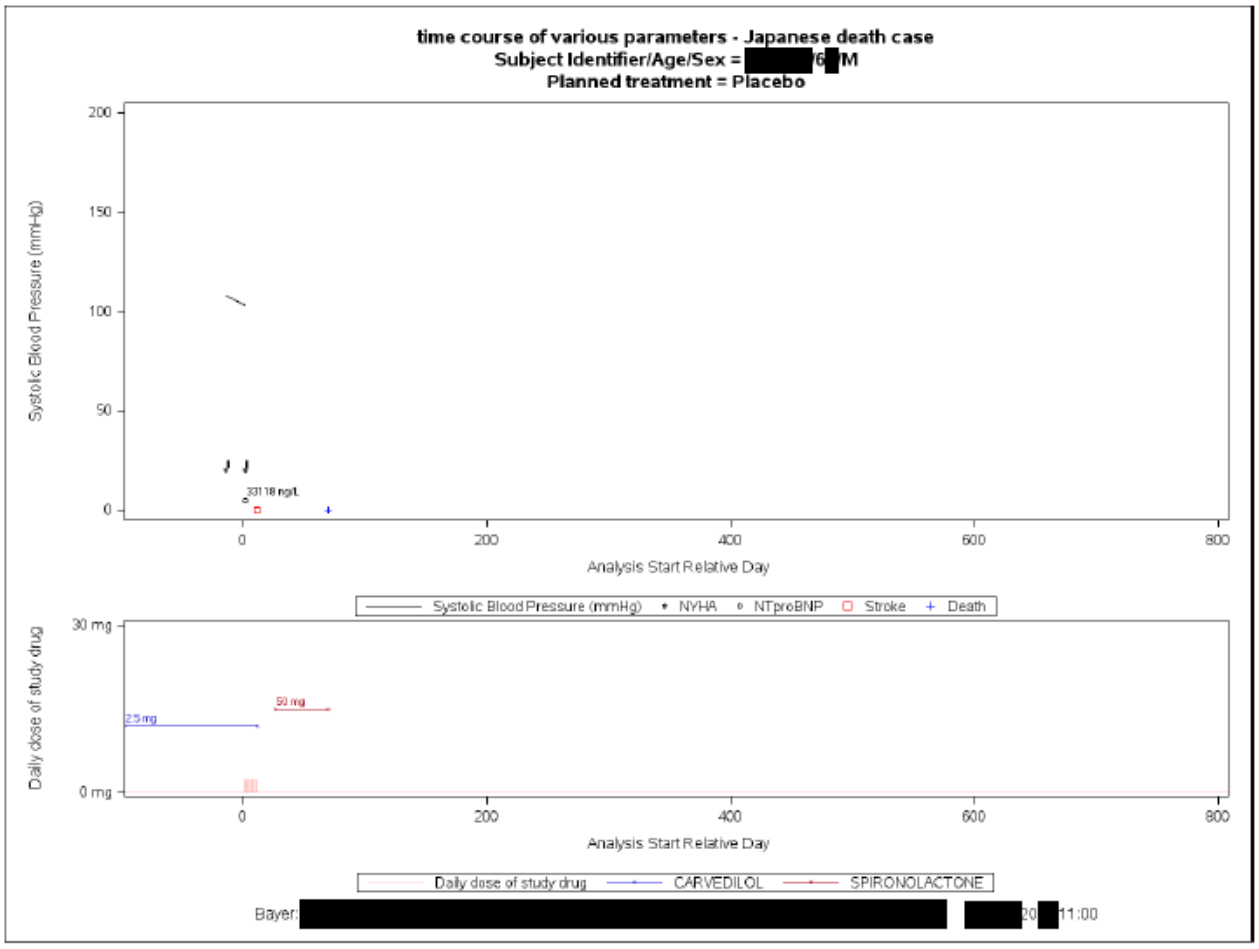
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
11	69	Stroke	Hospitalization	Stroke
69		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]/6[redacted]/M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
3118 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Stroke
Death
Daily dose of study drug
30 mg
2.5 mg
50 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
SPIRONOLACTONE
Bayer[redacted]20[redacted]11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Death	死亡		Day 450
SAE	Hypoglycaemia	低血糖	Severe	Day 263
SAE	Hyperglycaemia	高血糖	Severe	Day 386

Age	Sex	Race	Ethnicity	Country
5[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 6 months, 15 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Alcoholic liver disease; Varices oesophageal; Osteoporosis; Diabetic neuropathy; Gastrooesophageal reflux disease; Diabetes mellitus; Hyperlipidaemia; Hypertension; Coronary artery disease; Cerebrovascular accident; Angina pectoris
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	azosemide, tolvaptan, acetylsalicylic acid, prasugrel hydrochloride, carvedilol, epoetin beta, alfacalcidol, insulin lispro, esomeprazole magnesium, vonoprazan fumarate, mecobalamin, heparinoid, amlodipine, telmisartan

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-30	245 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-112	44 %		
1		NYHA CLASS II	49.1 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 16 年前から糖尿病があった。

第 263 日に被験者は自宅で不穏状態になった後、低血糖のため入院した。皮膚擦過傷（非重篤な有害事象）及び貧血（非重篤な有害事象）と診断された。シアノコバラミン／ピリドキシン塩酸塩／チアミンジスルフィド、アシクロビル、ミダゾラム、フェンタニル、プロポフォール、ロクロニウム臭化物、ヒトインスリン、グルコース、グアイアズレン、インスリングラルギン、ボグリボース、インスリンリスプロ及び含

糖酸化鉄が投与された。第 265 日に貧血は消失した。第 268 日に低血糖及び皮膚擦過傷は消失し、被験者は退院し、帰宅した。低血糖のため治験薬の投与は中断され、第 269 日に 10mg で再開された。

被験者は他院を受診し（日付不明）、第 386 日に高血糖と診断された（血糖値は約 574mg/dL）。薬剤（詳細不明）が投与された。この入院に関する追加情報は報告されなかった。

第 450 日に被験者は原因不明で死亡した。治験責任（分担）医師は、「死亡に至る詳細が不明のため、因果関係の評価ができない」とし、治験薬との因果関係は否定できないと判断した。剖検の有無は不明であった。治験薬の最終投与日は第 450 日であった。死亡時に、高血糖の転帰は未回復であった。

治験責任（分担）医師により、低血糖及び高血糖は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	7	MK-1242	2.5	1
8	8	MK-1242	2.5	0
9	15	MK-1242	2.5	1
16	21	MK-1242	5	1
22	22	MK-1242	5	0
23	29	MK-1242	5	1
30	54	MK-1242	10	1
55	74	MK-1242	10	0
75	99	MK-1242	10	1
100	152	MK-1242	10	1
153	165	MK-1242	10	0
166	218	MK-1242	10	1
219	262	MK-1242	10	1
263	268	MK-1242	10	0
269	290	MK-1242	10	1
291	309	MK-1242	10	0
310	329	MK-1242	10	1
330	361	MK-1242	10	1
362	385	MK-1242	10	0
386	418	MK-1242	10	1
419	423	MK-1242	10	0
424	434	MK-1242	10	1
435	449	MK-1242	10	1
450	450	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-30	177	104	87	
1	158	104	91	5[redacted].1
1	137	81	97	
15	151	93	91	5[redacted].2
29	143	86	86	5[redacted].8

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
57	126	85	97	5[redacted]5
99	145	87	82	5[redacted].2
127	166	95	85	5[redacted]
155	140	78	94	5[redacted]
190	185	112	89	5[redacted].4
218	173	103	92	5[redacted].6
253	182	112	92	5[redacted].7
295	133	84	90	4[redacted].5
330	168	104	93	5[redacted].8
365	189	112	81	5[redacted].2
400	148	92	94	4[redacted].7
435	193	115	83	5[redacted].3

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	66(H)	58(H)	3.762	140(H)
57	116(H)	350(H)		
99	94(H)	149(H)	5.472	215(H)
218	95(H)	52(H)	4.104	186(H)
330	120(H)	74(H)	7.353	196(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-30	110.5(H)
1	132.6(H)
99	141.44(H)
218	114.92
330	123.76

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

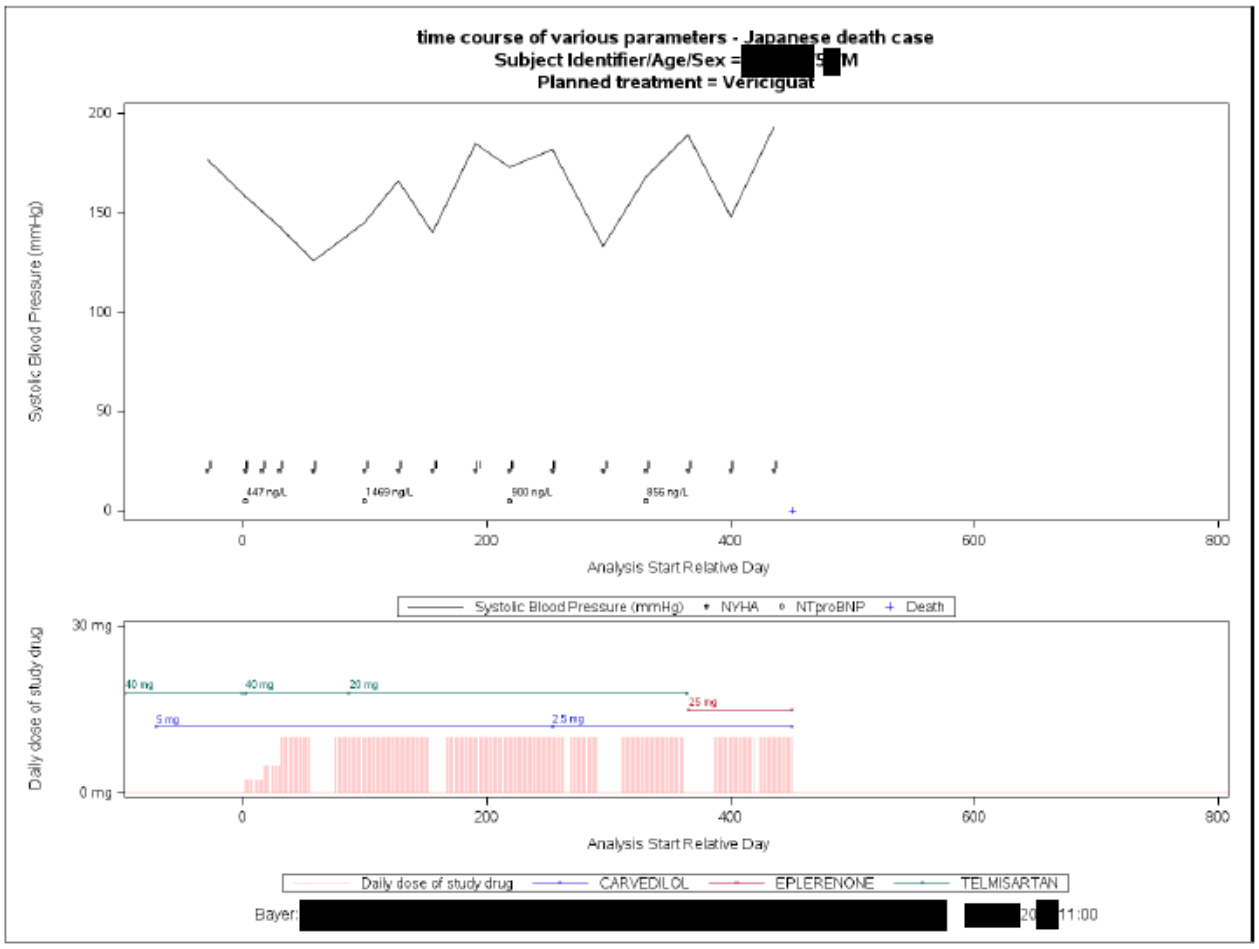
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
450		Undetermined Cause Of Death	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
Non-CV Death	Pneumonia	肺炎		Day 464
SAE	Inguinal hernia	鼠径ヘルニア	Severe	Day 107

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 1 year, 5 months, 16 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Diabetes mellitus; Hypertension; Peripheral arterial occlusive disease; Chronic obstructive pulmonary disease; Atrial fibrillation; Anaemia; Coronary artery disease; Myocardial infarction; Hyperlipidaemia; Chronic kidney disease; Ventricular extrasystoles; Hyperuricaemia; Aortic aneurysm; Spinal osteoarthritis; Benign prostatic hyperplasia; Lumbar spinal stenosis; Constipation; Intraductal papillary mucinous neoplasm; Rhinitis allergic; Haematoma muscle; Inguinal hernia; Echocardiogram
History of Medical/ Surgical Procedures	Coronary artery bypass; Percutaneous coronary intervention

Concomitant Medications at Randomization	fluvastatin sodium, acetylsalicylic acid, silodosin, distigmine bromide, bromhexine hydrochloride, tolvaptan, febuxostat, warfarin potassium, bisoprolol fumarate, eplerenone, ambroxol hydrochloride, fluticasone propionate;formoterol fumarate, theophylline, eicosapentaenoic acid ethyl ester, esomeprazole magnesium, fudosteine, loratadine, perindopril erbumine, trichlormethiazide, azosemide, olodaterol hydrochloride;tiotropium bromide monohydrate, sodium picosulfate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-25	2423 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-22	23 %		
1		NYHA CLASS II	25.9 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れと同年に診断された単径ヘルニアがあった。

第 107 日に被験者は単径ヘルニアの悪化のため入院した。ハルトマン手術及びヘルニア修復が行われた。単径ヘルニアのため治験薬の投与は中断され、第 123 日に再開した。第 149 日に単径ヘルニアは消失し、被験者は退院し、帰宅した。

第 454 日に被験者は肺炎のため入院した。セフメタゾールナトリウム、アミノフィリン、セフトリアキソンナトリウム水和物、ドパミン塩酸塩及びノルエピネフリンが投与された。第 464 日に被験者は肺炎のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。治験薬の最終投与日は第 445 日であった。

治験責任（分担）医師により、単径ヘルニアは治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	14	placebo	0	1
15	25	placebo	0	1
26	46	placebo	0	1
47	67	placebo	0	1
68	102	placebo	0	1
103	106	placebo	0	1
107	122	placebo	0	0
123	158	placebo	0	1
159	179	placebo	0	1
180	207	placebo	0	1
208	242	placebo	0	1
243	270	placebo	0	1
271	298	placebo	0	1
299	326	placebo	0	1
327	347	placebo	0	1
348	382	placebo	0	1
383	410	placebo	0	1
411	417	placebo	0	1
418	419	placebo	0	0
420	444	placebo	0	1
445	445	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-21	100	56	92	
1	100	49	90	4[redacted]
1	99	48	97	
15	97	59	88	4[redacted]
26	97	56	89	4[redacted].6
47	95	55	96	4[redacted].2

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
68	94	54	94	4[redacted]6
103	99	48	90	4[redacted]
159	94	57	88	4[redacted]4
180	99	52	69	4[redacted]6
208	98	47	89	4[redacted]4
243	98	49	87	4[redacted]
271	99	42	71	4[redacted]2
299	93	50	84	4[redacted]
327	101	49	89	4[redacted]
348	85	44	74	4[redacted]8
383	103	59	89	4[redacted]6
411	88	54	97	3[redacted]6
446	96	60	79	4[redacted]8

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	13	25	7.524	100
103	9(L)	18	5.814	86
208	8(L)	17	7.182	89
327	12	24	5.472	91

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-21	159.12(H)
1	212.16(H)
103	194.48(H)
208	203.32(H)
327	229.84(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

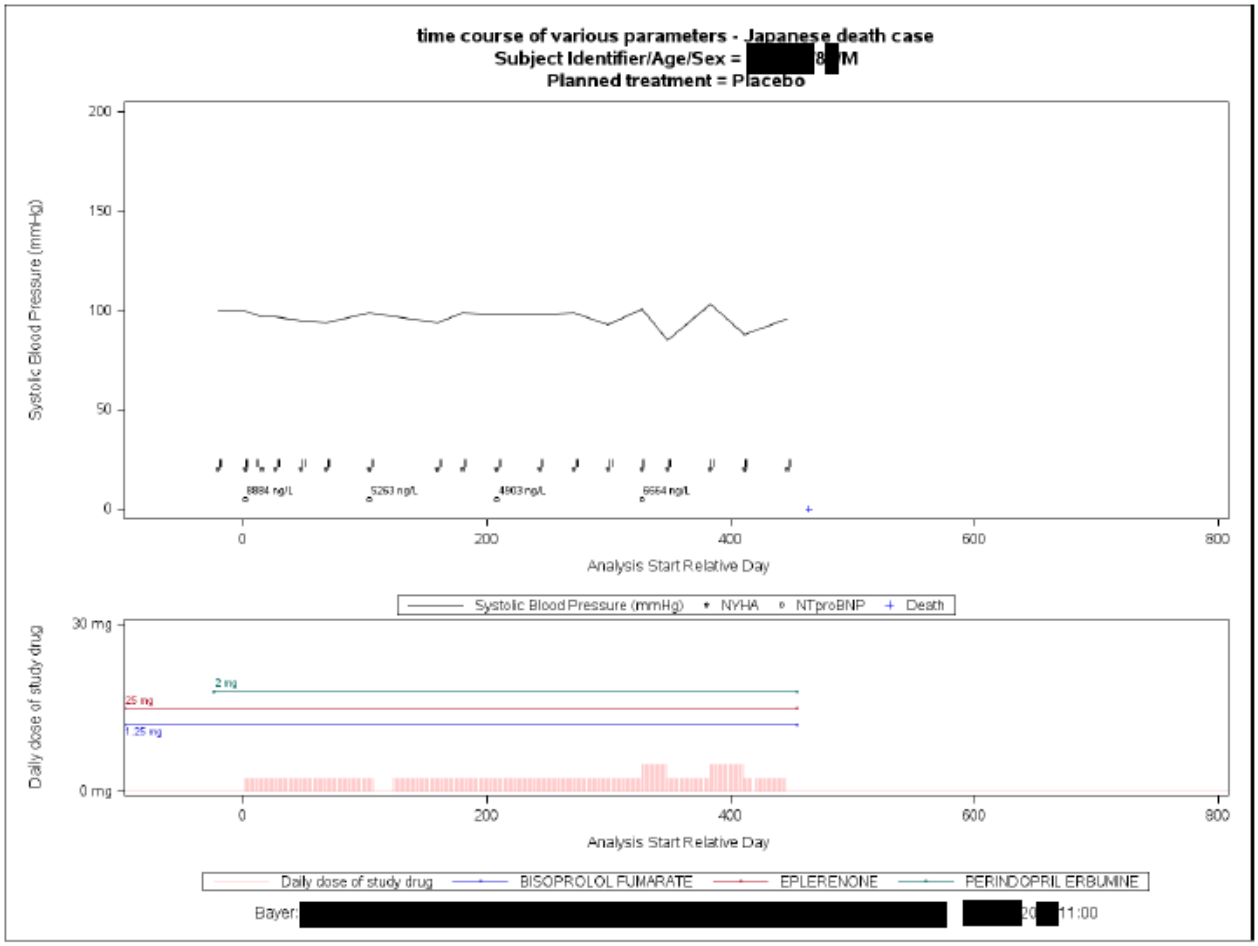
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
464		Non-CV Event	Death	Non-CV Event

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8 M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
8884 ng/L
5263 ng/L
4803 ng/L
6664 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
2 mg
25 mg
1.25 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
EPLERENONE
PERINDOPRIL ERBUMINE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Congestive cardiomyopathy	うっ血性心筋症		Day 251
SAE	Sepsis	敗血症	Severe	Day 227
SAE	Subdural haemorrhage	硬膜下出血	Severe	Day 240
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 224
Event of Clinical Interest	Hepatic function abnormal	肝機能異常	Mild	Day 225

Age	Sex	Race	Ethnicity	Country
4[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 3 years, 11 months, 22 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Diabetes mellitus; Hyperlipidaemia; Hypertension; Back pain; Hyperuricaemia; Renal cyst; Coronary artery disease; Myocardial infarction; Chronic kidney disease; Ventricular tachycardia; Cholelithiasis
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	esomeprazole magnesium, acetylsalicylic acid;clopidogrel bisulfate, febuxostat, tolvaptan, dapagliflozin propanediol monohydrate, carvedilol, amiodarone hydrochloride, metformin hydrochloride, sitagliptin phosphate, charcoal, activated, loxoprofen sodium, azosemide, trichlormethiazide, rosuvastatin calcium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-14	523 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
1	21 %	NYHA CLASS II	23.3 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

