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2.7.3.7.1　　付表及び付図

表 2.7.3.7-1 ベースラインの心不全に対する標準治療（アジア／太平洋地域）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	592		591		1183	
Subjects with data	591		591		1182	
With one or more SOC treatments	589	(99.7)	588	(99.5)	1177	(99.6)
With no SOC treatment	2	(0.3)	3	(0.5)	5	(0.4)
Beta Blocker						
Yes	528	(89.3)	528	(89.3)	1056	(89.3)
No	63	(10.7)	63	(10.7)	126	(10.7)
Reasons for not on the treatment						
Contraindication	9	(1.5)	4	(0.7)	13	(1.1)
Side effect or treatment intolerance	7	(1.2)	13	(2.2)	20	(1.7)
Subject or physician preference	42	(7.1)	42	(7.1)	84	(7.1)
Other	5	(0.8)	4	(0.7)	9	(0.8)
ACE-I or ARB						
Yes	416	(70.4)	425	(71.9)	841	(71.2)
No	175	(29.6)	166	(28.1)	341	(28.8)
Reasons for not on the treatment						
Contraindication	5	(0.8)	7	(1.2)	12	(1.0)
Side effect or treatment intolerance	22	(3.7)	24	(4.1)	46	(3.9)
Subject currently taking the combination of Sacubitril/Valsartan	62	(10.5)	44	(7.4)	106	(9.0)
Subject or physician preference	79	(13.4)	80	(13.5)	159	(13.5)
Other	7	(1.2)	11	(1.9)	18	(1.5)
MRA						
Yes	386	(65.3)	418	(70.7)	804	(68.0)
No	205	(34.7)	173	(29.3)	378	(32.0)
Reasons for not on the treatment						
Contraindication	5	(0.8)	7	(1.2)	12	(1.0)
Not indicated by treatment guidelines	37	(6.3)	21	(3.6)	58	(4.9)
Side effect or treatment intolerance	31	(5.2)	29	(4.9)	60	(5.1)
Subject or physician preference	126	(21.3)	110	(18.6)	236	(20.0)
Other	6	(1.0)	6	(1.0)	12	(1.0)
Sacubitril/Valsartan						
Yes	104	(17.6)	108	(18.3)	212	(17.9)
No	487	(82.4)	483	(81.7)	970	(82.1)
Reasons for not on the treatment						
Contraindication	9	(1.5)	7	(1.2)	16	(1.4)
Sacubitril/Valsartan						
Not indicated by treatment guidelines	69	(11.7)	76	(12.9)	145	(12.3)
Side effect or treatment intolerance	4	(0.7)	1	(0.2)	5	(0.4)
Subject or physician preference	161	(27.2)	151	(25.5)	312	(26.4)
Treatment Not Available	225	(38.1)	215	(36.4)	440	(37.2)
Other	19	(3.2)	33	(5.6)	52	(4.4)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
ICD						
Yes	87	(14.7)	91	(15.4)	178	(15.1)
No	504	(85.3)	500	(84.6)	1004	(84.9)
Reasons for not on the treatment						
Not indicated by treatment guidelines	197	(33.3)	198	(33.5)	395	(33.4)
Side effect or treatment intolerance	1	(0.2)	1	(0.2)	2	(0.2)
Subject or physician preference	168	(28.4)	155	(26.2)	323	(27.3)
Treatment Not Available	115	(19.5)	124	(21.0)	239	(20.2)
Other	23	(3.9)	22	(3.7)	45	(3.8)
Biventricular Pacemaker						
Yes	66	(11.2)	59	(10.0)	125	(10.6)
No	525	(88.8)	532	(90.0)	1057	(89.4)
Reasons for not on the treatment						
Not indicated by treatment guidelines	216	(36.5)	233	(39.4)	449	(38.0)
Side effect or treatment intolerance	1	(0.2)	0	(0.0)	1	(0.1)
Subject or physician preference	172	(29.1)	156	(26.4)	328	(27.7)
Treatment Not Available	119	(20.1)	121	(20.5)	240	(20.3)
Other	17	(2.9)	22	(3.7)	39	(3.3)
Standard of Care Device						
No Device	475	(80.4)	477	(80.7)	952	(80.5)
ICD Only	50	(8.5)	55	(9.3)	105	(8.9)
Biventricular Pacemaker Only	29	(4.9)	23	(3.9)	52	(4.4)
ICD and Biventricular Pacemaker	37	(6.3)	36	(6.1)	73	(6.2)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	518	(87.6)	527	(89.2)	1045	(88.4)
No	73	(12.4)	64	(10.8)	137	(11.6)
Two or more SOC Medications						
No	63	(10.7)	51	(8.6)	114	(9.6)
Yes	528	(89.3)	540	(91.4)	1068	(90.4)
MRA + Any RAS Inhibitor	35	(5.9)	34	(5.8)	69	(5.8)
Beta Blocker + Any RAS Inhibitor	149	(25.2)	130	(22.0)	279	(23.6)
MRA + Beta Blocker	29	(4.9)	30	(5.1)	59	(5.0)
MRA + Beta Blocker + Any RAS Inhibitor	315	(53.3)	346	(58.5)	661	(55.9)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.
Source: 5.3.5.1.6 16493_Additional analysis/Table 21

表 2.7.3.7-2 ベースラインの心不全に対する標準治療（東ヨーロッパ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	848		846		1694	
Subjects with data	848		845		1693	
With one or more SOC treatments	847	(99.9)	844	(99.9)	1691	(99.9)
With no SOC treatment	1	(0.1)	1	(0.1)	2	(0.1)
Beta Blocker						
Yes	816	(96.2)	795	(94.1)	1611	(95.2)
No	32	(3.8)	50	(5.9)	82	(4.8)
Reasons for not on the treatment						
Contraindication	9	(1.1)	8	(0.9)	17	(1.0)
Side effect or treatment intolerance	6	(0.7)	8	(0.9)	14	(0.8)
Subject or physician preference	16	(1.9)	30	(3.6)	46	(2.7)
Other	1	(0.1)	4	(0.5)	5	(0.3)
ACE-I or ARB						
Yes	700	(82.5)	693	(82.0)	1393	(82.3)
No	148	(17.5)	152	(18.0)	300	(17.7)
Reasons for not on the treatment						
Contraindication	15	(1.8)	13	(1.5)	28	(1.7)
Side effect or treatment intolerance	20	(2.4)	22	(2.6)	42	(2.5)
Subject currently taking the combination of Sacubitril/Valsartan	23	(2.7)	32	(3.8)	55	(3.2)
Subject or physician preference	82	(9.7)	75	(8.9)	157	(9.3)
Other	8	(0.9)	10	(1.2)	18	(1.1)
MRA						
Yes	673	(79.4)	649	(76.8)	1322	(78.1)
No	175	(20.6)	196	(23.2)	371	(21.9)
Reasons for not on the treatment						
Contraindication	20	(2.4)	29	(3.4)	49	(2.9)
Not indicated by treatment guidelines	32	(3.8)	39	(4.6)	71	(4.2)
Side effect or treatment intolerance	11	(1.3)	17	(2.0)	28	(1.7)
Subject or physician preference	103	(12.1)	96	(11.4)	199	(11.8)
Other	9	(1.1)	15	(1.8)	24	(1.4)
Sacubitril/Valsartan						
Yes	38	(4.5)	49	(5.8)	87	(5.1)
No	810	(95.5)	796	(94.2)	1606	(94.9)
Reasons for not on the treatment						
Contraindication	13	(1.5)	11	(1.3)	24	(1.4)
Sacubitril/Valsartan						
Not indicated by treatment guidelines	241	(28.4)	238	(28.2)	479	(28.3)
Side effect or treatment intolerance	6	(0.7)	7	(0.8)	13	(0.8)
Subject or physician preference	300	(35.4)	267	(31.6)	567	(33.5)
Treatment Not Available	197	(23.2)	204	(24.1)	401	(23.7)
Other	53	(6.3)	69	(8.2)	122	(7.2)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
ICD						
Yes	220	(25.9)	234	(27.7)	454	(26.8)
No	628	(74.1)	611	(72.3)	1239	(73.2)
Reasons for not on the treatment						
Not indicated by treatment guidelines	321	(37.9)	307	(36.3)	628	(37.1)
Side effect or treatment intolerance	3	(0.4)	1	(0.1)	4	(0.2)
Subject or physician preference	208	(24.5)	208	(24.6)	416	(24.6)
Treatment Not Available	36	(4.2)	33	(3.9)	69	(4.1)
Other	60	(7.1)	62	(7.3)	122	(7.2)
Biventricular Pacemaker						
Yes	94	(11.1)	124	(14.7)	218	(12.9)
No	754	(88.9)	721	(85.3)	1475	(87.1)
Reasons for not on the treatment						
Not indicated by treatment guidelines	439	(51.8)	435	(51.5)	874	(51.6)
Side effect or treatment intolerance	3	(0.4)	3	(0.4)	6	(0.4)
Subject or physician preference	230	(27.1)	209	(24.7)	439	(25.9)
Treatment Not Available	30	(3.5)	29	(3.4)	59	(3.5)
Other	52	(6.1)	45	(5.3)	97	(5.7)
Standard of Care Device						
No Device	605	(71.3)	581	(68.8)	1186	(70.1)
ICD Only	149	(17.6)	140	(16.6)	289	(17.1)
Biventricular Pacemaker Only	23	(2.7)	30	(3.6)	53	(3.1)
ICD and Biventricular Pacemaker	71	(8.4)	94	(11.1)	165	(9.7)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	737	(86.9)	741	(87.7)	1478	(87.3)
No	111	(13.1)	104	(12.3)	215	(12.7)
Two or more SOC Medications						
No	47	(5.5)	61	(7.2)	108	(6.4)
Yes	801	(94.5)	784	(92.8)	1585	(93.6)
MRA + Any RAS Inhibitor	20	(2.4)	31	(3.7)	51	(3.0)
Beta Blocker + Any RAS Inhibitor	132	(15.6)	140	(16.6)	272	(16.1)
MRA + Beta Blocker	71	(8.4)	56	(6.6)	127	(7.5)
MRA + Beta Blocker + Any RAS Inhibitor	578	(68.2)	557	(65.9)	1135	(67.0)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.
Source: 5.3.5.1.6 16493_Additional analysis/Table 22