治験責任（分担）医師の判断により治験薬の投与が中止され、最終投与日は第 224 日であった。

第 225 日に被験者は心不全のため入院し、慢性腎臓病の悪化（非重篤な有害事象）及び肝機能異常（非重篤な有害事象）と診断された。心室補助人工心臓が装着され、肺補助装置療法（経皮的心肺補助）が施行された。X 線検査で肺うっ血及び胸水が、心エコー検査で左室のびまん性運動低下が認められた。心電図は正常であった。スワン・ガンツカテーテルで循環不全が認められた。また、心血管造影、大動脈内バルーン留置及び持続的血液ろ過透析が行われた。第 226 日に輸血が行われた。第 227 日に敗血症が発現した。第 230 日に血液灌流が行われた。意識の低下が認められた。第 240 日に頭部 CT 検査で硬膜下血腫と診断された。ミルリノン、ドブタミン塩酸塩、メロペネム、コルチコステロイド（詳細不明のステロイド）、その他の治療薬（詳細不明の昇圧薬）、アドレナリン及びドパミン作動薬（詳細不明のカテコールアミン）が投与された。第 242 日に挿管された。第 249 日に気管切開が行われた。意識は改善せず、状態は悪化した。第 251 日に被験者はうっ血型心筋症のため死亡した（目撃者なしと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。敗血症、慢性腎臓病の悪化及び硬膜下血腫の転帰は未回復であった。肝機能異常の転帰は不明と報告された。

治験責任（分担）医師により、敗血症、硬膜下血腫及び肝機能異常は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	14	MK-1242	2.5	1
15	28	MK-1242	5	1
29	56	MK-1242	10	1
57	91	MK-1242	10	1
92	119	MK-1242	10	1
120	147	MK-1242	10	1
148	182	MK-1242	10	1
183	210	MK-1242	10	1
211	224	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-14	128	92	76	
1	118	88	72	8[redacted]2
1	128	89	66	
15	108	77	73	8[redacted]6
29	117	86	73	8[redacted]4
57	112	84	84	9[redacted]2
92	113	82	71	9[redacted]4
120	107	81	72	8[redacted]6
148	94	60	80	8[redacted]4
183	117	96	82	8[redacted]4
211	111	83	85	8[redacted]2

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	26	11	12.654	68
120	32	15	14.022	70
225	78(H)	138(H)	78.318(H)	345(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-14	257.244(H)
1	256.36(H)
120	229.84(H)
225	317.356(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

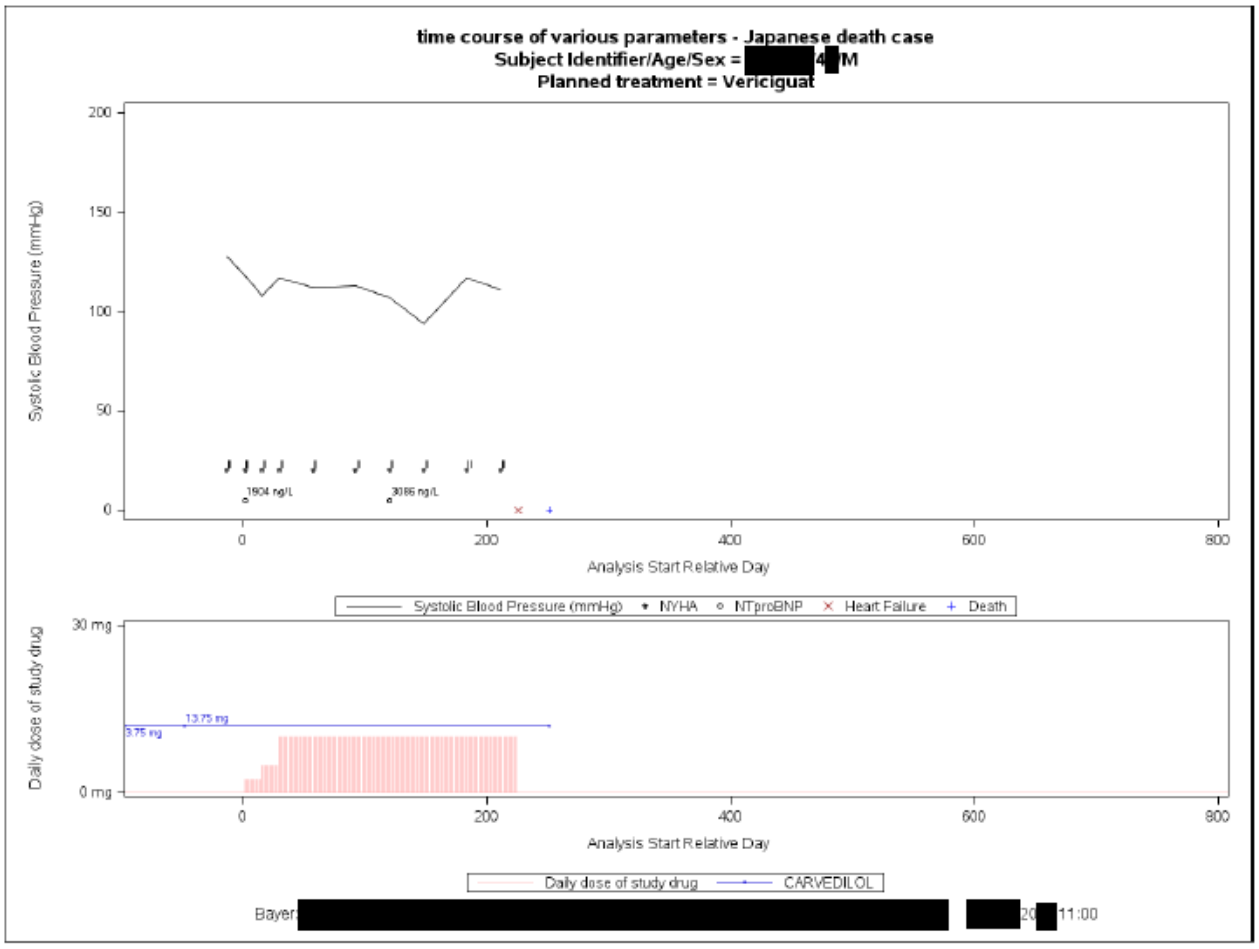
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
225	251	Heart Failure	Hospitalization	Heart Failure
251		Other Cardiovascular Event	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]4[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
1904 ng/L
3086 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
13.75 mg
3.75 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
Bayer[redacted]20[redacted]11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	うっ血性心筋症		Day 749

Age	Sex	Race	Ethnicity	Country
4[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 1419 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization

Medical History	Congestive cardiomyopathy, Hand fracture, Humerus fracture, Hyperlipidaemia, Hyperuricaemia, Insomnia, Ejection fraction, Mitral valve incompetence, Tricuspid valve incompetence
History of Medical/ Surgical Procedures	Mitral valve repair

Concomitant Medications at Randomization	rabeprazole sodium, amiodarone hydrochloride, eplerenone, furosemide, tolvaptan, enalapril maleate, carvedilol, febuxostat, flunitrazepam, triazolam, warfarin

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	292 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
1	27 %	NYHA CLASS II	80.1 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 561 日に足骨折（非重篤な有害事象）が発現した。

第 749 日に被験者が自宅で死亡していたことが判明した。翌日、剖検が実施され、死因は拡張型心筋症の可能性が高く、死亡日は第 749 日であると推測された。治験責任（分担）医師により、死因は合併症の拡張型心筋症であり、治験薬と関連なしと判断された。治験薬の最終投与日は 743 日であった。死亡時に、足骨折の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	14	MK-1242	2.5	1
15	28	MK-1242	2.5	1
29	84	MK-1242	2.5	1
85	105	MK-1242	5	1
106	225	MK-1242	5	1
226	337	MK-1242	5	1
338	421	MK-1242	5	1
422	540	MK-1242	5	1
541	659	MK-1242	5	1
660	743	MK-1242	5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-21	100	57	64	
1	101	58	63	6[redacted].4
1	101	63	62	
15	90	49	54	6[redacted].9
29	96	60	62	6[redacted].3
57	95	53	58	6[redacted].2
85	101	66	57	6[redacted]
106	98	48	53	6[redacted].2
134	94	55	49	6[redacted].2
162	94	55	41	6[redacted].7
197	98	64	42	6[redacted].2
225	95	52	62	6[redacted].3
253	90	50	55	6[redacted].7
288	94	54	55	6[redacted].1
309	96	53	54	6[redacted].2
337	97	57	51	6[redacted].5
365	91	50	55	6[redacted].6
393	94	53	57	6[redacted].5
421	94	56	56	6[redacted].5
456	91	51	56	6[redacted].9
484	96	61	59	6[redacted].9
519	92	53	57	6[redacted].9
540	90	49	62	6[redacted].2
568	93	45	60	6[redacted]
596	90	54	54	6[redacted].4
624	90	54	59	6[redacted].6
659	90	51	51	6[redacted].2
687	91	52	53	6[redacted].7
715	91	54	56	6[redacted]
743	91	52	49	6[redacted].4

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	9 (L)	15	5.472	66
106	7 (L)	16	5.814	68
225	8 (L)	11	10.089	55
337	11	18	4.788	63
659	11	14	9.918	52

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	88.4
106	97.24
225	79.56
337	61.88
659	88.4

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

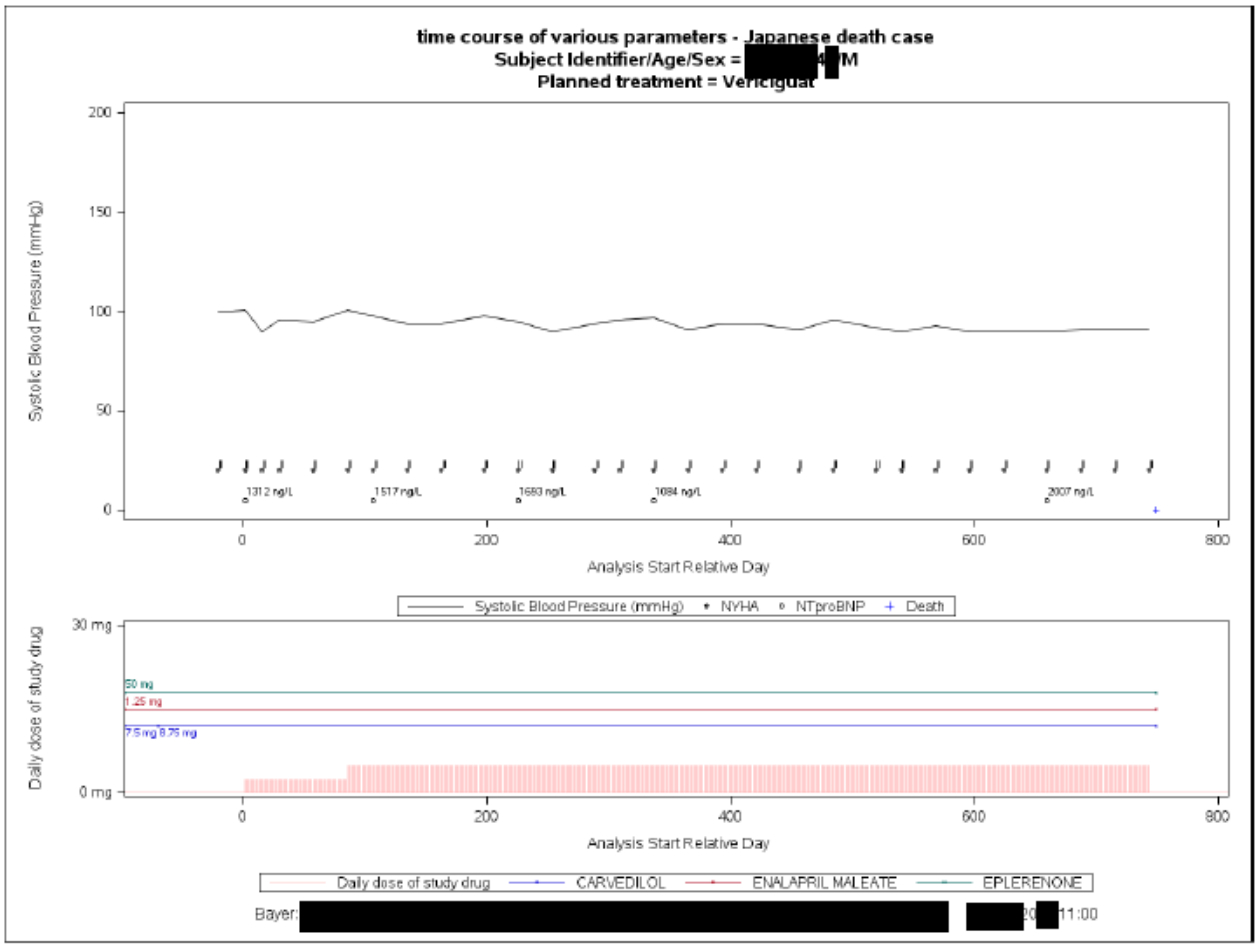
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
749		Undetermined Cause Of Death	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted] M
Planned treatment = Verlcigual
Systolic Blood Pressure (mmHg)
200
150
100
50
0
1312 ng/L
1517 ng/L
1683 ng/L
1084 ng/L
2907 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
0 mg
1.25 mg
7.5 mg
8.75 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
ENALAPRIL MALEATE
EPLERENONE
Bayer
11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Ventricular tachycardia	心室性頻脈		Day 354
SAE	Cardiac failure	心不全	Severe	Day 207

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 14 years, 7 months, 5 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Psoriasis; Hyperuricaemia; Ventricular tachycardia; Chronic kidney disease; Hyperlipidaemia; Constipation; Insomnia; Benign prostatic hyperplasia; Cerebrovascular accident; Atrial fibrillation; Peripheral arterial occlusive disease; Anaemia; Echocardiogram
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Implantable defibrillator insertion; Cardiac resynchronisation therapy

Concomitant Medications at Randomization	esomeprazole magnesium, rosuvastatin calcium, acetylsalicylic acid, silodosin, febuxostat, limaprost alfadex, zolpidem tartrate, carvedilol, sennoside a+b, furosemide, amiodarone hydrochloride, warfarin potassium, tolvaptan

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	2399 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-18	27 %		
1		NYHA CLASS II	32.1 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 3 年前から心室性頻脈があった。

第 171 日に被験者は心不全のため入院し、フロセミド、ワルファリンカリウム及びフロセミドナトリウムが投与された。第 185 日に被験者は退院し、自宅で医療サービスを受けることになった。

第 207 日に呼吸困難が発現した後、被験者は心不全増悪のため入院し、気管支炎（非重篤な有害事象）と

診断された。X線検査及びCT検査で肺うっ血の悪化が認められた。心エコー検査で高度の心機能障害及び僧帽弁逆流が認められた。心不全に対してフロセミドナトリウム、フロセミド及びアミオダロン塩酸塩が、気管支炎に対してセフトリアキソンナトリウム及びアンピシリンナトリウムが投与された。第222日に気管支炎は消失した。第236日にX線検査で肺うっ血の改善が認められたが、胸水は残存していた。第240日に心不全の増悪は回復し、被験者は退院し、自宅で医療サービスを受けることになった。

第320日に被験者は心不全のため入院し、ビソプロロールフマル酸塩、フロセミドナトリウム、メキシレチン塩酸塩、トルバプタン及びフロセミドが投与された。X線検査で肺うっ血の悪化が認められた。第347日に被験者は退院し、自宅で医療サービスを受けることになった。

第354日に呼吸が停止し、被験者は病院へ搬送された。エピネフリン及び炭酸水素ナトリウムが投与された。X線検査で右胸水及び軽度の肺うっ血が認められた。同日に被験者は心室性頻脈のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。治験薬の最終投与日は第353日であった。

治験責任（分担）医師により、心不全は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	15	MK-1242	2.5	1
16	21	MK-1242	5	1
22	22	MK-1242	5	0
23	29	MK-1242	5	1
30	57	MK-1242	10	1
58	86	MK-1242	10	1
87	114	MK-1242	10	1
115	142	MK-1242	10	1
143	170	MK-1242	10	1
171	203	MK-1242	10	1
204	207	MK-1242	10	1
208	208	MK-1242	10	0
209	236	MK-1242	10	1
237	269	MK-1242	10	1
270	302	MK-1242	10	1
303	320	MK-1242	10	1
321	325	MK-1242	10	0
326	335	MK-1242	10	1
336	352	MK-1242	10	1
353	353	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-7	128	65	62	
1	122	67	60	6[redacted]4
1	121	63	63	
15	105	62	59	6[redacted]45

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
29	110	61	57	6[redacted]85
57	101	56	60	6[redacted]95
86	126	60	71	6[redacted]05
114	108	57	62	6[redacted]
142	102	58	63	6[redacted]15
170	121	62	59	6[redacted]9
236	115	57	64	5[redacted]1
253	105	64	71	5[redacted]14
267	104	51	63	5[redacted]2
296	112	55	66	5[redacted]65
305	100	48	69	5[redacted]75
319	103	60	53	5[redacted]66
351	92	59	68	5[redacted]8

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	14	25	7.866	108
114	10	20	5.643	110
236	6(L)	15	8.55	109
351	15	24	8.892	124(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-21	151.164(H)
1	176.8(H)
114	159.12(H)
236	203.32(H)
351	221(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

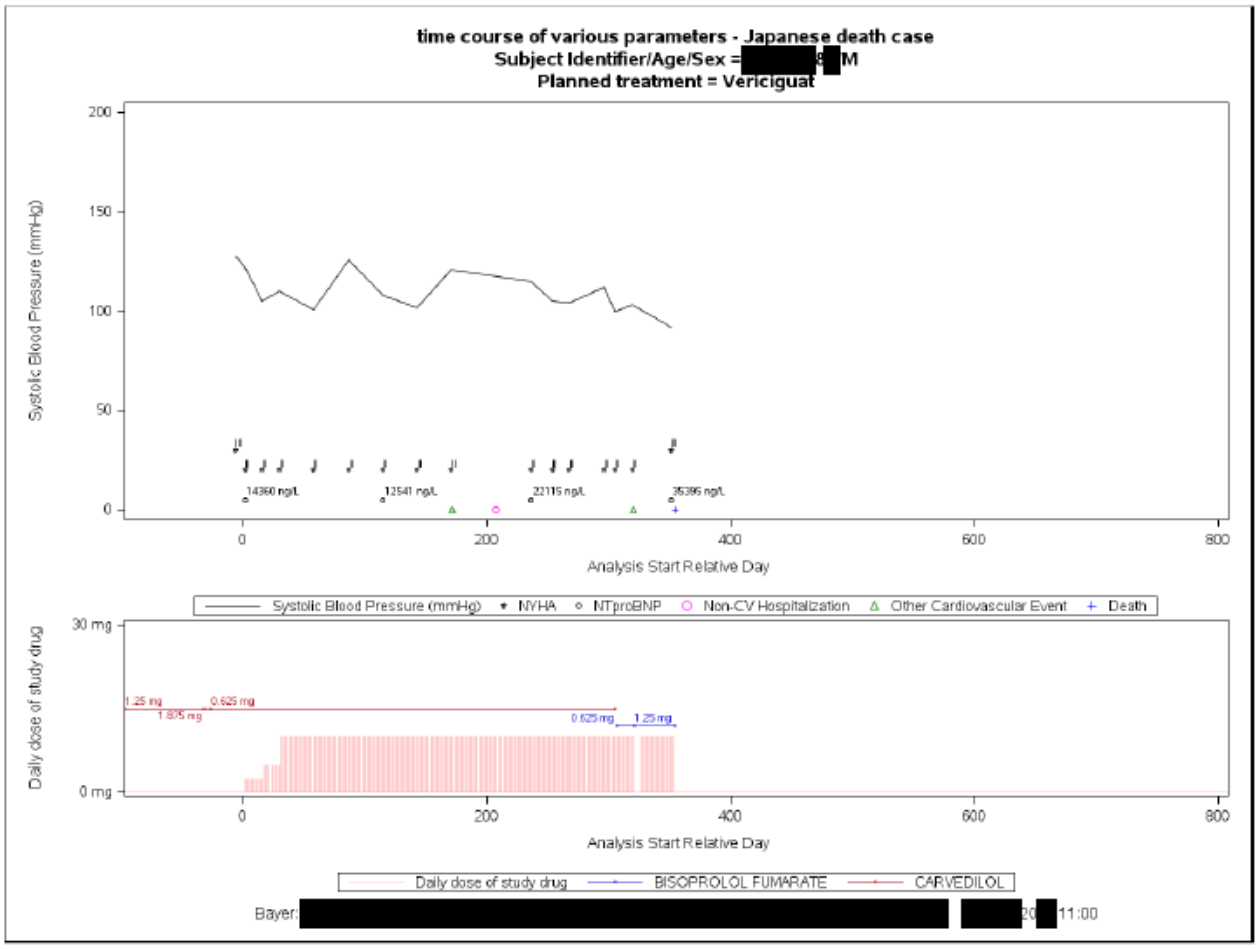
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
171	185	Heart Failure	Hospitalization	Other Cardiovascular Event
207	240	Heart Failure	Hospitalization	Non-CV Hospitalization
320	347	Heart Failure	Hospitalization	Other Cardiovascular Event
354		Sudden Cardiac Death	Death	Sudden Cardiac Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
Non-CV Death	Road traffic accident	交通事故		Day 87
SAE	Hypotension	低血圧	Severe	Day 70
Event of Clinical Interest	Hypotension	低血圧	Severe	Day 70