表 2.7.3.7-3 ベースラインの心不全に対する標準治療（ラテン及び南アメリカ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	362		362		724	
Subjects with data	362		362		724	
With one or more SOC treatments	362	(100)	361	(99.7)	723	(99.9)
With no SOC treatment	0	(0.0)	1	(0.3)	1	(0.1)
Beta Blocker						
Yes	330	(91.2)	338	(93.4)	668	(92.3)
No	32	(8.8)	24	(6.6)	56	(7.7)
Reasons for not on the treatment						
Contraindication	2	(0.6)	5	(1.4)	7	(1.0)
Side effect or treatment intolerance	8	(2.2)	4	(1.1)	12	(1.7)
Subject or physician preference	21	(5.8)	11	(3.0)	32	(4.4)
Other	1	(0.3)	4	(1.1)	5	(0.7)
ACE-I or ARB						
Yes	307	(84.8)	300	(82.9)	607	(83.8)
No	55	(15.2)	62	(17.1)	117	(16.2)
Reasons for not on the treatment						
Contraindication	10	(2.8)	7	(1.9)	17	(2.3)
Side effect or treatment intolerance	2	(0.6)	4	(1.1)	6	(0.8)
Subject currently taking the combination of Sacubitril/Valsartan	21	(5.8)	21	(5.8)	42	(5.8)
Subject or physician preference	21	(5.8)	30	(8.3)	51	(7.0)
Other	1	(0.3)	0	(0.0)	1	(0.1)
MRA						
Yes	290	(80.1)	293	(80.9)	583	(80.5)
No	72	(19.9)	69	(19.1)	141	(19.5)
Reasons for not on the treatment						
Contraindication	6	(1.7)	8	(2.2)	14	(1.9)
Not indicated by treatment guidelines	5	(1.4)	11	(3.0)	16	(2.2)
Side effect or treatment intolerance	2	(0.6)	5	(1.4)	7	(1.0)
Subject or physician preference	50	(13.8)	42	(11.6)	92	(12.7)
Other	9	(2.5)	3	(0.8)	12	(1.7)
Sacubitril/Valsartan						
Yes	33	(9.1)	31	(8.6)	64	(8.8)
No	329	(90.9)	331	(91.4)	660	(91.2)
Reasons for not on the treatment						
Contraindication	4	(1.1)	5	(1.4)	9	(1.2)
Sacubitril/Valsartan						
Not indicated by treatment guidelines	75	(20.7)	80	(22.1)	155	(21.4)
Side effect or treatment intolerance	1	(0.3)	4	(1.1)	5	(0.7)
Subject or physician preference	180	(49.7)	170	(47.0)	350	(48.3)
Treatment Not Available	50	(13.8)	54	(14.9)	104	(14.4)
Other	19	(5.2)	18	(5.0)	37	(5.1)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
ICD						
Yes	40	(11.0)	41	(11.3)	81	(11.2)
No	322	(89.0)	321	(88.7)	643	(88.8)
Reasons for not on the treatment						
Not indicated by treatment guidelines	138	(38.1)	163	(45.0)	301	(41.6)
Side effect or treatment intolerance	1	(0.3)	0	(0.0)	1	(0.1)
Subject or physician preference	125	(34.5)	121	(33.4)	246	(34.0)
Treatment Not Available	32	(8.8)	21	(5.8)	53	(7.3)
Other	26	(7.2)	16	(4.4)	42	(5.8)
Biventricular Pacemaker						
Yes	30	(8.3)	16	(4.4)	46	(6.4)
No	332	(91.7)	346	(95.6)	678	(93.6)
Reasons for not on the treatment						
Not indicated by treatment guidelines	159	(43.9)	184	(50.8)	343	(47.4)
Side effect or treatment intolerance	2	(0.6)	0	(0.0)	2	(0.3)
Subject or physician preference	115	(31.8)	122	(33.7)	237	(32.7)
Treatment Not Available	24	(6.6)	16	(4.4)	40	(5.5)
Other	32	(8.8)	24	(6.6)	56	(7.7)
Standard of Care Device						
No Device	302	(83.4)	311	(85.9)	613	(84.7)
ICD Only	30	(8.3)	35	(9.7)	65	(9.0)
Biventricular Pacemaker Only	20	(5.5)	10	(2.8)	30	(4.1)
ICD and Biventricular Pacemaker	10	(2.8)	6	(1.7)	16	(2.2)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	338	(93.4)	330	(91.2)	668	(92.3)
No	24	(6.6)	32	(8.8)	56	(7.7)
Two or more SOC Medications						
No	20	(5.5)	16	(4.4)	36	(5.0)
Yes	342	(94.5)	346	(95.6)	688	(95.0)
MRA + Any RAS Inhibitor	23	(6.4)	16	(4.4)	39	(5.4)
Beta Blocker + Any RAS Inhibitor	53	(14.6)	54	(14.9)	107	(14.8)
MRA + Beta Blocker	12	(3.3)	22	(6.1)	34	(4.7)
MRA + Beta Blocker + Any RAS Inhibitor	254	(70.2)	254	(70.2)	508	(70.2)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.
Source: 5.3.5.1.6 16493_Additional analysis/Table 23

表 2.7.3.7-4 ベースラインの心不全に対する標準治療（北アメリカ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	281		279		560	
Subjects with data	277		278		555	
With one or more SOC treatments	276	(99.6)	277	(99.6)	553	(99.6)
With no SOC treatment	1	(0.4)	1	(0.4)	2	(0.4)
Beta Blocker						
Yes	264	(95.3)	266	(95.7)	530	(95.5)
No	13	(4.7)	12	(4.3)	25	(4.5)
Reasons for not on the treatment						
Contraindication	1	(0.4)	0	(0.0)	1	(0.2)
Side effect or treatment intolerance	2	(0.7)	7	(2.5)	9	(1.6)
Subject or physician preference	7	(2.5)	3	(1.1)	10	(1.8)
Other	3	(1.1)	2	(0.7)	5	(0.9)
ACE-I or ARB						
Yes	158	(57.0)	153	(55.0)	311	(56.0)
No	119	(43.0)	125	(45.0)	244	(44.0)
Reasons for not on the treatment						
Contraindication	8	(2.9)	5	(1.8)	13	(2.3)
Side effect or treatment intolerance	16	(5.8)	24	(8.6)	40	(7.2)
Subject currently taking the combination of Sacubitril/Valsartan	46	(16.6)	45	(16.2)	91	(16.4)
Subject or physician preference	39	(14.1)	41	(14.7)	80	(14.4)
Other	10	(3.6)	10	(3.6)	20	(3.6)
MRA						
Yes	137	(49.5)	150	(54.0)	287	(51.7)
No	140	(50.5)	128	(46.0)	268	(48.3)
Reasons for not on the treatment						
Contraindication	8	(2.9)	13	(4.7)	21	(3.8)
Not indicated by treatment guidelines	28	(10.1)	19	(6.8)	47	(8.5)
Side effect or treatment intolerance	14	(5.1)	14	(5.0)	28	(5.0)
Subject or physician preference	80	(28.9)	72	(25.9)	152	(27.4)
Other	10	(3.6)	10	(3.6)	20	(3.6)
Sacubitril/Valsartan						
Yes	74	(26.7)	73	(26.3)	147	(26.5)
No	203	(73.3)	205	(73.7)	408	(73.5)
Reasons for not on the treatment						
Contraindication	13	(4.7)	10	(3.6)	23	(4.1)
Sacubitril/Valsartan						
Not indicated by treatment guidelines	29	(10.5)	33	(11.9)	62	(11.2)
Side effect or treatment intolerance	16	(5.8)	15	(5.4)	31	(5.6)
Subject or physician preference	117	(42.2)	113	(40.6)	230	(41.4)
Treatment Not Available	3	(1.1)	4	(1.4)	7	(1.3)
Other	25	(9.0)	30	(10.8)	55	(9.9)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
ICD						
Yes	152	(54.9)	147	(52.9)	299	(53.9)
No	125	(45.1)	131	(47.1)	256	(46.1)
Reasons for not on the treatment						
Not indicated by treatment guidelines	65	(23.5)	58	(20.9)	123	(22.2)
Side effect or treatment intolerance	1	(0.4)	2	(0.7)	3	(0.5)
Subject or physician preference	44	(15.9)	57	(20.5)	101	(18.2)
Treatment Not Available	2	(0.7)	1	(0.4)	3	(0.5)
Other	13	(4.7)	13	(4.7)	26	(4.7)
Biventricular Pacemaker						
Yes	70	(25.3)	77	(27.7)	147	(26.5)
No	207	(74.7)	201	(72.3)	408	(73.5)
Reasons for not on the treatment						
Not indicated by treatment guidelines	110	(39.7)	105	(37.8)	215	(38.7)
Side effect or treatment intolerance	0	(0.0)	1	(0.4)	1	(0.2)
Subject or physician preference	75	(27.1)	80	(28.8)	155	(27.9)
Treatment Not Available	2	(0.7)	0	(0.0)	2	(0.4)
Other	20	(7.2)	15	(5.4)	35	(6.3)
Standard of Care Device						
No Device	117	(42.2)	118	(42.4)	235	(42.3)
ICD Only	90	(32.5)	83	(29.9)	173	(31.2)
Biventricular Pacemaker Only	8	(2.9)	13	(4.7)	21	(3.8)
ICD and Biventricular Pacemaker	62	(22.4)	64	(23.0)	126	(22.7)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	231	(83.4)	221	(79.5)	452	(81.4)
No	46	(16.6)	57	(20.5)	103	(18.6)
Two or more SOC Medications						
No	37	(13.4)	40	(14.4)	77	(13.9)
Yes	240	(86.6)	238	(85.6)	478	(86.1)
MRA + Any RAS Inhibitor	4	(1.4)	6	(2.2)	10	(1.8)
Beta Blocker + Any RAS Inhibitor	104	(37.5)	90	(32.4)	194	(35.0)
MRA + Beta Blocker	15	(5.4)	20	(7.2)	35	(6.3)
MRA + Beta Blocker + Any RAS Inhibitor	117	(42.2)	122	(43.9)	239	(43.1)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.
Source: 5.3.5.1.6 16493_Additional analysis/Table 24