Age	Sex	Race	Ethnicity	Country
7[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 4 years, 11 months, 11 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Hypertension; Atrial fibrillation; Bundle branch block right; Lumbar spinal stenosis; Hyperlipidaemia; Angina pectoris; Chronic kidney disease; Hyperuricaemia; Peripheral arterial occlusive disease; Peripheral artery aneurysm; Echocardiogram; Deafness
History of Medical/ Surgical Procedures	Coronary artery bypass; Percutaneous coronary intervention

Concomitant Medications at Randomization	glyceryl trinitrate, pitavastatin calcium, clopidogrel bisulfate, irbesartan, allopurinol, furosemide, bisoprolol fumarate, spironolactone, apixaban, trichlormethiazide, lansoprazole, adenosine triphosphate, disodium salt, mecobalamin, angelica archangelica root;astragalus spp. root;atractylodes spp. rhizome;bupleurum falcatum root;dimocarpus longan aril;gardenia jasminoides fruit;glycyrrhiza spp. root;paeonia x suffruticosa root

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-27	1409 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-266	43 %		
1		NYHA CLASS III	29.2 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 29 日に偶発的過量投与（非重篤な有害事象）が認められ、これに伴う副作用はなかった。被験者は第 29 日～第 56 日まで治験薬を 1 日 3 錠服用していた。治験薬の正しい服用方法が再教育され、第 56 日に過量投与は消失した。

第 70 日に被験者は転倒し、下肢の脱力及び起立不能を伴う低血圧のため入院した。血圧は 74/53mmHg 及び 88/36mmHg であった。トリクロルメチアジドの投与が中止された。低血圧のため治験薬の投与は中断され、第 73 日に再開された。第 76 日に低血圧は消失し、被験者は退院し、帰宅した。

第 87 日に被験者は運転中の自損の交通事故のため入院した。プロポフォール、ノルエピネフリン、エピネフリン、ドパミン塩酸塩、塩化カルシウム二水和物／塩化カリウム／塩化ナトリウム／乳酸ナトリウム、重炭酸ナトリウム、濃厚赤血球及び血漿が投与された。同日に被験者は交通事故のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。治験薬の最終投与日は第 86 日であった。

治験責任（分担）医師により、低血圧は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	14	placebo	0	1
15	28	placebo	0	1
29	56	placebo	0	3
57	69	placebo	0	1
70	72	placebo	0	0
73	85	placebo	0	1
86	86	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-14	112	46	59	
1	118	46	61	[redacted].9
1	123	55	61	
15	118	55	65	[redacted].9
29	116	51	48	[redacted].5
57	120	55	54	[redacted].9
73	110	47	47	[redacted].9
85	93	37	57	[redacted].4

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	12	18	22.914(H)	144(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-27	155.584(H)
1	194.48(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

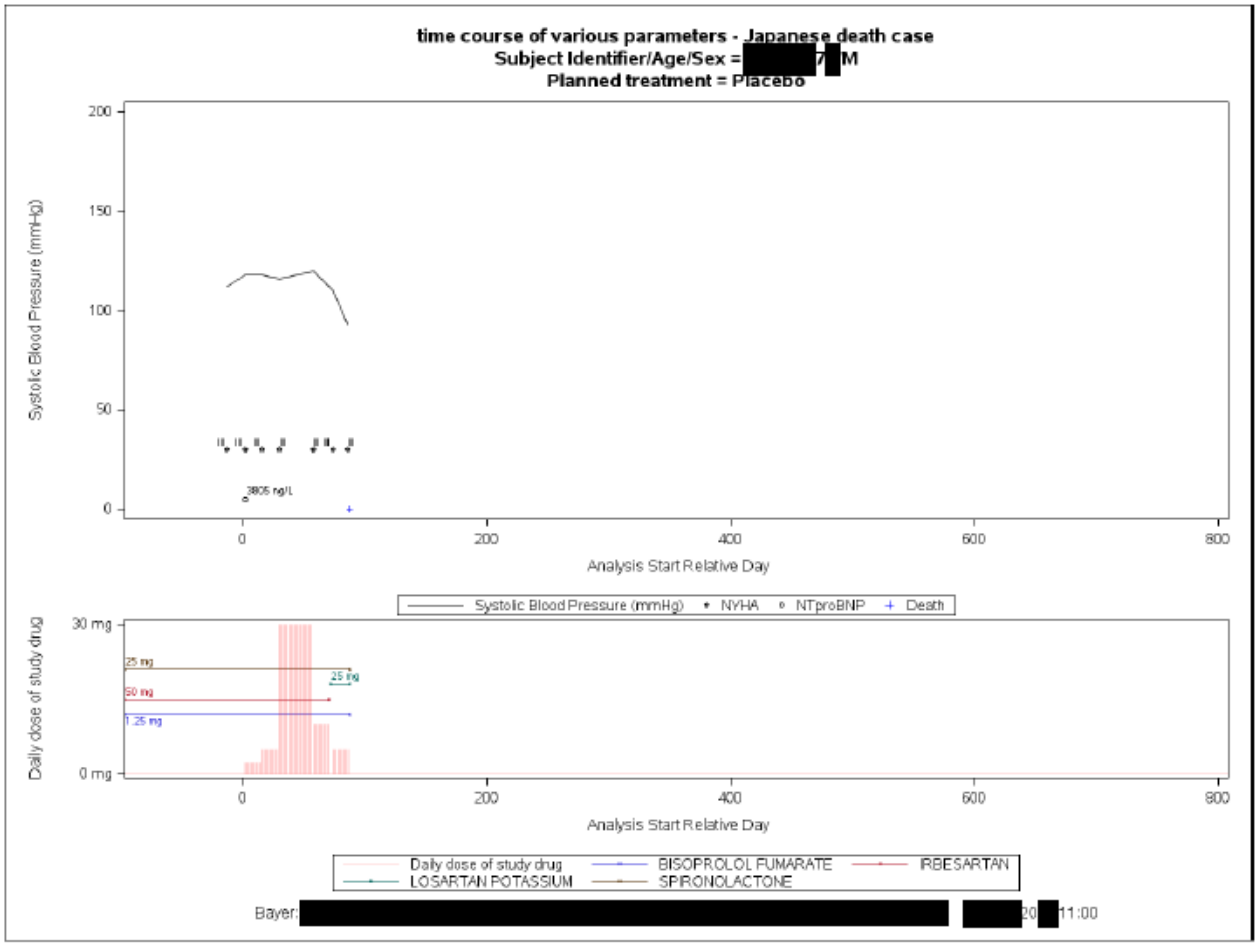
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
87		Non-CV Event	Death	Non-CV Event

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
Non-CV Death	Pneumonia	肺炎		Day 307
SAE	Hypokalaemia	低カリウム血症	Severe	Day 35
SAE	Alcoholic pancreatitis	アルコール性膵炎	Severe	Day 235
SAE	Pneumonia	肺炎	Severe	Day 291
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 234

Age	Sex	Race	Ethnicity	Country
6[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 8 years, 4 months, 24 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Hypertension; Ventricular tachycardia; Ventricular extrasystoles; Gastrooesophageal reflux disease; Insomnia; Deafness; Coronary artery disease; Myocardial infarction; Diabetes mellitus; Hyperlipidaemia; Peripheral arterial occlusive disease; Angina pectoris; Infectious pleural effusion; Pneumonia; Hypokalaemia; Alcohol use; Chronic gastritis; Alcoholic liver disease; Diarrhoea; Hyperuricaemia; Back pain; Echocardiogram
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	suvorexant, eplerenone, azosemide, perindopril, carvedilol, eszopiclone, mitiglinide calcium, acetylsalicylic acid;lansoprazole, rosuvastatin calcium, topiroxostat, ipragliflozin l-proline;sitagliptin phosphate monohydrate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-16	351 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-77	21 %		
1		NYHA CLASS II	97.6 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 2 年前から低カリウム血症、肺炎及びアルコール摂取が、約 1 年前からアルコール性肝障害があった。

第 35 日、脱力及び起立不能の発現後に、被験者は低カリウム血症の悪化のため入院した。低マグネシウム血症（非重篤な有害事象）も認められた。塩化カリウム、電解質 NOS、塩化カルシウム二水和物／塩化カリウム／酢酸ナトリウム三水和物／塩化ナトリウム／シアノコバラミン／ピリドキシン塩酸塩／チアミンジスルフィド、硫酸マグネシウム、リン酸二カリウムが投与された。第 36 日に便秘（非重篤な有害事象）が発現し、酸化マグネシウムが投与された。第 39 日に低マグネシウム血症、第 42 日に便秘が消失した。第 46 日に低カリウム血症が消失し、被験者は退院し、帰宅した。

第 235 日、心窩部痛の発現後に、被験者は急性アルコール性膵炎のため入院した。アルコール性膵炎のため治験薬の投与は中断された。その後、治験責任（分担）医師の判断により中止され、治験薬の最終投与日は第 234 日であった。ナファモスタットメシル酸塩、アンピシリンナトリウム／スルバクタムナトリウム、塩化カルシウム二水和物／塩化カリウム／酢酸ナトリウム三水和物／塩化ナトリウム、ペンタゾシン、アンピシリンナトリウム／スルバクタムナトリウム、塩化カリウムが投与された。第 246 日に急性アルコール性膵炎は消失し、被験者は退院し、帰宅した。

第 291 日、呼吸困難の発現後に、被験者は肺炎のため入院した。胸部 X 線検査で肺炎が確認された。被験者は心肺停止となり、蘇生により回復したが、意識は回復しなかった（日付不明）。心電図及び不整脈に関する事象は認められなかった。低酸素症が心肺停止を引き起こした可能性があると報告された。スルバクタムナトリウム、パラセタモール、メロペネム、ドブタミン塩酸塩、ニトログリセリン、フロセミド、カンレノ酸カリウム、カルベジロール、ペリンドプリルエルブミン、エプレレノン及びアゾセミドが投与された。第 307 日に被験者は肺炎のため死亡した（目撃者なしと報告された）。剖検は実施されなかった。

治験責任（分担）医師により、肺炎、低カリウム血症及びアルコール性膵炎は治験薬と関連なしと判断された。

Table 1.Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	4	MK-1242	2.5	0
5	14	MK-1242	2.5	1
15	28	MK-1242	5	1
29	34	MK-1242	10	1
35	36	MK-1242	10	0
37	56	MK-1242	10	1
57	84	MK-1242	10	1
85	112	MK-1242	10	1
113	154	MK-1242	10	1
155	182	MK-1242	10	1
183	187	MK-1242	10	0
188	210	MK-1242	10	1
211	233	MK-1242	10	1
234	234	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-2	68	48	93	
1	127	74	116	5[redacted]3
1	114	73	111	
15	115	66	116	5[redacted].8
29	107	71	112	5[redacted].1
57	123	76	107	5[redacted]
85	117	61	108	6[redacted].4
113	101	66	93	5[redacted].9
155	158	98	121	5[redacted].6
211	147	103	107	5[redacted].6
251	97	67	98	5[redacted].9
274	114	71	88	5[redacted].5

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	37	108(H)	16.758	84
113	32	95(H)	26.163(H)	83
211	41(H)	160(H)	17.955	88
235	169(H)	380(H)		
245	158(H)	202(H)		

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-16	76.024
1	70.72
113	88.4
211	88.4

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

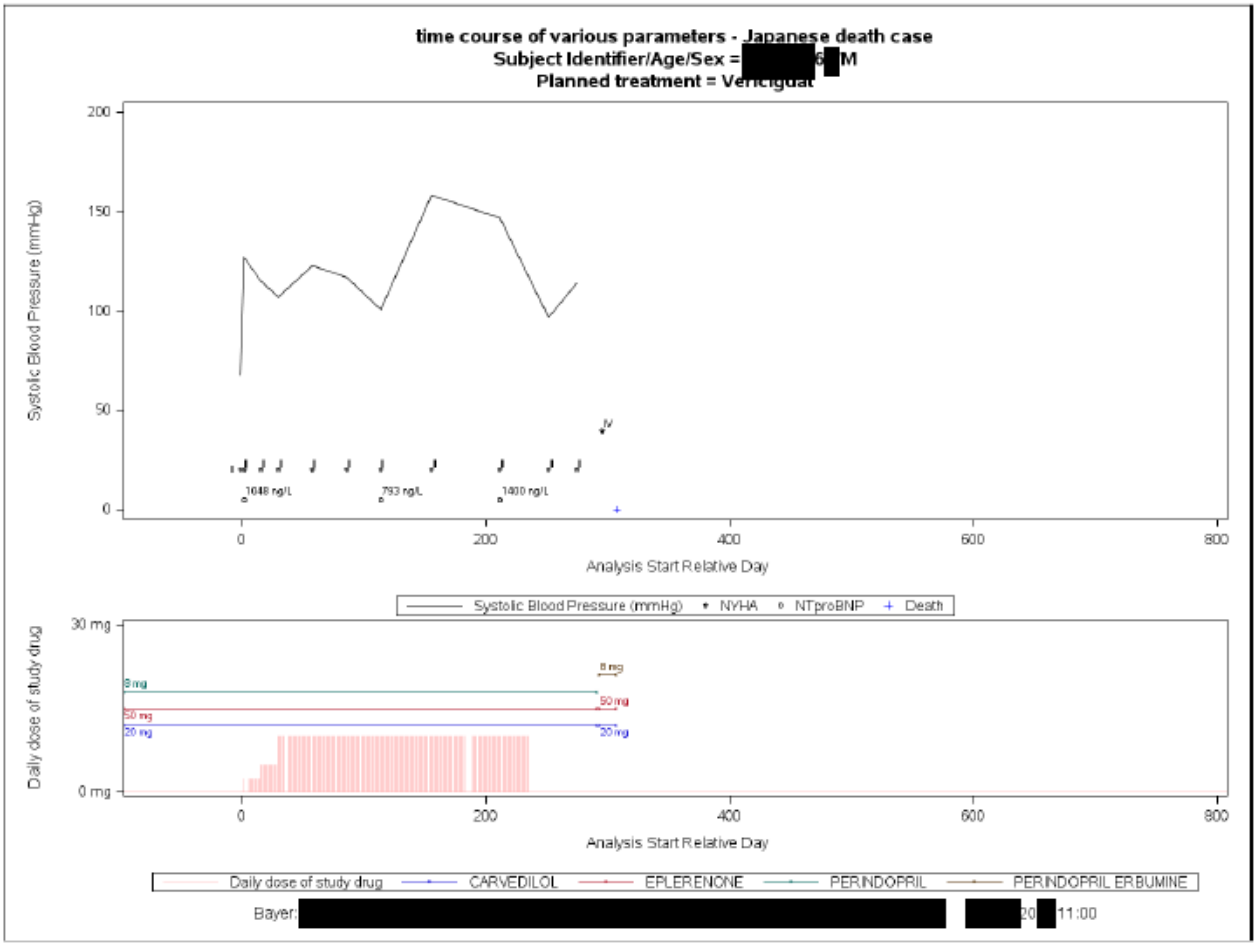
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
307		Non-CV Event	Death	Non-CV Event

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted] M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
1048 ng/L
793 ng/L
1400 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
0 mg
8 mg
50 mg
20 mg
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
EPLERENONE
PERINDOPRIL
PERINDOPRIL ERBUMINE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure	心不全		Day 419
SAE	Skin bacterial infection	皮膚細菌感染	Severe	Day 365
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 395
Event of Clinical Interest	Syncope	失神	Mild	Day 126

Age	Sex	Race	Ethnicity	Country
7[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 3 years, 10 months, 18 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Hyperlipidaemia; Constipation; Hyperuricaemia; Hepatic steatosis; Chronic kidney disease; Liver disorder; Hypothyroidism; Papuloerythroderma of Ofuji; Subcutaneous abscess; Pruritus; Echocardiogram; Diabetes mellitus
History of Medical/ Surgical Procedures	Cardiac resynchronisation therapy

Concomitant Medications at Randomization	dexchlorpheniramine maleate, white soft paraffin, betamethasone butyrate propionate, prednisolone valeroacetate, diflorasone diacetate, spironolactone, furosemide, ursodeoxycholic acid, pimobendan, bisoprolol fumarate, warfarin, febuxostat, fexofenadine hydrochloride, cepharanthine, magnesium oxide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	2373 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-32	19 %		
1		NYHA CLASS III	40 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れと同年の丘疹ー紅皮症（太藤）、皮下組織膿瘍及びそう痒症があった。

第 30 日に中毒性皮疹（非重篤な有害事象）が発現し、プレドニゾロンが投与され、*d*ークロルフェニラミ

ンマレイン酸塩、白色軟パラフィン、ベタメタゾン酪酸エステルプロピオン酸エステル及びプレドニゾロン吉草酸エステル酢酸エステルの投与が継続された。

第 126 日に失神（非重篤な有害事象、2 分間持続）が発現し、被験者は立位から転倒し、頭部を強打した。皮下血腫（非重篤な有害事象）及び頭部挫創（非重篤な有害事象）と診断された。血圧の測定値は報告されなかった。グアイアズレンが投与された。第 130 日に被験者はその後に失神が発現していないことを報告した。第 197 日に皮下血腫及び頭部挫創は消失した。

第 346 日～第 356 日に被験者は心不全のため入院した。

第 365 日に、足の皮膚潰瘍から滲出液が認められ、皮膚細菌感染及び全身皮膚潰瘍（非重篤な有害事象）と診断された。第 368 日に滲出液の微生物培養検査の結果は陽性であり、スルファジアジン銀及びセフジニルが投与され、ジフロラゾン酢酸エステル、フェキソフェナジン塩酸塩及びセファランチンの投与が継続された。第 374 日に被験者は皮膚細菌感染、及び皮膚細菌感染に続発した心不全増悪のため入院した。白色軟パラフィン、スルファジアジン銀及びセフジニルが投与された。第 377 日に表皮融解（非重篤な有害事象）が発現し、グアイアズレンが投与された。スピロノラクトン及びピモベンダンも投与された。第 382 日に誤嚥性肺炎（非重篤な有害事象）が発現し、スルバクタムナトリウム／アンピシリンナトリウムが投与された。第 390 日に誤嚥性肺炎は消失した。第 391 日に尿路感染（非重篤な有害事象）が発現し、セフトリアキソンナトリウム及びパラセタモールが投与された。治験責任（分担）医師の判断により治験薬の投与は中止され、最終投与日は第 395 日であった。第 401 日に 2 回目の誤嚥性肺炎（非重篤な有害事象）が発現し、クリンダマイシンリン酸エステルが投与された。第 404 日に皮膚カンジダ（非重篤な有害事象）が発現し、ケトコナゾールが投与された。第 419 日に被験者は心不全のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、中毒性皮疹、皮膚細菌感染、皮膚潰瘍、表皮融解、尿路感染、誤嚥性肺炎及び皮膚カンジダの転帰は未回復であった。

治験責任（分担）医師により、皮膚細菌感染及び失神は治験薬と関連なしと判断された。

Table 1.Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	14	MK-1242	2.5	1
15	31	MK-1242	5	1
32	56	MK-1242	10	1
57	79	MK-1242	10	1
80	82	MK-1242	10	0
83	105	MK-1242	10	1
106	161	MK-1242	10	1
162	181	MK-1242	10	1
182	182	MK-1242	10	0
183	185	MK-1242	10	1
186	186	MK-1242	10	0
187	210	MK-1242	10	1
211	238	MK-1242	10	1
239	239	MK-1242	10	0
240	266	MK-1242	10	1
267	290	MK-1242	10	1
291	291	MK-1242	10	0

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
292	315	MK-1242	10	1
316	343	MK-1242	10	1
344	357	MK-1242	10	1
358	358	MK-1242	10	0
359	371	MK-1242	10	1
372	394	MK-1242	5	1
395	395	MK-1242	5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	101	65	69	5[redacted].6
1	101	65	69	
1	102	66	72	
15	102	63	71	5[redacted].4
32	102	61	69	5[redacted].1
57	107	61	67	5[redacted].8
106	104	63	67	5[redacted].5
162	103	54	59	5[redacted].9
211	102	66	64	5[redacted].9
267	102	63	73	5[redacted].7
316	102	75	69	5[redacted].2
344	99	62	69	5[redacted].2
372	80	62	76	5[redacted].3
397	79	63	68	4[redacted].9

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	14	27	13.68	139(H)
106	12	23	10.431	118(H)
211	13	30	11.799	142(H)
316	23	28	15.219	109

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	154.7(H)
1	150.28(H)
106	132.6(H)
211	106.08
316	159.12(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