表 2.7.3.7-5 ベースラインの心不全に対する標準治療（西ヨーロッパ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	443		446		889	
Subjects with data	443		443		886	
With one or more SOC treatments	443	(100)	443	(100)	886	(100)
Beta Blocker						
Yes	411	(92.8)	415	(93.7)	826	(93.2)
No	32	(7.2)	28	(6.3)	60	(6.8)
Reasons for not on the treatment						
Contraindication	7	(1.6)	2	(0.5)	9	(1.0)
Side effect or treatment intolerance	8	(1.8)	12	(2.7)	20	(2.3)
Subject or physician preference	13	(2.9)	13	(2.9)	26	(2.9)
Other	4	(0.9)	1	(0.2)	5	(0.6)
ACE-I or ARB						
Yes	266	(60.0)	282	(63.7)	548	(61.9)
No	177	(40.0)	161	(36.3)	338	(38.1)
Reasons for not on the treatment						
Contraindication	12	(2.7)	4	(0.9)	16	(1.8)
Side effect or treatment intolerance	27	(6.1)	19	(4.3)	46	(5.2)
Subject currently taking the combination of Sacubitril/Valsartan	63	(14.2)	66	(14.9)	129	(14.6)
Subject or physician preference	69	(15.6)	60	(13.5)	129	(14.6)
Other	6	(1.4)	12	(2.7)	18	(2.0)
MRA						
Yes	261	(58.9)	288	(65.0)	549	(62.0)
No	182	(41.1)	155	(35.0)	337	(38.0)
Reasons for not on the treatment						
Contraindication	23	(5.2)	14	(3.2)	37	(4.2)
Not indicated by treatment guidelines	24	(5.4)	25	(5.6)	49	(5.5)
Side effect or treatment intolerance	28	(6.3)	20	(4.5)	48	(5.4)
Subject or physician preference	99	(22.3)	88	(19.9)	187	(21.1)
Other	8	(1.8)	8	(1.8)	16	(1.8)
Sacubitril/Valsartan						
Yes	111	(25.1)	110	(24.8)	221	(24.9)
No	332	(74.9)	333	(75.2)	665	(75.1)
Reasons for not on the treatment						
Contraindication	24	(5.4)	14	(3.2)	38	(4.3)
Not indicated by treatment guidelines	98	(22.1)	90	(20.3)	188	(21.2)
Sacubitril/Valsartan						
Side effect or treatment intolerance	19	(4.3)	17	(3.8)	36	(4.1)
Subject or physician preference	170	(38.4)	183	(41.3)	353	(39.8)
Treatment Not Available	7	(1.6)	9	(2.0)	16	(1.8)
Other	14	(3.2)	20	(4.5)	34	(3.8)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
ICD						
Yes	197	(44.5)	190	(42.9)	387	(43.7)
No	246	(55.5)	253	(57.1)	499	(56.3)
Reasons for not on the treatment						
Not indicated by treatment guidelines	121	(27.3)	105	(23.7)	226	(25.5)
Side effect or treatment intolerance	1	(0.2)	1	(0.2)	2	(0.2)
Subject or physician preference	105	(23.7)	130	(29.3)	235	(26.5)
Treatment Not Available	7	(1.6)	3	(0.7)	10	(1.1)
Other	12	(2.7)	14	(3.2)	26	(2.9)
Biventricular Pacemaker						
Yes	110	(24.8)	93	(21.0)	203	(22.9)
No	333	(75.2)	350	(79.0)	683	(77.1)
Reasons for not on the treatment						
Not indicated by treatment guidelines	186	(42.0)	171	(38.6)	357	(40.3)
Side effect or treatment intolerance	1	(0.2)	1	(0.2)	2	(0.2)
Subject or physician preference	123	(27.8)	151	(34.1)	274	(30.9)
Treatment Not Available	8	(1.8)	5	(1.1)	13	(1.5)
Other	15	(3.4)	22	(5.0)	37	(4.2)
Standard of Care Device						
No Device	209	(47.2)	230	(51.9)	439	(49.5)
ICD Only	124	(28.0)	120	(27.1)	244	(27.5)
Biventricular Pacemaker Only	37	(8.4)	23	(5.2)	60	(6.8)
ICD and Biventricular Pacemaker	73	(16.5)	70	(15.8)	143	(16.1)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	370	(83.5)	391	(88.3)	761	(85.9)
No	73	(16.5)	52	(11.7)	125	(14.1)
Two or more SOC Medications						
No	54	(12.2)	42	(9.5)	96	(10.8)
Yes	389	(87.8)	401	(90.5)	790	(89.2)
MRA + Any RAS Inhibitor	9	(2.0)	13	(2.9)	22	(2.5)
Beta Blocker + Any RAS Inhibitor	131	(29.6)	118	(26.6)	249	(28.1)
MRA + Beta Blocker	33	(7.4)	20	(4.5)	53	(6.0)
MRA + Beta Blocker + Any RAS Inhibitor	216	(48.8)	250	(56.4)	466	(52.6)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.
Source: 5.3.5.1.6 16493_Additional analysis/Table 25

表 2.7.3.7-6　試験期間における心不全に対する標準治療（アジア／太平洋地域）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	592		591		1183	
Subjects with Follow Up	588		587		1175	
With SOC during Follow Up	588	(100.0)	584	(99.5)	1172	(99.7)
Without SOC during Follow Up	0	(0.0)	3	(0.5)	3	(0.3)
Day 2 to Day 21	**588**		**587**		**1175**	
Subject with any SOC Medication	587	(99.8)	582	(99.1)	1169	(99.5)
Beta Blocker	530	(90.1)	523	(89.1)	1053	(89.6)
ACE-I or ARB	418	(71.1)	425	(72.4)	843	(71.7)
MRA	393	(66.8)	425	(72.4)	818	(69.6)
Sacubitril/Valsartan	106	(18.0)	111	(18.9)	217	(18.5)
Day 22 to Day 56	**580**		**582**		**1162**	
Subject with any SOC Medication	579	(99.8)	575	(98.8)	1154	(99.3)
Beta Blocker	522	(90.0)	519	(89.2)	1041	(89.6)
ACE-I or ARB	412	(71.0)	412	(70.8)	824	(70.9)
MRA	390	(67.2)	420	(72.2)	810	(69.7)
Sacubitril/Valsartan	102	(17.6)	112	(19.2)	214	(18.4)
Day 57 to Week 16	**559**		**564**		**1123**	
Subject with any SOC Medication	558	(99.8)	558	(98.9)	1116	(99.4)
Beta Blocker	502	(89.8)	501	(88.8)	1003	(89.3)
ACE-I or ARB	390	(69.8)	395	(70.0)	785	(69.9)
MRA	382	(68.3)	401	(71.1)	783	(69.7)
Sacubitril/Valsartan	106	(19.0)	117	(20.7)	223	(19.9)
Week 17 to Week 32	**553**		**551**		**1104**	
Subject with any SOC Medication	550	(99.5)	546	(99.1)	1096	(99.3)
Beta Blocker	497	(89.9)	493	(89.5)	990	(89.7)
ACE-I or ARB	381	(68.9)	384	(69.7)	765	(69.3)
MRA	383	(69.3)	395	(71.7)	778	(70.5)
Sacubitril/Valsartan	125	(22.6)	130	(23.6)	255	(23.1)
Week 33 to Week 48	**459**		**467**		**926**	
Subject with any SOC Medication	454	(98.9)	459	(98.3)	913	(98.6)
Beta Blocker	405	(88.2)	416	(89.1)	821	(88.7)
ACE-I or ARB	311	(67.8)	317	(67.9)	628	(67.8)
MRA	310	(67.5)	338	(72.4)	648	(70.0)
Sacubitril/Valsartan	96	(20.9)	109	(23.3)	205	(22.1)
Week 49 to Week 64	**344**		**348**		**692**	
Subject with any SOC Medication	337	(98.0)	339	(97.4)	676	(97.7)
Beta Blocker	305	(88.7)	306	(87.9)	611	(88.3)
ACE-I or ARB	230	(66.9)	236	(67.8)	466	(67.3)
MRA	216	(62.8)	241	(69.3)	457	(66.0)
Sacubitril/Valsartan	68	(19.8)	81	(23.3)	149	(21.5)
Week 65 to Week 80	**230**		**234**		**464**	
Subject with any SOC Medication	223	(97.0)	226	(96.6)	449	(96.8)
Beta Blocker	201	(87.4)	199	(85.0)	400	(86.2)
ACE-I or ARB	157	(68.3)	150	(64.1)	307	(66.2)
MRA	136	(59.1)	154	(65.8)	290	(62.5)
Sacubitril/Valsartan	42	(18.3)	46	(19.7)	88	(19.0)
Week 81 to Week 96	**156**		**173**		**329**	
Subject with any SOC Medication	152	(97.4)	165	(95.4)	317	(96.4)
Beta Blocker	138	(88.5)	149	(86.1)	287	(87.2)
ACE-I or ARB	108	(69.2)	108	(62.4)	216	(65.7)
MRA	95	(60.9)	107	(61.8)	202	(61.4)
Sacubitril/Valsartan	30	(19.2)	35	(20.2)	65	(19.8)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Week 97 to Week 112	**109**		**118**		**227**	
Subject with any SOC Medication	108	(99.1)	110	(93.2)	218	(96.0)
Beta Blocker	98	(89.9)	97	(82.2)	195	(85.9)
ACE-I or ARB	73	(67.0)	70	(59.3)	143	(63.0)
MRA	61	(56.0)	71	(60.2)	132	(58.1)
Sacubitril/Valsartan	19	(17.4)	24	(20.3)	43	(18.9)
Week 113 to Week 128	**58**		**61**		**119**	
Subject with any SOC Medication	56	(96.6)	57	(93.4)	113	(95.0)
Beta Blocker	52	(89.7)	51	(83.6)	103	(86.6)
ACE-I or ARB	38	(65.5)	35	(57.4)	73	(61.3)
MRA	31	(53.4)	38	(62.3)	69	(58.0)
Sacubitril/Valsartan	9	(15.5)	11	(18.0)	20	(16.8)
Week 129 to Week 144	**10**		**11**		**21**	
Subject with any SOC Medication	10	(100.0)	10	(90.9)	20	(95.2)
Beta Blocker	9	(90.0)	8	(72.7)	17	(81.0)
ACE-I or ARB	8	(80.0)	5	(45.5)	13	(61.9)
MRA	7	(70.0)	6	(54.5)	13	(61.9)
Sacubitril/Valsartan	3	(30.0)	3	(27.3)	6	(28.6)