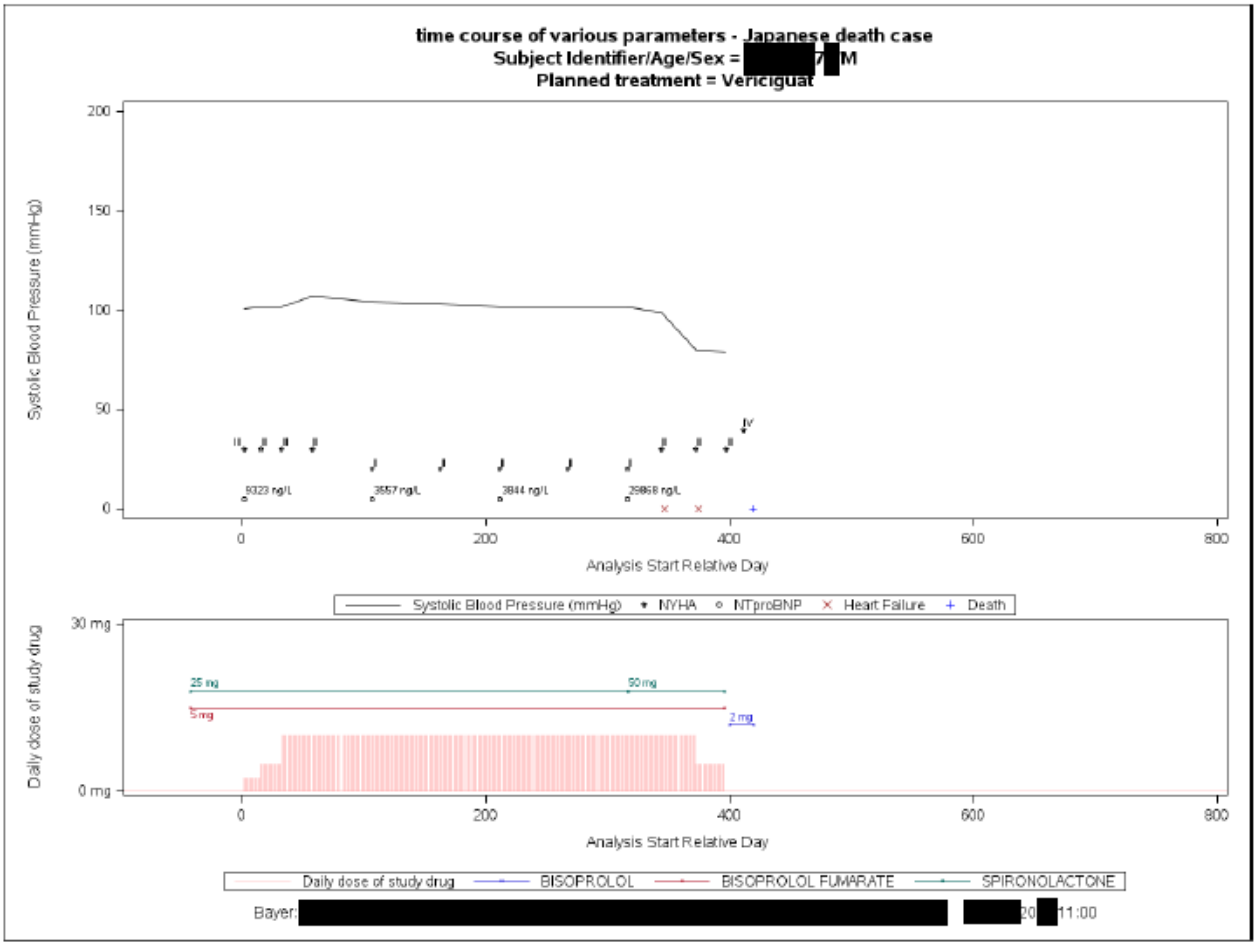
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
346	356	Heart Failure	Hospitalization	Heart Failure
374	419	Heart Failure	Hospitalization	Heart Failure
419		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure	心不全		Day 90
SAE	Large intestinal ulcer perforation	穿孔性大腸潰瘍	Severe	Day 81

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 4 years, 2 months, 26 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Diabetes mellitus; Anaemia; Deafness unilateral; Coronary artery disease; Myocardial infarction; Peripheral arterial occlusive disease; Angina pectoris; Constipation; Bundle branch block right; Ventricular extrasystoles; Nephrosclerosis; Atrial fibrillation; Hyperuricaemia; Bronchitis; Inguinal hernia; Pruritus; Facial bones fracture; Pneumonia bacterial
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	acetylsalicylic acid, famotidine, torasemide, rivaroxaban, sennoside a+b, tolvaptan, febuxostat, eplerenone, furosemide, crotamiton;hydrocortisone, amiodarone hydrochloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-13	1975 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-13	34 %		
1		NYHA CLASS II	38.8 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 61 年前から喫煙が、約 6 年前から便秘があった。また、腹部ステントグラフトの治療歴があった（日付不明）。

第 79 日に被験者は心不全のため入院し、腎機能障害（非重篤な有害事象）と診断された。胸部 X 線で胸水、心エコーで左室駆出率の低値、心電図検査で心室性期外収縮、完全右脚ブロック及び ST 低下が認め

られた。第 80 日に被験者は 2 日間便秘であることを報告し、センノシド a+b、ピコスルファートナトリウム及びグリセロールが投与された。第 81 日に悪心が発現し、塩酸メトクロプラミドが投与された。第 82 日に腹痛が発現し、腹部 CT で右鼠径ヘルニア及び「小腸伸展」が認められた。第 83 日及び第 84 日に腹部 CT で右鼠径ヘルニア、S 状結腸の壁肥厚及び浮腫が認められた。第 84 日に穿孔性大腸潰瘍と診断され（発現日は第 81 日）、S 状結腸切除術が施行された。フェンタニル、塩酸レミフェンタニル、ヘパリンナトリウム、リドカイン塩酸塩、レバロルファン酒石酸塩、フロモキセフナトリウム、エフェドリン、ミダゾラム、ミルリノン、フェニレフリン塩酸塩、スガマデクスナトリウム、ロピバカイン塩酸塩、ロクロニウム臭化物が投与され、赤血球輸血が行われた。穿孔性大腸潰瘍のため治験薬の投与は中断され、その後再開されず、最終投与日は第 83 日であった。血圧は 96～98／55～60mmHg であった（日付不明）。第 84 日にドパミン塩酸塩の投与が開始された。第 86 日、第 89 日及び第 90 日の胸部 X 線検査で胸水及び肺うっ血が認められた。アセチルサリチル酸、アミオダロン塩酸塩、リバーロキサバン、フロセミドナトリウム、ニコランジル、アトロピン、イソプレナリン塩酸塩及びカルペリチドが投与された。第 89 日に肝機能検査値異常（非重篤な有害事象）と診断された。第 90 日に腹部 CT で右鼠径ヘルニア、上行結腸から横行結腸にかけての浮腫、及び S 状結腸に硬い便の貯留が認められた。同日に被験者は心不全のため突然死した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、腎機能障害、穿孔性大腸潰瘍及び肝機能検査異常の転帰は未回復であった。

治験責任（分担）医師により、穿孔性大腸潰瘍は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	12	MK-1242	2.5	1
13	26	MK-1242	5	1
27	36	MK-1242	10	1
37	37	MK-1242	10	0
38	47	MK-1242	10	1
48	78	MK-1242	10	1
79	82	MK-1242	10	1
83	83	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	105	50	81	5[redacted]96
1	105	50	81	
1	110	56	77	
13	103	47	67	6[redacted]7
27	104	55	70	6[redacted]9
48	116	58	81	6[redacted]3
79	101	56	72	6[redacted]8

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	11	18	6.156	99

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	159.12(H)
1	150.28(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

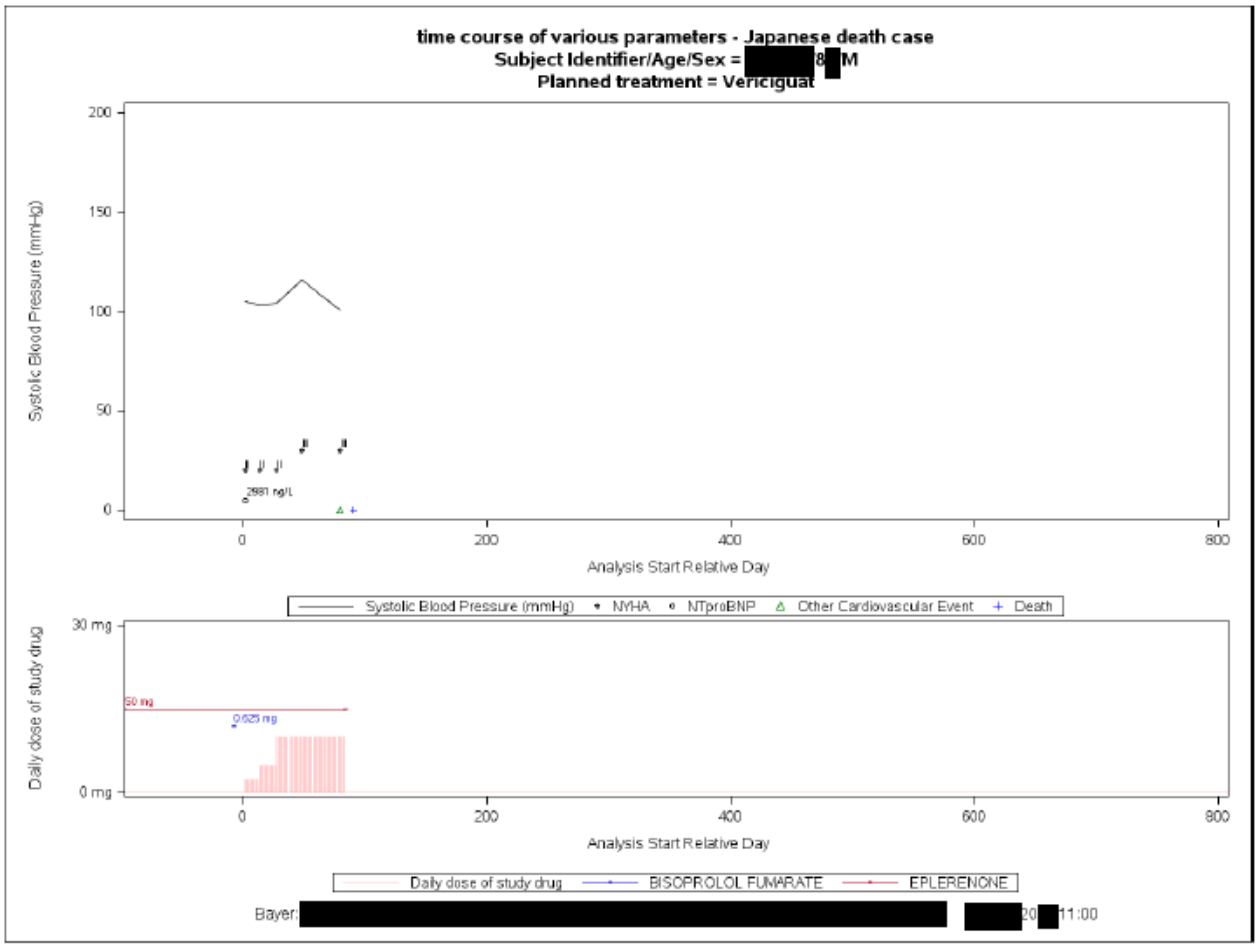
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
79	90	Heart Failure	Hospitalization	Other Cardiovascular Event
90		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8 M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
2981 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
0 mg
10 mg
0.625 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
EPLERENONE
Bayer: [redacted] 20[redacted]11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Marasmus	マラスムス		Day 180
SAE	Marasmus	マラスムス	Severe	Day 108
Discontinuation of Study Medication Due to AE	Marasmus	マラスムス	Severe	Day 108

Age	Sex	Race	Ethnicity	Country
9[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 2 years, 9 months, 17 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Chronic kidney disease; Hypertension; Diabetes mellitus; Cerebrovascular accident; Lumbar spinal stenosis; Intervertebral disc protrusion; Hypothyroidism; Chronic obstructive pulmonary disease; Bundle branch block left; Hyperlipidaemia; Cataract; Hyperkalaemia; Inguinal hernia; Dry eye; Echocardiogram; Conjunctivitis; Blepharitis; Constipation
History of Medical/ Surgical Procedures	Cardiac resynchronisation therapy

Concomitant Medications at Randomization	acetylsalicylic acid, esomeprazole magnesium, ast 120, glycopyrronium bromide;indacaterol maleate, mitiglinide calcium;voglibose, azosemide, levothyroxine sodium, pirenoxine, tolvaptan, atorvastatin, pimobendan, bisoprolol fumarate, insulin degludec, calcium polystyrene sulfonate, ketoprofen, magnesium oxide, tosufloxacin tosilate, fluorometholone, methylprednisolone;neomycin sulfate, amlodipine, trichlormethiazide, enalapril maleate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	788 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-10	30 %		
1		NYHA CLASS II	21.4 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者は第 21 日～第 31 日及び第 51 日～第 64 日に心不全のため入院した。

第 108 日、疲労及び胸痛が発現した後、被験者は入院し、マラスムスと診断された。非重篤な有害事象として、第 110 日に低カリウム血症、第 111 日に新規発症心房細動、第 114 日に喀血、第 117 日に低血糖が発現した。低カリウム血症、喀血及び低血糖は 23 時間持続し、発現日当日に消失した。フロセミド、グルコン酸カリウム、アミオダロン塩酸塩、ワルファリン、ヘパリンナトリウム、ピコスルファートナトリウム、重炭酸ナトリウム／リン酸二水素ナトリウム（無水）、ヒトインスリン、グルコース、トルバプタン及びポリスチレンスルホン酸カルシウムが投与された。マラスムスのため治験薬の投与は中止され、最終投与日は第 119 日であった。第 133 日に被験者は退院し、長期療養施設に入所した。

第 180 日に被験者はマラスムス（医師報告用語は“geromarasmus”）のため死亡した（目撃者なしと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、新規発症心房細動の転帰は未回復であった。

治験責任（分担）医師により、マラスムスは治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	15	MK-1242	2.5	1
16	29	MK-1242	5	1
30	43	MK-1242	10	1
44	50	MK-1242	2.5	1
51	51	MK-1242	10	0
52	57	MK-1242	10	1
58	68	MK-1242	10	1
69	75	MK-1242	10	1
76	85	MK-1242	10	1
86	92	MK-1242	10	1
93	107	MK-1242	10	1
108	108	MK-1242	10	0
109	118	MK-1242	10	1
119	119	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	129	54	60	5[redacted]3
1	129	54	60	
1	133	58	60	
15	152	63	60	5[redacted]1
29	139	57	60	5[redacted]3
43	141	59	63	5[redacted]1
57	121	52	61	5[redacted]5
68	148	59	60	5[redacted]5
75	144	55	60	5[redacted]6
85	135	57	60	5[redacted]9
92	143	60	60	5[redacted]8
120	111	52	60	5[redacted]2
124	118	51	60	5[redacted]8

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	32	39	5.814	71
120	20	32	5.472	71
124	19	29	4.275	71

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	236.912(H)
1	247.52(H)
110	377.468(H)
120	512.72(H)
124	397.8(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

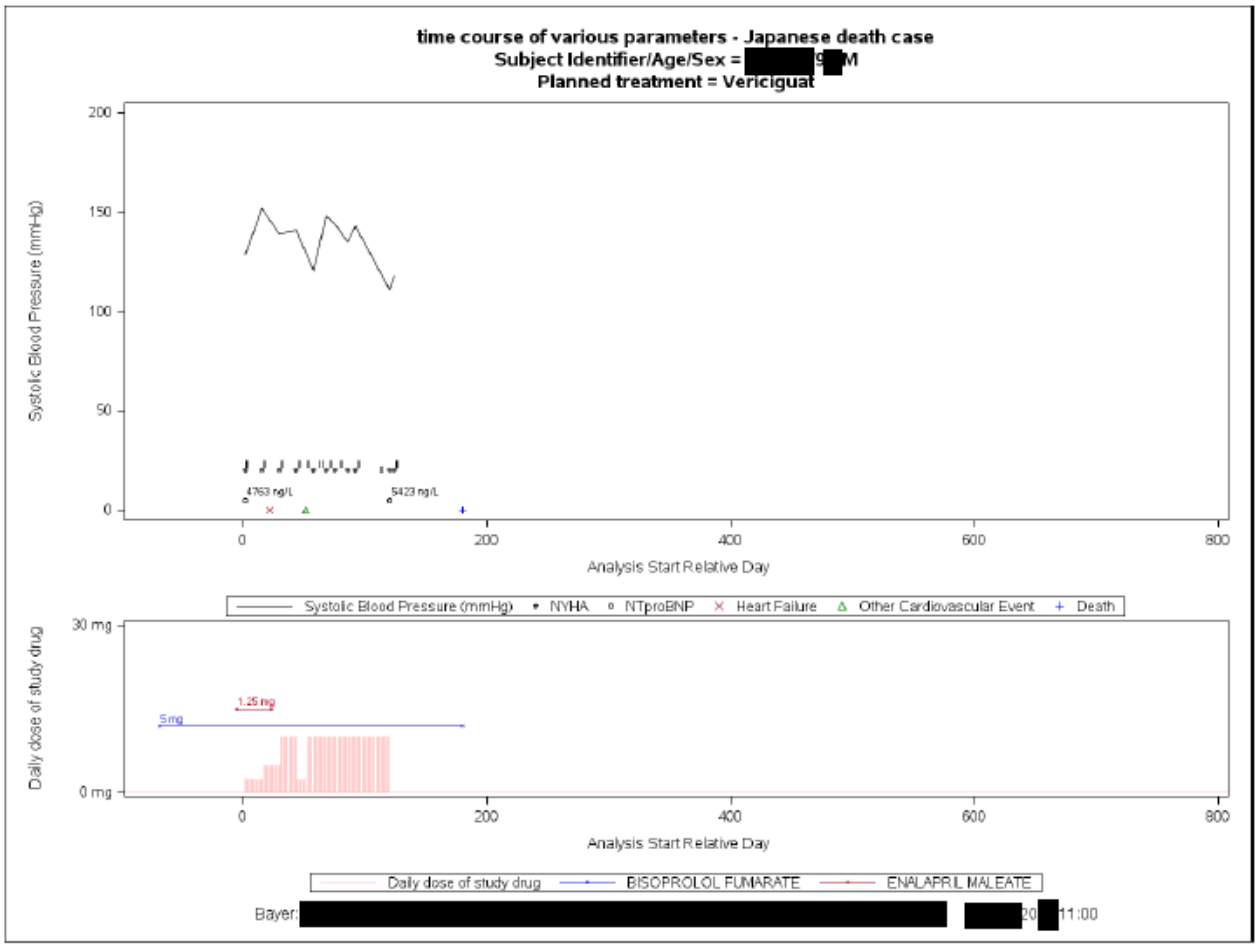
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
21	31	Heart Failure	Hospitalization	Heart Failure
51	64	Heart Failure	Hospitalization	Other Cardiovascular Event
180		Non-CV Event	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
4763 ng/L
5423 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
1.25 mg
5mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
ENALAPRIL MALEATE
Bayer [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure	心不全		Day 289
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 260

Age	Sex	Race	Ethnicity	Country
6[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 6 years, 10 months, 5 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Bundle branch block left; Ventricular tachycardia; Hyperuricaemia; Atrial fibrillation; Diabetes mellitus; Hyperlipidaemia; Echocardiogram; Hypokalaemia
History of Medical/ Surgical Procedures	Implantable defibrillator insertion

Concomitant Medications at Randomization	digoxin, dapagliflozin propanediol monohydrate, pimobendan, bisoprolol fumarate, amiodarone hydrochloride, docarpamine, furosemide, tolvaptan, trichlormethiazide, azosemide, warfarin, febuxostat, rosuvastatin calcium, vonoprazan fumarate, mosapride citrate, potassium chloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1		342.1 pmol/L

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-126	17 %		
1		NYHA CLASS II	68.1 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

治験責任（分担）医師の判断により治験薬の投与が中止され、最終投与日は第 260 日であった。

第 264 日に被験者は心不全のため入院した。心電図でペーシングリズムの心房細動、胸部 X 線検査で心胸郭比 75%及び胸水が認められた。酸素が投与された。第 289 日に心室細動が発現し、被験者は心不全のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検の有無は不明であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	14	placebo	0	1
15	31	placebo	0	1
32	53	placebo	0	1
54	62	placebo	0	1
63	64	placebo	0	0
65	88	placebo	0	1
89	102	placebo	0	1
103	130	placebo	0	1
131	144	placebo	0	1
145	172	placebo	0	1
173	185	placebo	0	1
186	186	placebo	0	0
187	200	placebo	0	1
201	216	placebo	0	1
217	219	placebo	0	0
220	235	placebo	0	1
236	259	placebo	0	1
260	260	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	101	71	69	7[redacted]3
1	101	71	69	
1	107	74	65	
15	102	73	66	7[redacted].6
32	110	72	68	7[redacted].8
54	107	77	67	7[redacted].5
89	89	67	57	6[redacted]
103	105	82	74	6[redacted].9
131	96	73	74	6[redacted].6
145	92	69	62	5[redacted].2
173	105	76	64	6[redacted]
201	98	75	60	6[redacted].4
236	99	71	62	6[redacted].2
264	82	62	60	6[redacted].4

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	46(H)	50(H)	20.691(H)	67
103	36	52(H)	25.137(H)	79
201	17	33	19.836(H)	69

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	107.848(H)
1	97.24
103	79.56
201	70.72