SOC: Standard of Care.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 26

表 2.7.3.7-7 試験期間における心不全に対する標準治療（東ヨーロッパ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	848		846		1694	
Subjects with Follow Up	839		836		1675	
With SOC during Follow Up	839	(100.0)	835	(99.9)	1674	(99.9)
Without SOC during Follow Up	0	(0.0)	1	(0.1)	1	(0.1)
Day 2 to Day 21	**839**		**836**		**1675**	
Subject with any SOC Medication	839	(100.0)	835	(99.9)	1674	(99.9)
Beta Blocker	811	(96.7)	789	(94.4)	1600	(95.5)
ACE-I or ARB	698	(83.2)	693	(82.9)	1391	(83.0)
MRA	675	(80.5)	649	(77.6)	1324	(79.0)
Sacubitril/Valsartan	41	(4.9)	52	(6.2)	93	(5.6)
Day 22 to Day 56	**831**		**825**		**1656**	
Subject with any SOC Medication	831	(100.0)	824	(99.9)	1655	(99.9)
Beta Blocker	800	(96.3)	779	(94.4)	1579	(95.4)
ACE-I or ARB	688	(82.8)	686	(83.2)	1374	(83.0)
MRA	674	(81.1)	641	(77.7)	1315	(79.4)
Sacubitril/Valsartan	43	(5.2)	62	(7.5)	105	(6.3)
Day 57 to Week 16	**774**		**777**		**1551**	
Subject with any SOC Medication	773	(99.9)	776	(99.9)	1549	(99.9)
Beta Blocker	740	(95.6)	731	(94.1)	1471	(94.8)
ACE-I or ARB	640	(82.7)	643	(82.8)	1283	(82.7)
MRA	631	(81.5)	607	(78.1)	1238	(79.8)
Sacubitril/Valsartan	45	(5.8)	60	(7.7)	105	(6.8)
Week 17 to Week 32	**758**		**761**		**1519**	
Subject with any SOC Medication	757	(99.9)	759	(99.7)	1516	(99.8)
Beta Blocker	727	(95.9)	716	(94.1)	1443	(95.0)
ACE-I or ARB	626	(82.6)	631	(82.9)	1257	(82.8)
MRA	615	(81.1)	599	(78.7)	1214	(79.9)
Sacubitril/Valsartan	50	(6.6)	67	(8.8)	117	(7.7)
Week 33 to Week 48	**652**		**635**		**1287**	
Subject with any SOC Medication	651	(99.8)	632	(99.5)	1283	(99.7)
Beta Blocker	625	(95.9)	601	(94.6)	1226	(95.3)
ACE-I or ARB	533	(81.7)	528	(83.1)	1061	(82.4)
MRA	514	(78.8)	497	(78.3)	1011	(78.6)
Sacubitril/Valsartan	38	(5.8)	52	(8.2)	90	(7.0)
Week 49 to Week 64	**500**		**486**		**986**	
Subject with any SOC Medication	499	(99.8)	483	(99.4)	982	(99.6)
Beta Blocker	479	(95.8)	461	(94.9)	940	(95.3)
ACE-I or ARB	406	(81.2)	405	(83.3)	811	(82.3)
MRA	389	(77.8)	379	(78.0)	768	(77.9)
Sacubitril/Valsartan	33	(6.6)	41	(8.4)	74	(7.5)
Week 65 to Week 80	**403**		**386**		**789**	
Subject with any SOC Medication	402	(99.8)	385	(99.7)	787	(99.7)
Beta Blocker	385	(95.5)	365	(94.6)	750	(95.1)
ACE-I or ARB	325	(80.6)	320	(82.9)	645	(81.7)
MRA	311	(77.2)	290	(75.1)	601	(76.2)
Sacubitril/Valsartan	28	(6.9)	37	(9.6)	65	(8.2)
Week 81 to Week 96	**335**		**316**		**651**	
Subject with any SOC Medication	334	(99.7)	314	(99.4)	648	(99.5)
Beta Blocker	322	(96.1)	298	(94.3)	620	(95.2)
ACE-I or ARB	273	(81.5)	264	(83.5)	537	(82.5)
MRA	260	(77.6)	241	(76.3)	501	(77.0)
Sacubitril/Valsartan	18	(5.4)	30	(9.5)	48	(7.4)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Week 97 to Week 112	**249**		**225**		**474**	
Subject with any SOC Medication	249	(100.0)	225	(100.0)	474	(100.0)
Beta Blocker	243	(97.6)	212	(94.2)	455	(96.0)
ACE-I or ARB	201	(80.7)	196	(87.1)	397	(83.8)
MRA	198	(79.5)	175	(77.8)	373	(78.7)
Sacubitril/Valsartan	18	(7.2)	17	(7.6)	35	(7.4)
Week 113 to Week 128	**158**		**131**		**289**	
Subject with any SOC Medication	158	(100.0)	131	(100.0)	289	(100.0)
Beta Blocker	155	(98.1)	121	(92.4)	276	(95.5)
ACE-I or ARB	117	(74.1)	113	(86.3)	230	(79.6)
MRA	128	(81.0)	108	(82.4)	236	(81.7)
Sacubitril/Valsartan	16	(10.1)	12	(9.2)	28	(9.7)
Week 129 to Week 144	**42**		**32**		**74**	
Subject with any SOC Medication	42	(100.0)	32	(100.0)	74	(100.0)
Beta Blocker	42	(100.0)	30	(93.8)	72	(97.3)
ACE-I or ARB	32	(76.2)	31	(96.9)	63	(85.1)
MRA	37	(88.1)	26	(81.3)	63	(85.1)
Sacubitril/Valsartan	3	(7.1)	1	(3.1)	4	(5.4)

SOC: Standard of Care.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 27

表 2.7.3.7-8 試験期間における心不全に対する標準治療（ラテン及び南アメリカ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	362		362		724	
Subjects with Follow Up	360		358		718	
With SOC during Follow Up	360	(100.0)	357	(99.7)	717	(99.9)
Without SOC during Follow Up	0	(0.0)	1	(0.3)	1	(0.1)
Day 2 to Day 21	**360**		**358**		**718**	
Subject with any SOC Medication	360	(100.0)	357	(99.7)	717	(99.9)
Beta Blocker	328	(91.1)	334	(93.3)	662	(92.2)
ACE-I or ARB	307	(85.3)	300	(83.8)	607	(84.5)
MRA	289	(80.3)	292	(81.6)	581	(80.9)
Sacubitril/Valsartan	33	(9.2)	31	(8.7)	64	(8.9)
Day 22 to Day 56	**358**		**353**		**711**	
Subject with any SOC Medication	358	(100.0)	352	(99.7)	710	(99.9)
Beta Blocker	327	(91.3)	328	(92.9)	655	(92.1)
ACE-I or ARB	305	(85.2)	294	(83.3)	599	(84.2)
MRA	284	(79.3)	284	(80.5)	568	(79.9)
Sacubitril/Valsartan	35	(9.8)	32	(9.1)	67	(9.4)
Day 57 to Week 16	**339**		**335**		**674**	
Subject with any SOC Medication	338	(99.7)	334	(99.7)	672	(99.7)
Beta Blocker	309	(91.2)	310	(92.5)	619	(91.8)
ACE-I or ARB	287	(84.7)	272	(81.2)	559	(82.9)
MRA	273	(80.5)	269	(80.3)	542	(80.4)
Sacubitril/Valsartan	36	(10.6)	35	(10.4)	71	(10.5)
Week 17 to Week 32	**330**		**325**		**655**	
Subject with any SOC Medication	330	(100.0)	323	(99.4)	653	(99.7)
Beta Blocker	301	(91.2)	303	(93.2)	604	(92.2)
ACE-I or ARB	283	(85.8)	267	(82.2)	550	(84.0)
MRA	268	(81.2)	263	(80.9)	531	(81.1)
Sacubitril/Valsartan	41	(12.4)	40	(12.3)	81	(12.4)
Week 33 to Week 48	**289**		**283**		**572**	
Subject with any SOC Medication	289	(100.0)	283	(100.0)	572	(100.0)
Beta Blocker	263	(91.0)	263	(92.9)	526	(92.0)
ACE-I or ARB	238	(82.4)	229	(80.9)	467	(81.6)
MRA	227	(78.5)	229	(80.9)	456	(79.7)
Sacubitril/Valsartan	34	(11.8)	36	(12.7)	70	(12.2)
Week 49 to Week 64	**202**		**202**		**404**	
Subject with any SOC Medication	202	(100.0)	202	(100.0)	404	(100.0)
Beta Blocker	185	(91.6)	183	(90.6)	368	(91.1)
ACE-I or ARB	162	(80.2)	162	(80.2)	324	(80.2)
MRA	160	(79.2)	157	(77.7)	317	(78.5)
Sacubitril/Valsartan	28	(13.9)	22	(10.9)	50	(12.4)
Week 65 to Week 80	**132**		**129**		**261**	
Subject with any SOC Medication	132	(100.0)	129	(100.0)	261	(100.0)
Beta Blocker	122	(92.4)	120	(93.0)	242	(92.7)
ACE-I or ARB	107	(81.1)	107	(82.9)	214	(82.0)
MRA	109	(82.6)	102	(79.1)	211	(80.8)
Sacubitril/Valsartan	20	(15.2)	15	(11.6)	35	(13.4)
Week 81 to Week 96	**89**		**88**		**177**	
Subject with any SOC Medication	89	(100.0)	87	(98.9)	176	(99.4)
Beta Blocker	82	(92.1)	82	(93.2)	164	(92.7)
ACE-I or ARB	73	(82.0)	70	(79.5)	143	(80.8)
MRA	76	(85.4)	72	(81.8)	148	(83.6)
Sacubitril/Valsartan	11	(12.4)	12	(13.6)	23	(13.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Week 97 to Week 112	**46**		**49**		**95**	
Subject with any SOC Medication	45	(97.8)	48	(98.0)	93	(97.9)
Beta Blocker	41	(89.1)	47	(95.9)	88	(92.6)
ACE-I or ARB	38	(82.6)	35	(71.4)	73	(76.8)
MRA	42	(91.3)	40	(81.6)	82	(86.3)
Sacubitril/Valsartan	5	(10.9)	8	(16.3)	13	(13.7)
Week 113 to Week 128	**14**		**14**		**28**	
Subject with any SOC Medication	14	(100.0)	13	(92.9)	27	(96.4)
Beta Blocker	14	(100.0)	13	(92.9)	27	(96.4)
ACE-I or ARB	11	(78.6)	9	(64.3)	20	(71.4)
MRA	13	(92.9)	11	(78.6)	24	(85.7)
Sacubitril/Valsartan	1	(7.1)	1	(7.1)	2	(7.1)
Week 129 to Week 144	**1**		**1**		**2**	
Subject with any SOC Medication	1	(100.0)	1	(100.0)	2	(100.0)
Beta Blocker	1	(100.0)	1	(100.0)	2	(100.0)
ACE-I or ARB	0		1	(100.0)	1	(50.0)
MRA	1	(100.0)	1	(100.0)	2	(100.0)
Sacubitril/Valsartan	1	(100.0)	0		1	(50.0)