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

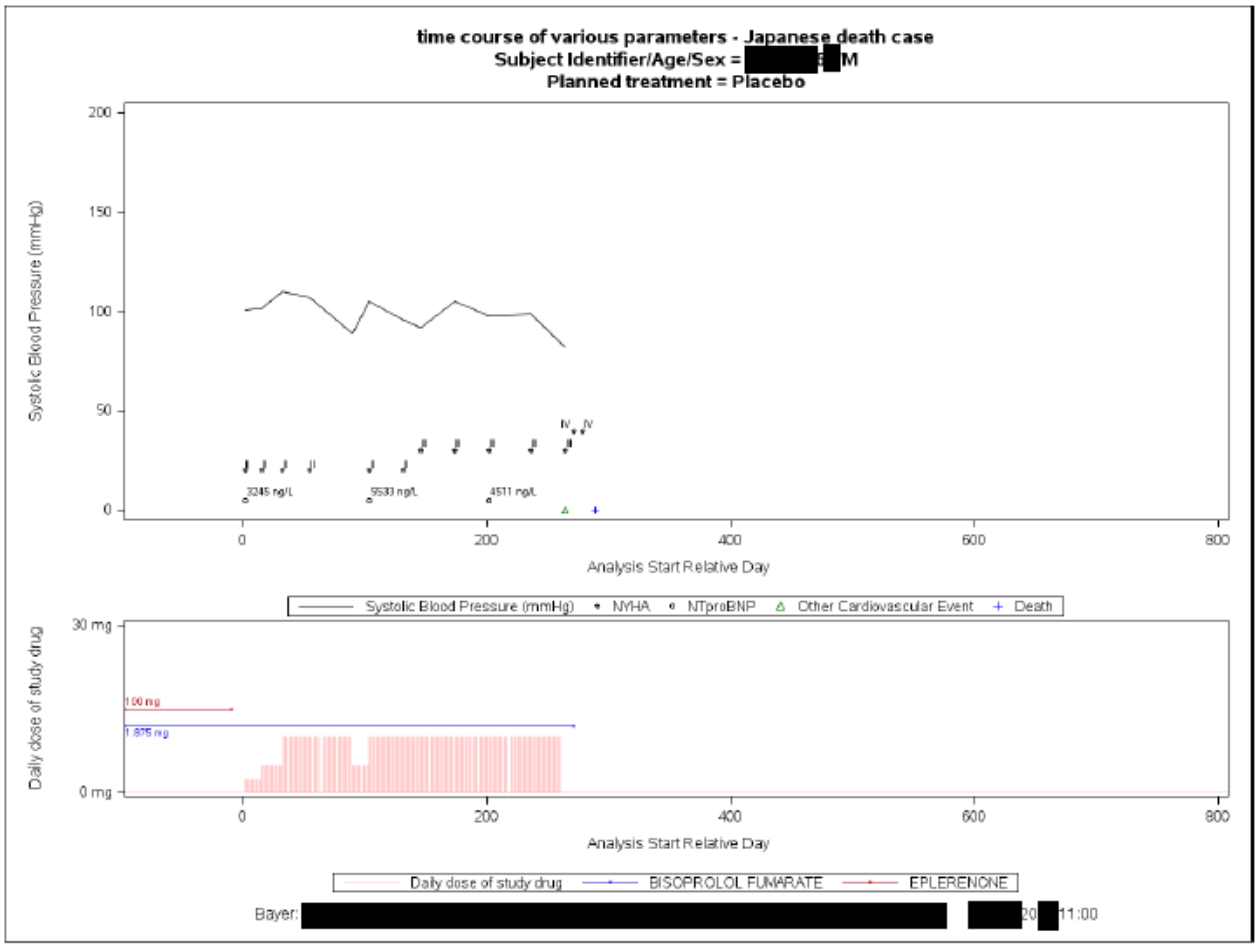
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
264	289	Heart Failure	Hospitalization	Other Cardiovascular Event
289		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted] M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
7245 ng/L
9533 ng/L
4511 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
0 mg
100 mg
1,875 mg
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
EPLERENONE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure	心不全		Day 204
SAE	Hypothermia	低体温	Severe	Day 167
SAE	Hypothermia	低体温	Severe	Day 189
Discontinuation of Study Medication Due to Other Reason	Noncompliance			Day 101

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 8 months, 14 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Haematochezia; Hypertension; Angina pectoris; Constipation; Coronary artery disease; Hyperuricaemia; Atrial fibrillation; Cardiac failure; Anaemia; Rheumatoid arthritis; Bronchitis chronic; Renal impairment; Hypothyroidism; Echocardiogram; Mitral valve incompetence
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Cardiac pacemaker insertion

Concomitant Medications at Randomization	sennoside a+b, ferrous sodium citrate, levothyroxine sodium, carbocisteine, febuxostat, spironolactone, furosemide, enalapril maleate, edoxaban tosilate, potassium chloride, carvedilol

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	1275 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-7	38 %		
1		NYHA CLASS III	81 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

服薬不遵守のため、治験薬の投与は中止され、最終投与日は第 101 日であった。

第 155 日に AST 増加、ALT 増加、血中ビリルビン増加及び廃用症候群（いずれも非重篤な有害事象）と診

断された。第 171 日、飲食不能となった後に意識が低下し、被験者は低体温（発現日は第 167 日）のため入院した。バイタルサインは体温 81.3°F、血圧 84／43mmHg であった。炭水化物（NOS）／塩化カリウム／塩化ナトリウム／乳酸ナトリウム、ノルエピネフリン、硫酸銅五水和物／塩化第二鉄六水和物／塩化マンガン四水和物／ヨウ化カリウム／硫酸亜鉛七水和物、シアノコバラミン／ピリドキシン塩酸塩／チアミンジスルフィド、アミノ酸（NOS）／電解質（NOS）／グルコース／チアミン塩酸塩が投与された。第 172 日に CRP 増加（非重篤な有害事象）が発現した。第 185 日に低体温は消失し、被験者は退院し、帰宅した。

第 189 日、飲食不能となった後に、被験者は低体温のため入院した。バイタルサインは体温 83.5°F、血圧 117／87mmHg であった。グルコース／塩化ナトリウム／乳酸ナトリウム、アミノ酸（NOS）／電解質（NOS）／グルコース／塩酸チアミン、塩化カルシウム二水和物／塩化カリウム／塩化ナトリウム／乳酸ナトリウムが投与された。第 204 日、心拍数が徐々に増加した後に無脈となり（詳細不明）、被験者は心不全のため死亡した（目撃者ありと報告された）。剖検は実施されなかった。死亡時に、2 回目の低体温、AST 増加、ALT 増加、血中ビリルビン増加、廃用症候群及び CRP 増加の転帰は未回復であった。

治験責任（分担）医師により、低体温（両事象）は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration Mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	6	MK-1242	2.5	1
7	8	MK-1242	2.5	0
9	15	MK-1242	2.5	1
16	28	MK-1242	5	1
29	50	MK-1242	10	1
51	73	MK-1242	10	1
74	76	MK-1242	10	0
77	100	MK-1242	10	1
101	101	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-7	133	92	77	
1	112	72	77	4[redacted]
1	114	67	77	
15	127	75	78	4[redacted].5
29	138	87	84	4[redacted].7
50	127	79	79	4[redacted].4
101	123	57	95	4[redacted].4
192	95	48	71	

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	7(L)	13	12.483	96
101	30	47(H)	15.903	111
155	55(H)	100(H)	37.62(H)	
192	838(H)	1425(H)	28.899(H)	139(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	80.444
1	79.56
101	123.76
192	291.72(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
64		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
66		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
93		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
100		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
101		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
108		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
110		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
113		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
117		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
120		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
122		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
129		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
134		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria

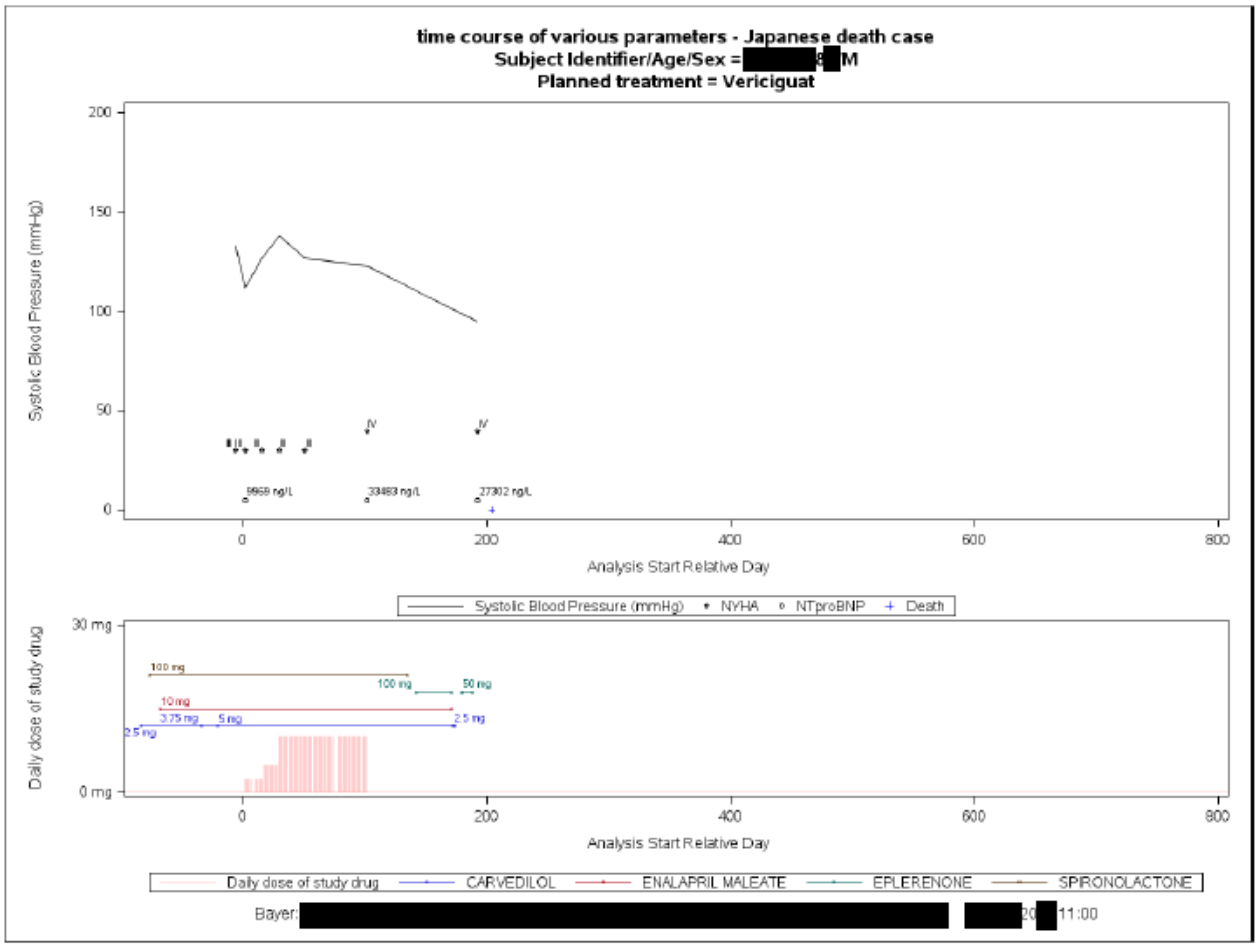
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
141		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
155		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
162		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
204		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	急性心不全		Day 478

Age	Sex	Race	Ethnicity	Country
8[redacted]	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 805 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Atrial fibrillation, Cerebrovascular accident, Chronic kidney disease, Diabetes mellitus, Hyperlipidaemia, Hypertension, Hyperuricaemia, Coronary artery disease, Echocardiogram, Myocardial infarction
History of Medical/ Surgical Procedures	Coronary artery bypass

Concomitant Medications at Randomization	atorvastatin calcium, bisoprolol, warfarin potassium, febuxostat, imidapril hydrochloride, azosemide, spironolactone

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-7	ng/L	3552 pg/ml

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-36	37 %		
1		NYHA CLASS II	53.1 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 221 日に緑内障（非重篤な有害事象）、第 344 日にそう痒症（非重篤な有害事象）が発現した。

被験者は、第 478 日に急性心不全のため死亡した。治験責任（分担）医師は、「情報不足のため因果関係は評価できない」とし、因果関係は否定できないと判断した。剖検の有無は不明であった。死亡時に、緑内障とそう痒症の転帰は未回復であった。治験薬の最終投与日は第 477 日であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	14	MK-1242	2.5	1
15	26	MK-1242	2.5	1
27	56	MK-1242	5	1
57	84	MK-1242	10	1
85	101	MK-1242	10	1
102	103	MK-1242	10	0
104	119	MK-1242	10	1
120	120	MK-1242	10	0
121	157	MK-1242	10	1
158	158	MK-1242	10	0
159	174	MK-1242	10	1
175	175	MK-1242	10	0
176	210	MK-1242	10	1
211	238	MK-1242	10	1
239	336	MK-1242	10	1
337	350	MK-1242	10	1
351	439	MK-1242	10	1
440	476	MK-1242	10	1
477	477	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-7	111	76	79	
1	105	73	81	5[redacted]
1	109	69	76	
15	95	72	89	5[redacted].4
27	126	72	70	5[redacted].2
57	107	78	76	5[redacted].4
85	111	73	75	5[redacted].5
120	103	73	86	5[redacted].8
211	119	84	83	5[redacted]
239	121	81	67	5[redacted].4
337	103	61	76	5[redacted].8
351	110	62	73	5[redacted].3
440	112	74	86	5[redacted].7

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	16	26	10.773	109
120	14	27	22.914(H)	90
239	14	29	22.743(H)	91
337	13	29	25.137(H)	89

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-7	138.788(H)
1	114.92
120	150.28(H)
239	123.76
337	150.28(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

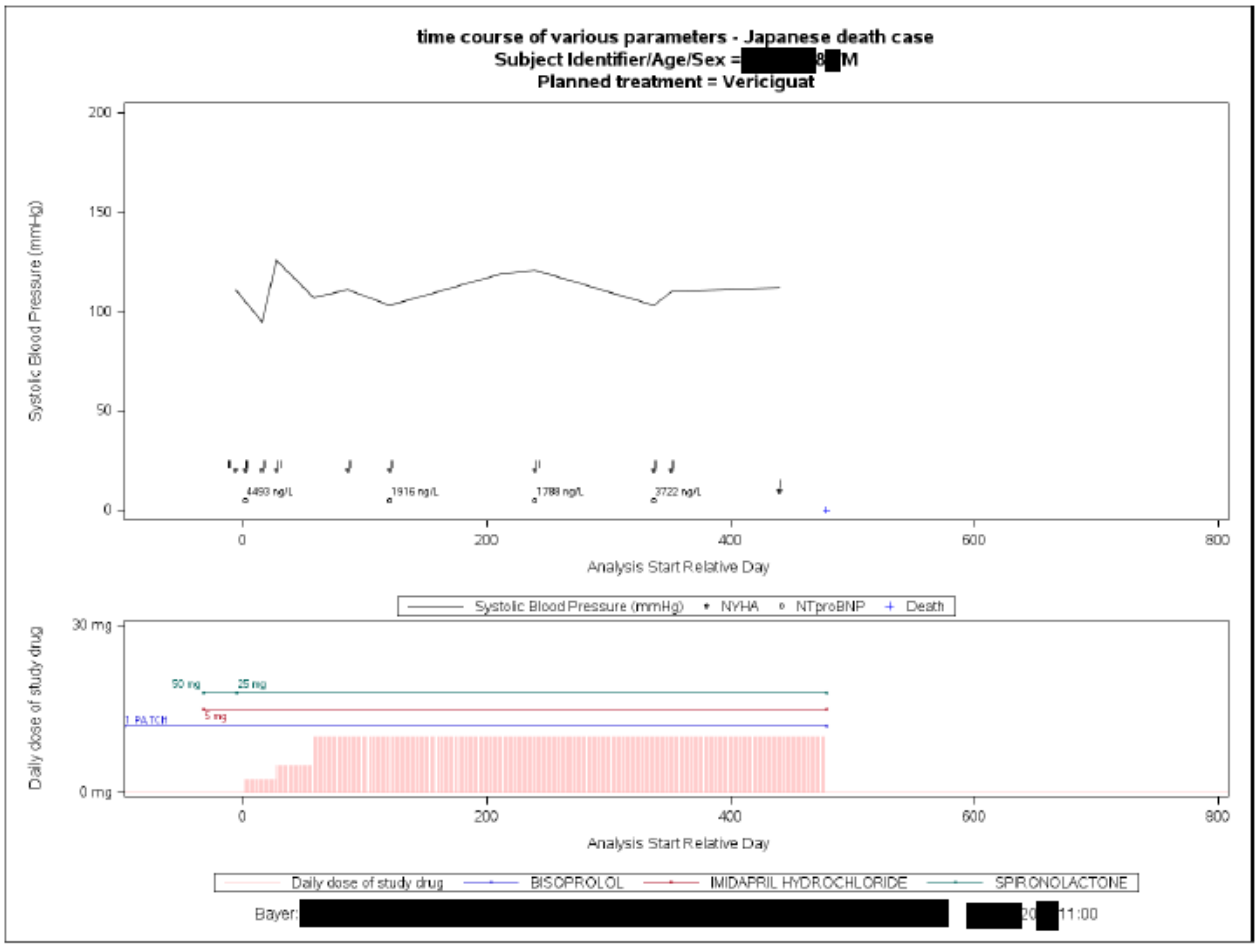
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
478		Heart Failure	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
4493 ng/L
1916 ng/L
1788 ng/L
3722 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
90 mg
25 mg
1 PATCH
5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL
IMIDAPRIL HYDROCHLORIDE
SPIRONOLACTONE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Congestive cardiomyopathy	うっ血性心筋症		Day 184
SAE	Syncope	失神	Severe	Day 177
Event of Clinical Interest	Syncope	失神	Severe	Day 177

Age	Sex	Race	Ethnicity	Country
5[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 9 years, 7 months, 16 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Seasonal allergy; Congestive cardiomyopathy; Cerebrovascular accident; Back pain; Atrial fibrillation; Echocardiogram; Insomnia; Atrial tachycardia; Diabetes mellitus
History of Medical/ Surgical Procedures	Cardiac resynchronisation therapy; Implantable defibrillator insertion

Concomitant Medications at Randomization	lansoprazole, edoxaban tosilate, spironolactone, furosemide, carvedilol, amiodarone hydrochloride, pimobendan, zolpidem tartrate, triazolam, ketoprofen

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	704 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-77	27 %		
1		NYHA CLASS III	78.2 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 9 年前からうっ血性心筋症があった。

被験者は第 68 日～第 79 日及び第 159 日～第 177 日目に心不全のため入院した。第 113 日に血圧低値がみられ、治験薬の投与が中断された。その後再開されず、治験薬の最終投与日は第 113 日であった。

第 177 日に被験者は拡張型心筋症の悪化及び失神（座位で約 5 分間の突然の意識消失）のため入院した。

頭部 CT 検査で出血や梗塞は認められず、心電図の変化はなく、意識消失は血管迷走神経反射によるものであった。ミドドリン塩酸塩が投与された。第 182 日に心室頻拍、呼吸停止、意識消失及び脈拍微弱が認められた。気道確保デバイス挿入、蘇生及び除細動が行われた。トルバプタン、フロセミド、メトクロプラミド及びセレコキシブが投与された。第 184 日に圧迫部位の胸痛を訴えた後、心肺停止状態で発見された。蘇生及び除細動が行われ、エピネフリン、重炭酸ナトリウム及びグルコン酸カルシウムが投与された。第 184 日に被験者はうっ血性心筋症のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。

治験責任（分担）医師により、失神は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	15	placebo	0	1
16	29	placebo	0	1
30	66	placebo	0	1
67	68	placebo	0	1
69	69	placebo	0	0
70	113	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	110	74	69	4[redacted].5
1	110	74	69	
1	102	68	69	
15	105	72	70	4[redacted].9
29	96	55	70	4[redacted].8
66	89	59	70	
78	93	63	70	
113	83	57	70	4[redacted]

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	29	30	7.695	90
113	83(H)	87(H)	10.944	164(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	88.4
1	88.4