SOC: Standard of Care.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 28

表 2.7.3.7-9 試験期間における心不全に対する標準治療（北アメリカ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	281		279		560	
Subjects with Follow Up	277		279		556	
With SOC during Follow Up	276	(99.6)	278	(99.6)	554	(99.6)
Without SOC during Follow Up	1	(0.4)	1	(0.4)	2	(0.4)
Day 2 to Day 21	**277**		**279**		**556**	
Subject with any SOC Medication	275	(99.3)	278	(99.6)	553	(99.5)
Beta Blocker	263	(94.9)	268	(96.1)	531	(95.5)
ACE-I or ARB	159	(57.4)	153	(54.8)	312	(56.1)
MRA	137	(49.5)	155	(55.6)	292	(52.5)
Sacubitril/Valsartan	79	(28.5)	75	(26.9)	154	(27.7)
Day 22 to Day 56	**275**		**279**		**554**	
Subject with any SOC Medication	273	(99.3)	278	(99.6)	551	(99.5)
Beta Blocker	260	(94.5)	267	(95.7)	527	(95.1)
ACE-I or ARB	159	(57.8)	154	(55.2)	313	(56.5)
MRA	136	(49.5)	154	(55.2)	290	(52.3)
Sacubitril/Valsartan	81	(29.5)	83	(29.7)	164	(29.6)
Day 57 to Week 16	**269**		**269**		**538**	
Subject with any SOC Medication	266	(98.9)	269	(100.0)	535	(99.4)
Beta Blocker	255	(94.8)	258	(95.9)	513	(95.4)
ACE-I or ARB	155	(57.6)	149	(55.4)	304	(56.5)
MRA	131	(48.7)	153	(56.9)	284	(52.8)
Sacubitril/Valsartan	82	(30.5)	84	(31.2)	166	(30.9)
Week 17 to Week 32	**261**		**263**		**524**	
Subject with any SOC Medication	258	(98.9)	262	(99.6)	520	(99.2)
Beta Blocker	245	(93.9)	252	(95.8)	497	(94.8)
ACE-I or ARB	142	(54.4)	140	(53.2)	282	(53.8)
MRA	126	(48.3)	155	(58.9)	281	(53.6)
Sacubitril/Valsartan	92	(35.2)	84	(31.9)	176	(33.6)
Week 33 to Week 48	**231**		**230**		**461**	
Subject with any SOC Medication	227	(98.3)	228	(99.1)	455	(98.7)
Beta Blocker	214	(92.6)	218	(94.8)	432	(93.7)
ACE-I or ARB	107	(46.3)	120	(52.2)	227	(49.2)
MRA	110	(47.6)	133	(57.8)	243	(52.7)
Sacubitril/Valsartan	83	(35.9)	77	(33.5)	160	(34.7)
Week 49 to Week 64	**177**		**174**		**351**	
Subject with any SOC Medication	174	(98.3)	172	(98.9)	346	(98.6)
Beta Blocker	164	(92.7)	163	(93.7)	327	(93.2)
ACE-I or ARB	83	(46.9)	96	(55.2)	179	(51.0)
MRA	93	(52.5)	101	(58.0)	194	(55.3)
Sacubitril/Valsartan	62	(35.0)	55	(31.6)	117	(33.3)
Week 65 to Week 80	**128**		**120**		**248**	
Subject with any SOC Medication	125	(97.7)	118	(98.3)	243	(98.0)
Beta Blocker	122	(95.3)	111	(92.5)	233	(94.0)
ACE-I or ARB	64	(50.0)	62	(51.7)	126	(50.8)
MRA	63	(49.2)	63	(52.5)	126	(50.8)
Sacubitril/Valsartan	43	(33.6)	38	(31.7)	81	(32.7)
Week 81 to Week 96	**103**		**96**		**199**	
Subject with any SOC Medication	99	(96.1)	94	(97.9)	193	(97.0)
Beta Blocker	96	(93.2)	89	(92.7)	185	(93.0)
ACE-I or ARB	52	(50.5)	50	(52.1)	102	(51.3)
MRA	49	(47.6)	49	(51.0)	98	(49.2)
Sacubitril/Valsartan	34	(33.0)	29	(30.2)	63	(31.7)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Week 97 to Week 112	**64**		**58**		**122**	
Subject with any SOC Medication	62	(96.9)	57	(98.3)	119	(97.5)
Beta Blocker	59	(92.2)	55	(94.8)	114	(93.4)
ACE-I or ARB	32	(50.0)	31	(53.4)	63	(51.6)
MRA	29	(45.3)	30	(51.7)	59	(48.4)
Sacubitril/Valsartan	21	(32.8)	13	(22.4)	34	(27.9)
Week 113 to Week 128	**38**		**29**		**67**	
Subject with any SOC Medication	37	(97.4)	28	(96.6)	65	(97.0)
Beta Blocker	34	(89.5)	28	(96.6)	62	(92.5)
ACE-I or ARB	23	(60.5)	16	(55.2)	39	(58.2)
MRA	15	(39.5)	13	(44.8)	28	(41.8)
Sacubitril/Valsartan	10	(26.3)	9	(31.0)	19	(28.4)
Week 129 to Week 144	**10**		**6**		**16**	
Subject with any SOC Medication	9	(90.0)	6	(100.0)	15	(93.8)
Beta Blocker	9	(90.0)	6	(100.0)	15	(93.8)
ACE-I or ARB	7	(70.0)	3	(50.0)	10	(62.5)
MRA	5	(50.0)	2	(33.3)	7	(43.8)
Sacubitril/Valsartan	2	(20.0)	4	(66.7)	6	(37.5)

SOC: Standard of Care.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 29

表 2.7.3.7-10　試験期間における心不全に対する標準治療（西ヨーロッパ）（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	443		446		889	
Subjects with Follow Up	441		442		883	
With SOC during Follow Up	439	(99.5)	441	(99.8)	880	(99.7)
Without SOC during Follow Up	2	(0.5)	1	(0.2)	3	(0.3)
Day 2 to Day 21	**441**		**442**		**883**	
Subject with any SOC Medication	438	(99.3)	441	(99.8)	879	(99.5)
Beta Blocker	411	(93.2)	414	(93.7)	825	(93.4)
ACE-I or ARB	270	(61.2)	285	(64.5)	555	(62.9)
MRA	271	(61.5)	297	(67.2)	568	(64.3)
Sacubitril/Valsartan	116	(26.3)	120	(27.1)	236	(26.7)
Day 22 to Day 56	**436**		**435**		**871**	
Subject with any SOC Medication	433	(99.3)	434	(99.8)	867	(99.5)
Beta Blocker	409	(93.8)	413	(94.9)	822	(94.4)
ACE-I or ARB	266	(61.0)	278	(63.9)	544	(62.5)
MRA	269	(61.7)	289	(66.4)	558	(64.1)
Sacubitril/Valsartan	115	(26.4)	127	(29.2)	242	(27.8)
Day 57 to Week 16	**418**		**413**		**831**	
Subject with any SOC Medication	415	(99.3)	412	(99.8)	827	(99.5)
Beta Blocker	396	(94.7)	393	(95.2)	789	(94.9)
ACE-I or ARB	262	(62.7)	255	(61.7)	517	(62.2)
MRA	258	(61.7)	278	(67.3)	536	(64.5)
Sacubitril/Valsartan	114	(27.3)	129	(31.2)	243	(29.2)
Week 17 to Week 32	**410**		**399**		**809**	
Subject with any SOC Medication	406	(99.0)	397	(99.5)	803	(99.3)
Beta Blocker	384	(93.7)	382	(95.7)	766	(94.7)
ACE-I or ARB	251	(61.2)	235	(58.9)	486	(60.1)
MRA	255	(62.2)	267	(66.9)	522	(64.5)
Sacubitril/Valsartan	115	(28.0)	133	(33.3)	248	(30.7)
Week 33 to Week 48	**369**		**361**		**730**	
Subject with any SOC Medication	365	(98.9)	359	(99.4)	724	(99.2)
Beta Blocker	342	(92.7)	343	(95.0)	685	(93.8)
ACE-I or ARB	222	(60.2)	212	(58.7)	434	(59.5)
MRA	232	(62.9)	239	(66.2)	471	(64.5)
Sacubitril/Valsartan	113	(30.6)	121	(33.5)	234	(32.1)
Week 49 to Week 64	**311**		**302**		**613**	
Subject with any SOC Medication	307	(98.7)	302	(100.0)	609	(99.3)
Beta Blocker	289	(92.9)	287	(95.0)	576	(94.0)
ACE-I or ARB	188	(60.5)	177	(58.6)	365	(59.5)
MRA	198	(63.7)	196	(64.9)	394	(64.3)
Sacubitril/Valsartan	97	(31.2)	105	(34.8)	202	(33.0)
Week 65 to Week 80	**245**		**237**		**482**	
Subject with any SOC Medication	243	(99.2)	237	(100.0)	480	(99.6)
Beta Blocker	226	(92.2)	228	(96.2)	454	(94.2)
ACE-I or ARB	142	(58.0)	128	(54.0)	270	(56.0)
MRA	151	(61.6)	152	(64.1)	303	(62.9)
Sacubitril/Valsartan	75	(30.6)	86	(36.3)	161	(33.4)
Week 81 to Week 96	**184**		**183**		**367**	
Subject with any SOC Medication	183	(99.5)	182	(99.5)	365	(99.5)
Beta Blocker	169	(91.8)	173	(94.5)	342	(93.2)
ACE-I or ARB	109	(59.2)	102	(55.7)	211	(57.5)
MRA	118	(64.1)	112	(61.2)	230	(62.7)
Sacubitril/Valsartan	57	(31.0)	65	(35.5)	122	(33.2)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Week 97 to Week 112	**121**		**131**		**252**	
Subject with any SOC Medication	120	(99.2)	129	(98.5)	249	(98.8)
Beta Blocker	111	(91.7)	125	(95.4)	236	(93.7)
ACE-I or ARB	75	(62.0)	68	(51.9)	143	(56.7)
MRA	78	(64.5)	85	(64.9)	163	(64.7)
Sacubitril/Valsartan	34	(28.1)	54	(41.2)	88	(34.9)
Week 113 to Week 128	**68**		**72**		**140**	
Subject with any SOC Medication	67	(98.5)	71	(98.6)	138	(98.6)
Beta Blocker	60	(88.2)	70	(97.2)	130	(92.9)
ACE-I or ARB	41	(60.3)	38	(52.8)	79	(56.4)
MRA	43	(63.2)	46	(63.9)	89	(63.6)
Sacubitril/Valsartan	18	(26.5)	27	(37.5)	45	(32.1)
Week 129 to Week 144	**9**		**13**		**22**	
Subject with any SOC Medication	9	(100.0)	13	(100.0)	22	(100.0)
Beta Blocker	7	(77.8)	13	(100.0)	20	(90.9)
ACE-I or ARB	3	(33.3)	7	(53.8)	10	(45.5)
MRA	5	(55.6)	8	(61.5)	13	(59.1)
Sacubitril/Valsartan	5	(55.6)	7	(53.8)	12	(54.5)

SOC: Standard of Care.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 30

表 2.7.3.7-11 ガイドラインの基準に基づく心不全に対する標準治療（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2526		2524		5050	
Beta Blocker						
Subjects with Data*	2512		2516		5028	
Subjects Meeting Guideline Derived Criteria†	2275		2266		4541	
Used	2172	(95.5)	2166	(95.6)	4338	(95.5)
Not Used	103	(4.5)	100	(4.4)	203	(4.5)
RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Subjects with Data*	2512		2516		5028	
Subjects Meeting Guideline Derived Criteria†	2151		2149		4300	
Used	2032	(94.5)	2041	(95.0)	4073	(94.7)
Not Used	119	(5.5)	108	(5.0)	227	(5.3)
MRA						
Subjects with Data*	2490		2500		4990	
Subjects Meeting Guideline Derived Criteria†	1719		1732		3451	
Used	1329	(77.3)	1395	(80.5)	2724	(78.9)
Not Used	390	(22.7)	337	(19.5)	727	(21.1)
Sacubitril/Valsartan						
Subjects with Data*	2512		2516		5028	
Subjects Meeting Guideline Derived Criteria†	2227		2243		4470	
Used	344	(15.4)	350	(15.6)	694	(15.5)
Not Used	1883	(84.6)	1893	(84.4)	3776	(84.5)
ICD						
Subjects with Data*	2512		2516		5028	
Subjects Meeting Guideline Derived Criteria†	1726		1744		3470	
Used	558	(32.3)	557	(31.9)	1115	(32.1)
Not Used	1168	(67.7)	1187	(68.1)	2355	(67.9)

*Subjects with data on guideline derived criteria and use of SOC medication.

†Guideline Derived Criteria:

Betablocker: All subjects with a baseline LVEF ≤ 40% without known contraindication or intolerance to betablocker.

RAS Inhibitor: All subjects with a baseline LVEF ≤ 40% without known contraindication or intolerance to ACEI/ARB or ARNI

MRA: For Western Europe region and Eastern European region (except South Africa and Israel), includes all subjects with a baseline LVEF ≤ 35% without known contraindication or intolerance to MRA. For all other countries, includes all subjects with a baseline LVEF ≤ 35% and a baseline eGFR > 30ml/min/1.73m^2 without known contraindication or intolerance to MRA.

Sacubitril/Valsartan: All subjects with a baseline LVEF ≤ 40% without known contraindication or intolerance to Sacubitril/Valsartan.

ICD: For Western Europe region and Eastern European region (except South Africa and Israel), includes all subjects with a baseline LVEF ≤ 30% without known intolerance to ICD. For all other countries, includes all subjects with a baseline LVEF ≤ 35% without known intolerance to ICD.