Study Day	CREAT µmol/L
113	97.24

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

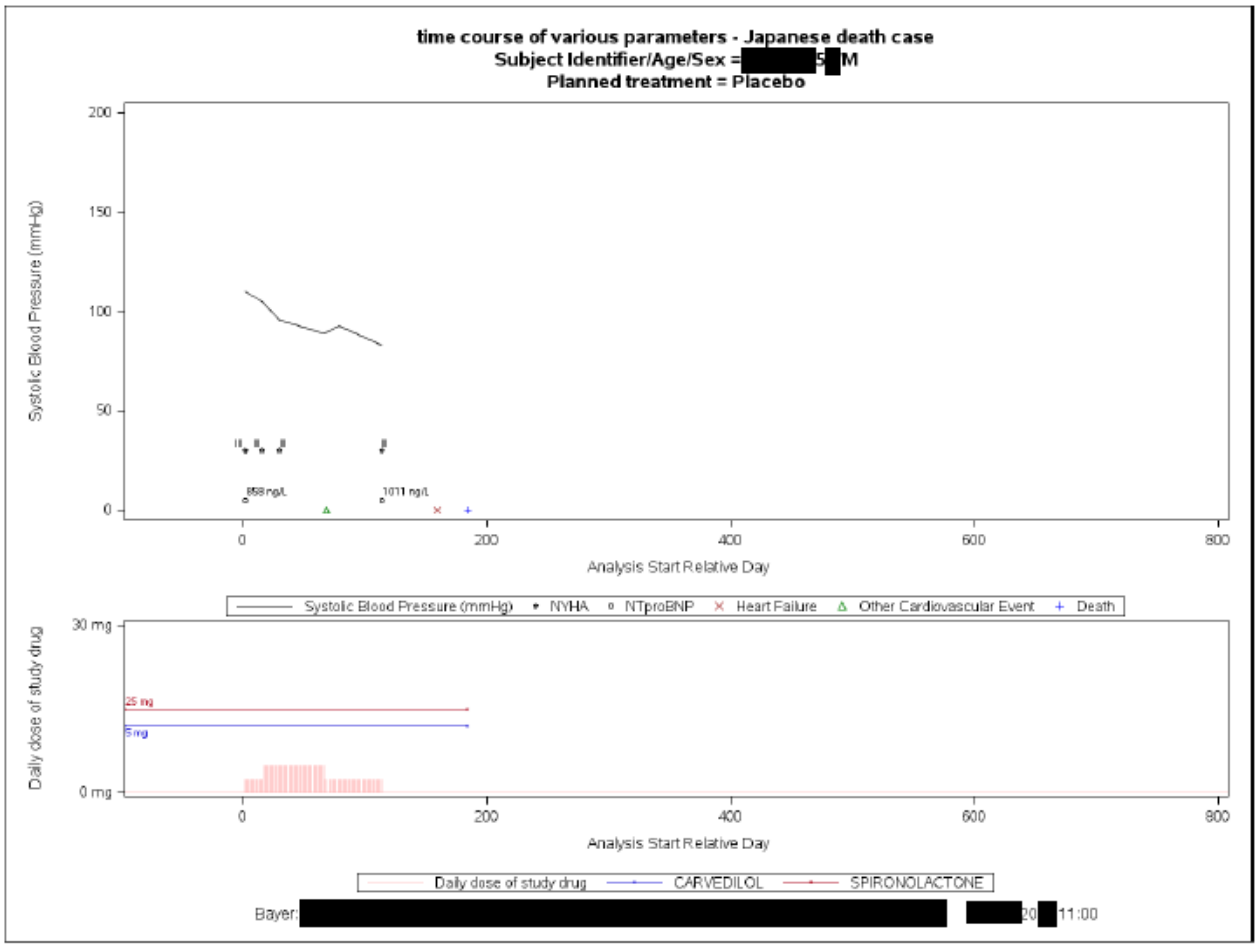
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
66		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
68	79	Heart Failure	Hospitalization	Other Cardiovascular Event
155		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
159	177	Heart Failure	Hospitalization	Heart Failure
184		Sudden Cardiac Death	Death	Sudden Cardiac Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted] 5 M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
858 ng/L
1011 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
25 mg
5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
SPIRONOLACTONE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cerebrovascular accident	脳血管発作		Day 231
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 186

Age	Sex	Race	Ethnicity	Country
7[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 2 years, 6 months, 12 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Diabetes mellitus; Hyperlipidaemia; Hypertension; Chronic obstructive pulmonary disease; Constipation; Pruritus; Renal neoplasm; Coronary artery disease; Myocardial infarction; Large intestine polyp; Chronic kidney disease; Hyperuricaemia; Cerebrovascular accident; Gout; Atrial fibrillation; Inguinal hernia; Echocardiogram; Cataract; Eczema asteatotic; Anaemia
History of Medical/ Surgical Procedures	Aortic valve replacement; Mitral valve replacement; Percutaneous coronary intervention; Cardiac resynchronisation therapy; Implantable defibrillator insertion

Concomitant Medications at Randomization	spironolactone, pimobendan, warfarin, digoxin, umeclidinium bromide;vilanterol trifenatate, dexamethasone valerate, carvedilol, ferrous sodium citrate, tolvaptan, acetylsalicylic acid, lansoprazole, atorvastatin, moxifloxacin hydrochloride, sennoside a+b, magnesium oxide, furosemide, betamethasone sodium phosphate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-1	1409 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-8	41 %		
1		NYHA CLASS IV	35 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

被験者の病歴には、本試験組入れの約 2 年前から脳血管発作があった。

被験者は第 72 日～第 84 日及び第 107 日～第 119 日に心不全のため入院した。

第 149 日に被験者は心不全のため入院した。胸部 X 線検査で胸水の増加が認められた。第 152 日～第 156 日に鼻出血（非重篤な有害事象）が発現した。第 155 日に認知症（非重篤な有害事象）が発現した。治験責任（分担）医師の判断により治験薬の投与は中止され、最終投与日は第 186 日であった。フロセミド、パラセタモール、ジフェンヒドラミン塩酸塩／ヒドロコルチゾン酢酸エステル／硫酸ネオマイシン、白色軟パラフィン、ワルファリン及びクエチアピンフマル酸塩が投与された。第 231 日に被験者は脳血管発作のため死亡した（目撃者ありと報告された）。剖検は実施されなかった。死亡時に、認知症の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	11	MK-1242	2.5	1
12	25	MK-1242	5	1
26	31	MK-1242	10	1
32	34	MK-1242	10	0
35	40	MK-1242	5	1
41	41	MK-1242	5	0
42	47	MK-1242	5	1
48	76	MK-1242	10	1
77	107	MK-1242	10	1
108	109	MK-1242	10	1
110	147	MK-1242	10	1
148	149	MK-1242	10	0
150	185	MK-1242	10	1
186	186	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-1	114	49	80	
1	115	49	80	5[redacted].4
1	114	48	79	
11	119	46	80	5[redacted].6
25	115	46	80	5[redacted].8
32	123	49	80	
34	105	44	80	
47	114	48	80	
76	108	44	80	5[redacted].3
107	114	44	80	6[redacted].3
109	112	45	80	
186				5[redacted].4

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	17	25	27.189(H)	86

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
107	26	32	27.189(H)	85

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-1	163.54(H)
1	167.96(H)
107	185.64(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

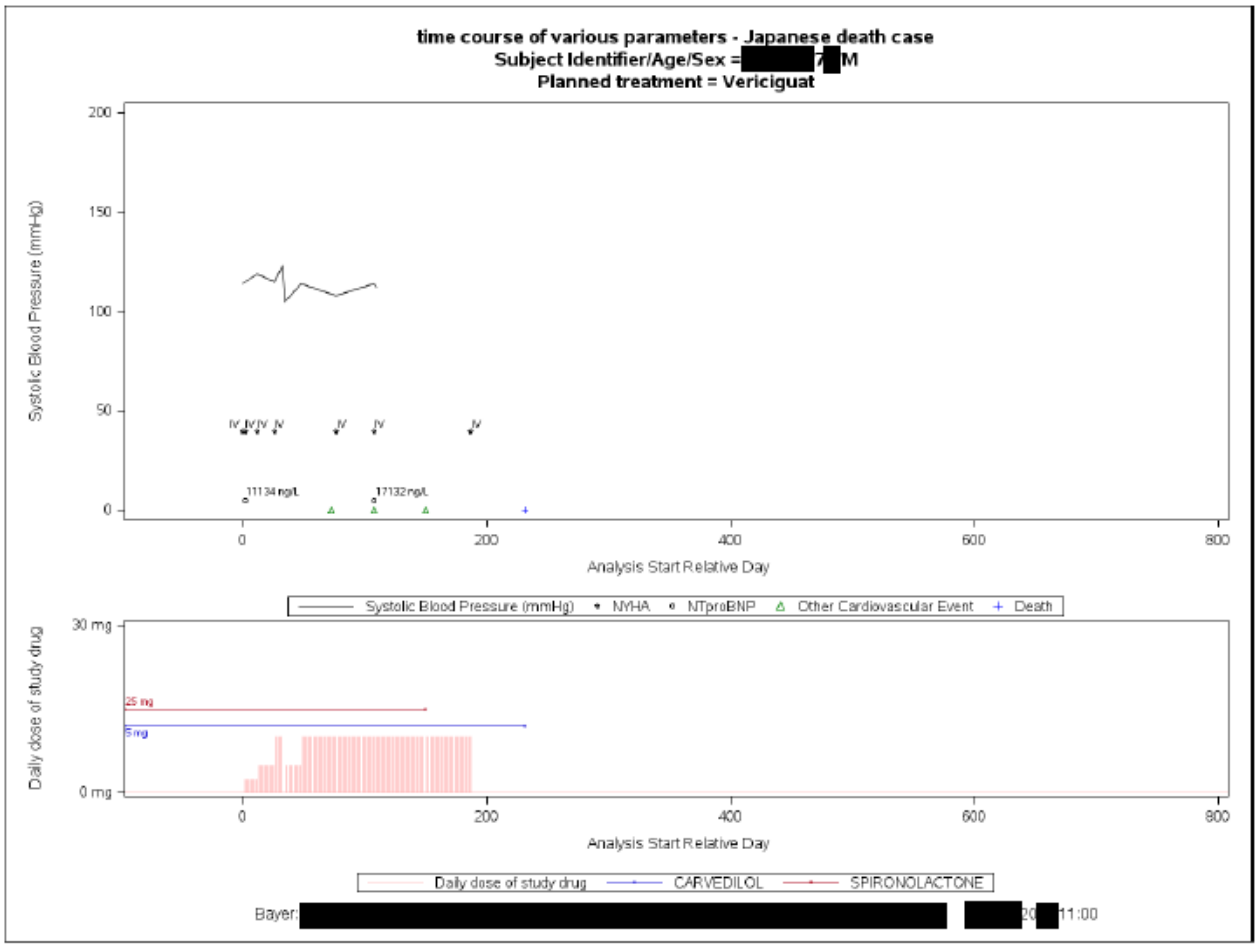
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
72	84	Heart Failure	Hospitalization	Other Cardiovascular Event
107	119	Heart Failure	Hospitalization	Other Cardiovascular Event
149	231	Heart Failure	Hospitalization	Other Cardiovascular Event
231		Stroke	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]7[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
IV IV IV IV IV IV
11134 ng/L
17132 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
25 mg
5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
SPIRONOLACTONE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	うっ血性心不全		Day 18

Age	Sex	Race	Ethnicity	Country
7[redacted]	Female	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 1852 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization

Medical History	Anaemia, Atrioventricular block first degree, Gastrooesophageal reflux disease, Hyperlipidaemia, Hypertension, Intracardiac mass, Large intestine polyp, Renal impairment, Rhinitis allergic, Colon cancer, Echocardiogram, Pneumonia
History of Medical/ Surgical Procedures	

Concomitant Medications at Randomization	esomeprazole magnesium, azosemide, atorvastatin, carvedilol, enalapril, ferrous sodium citrate, trichlormethiazide, warfarin

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-14	526 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-122	24 %		
1		NYHA CLASS II	53.8 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 18 日に被験者が自宅にて死亡しているところを家族により発見された。検視の結果、うっ血性心不全の増悪により死亡したと判断された。剖検は実施されなかった。治験薬の最終投与日は第 17 日であった。

治験薬の増量の影響が否定できないとして、治験担当医師は、治験薬との因果関係は否定できないと判断した。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	15	placebo	0	1
16	16	placebo	0	1
17	17	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	102	51	65	
1	102	51	65	4[redacted].7
1	115	59	77	
15	100	53	74	4[redacted].6

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	17	25	4.104	106

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-14	76.024(H)
1	88.4

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

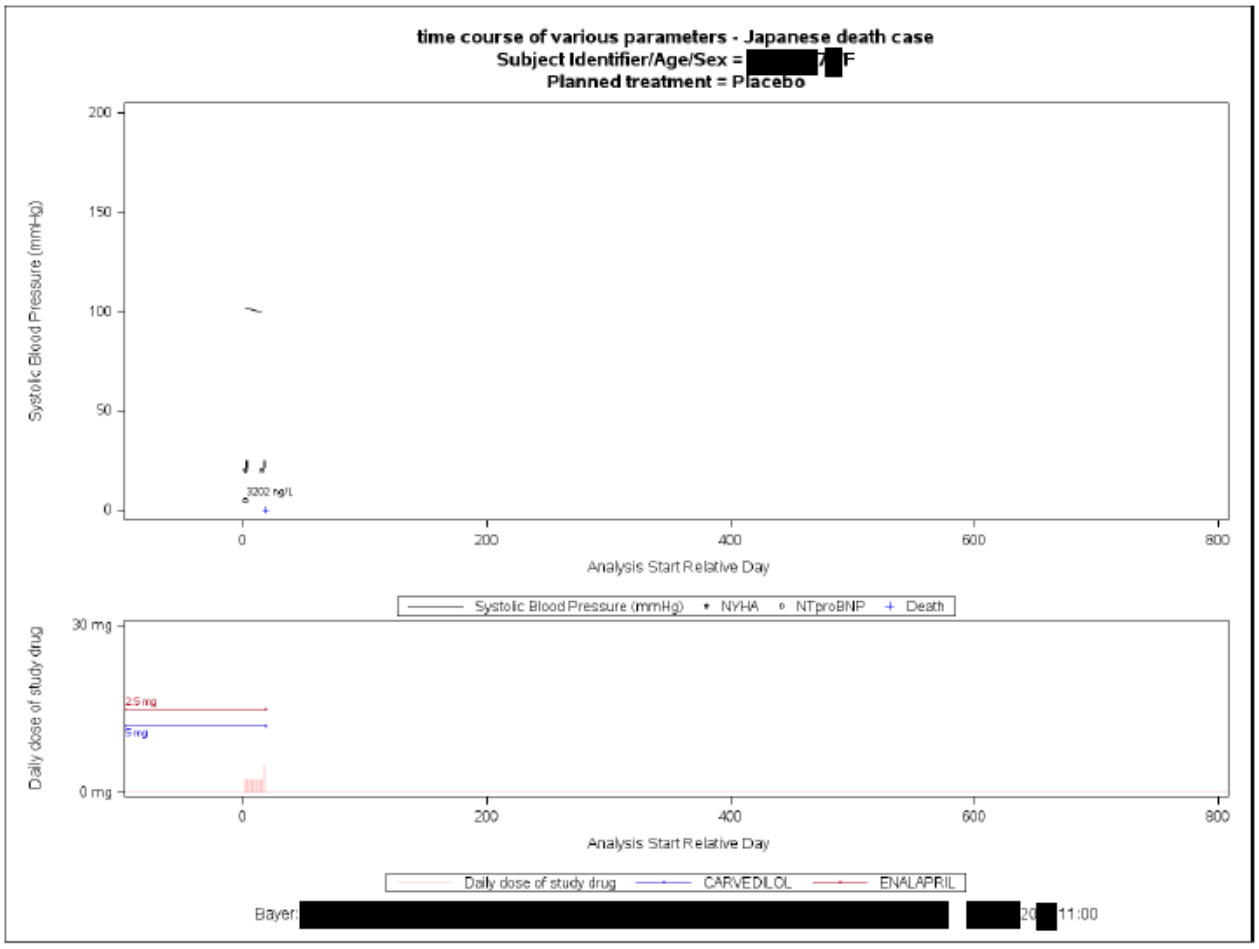
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
18		Heart Failure	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]F
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
3202 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
25 mg
5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
ENALAPRIL
Bayer [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure	心不全		Day 65
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 52

Age	Sex	Race	Ethnicity	Country
7[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 2 years, 10 months, 7 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Hyperuricaemia; Coronary artery disease; Diabetes mellitus; Hyperlipidaemia; Hypertension; Peripheral arterial occlusive disease; Renal failure; Lumbar hernia; Angina pectoris; Pneumonia; Constipation; Insomnia; Hepatic function abnormal; Carotid artery stenosis; Photosensitivity reaction; Echocardiogram; Hypokalaemia; Groin pain; Epistaxis; Atrial fibrillation; Atrial flutter; Anaemia
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Cardiac resynchronisation therapy; Mitral valve replacement

Concomitant Medications at Randomization	allopurinol, acetylsalicylic acid, clopidogrel bisulfate, rabeprazole sodium, linagliptin, pimobendan, ursodeoxycholic acid, brotizolam, glimepiride, tolvaptan, bepridil hydrochloride monohydrate, trichlormethiazide, digoxin, ferrous sodium citrate, carvedilol, potassium aspartate, furosemide, warfarin, candesartan cilexetil

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-23	916 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-23	18 %		
1		NYHA CLASS II	19 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 15 日に心不全の増悪（非重篤な有害事象）が発現し、本事象のため治験薬の投与が中断された。第 29 日に心不全の増悪は回復し、治験薬の投与は 2.5mg で再開された。

第 52 日に心不全の増悪（非重篤な有害事象）が発現し、トルバプタンが投与された。心不全の増悪のため治験薬の投与は中断された。その後、治験責任（分担）医師の判断により中止され、治験薬の最終投与日は第 52 日であった。第 56 日に心不全の増悪は回復したが、後遺症（詳細不明）があり、追加治療としてワルファリン及びトリクロルメチアジドが投与された。

第 57 日に被験者は心不全のため入院した。第 64 日に胸部 CT 検査で胸水が認められた。第 65 日に発熱（非重篤な有害事象）が認められた。カルペリチド、ドパミン塩酸塩、フロセミドナトリウム、アゾセミド、シベレスタットナトリウム、パラセタモール及びジクロフェナクナトリウムが投与された。第 65 日、心室細動の発現後に、被験者は心不全の増悪のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、発熱の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	13	MK-1242	2.5	1
14	15	MK-1242	2.5	0
16	28	MK-1242	2.5	0
29	43	MK-1242	2.5	1
44	51	MK-1242	5	1
52	52	MK-1242	5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-23	101	48	73	
1	101	41	90	5[redacted]6
1	91	42	74	
16	99	50	90	5[redacted]8
29	110	63	89	6[redacted]8
43	101	65	98	6[redacted]8
57	96	67	103	7[redacted]6

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	11	17	22.401(H)	187(H)
57	13	21	30.609(H)	158(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-23	190.944(H)

Study Day	CREAT µmol/L
1	282.88(H)
57	318.24(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

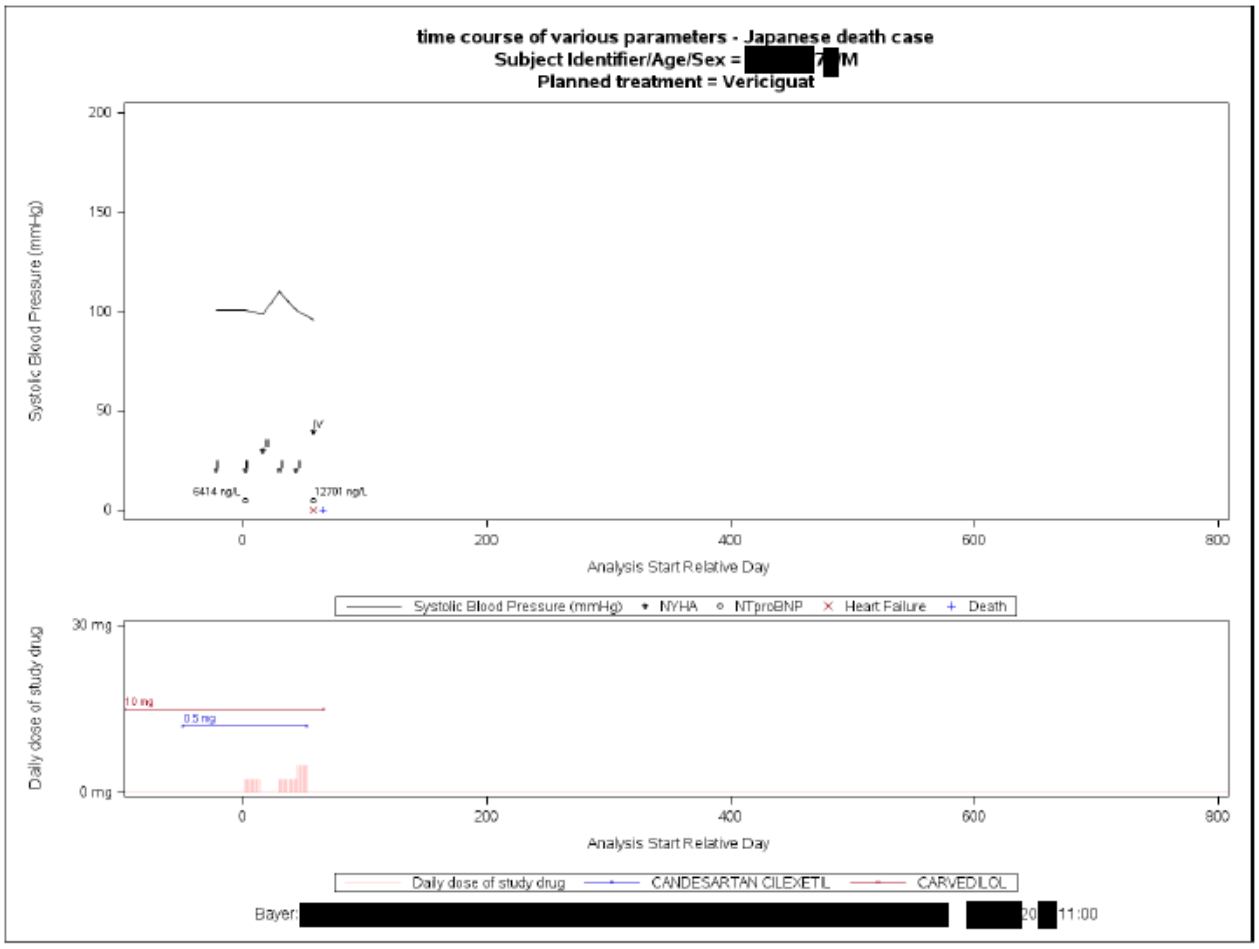
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
15		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
52		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
57	65	Heart Failure	Hospitalization	Heart Failure
65		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]7[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
6414 ng/L
12701 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
10 mg
0.5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CANDESARTAN CILEXETIL
CARVEDILOL
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	心不全		Day 207

Age	Sex	Race	Ethnicity	Country
8[redacted]	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 1429 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Bronchitis chronic, Chorioretinopathy, Chronic kidney disease, Constipation, Dementia, Gastrooesophageal reflux disease, Hyperuricaemia, Hypothyroidism, Punctate keratitis, Retinal haemorrhage, Sleep apnoea syndrome, Atrial fibrillation, Atrial flutter, Cerebrovascular accident, Congestive cardiomyopathy, Echocardiogram, Ventricular tachycardia
History of Medical/ Surgical Procedures	

Concomitant Medications at Randomization	amiodarone hydrochloride, chondroitin sulfate sodium;flavine adenine dinucleotide disodium, clopidogrel bisulfate, panax ginseng root;zanthoxylum piperitum pericarp;zingiber officinale processed rhizome, tolvaptan, kallidinogenase, iodolecithin, esomeprazole magnesium, perindopril erbumine, febuxostat, levothyroxine sodium, azosemide, ambroxol hydrochloride, warfarin potassium, carbazochrome sodium sulfonate, pimobendan

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-9	341 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-9	36 %		
1		NYHA CLASS III	22.8 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

非重篤な有害事象として、第 30 日に胸水、第 52 日に眼瞼浮腫と末梢性浮腫、第 203 日に腎不全が発現した。

第 174 日に息苦しいとの訴えがあり、被験者は緊急来院した。その際、胸水増加及び肺うっ血を認め入院

となった。入院中、血圧低下により治験薬の投与を中断したが、再開することなく、最終投与日は第 189 日であった、その後、第 207 日に心不全のため死亡した。治験責任（分担）医師により、治験薬中断後も症状改善なく悪化したことから、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、胸水と腎不全の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	placebo	0	1
2	12	placebo	0	1
13	29	placebo	0	1
30	83	placebo	0	1
84	88	placebo	0	0
89	110	placebo	0	1
111	189	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-8	96	51	53	
1	118	64	63	6[redacted]7
1	112	57	61	
13	113	66	78	6[redacted]8
30	129	71	77	6[redacted]3
55	112	66	77	6[redacted]9
111	112	62	73	6[redacted]4

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	14	21	5.814	79
111	19	29	7.011	88

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	240.448(H)
1	238.68(H)
111	247.52(H)
203	525.98(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

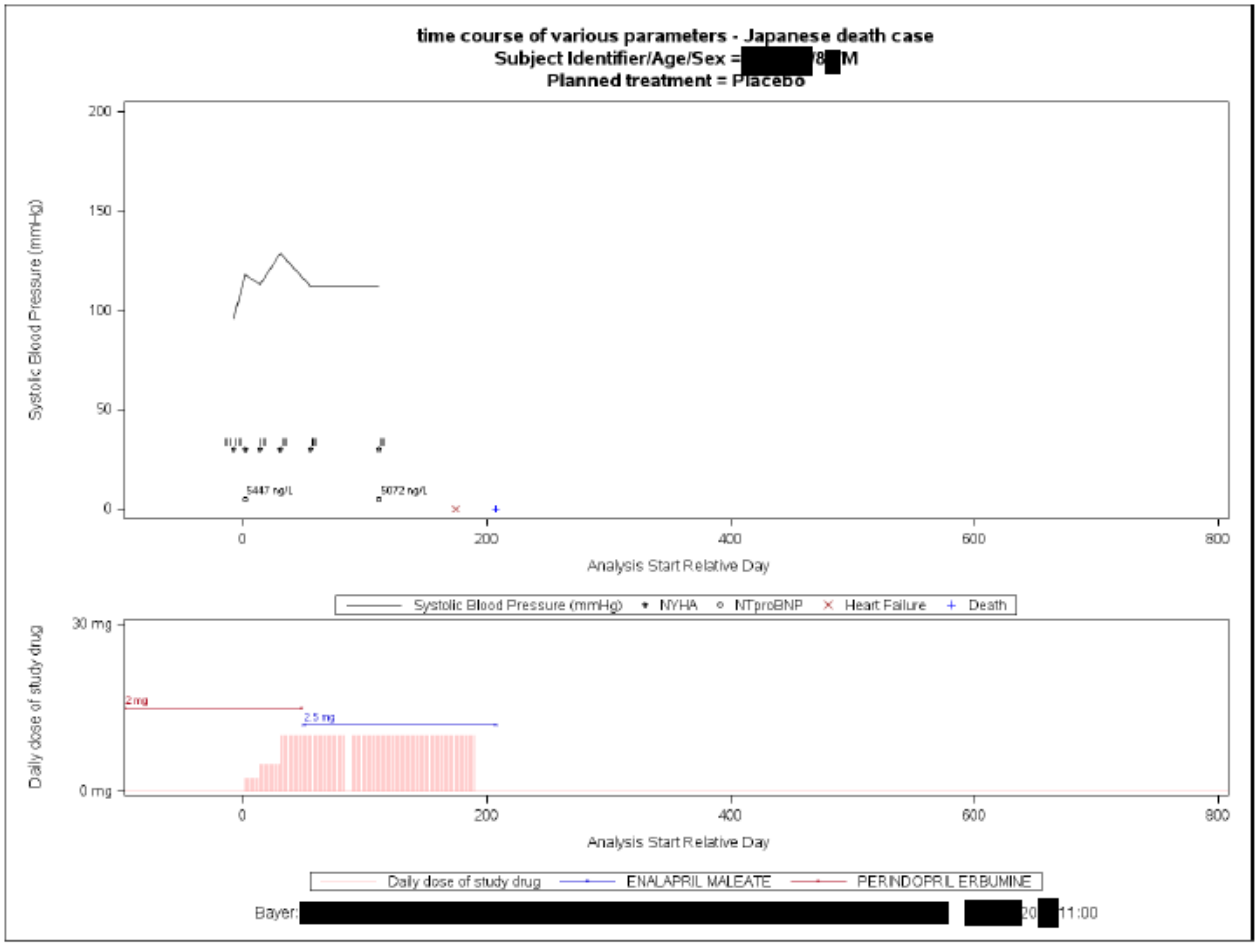
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
174	207	Heart Failure	Hospitalization	Heart Failure
207		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	心不全		Day 147

Age	Sex	Race	Ethnicity	Country
8[redacted]	Female	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 2995 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Anaemia, Atrial fibrillation, Bradycardia, Constipation, Dementia Alzheimer's type, Eczema, Hyperlipidaemia, Hyperuricaemia, Hypokalaemia, Hypothyroidism, Mitral valve incompetence, Osteoporosis, Tricuspid valve incompetence, Bundle branch block left, Echocardiogram, Gastroenteritis, Hypertension, Influenza, Nasopharyngitis, Pneumonia
History of Medical/ Surgical Procedures	Mitral valve replacement

Concomitant Medications at Randomization	eldecalcitol, magnesium oxide, atorvastatin calcium, panax ginseng root;zanthoxylum piperitum pericarp;zingiber officinale processed rhizome, levothyroxine sodium, lansoprazole, apixaban, potassium chloride, febuxostat, enalapril maleate, betamethasone valerate;gentamicin sulfate, azosemide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	1062 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-132	39 %		
1		NYHA CLASS III	42.9 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者は、第 19 日に心不全のため入院した。第 27 日に認知症（非重篤な有害事象）、不眠症（非重篤な有害事象）、そう痒症（非重篤な有害事象）、第 44 日に血便排泄（非重篤な有害事象）が発現した。第 68 日に退院した。

第 138 日に再び心不全のため入院した。第 138 日に譫妄（非重篤な有害事象）、高カリウム血症（非重篤な有害事象）、第 141 日に眼挫傷（左眼）（非重篤な有害事象）、第 143 日に眼挫傷（右眼）（非重篤な

有害事象）、第 147 日に急性腎障害（非重篤な有害事象）が発現した。被験者は、第 147 日に心不全のため死亡した。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検が実施され、剖検で確定した死因は、慢性心不全に続発した両肺うっ血水腫による呼吸不全であった。治験薬の最終投与日は第 144 日であった。死亡時に、認知症、不眠症、そう痒症、譫妄、高カリウム血症、眼挫傷、急性腎障害の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	29	MK-1242	2.5	1
30	36	MK-1242	5	1
37	58	MK-1242	2.5	0
59	68	MK-1242	2.5	1
69	75	MK-1242	5	1
76	78	MK-1242	5	0
79	85	MK-1242	5	1
86	113	MK-1242	2.5	1
114	141	MK-1242	5	1
142	143	MK-1242	5	0
144	144	MK-1242	5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	107	58	76	
1	107	58	76	4[redacted]6
1	91	44	60	
15	91	42	79	5[redacted]
29	106	41	85	5[redacted]5
58	116	42	70	4[redacted]
68	111	49	84	4[redacted]9
85	89	37	92	4[redacted]1
113	115	57	83	4[redacted]6

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	12	21	8.208	116(H)
113	9(L)	18	14.193	118(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
1	98.124(H)
1	106.08
113	106.08
147	276.692(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

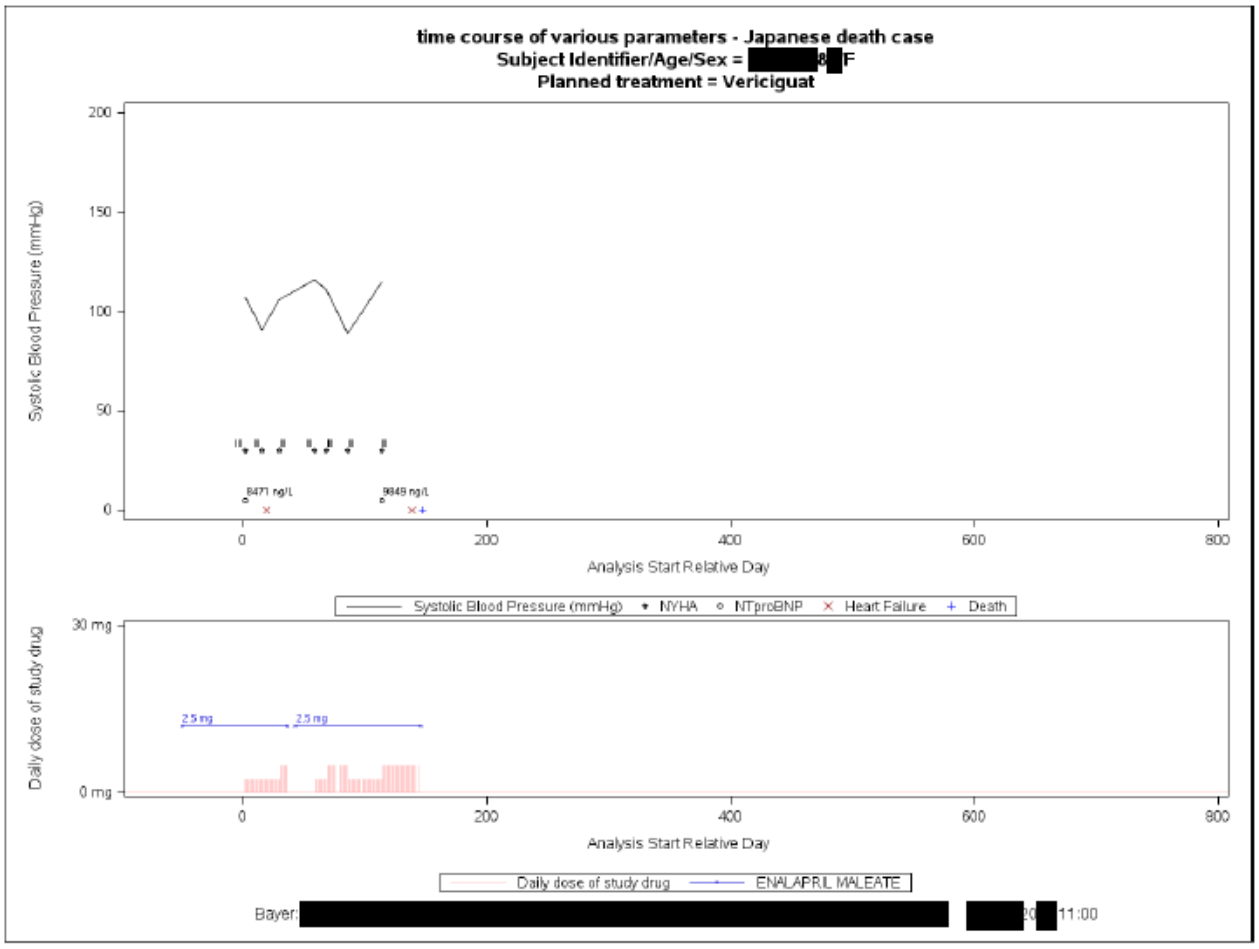
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
19	68	Heart Failure	Hospitalization	Heart Failure
138	147	Heart Failure	Hospitalization	Heart Failure
147		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8/F
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
8471 ng/L
9849 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
0 mg
2.5 mg
2.5 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
ENALAPRIL MALEATE
Bayer [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	突然死		Day 160

Age	Sex	Race	Ethnicity	Country
7[redacted]	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 226 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Anaemia, Chronic gastritis, Chronic kidney disease, Dry skin, Hypertension, Hypoalbuminaemia, Supraventricular extrasystoles, Ventricular extrasystoles, Atrial fibrillation, Dysphagia, Echocardiogram, Nasopharyngitis, Pneumonia, Skin candida
History of Medical/ Surgical Procedures	

Concomitant Medications at Randomization	edoxaban tosilate, lansoprazole, rosuvastatin, bisoprolol fumarate, enalapril maleate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-9	776 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-30	30 %		
1		NYHA CLASS II	94 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

第 113 日、治験の規定来院が実施された。被験者の血圧は 89/52 と低値であったため、規定により治験薬は中断された。その際、心不全症状及び検査結果に著変はみられなかった。その後、治験薬投与は再開されず、最終投与日は第 112 日であった。第 160 日、被験者が自宅で死亡していたとの連絡が医療機関へ入った。治験責任（分担）医師により、死因は突然死と判断された。治験の規定により治験薬投与を中断しているため、治験薬と関連なしと判断された。剖検は実施されなかった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	14	MK-1242	2.5	1
15	28	MK-1242	2.5	1
29	112	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-9	88	54	67	
1	118	78	76	4[redacted]
1	91	58	84	
15	97	60	71	4[redacted].6
29	98	64	62	4[redacted].8
113	89	52	68	4[redacted].6

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	9(L)	17	2.736	91
113	14	20	5.985	78

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-9	100.776(H)
1	70.72
113	97.24

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

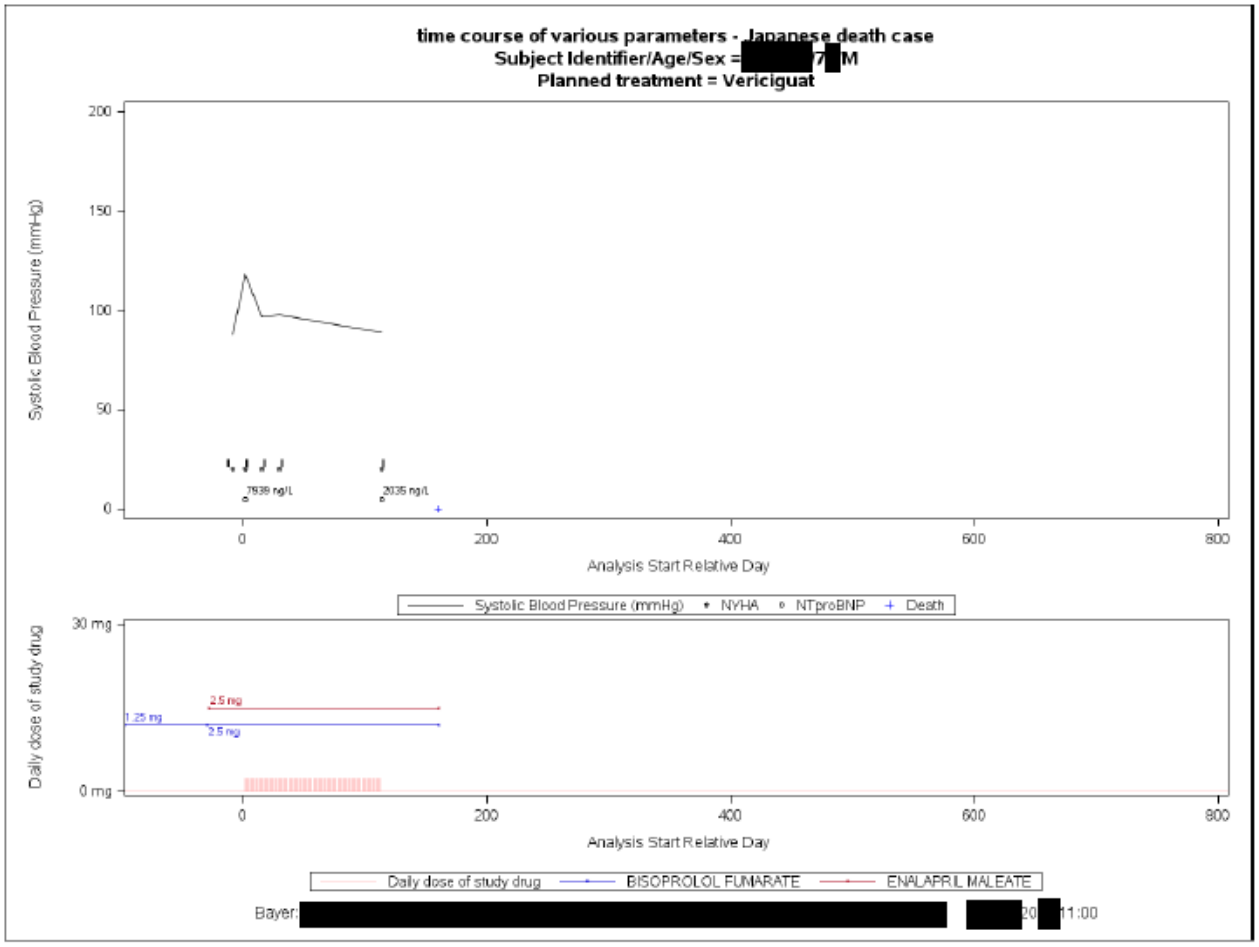
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
160		Sudden Cardiac Death	Death	Undetermined Cause Of Death

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]7 M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
7939 ng/L
2035 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Death
Daily dose of study drug
30 mg
0 mg
2.5 mg
1.25 mg
2.5 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
ENALAPRIL MALEATE
Bayer: [redacted] 11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term	Severity	Study Day (relative to treatment)
CV Death	心不全		Day 287

Age	Sex	Race	Ethnicity	Country
8[redacted]	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 1514 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Anaemia, Aortic valve incompetence, Asthma, Back pain, Benign prostatic hyperplasia, Bundle branch block right, Chronic gastritis, Chronic kidney disease, Colon adenoma, Conjunctivitis allergic, Constipation, Diabetes mellitus, Dry eye, Hyperlipidaemia, Hypertension, Hypertonic bladder, Hyperuricaemia, Insomnia, Peripheral arterial occlusive disease, Pruritus, Rash, Spinal osteoarthritis, Cerebrovascular accident, Echocardiogram, Herpes zoster, Myocardial infarction
History of Medical/ Surgical Procedures	Percutaneous coronary intervention, Cataract operation

Concomitant Medications at Randomization	glucose, magnesium oxide, torasemide, fluticasone propionate;salmeterol xinafoate, naftopidil, mirabegron, linagliptin, acetylsalicylic acid, sodium picosulfate, insulin glargine, hyaluronate sodium, trichlormethiazide, brotizolam, candesartan cilexetil, mosapride citrate, allopurinol, carvedilol, furosemide, pravastatin sodium, rabeprazole sodium, sennoside a+b, prednisolone valeroacetate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-17	ng/L	8775 pg/ml