Source: 5.3.5.1.6 16493_Additional analysis/Table 31

表 2.7.3.7-12 無作為割付け時の SGLT2 阻害薬の使用状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2526		2524		5050	
With SGLT2 inhibitor use	67	(2.7)	70	(2.8)	137	(2.7)
Without SGLT2 inhibitor use	2459	(97.3)	2454	(97.2)	4913	(97.3)
CANAGLIFLOZIN	7	(0.3)	4	(0.2)	11	(0.2)
CANAGLIFLOZIN HEMIHYDRATE;TENELIGLIPTIN HYDROBROMIDE	0	(0.0)	1	(0.0)	1	(0.0)
DAPAGLIFLOZIN	6	(0.2)	5	(0.2)	11	(0.2)
DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE	3	(0.1)	7	(0.3)	10	(0.2)
DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE;METFORMIN HYDROCHLORIDE	3	(0.1)	0	(0.0)	3	(0.1)
EMPAGLIFLOZIN	40	(1.6)	45	(1.8)	85	(1.7)
EMPAGLIFLOZIN;LINAGLIPTIN	1	(0.0)	0	(0.0)	1	(0.0)
EMPAGLIFLOZIN;METFORMIN HYDROCHLORIDE	3	(0.1)	3	(0.1)	6	(0.1)
IPRAGLIFLOZIN L-PROLINE	2	(0.1)	4	(0.2)	6	(0.1)
IPRAGLIFLOZIN L-PROLINE;SITAGLIPTIN PHOSPHATE MONOHYDRATE	1	(0.0)	1	(0.0)	2	(0.0)
TOFOGLIFLOZIN	1	(0.0)	1	(0.0)	2	(0.0)

Every subject is counted a single time for each applicable specific medication.
A specific medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Source: 5.3.5.1.6 16493_Additional analysis/Table 32

表 2.7.3.7-13 無作為割付け時のイバブラジンの使用状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2526		2524		5050	
With Ivabradine use	161	(6.4)	143	(5.7)	304	(6.0)
Without Ivabradine use	2365	(93.6)	2381	(94.3)	4746	(94.0)
IVABRADINE	93	(3.7)	70	(2.8)	163	(3.2)
IVABRADINE HYDROCHLORIDE	68	(2.7)	73	(2.9)	141	(2.8)

Every subject is counted a single time for each applicable specific medication.
A specific medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Source: 5.3.5.1.6 16493_Additional analysis/Table 33

表 2.7.3.7-14　死因が不確定であった死亡を除いた主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %†	KM% (95% CI)‡	n	(%)	Annual %†	KM% (95% CI)‡	HR (95% CI)§	p-Value‖
Primary Composite Endpoint	826	(32.7)	31.0	40.7 (38.3, 43.2)	899	(35.6)	35.0	44.0 (41.5, 46.6)	0.89 (0.81, 0.98)	0.020
Heart Failure Hospitalization	691	(27.4)			747	(29.6)				
Cardiovascular Death	135	(5.3)			152	(6.0)				

For subjects with multiple events, only the first event contributing to the composite endpoint is counted in the table.
† Total subjects with an event per 100 subject years at risk.
‡ Kaplan-Meier estimate and confidence interval at 2 years.
§ Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
‖ From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 35

表 2.7.3.7-15　治験責任（分担）医師の臨床イベント評価による主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %[†]	KM% (95% CI)[‡]	n	(%)	Annual %[†]	KM% (95% CI)[‡]	HR (95% CI)[§]	p-Value[‖]
Primary Composite Endpoint	1016	(40.2)	39.8	49.6 (47.1, 52.1)	1077	(42.7)	44.0	50.9 (48.4, 53.4)	0.92 (0.84, 1.00)	0.043
Heart Failure Hospitalization	830	(32.9)			891	(35.3)				
Cardiovascular Death	186	(7.4)			186	(7.4)				

For subjects with multiple events, only the first event contributing to the composite endpoint is counted in the table.
[†] Total subjects with an event per 100 subject years at risk.
[‡] Kaplan-Meier estimate and confidence interval at 2 years.
[§] Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[‖] From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 36

表 2.7.3.7-16　死因が不確定であった死亡を除いた副次評価項目（CV 死までの期間）の解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %†	KM% (95% CI)‡	n	(%)	Annual %†	KM% (95% CI)‡	HR (95% CI)§	p-Value‖
Cardiovascular Death	302	(12.0)	9.4	16.3 (14.5, 18.3)	340	(13.5)	10.7	18.8 (16.8, 21.0)	0.88 (0.75, 1.02)	0.097
Heart Failure	165	(6.5)			191	(7.6)				
Myocardial Infarction	10	(0.4)			11	(0.4)				
Stroke	7	(0.3)			16	(0.6)				
Other Cardiovascular Event	13	(0.5)			9	(0.4)				
Sudden Cardiac Death	107	(4.2)			113	(4.5)				

† Total subjects with an event per 100 subject years at risk.
‡ Kaplan-Meier estimate and confidence interval at 2 years.
§ Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
‖ From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 37

表 2.7.3.7-17　治験責任（分担）医師の臨床イベント評価による副次評価項目（CV 死までの期間）の解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %[†]	KM% (95% CI)[‡]	n	(%)	Annual %[†]	KM% (95% CI)[‡]	HR (95% CI)[§]	p-Value[‖]
Cardiovascular Death	419	(16.6)	13.1	22.2 (20.2, 24.4)	437	(17.3)	13.8	23.5 (21.4, 25.8)	0.95 (0.83, 1.08)	0.426
Heart Failure	187	(7.4)			200	(7.9)				
Myocardial Infarction	14	(0.6)			12	(0.5)				
Stroke	9	(0.4)			10	(0.4)				
Other Cardiovascular Event	25	(1.0)			29	(1.1)				
Sudden Cardiac Death	96	(3.8)			88	(3.5)				
Undetermined Cause Of Death	88	(3.5)			98	(3.9)				

[†] Total subjects with an event per 100 subject years at risk.
[‡] Kaplan-Meier estimate and confidence interval at 2 years.
[§] Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[‖] From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 38

表 2.7.3.7-18　治験責任（分担）医師の臨床イベント評価による副次評価項目（心不全による入院の初回発現までの期間）の解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %[†]	KM% (95% CI)[‡]	n	(%)	Annual %[†]	KM% (95% CI)[‡]	HR (95% CI)[§]	p-Value[‖]
Heart Failure Hospitalization	831	(32.9)	32.6	42.2 (39.7, 44.8)	901	(35.7)	36.8	44.0 (41.5, 46.5)	0.90 (0.82, 0.98)	0.023

[†] Total subjects with an event per 100 subject years at risk.
[‡] Kaplan-Meier estimate and confidence interval at 2 years.
[§] Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[‖] From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 39

表 2.7.3.7-19　CV 死、心不全による入院又は心不全による緊急来院の複合エンドポイントの初回発現までの期間（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %†	KM% (95% CI)‡	n	(%)	Annual %†	KM% (95% CI)‡	HR (95% CI)§	p-Value‖
Exploratory Composite Endpoint	928	(36.7)	35.3	45.0 (42.6, 47.5)	1011	(40.1)	40.0	48.7 (46.2, 51.2)	0.89 (0.82, 0.98)	0.013
Heart Failure Hospitalization	641	(25.4)			701	(27.8)				
Cardiovascular Death	198	(7.8)			216	(8.6)				
Urgent Heart Failure Visit	89	(3.5)			94	(3.7)				

For subjects with multiple events, only the first event contributing to the composite endpoint is counted in the table.
† Total subjects with an event per 100 subject years at risk.
‡ Kaplan-Meier estimate and confidence interval at 2 years.
§ Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
‖ From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 51

表 2.7.3.7-20　第 32 週の KCCQ Overall Summary Score（NYHA 分類クラスⅠ／Ⅱ）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Baseline		Week 32		Change from Baseline at Week 32		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI†)
Vericiguat	1334	65.1 (21.4)	1140	67.7 (28.9)	1059	2.8 (27.2)	2.4 (0.9, 3.9)
Placebo	1341	65.2 (20.5)	1133	67.6 (29.0)	1044	2.4 (29.0)	2.4 (0.8, 3.9)
Treatment Comparison					Difference in LS Means (95% CI)†		p-Value†
Vericiguat - Placebo					0.1 (-2.1, 2.2)		0.944

Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).

† Based on a longitudinal analysis of covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all post-randomization timepoints through Week 96.

For baseline and Week 32, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and Week 32.

CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 43

表 2.7.3.7-21　第 32 週の KCCQ Overall Summary Score（NYHA 分類クラスⅢ／Ⅳ）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Baseline		Week 32		Change from Baseline at Week 32		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI†)
Vericiguat	913	49.2 (21.7)	772	51.3 (32.5)	699	2.3 (30.0)	2.1 (0.1, 4.1)
Placebo	881	49.2 (21.8)	757	48.3 (33.1)	672	-1.7 (31.3)	-0.8 (-2.8, 1.3)
Treatment Comparison					Difference in LS Means (95% CI)†		p-Value†
Vericiguat - Placebo					2.9 (0.0, 5.8)		0.047

Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).

† Based on a longitudinal analysis of covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all post-randomization timepoints through Week 96.

For baseline and Week 32, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and Week 32.

CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 44

表 2.7.3.7-22　各評価時点の KCCQ Overall Summary Score（NYHA 分類クラスⅠ／Ⅱ）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

Visit	Treatment	Baseline			Value			Change from Baseline		
		N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	1334	65.1 (21.4)	68.2 [51.6, 81.8]						
	Placebo	1341	65.2 (20.5)	67.2 [51.2, 81.9]						
Day 28	Vericiguat	1189	65.4 (21.3)	68.8 [52.1, 82.0]	1276	72.5 (20.9)	77.3 [61.0, 89.0]	1189	7.0 (18.1)	5.6 [-2.6, 15.9]
	Placebo	1207	65.3 (20.3)	67.2 [51.6, 81.8]	1294	71.9 (21.1)	76.6 [61.2, 88.0]	1207	6.5 (19.0)	5.5 [-2.9, 15.4]
Week 16	Vericiguat	1177	65.3 (21.4)	68.5 [52.1, 81.8]	1261	70.6 (25.2)	77.1 [58.1, 90.6]	1177	5.4 (23.4)	5.7 [-3.8, 16.7]
	Placebo	1201	65.5 (20.3)	67.4 [52.1, 82.0]	1296	70.5 (24.7)	77.3 [58.3, 89.6]	1201	4.9 (24.3)	5.7 [-5.7, 17.7]
Week 32	Vericiguat	1059	65.2 (21.3)	68.5 [51.8, 81.8]	1140	67.7 (28.9)	76.0 [55.3, 89.6]	1059	2.8 (27.2)	5.8 [-5.7, 16.9]
	Placebo	1044	65.0 (20.6)	67.0 [51.0, 82.0]	1133	67.6 (29.0)	76.0 [54.7, 89.6]	1044	2.4 (29.0)	4.4 [-7.3, 18.2]
Week 48	Vericiguat	807	65.3 (21.6)	68.8 [52.1, 82.3]	861	63.7 (32.4)	74.5 [48.7, 89.3]	807	-1.1 (31.5)	4.2 [-10.7, 15.6]
	Placebo	817	64.4 (20.8)	66.9 [50.3, 81.0]	883	62.3 (32.6)	73.4 [46.9, 88.3]	817	-1.6 (32.5)	2.1 [-13.8, 17.7]
Week 96	Vericiguat	336	63.9 (21.4)	66.5 [50.9, 81.3]	369	46.8 (39.7)	56.3 [0.0, 85.4]	336	-16.5 (40.1)	-4.7 [-50.1, 12.0]
	Placebo	365	63.0 (21.0)	63.5 [49.0, 79.2]	402	46.5 (39.8)	59.4 [0.0, 83.8]	365	-17.0 (40.8)	-8.3 [-50.5, 12.5]
Week 144	Vericiguat	26	63.7 (23.1)	60.5 [50.0, 85.2]	29	2.2 (11.8)	0.0 [0.0, 0.0]	26	-61.2 (27.0)	-60.5 [-85.2, -47.4]
	Placebo	45	58.5 (24.4)	65.6 [36.7, 75.3]	49	5.4 (21.2)	0.0 [0.0, 0.0]	45	-52.7 (27.1)	-53.1 [-71.9, -32.3]