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
1	34 %		
1		NYHA CLASS II	26 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

非重篤な有害事象として、第 15 日に好酸球数増加、第 54 日に毛包炎、第 57 日に接触皮膚炎、第 91 日に皮膚擦過傷、第 263 日に肝機能異常及びインフルエンザが発現した。

被験者は、第 218 日～第 243 日に心不全のため入院した。入院中の院内検査より、もともと低下していた腎機能検査値がさらに低下してきたため、治験薬の投与が中断された。その後再開されず、治験薬の最終投与日は第 233 日であった。

第 260 日に再び心不全のため入院し、第 287 日に死亡した。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、好酸球数増加、毛包炎、接触皮膚炎の転帰は未回復であった。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	57	MK-1242	2.5	1
58	106	MK-1242	5	1
107	190	MK-1242	2.5	1
191	233	MK-1242	5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-17	110	48	64	
1	104	51	75	5[redacted].1
1	103	48	80	
15	103	49	71	5[redacted].5
29	91	41	69	5[redacted]
43	97	48	76	5[redacted].5
57	102	47	75	5[redacted].1
85	96	42	71	5[redacted].3
106	89	40	77	5[redacted].4
134	99	46	82	5[redacted].8
162	90	45	70	5[redacted].2
190	117	53	77	5[redacted].8
218	108	47	70	6[redacted].9
260	101	42	63	6[redacted].1

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	18	22	6.156	96
106	13	15	5.814	79
218	16	24	6.669	110

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
263	49(H)	48(H)		

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-17	210.392(H)
1	212.16(H)
106	274.04(H)
218	327.08(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

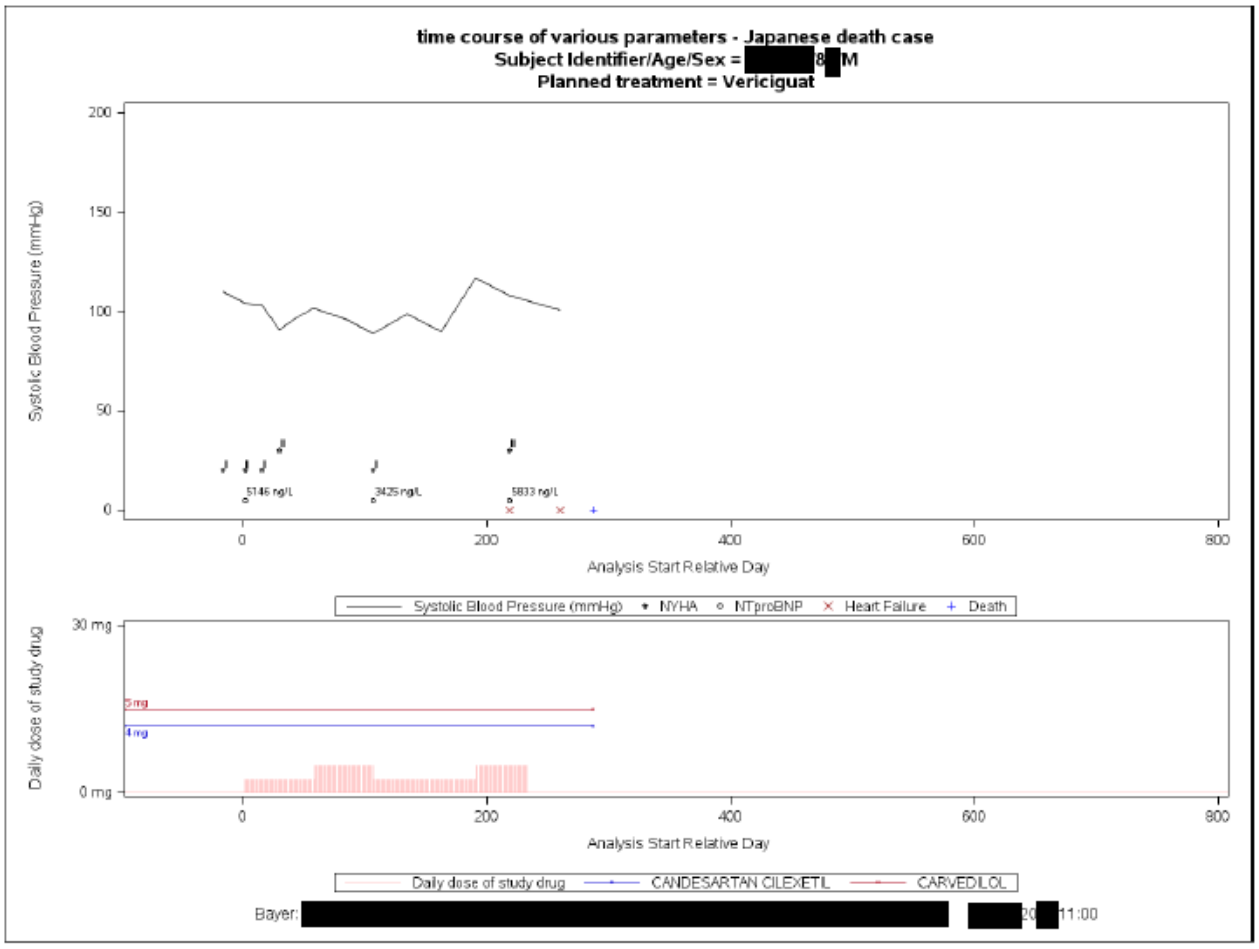
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
218	243	Heart Failure	Hospitalization	Heart Failure
260	287	Heart Failure	Hospitalization	Heart Failure
287		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]8[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
5146 ng/L
3425 ng/L
5833 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
5 mg
4 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CANDESARTAN CILEXETIL
CARVEDILOL
Bayer: [redacted] 20[redacted]11:00

Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Cardiac failure congestive	うっ血性心不全		Day 153
SAE	Gastric cancer	胃癌	Severe	Day 66

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Female	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 1 year, 6 months, 21 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Chronic gastritis; Corneal leukoma; Conjunctivitis; Parkinson's disease; Hepatitis C antibody positive; Spinal osteoarthritis; Insomnia; Depression; Essential tremor; Chronic kidney disease; Blood lactate dehydrogenase increased; Congestive cardiomyopathy; Diabetes mellitus; Atrial fibrillation; Constipation; Hyperuricaemia; Gamma-glutamyltransferase increased; Blood alkaline phosphatase increased; Echocardiogram; Anaemia
History of Medical/ Surgical Procedures	Cataract operation

Concomitant Medications at Randomization	pranoprofen, zonisamide, flunitrazepam, apixaban, bisoprolol fumarate, pramipexole dihydrochloride, primidone, sennoside a+b, tolvaptan, ramelteon, suvorexant, lansoprazole, furosemide, enalapril maleate, spironolactone, tofogliflozin, levodopa, milnacipran hydrochloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-29		

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.
* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-7	37 %		
1		NYHA CLASS III	42.9 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.
* Investigator reported.

Clinical Course of Events:

被験者の病歴には、慢性胃炎（期間不明、センノシド a+b により治療）、本試験開始の約 1 年前から便秘があった。癌の家族歴も報告された（2 人の兄弟は癌のため死亡、両親は癌の病歴なし）。

第 27 日に血圧低下（非重篤な有害事象）が認められた。本事象のため治験薬の投与が中断され、その後再開されず、最終投与日は第 27 日であった。

第 41 日に被験者は心不全のため入院した。第 66 日に上部消化管内視鏡検査、腹部 CT 検査及び組織診で胃癌、副腎転移、多発性肝腫瘍及び腹水が認められた。第 42 日以降、便秘はランソプラゾールにより治療された。癌治療は行われず、緩和ケアが行われた。第 92 日に被験者は退院し、帰宅した。

第 139 日に被験者は心不全のため入院した。グルコース／塩化ナトリウム／乳酸ナトリウム、ドブタミン塩酸塩、ドパミン塩酸塩及び塩酸モルヒネが投与された。第 153 日に被験者は心拍出量低下を伴ううっ血性心不全のため死亡した（目撃者ありと報告された）。治験責任（分担）医師により、治験薬と関連なしと判断された。剖検は実施されなかった。死亡時に、血圧低下及び胃癌の転帰は未回復であった。

治験責任（分担）医師により、胃癌は治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	27	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	105	49	73	3[redacted]8
1	105	49	73	
1	92	43	69	
13	100	45	63	3[redacted]8
27	82	34	53	4[redacted]9
41	94	37	59	4[redacted]7
104	76	29	55	3[redacted]
134	82	41	62	4[redacted]6

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	19	26	3.42	173(H)
104	11	23	3.42	204(H)

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-29	110.5(H)
1	106.08
104	141.44(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

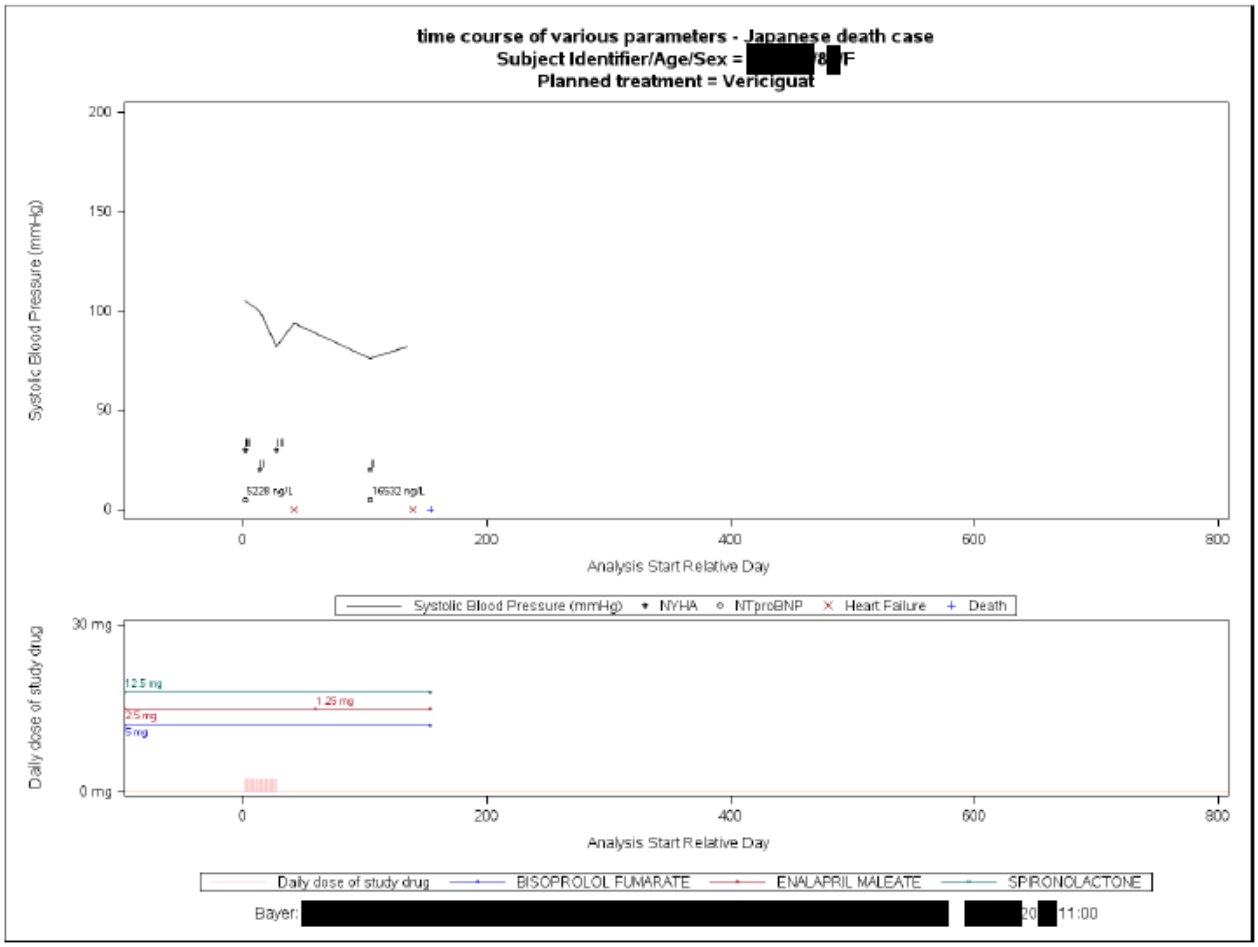
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
41	92	Heart Failure	Hospitalization	Heart Failure
134		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
139	153	Heart Failure	Hospitalization	Heart Failure
153		Heart Failure	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as "Not Hospitalized." 2) Deaths with an undetermined cause are considered as cardiovascular.



Subject Number: [redacted]

Treatment Arm: MK-1242 (Vericiguat) 2.5 mg / 5 mg / 10 mg + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Marasmus	マラスムス		Day 187
SAE	Marasmus	マラスムス	Severe	Day 181
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 120

Age	Sex	Race	Ethnicity	Country
8[redacted] years	Male	Asian	Not Hispanic or Latino	Japan

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction approximately 5 years, 6 months, 27 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Cognitive disorder; Diabetes mellitus; Chronic obstructive pulmonary disease; Atrioventricular block first degree; Hypertensive heart disease; Eczema asteatotic; Hyperkalaemia; Ventricular tachycardia; Hypertension; Coronary artery disease; Angina pectoris; Gastrooesophageal reflux disease; Aortic valve stenosis; Bundle branch block right; Hemiplegia; Cerebrovascular accident; Herpes zoster; Post herpetic neuralgia; Interstitial lung disease; Influenza; Echocardiogram
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Oxygen therapy

Concomitant Medications at Randomization	furosemide, lansoprazole, clopidogrel bisulfate, minocycline hydrochloride, bisoprolol fumarate, imidapril hydrochloride, empagliflozin, alogliptin benzoate, spironolactone, tolvaptan, sodium polystyrene sulfonate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-7	1166 ng/L	

BNP = brain natriuretic peptide; NT-proBNP = N-terminal fragment of the prohormone brain natriuretic peptide.

* May be obtained at local lab.

Baseline Measurements

Study Day	LVEF*	NYHA Class*	eGFR
-49	28 %		
1		NYHA CLASS III	63 mL/min/1.73 m2

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction;
NYHA = New York Heart Association.

* Investigator reported.

Clinical Course of Events:

被験者は第 74 日～第 162 日目に心不全のため入院した。

治験責任（分担）医師の判断により治験薬の投与が中止され、最終投与日は第 120 日であった。

第 181 日、食欲減退（非重篤な有害事象、発現日は第 163 日）及び脱水（非重篤な有害事象、発現日は第 176 日）の発現後に、被験者はマラスムスのため入院した。グルコース／塩化ナトリウム／乳酸ナトリウム、酸素が投与された。全身状態及び呼吸状況が悪化し、第 187 日に被験者はマラスムス（医師報告用語は“geromarasmus”）のため死亡した（目撃者ありと報告された）。剖検は実施されなかった。死亡時に、食欲減退及び脱水の転帰は未回復であった。

治験責任（分担）医師により、マラスムスは治験薬と関連なしと判断された。

Table 1. Study Medication Exposure

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
1	1	MK-1242	2.5	1
2	6	MK-1242	2.5	1
7	7	MK-1242	2.5	0
8	15	MK-1242	2.5	1
16	29	MK-1242	2.5	1
30	50	MK-1242	2.5	1
51	51	MK-1242	2.5	0
52	57	MK-1242	2.5	1
58	58	MK-1242	2.5	0
59	68	MK-1242	2.5	1
69	71	MK-1242	2.5	0
72	74	MK-1242	2.5	1
75	85	MK-1242	2.5	0
86	99	MK-1242	2.5	1
100	106	MK-1242	2.5	1
107	120	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-7	113	56	56	
1	106	50	57	4[redacted]2
1	106	46	56	
15	90	48	58	4[redacted].6
29	91	47	59	4[redacted].1
64	98	39	64	4[redacted].8
85	106	48	64	4[redacted].9
99	106	46	54	4[redacted].2
106	113	44	56	4[redacted].8
113	122	50	57	
176	126	67	70	3[redacted].8

bpm = beats per minute.

Table 3. Liver Function Laboratory Values

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
1	17	24	5.643	109
106	10	20	3.591	83

A = abnormal; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; H = high; L = low.

Table 4. Renal Function Laboratory Values

Study Day	CREAT µmol/L
-7	93.704
1	97.24
106	79.56
181	495.924(H)

A = abnormal; CREAT = creatinine; H = high; L = low.

Table 5. Potential Study Endpoints

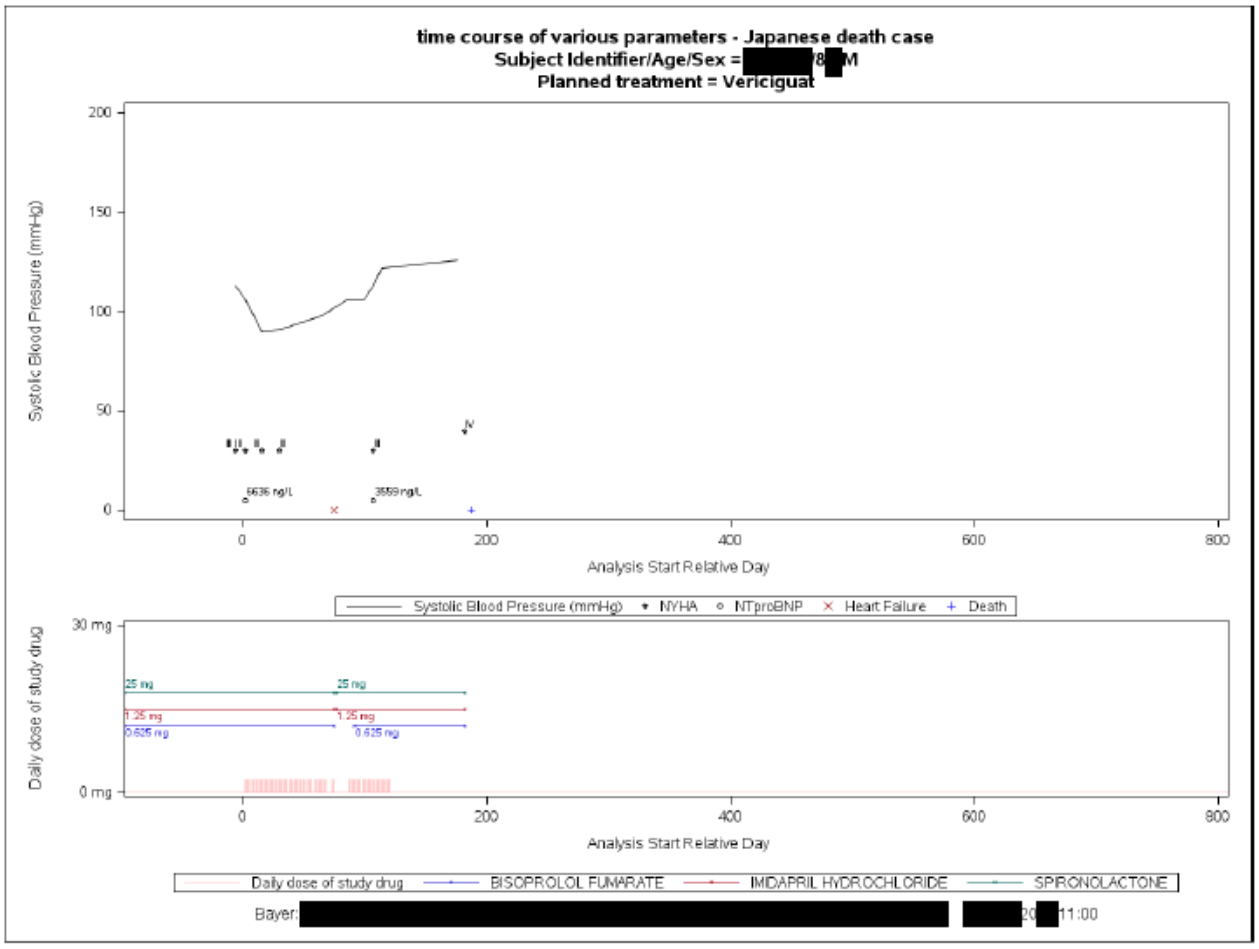
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
74	162	Heart Failure	Hospitalization	Heart Failure
187		Non-CV Event	Death	Heart Failure

CEC = Clinical Events Committee; CV = cardiovascular.

Table will be blank if no potential endpoints were reported.

* Event start and stop days are calculated based on the randomization day, whereas data listings present event start and stop days based on first dose of study medication.

† Notes: 1) Hospitalizations that were planned or scheduled, or hospitalizations lasting <24 hours, have been adjudicated as “Not Hospitalized.” 2) Deaths with an undetermined cause are considered as cardiovascular.


time course of various parameters - Japanese death case
Subject Identifier/Age/Sex = [redacted]/8[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
9636 ng/L
3559 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Death
Daily dose of study drug
30 mg
0 mg
25 mg
25 mg
1.25 mg
1.25 mg
0.625 mg
0.625 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
IMIDAPRIL HYDROCHLORIDE
SPIRONOLACTONE
Bayer[redacted]11:00