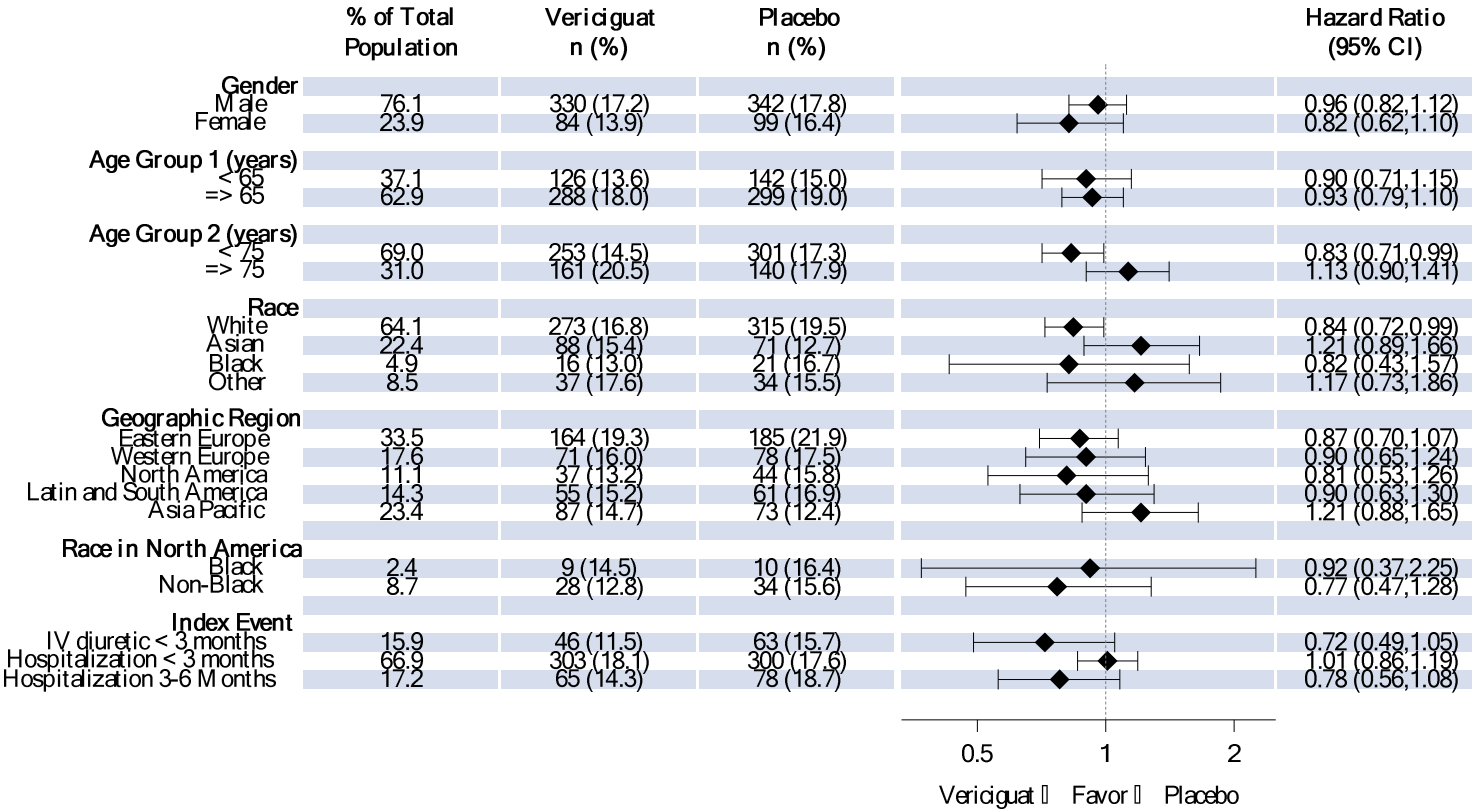
Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).
For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment at both baseline and the specific timepoint.
SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 45

表 2.7.3.7-23 各評価時点の KCCQ Overall Summary Score（NYHA 分類クラスⅢ／Ⅳ）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

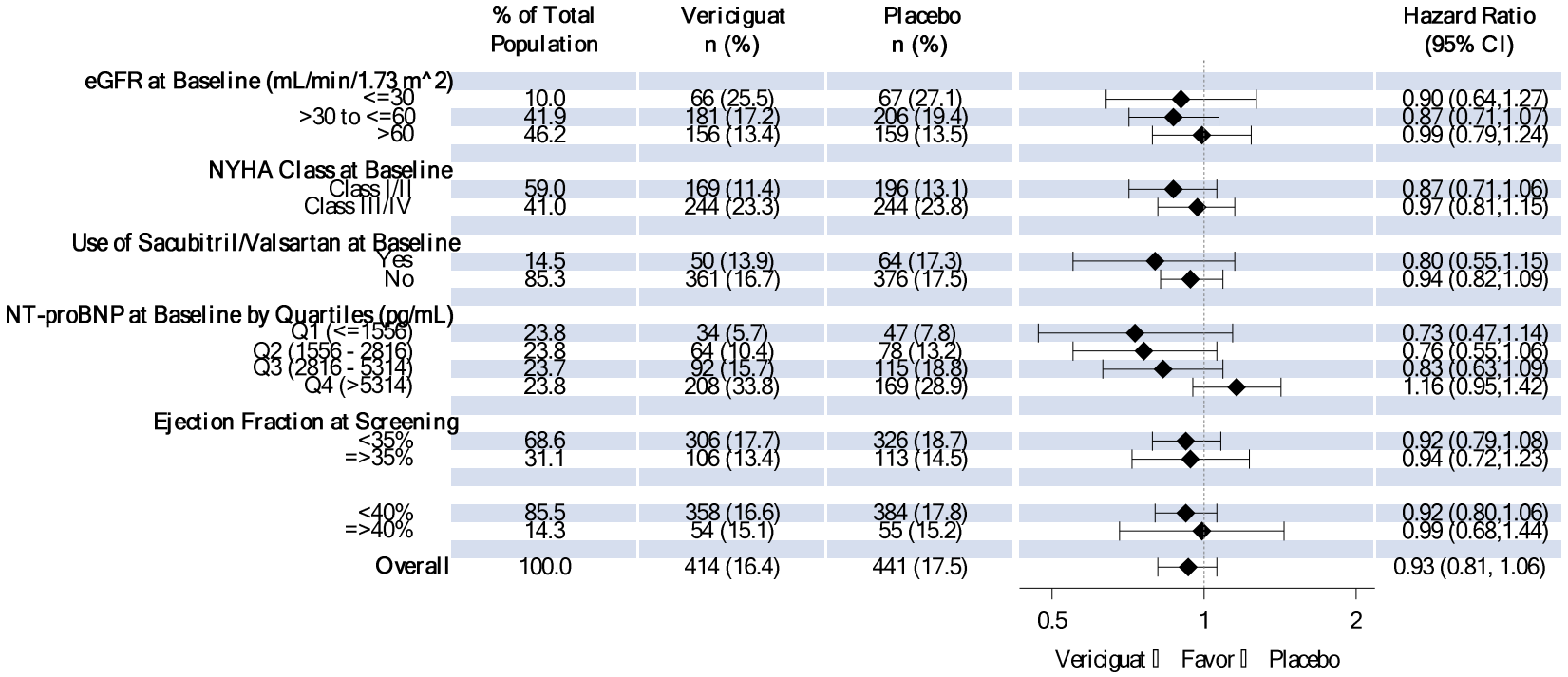
		Baseline			Value			Change from Baseline		
Visit	Treatment	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	913	49.2 (21.7)	48.7 [32.8, 64.8]						
	Placebo	881	49.2 (21.8)	48.2 [32.8, 65.4]						
Day 28	Vericiguat	813	49.5 (21.5)	49.2 [33.0, 65.1]	874	57.0 (24.0)	58.9 [41.1, 75.0]	813	7.4 (20.5)	6.8 [-3.6, 18.2]
	Placebo	778	49.9 (21.6)	48.4 [33.5, 65.9]	866	56.5 (24.4)	58.1 [39.6, 76.0]	778	6.7 (20.2)	5.5 [-4.6, 18.0]
Week 16	Vericiguat	781	49.1 (21.5)	48.4 [32.8, 63.5]	853	55.0 (28.7)	59.1 [39.1, 77.6]	781	5.8 (27.0)	7.0 [-8.3, 21.4]
	Placebo	757	50.0 (21.7)	49.0 [33.6, 65.6]	852	53.9 (29.4)	58.9 [34.2, 78.2]	757	3.5 (26.7)	4.7 [-10.2, 19.8]
Week 32	Vericiguat	699	49.0 (21.5)	48.4 [33.0, 63.5]	772	51.3 (32.5)	57.8 [25.9, 78.2]	699	2.3 (30.0)	5.2 [-14.1, 19.8]
	Placebo	672	49.4 (21.9)	48.4 [32.6, 65.9]	757	48.3 (33.1)	53.9 [16.4, 75.5]	672	-1.7 (31.3)	2.2 [-20.3, 19.3]
Week 48	Vericiguat	563	48.6 (21.6)	47.9 [32.8, 63.0]	621	46.6 (34.5)	53.6 [0.0, 76.6]	563	-1.8 (33.1)	2.1 [-24.5, 20.8]
	Placebo	549	48.9 (21.6)	47.7 [32.6, 64.8]	615	45.2 (34.6)	48.4 [0.0, 75.0]	549	-3.9 (34.2)	1.0 [-25.7, 21.4]
Week 96	Vericiguat	283	47.4 (21.4)	46.1 [32.8, 61.2]	315	31.3 (36.1)	0.0 [0.0, 68.0]	283	-14.7 (36.5)	-16.1 [-43.5, 15.1]
	Placebo	271	46.4 (21.0)	45.8 [30.7, 62.8]	308	26.0 (33.5)	0.0 [0.0, 57.4]	271	-21.2 (35.1)	-25.3 [-47.4, 5.7]
Week 144	Vericiguat	38	47.2 (24.0)	44.9 [25.0, 62.0]	46	0.0 (0.0)	0.0 [0.0, 0.0]	38	-47.2 (24.0)	-44.9 [-62.0, -25.0]
	Placebo	57	45.0 (22.5)	41.4 [29.7, 57.1]	62	0.0 (0.0)	0.0 [0.0, 0.0]	57	-45.0 (22.5)	-41.4 [-57.1, -29.7]

Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).
For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment at both baseline and the specific timepoint.
SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 46

図 2.7.3.7-1　副次評価項目（CV 死までの期間）における部分集団解析のフォレストプロット（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



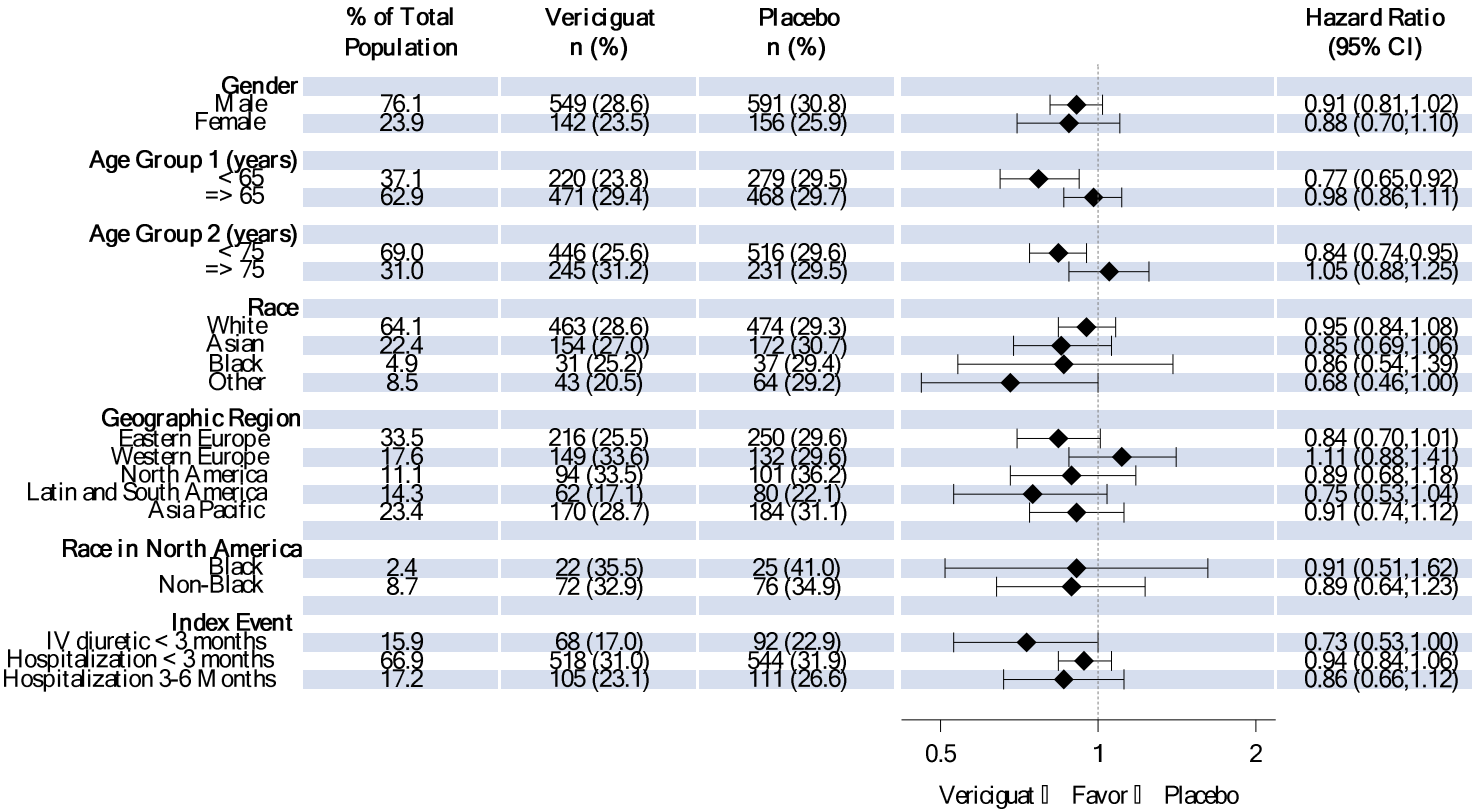
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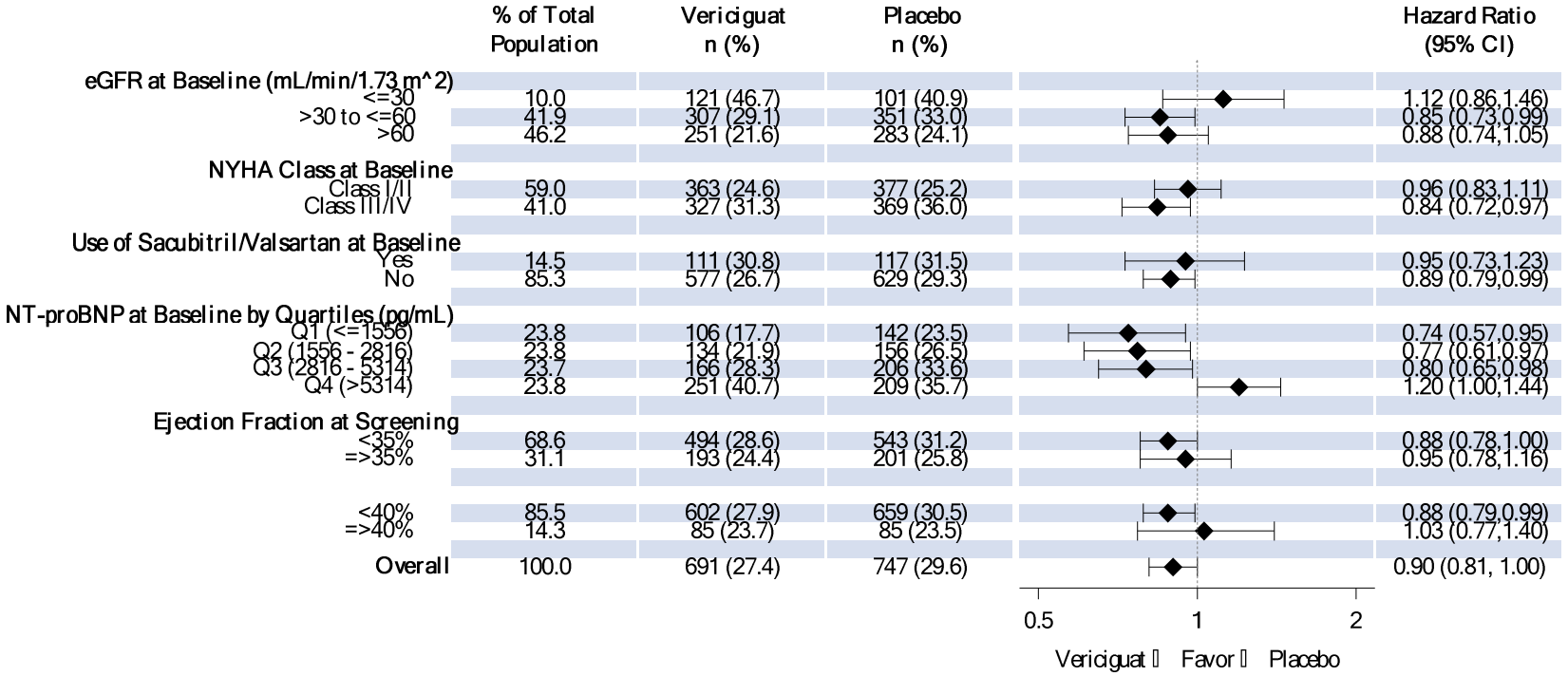
Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 2

図 2.7.3.7-2　副次評価項目（心不全による入院の初回発現までの期間）における部分集団解析のフォレストプロット（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



(Continued)



Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 3

表 2.7.3.7-24　副次評価項目（CV 死までの期間）における部分集団解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
Gender								
Male	330/1921 (17.2)	13.5	22.6 (20.3, 25.1)	342/1921 (17.8)	14.1	24.1 (21.6, 26.7)	0.96 (0.82,1.12)	0.360
Female	84/605 (13.9)	11.0	20.4 (16.3, 25.4)	99/603 (16.4)	13.4	22.4 (18.3, 27.4)	0.82 (0.62,1.10)	
Age Group 1 (years)								
< 65	126/926 (13.6)	10.7	18.4 (15.3, 22.0)	142/947 (15.0)	11.8	19.9 (16.8, 23.4)	0.90 (0.71,1.15)	0.824
≥ 65	288/1600 (18.0)	14.2	24.0 (21.5, 26.9)	299/1577 (19.0)	15.2	26.0 (23.2, 29.1)	0.93 (0.79,1.10)	
Age Group 2 (years)								
< 75	253/1741 (14.5)	11.4	19.8 (17.4, 22.4)	301/1741 (17.3)	13.7	23.7 (21.1, 26.5)	0.83 (0.71,0.99)	0.036
≥ 75	161/785 (20.5)	16.2	26.9 (23.1, 31.1)	140/783 (17.9)	14.4	23.6 (19.9, 27.9)	1.13 (0.90,1.41)	
Race								
White	273/1621 (16.8)	12.5	21.7 (19.4, 24.4)	315/1618 (19.5)	14.9	24.9 (22.3, 27.7)	0.84 (0.72,0.99)	0.157
Asian	88/571 (15.4)	13.3	22.7 (18.1, 28.2)	71/561 (12.7)	10.8	19.7 (15.0, 25.5)	1.21 (0.89,1.66)	
Black	16/123 (13.0)	11.6	18.9 (10.1, 33.9)	21/126 (16.7)	14.4	26.2 (16.9, 39.2)	0.82 (0.43,1.57)	
Other	37/210 (17.6)	16.5	25.2 (18.1, 34.4)	34/219 (15.5)	13.8	22.6 (16.1, 31.0)	1.17 (0.73,1.86)	
Geographic Region								
Eastern Europe	164/848 (19.3)	14.8	24.3 (21.0, 28.1)	185/846 (21.9)	17.2	28.4 (24.7, 32.4)	0.87 (0.70,1.07)	0.470
Western Europe	71/443 (16.0)	11.5	20.7 (16.4, 25.9)	78/446 (17.5)	12.8	20.8 (16.7, 25.8)	0.90 (0.65,1.24)	
North America	37/281 (13.2)	9.7	18.8 (13.3, 26.1)	44/279 (15.8)	12.0	21.5 (15.7, 29.0)	0.81 (0.53,1.26)	
Latin and South America	55/362 (15.2)	13.6	22.1 (17.0, 28.6)	61/362 (16.9)	15.1	24.3 (18.8, 31.2)	0.90 (0.63,1.30)	
Asia Pacific	87/592 (14.7)	12.4	21.0 (16.7, 26.1)	73/591 (12.4)	10.3	19.3 (14.9, 24.8)	1.21 (0.88,1.65)	
Race in North America								
Black	9/62 (14.5)	11.0	20.2 (9.5, 40.0)	10/61 (16.4)	12.2	20.5 (10.8, 37.0)	0.92 (0.37,2.25)	0.751
Non-Black	28/219 (12.8)	9.4	18.3 (12.4, 26.4)	34/218 (15.6)	12.0	22.0 (15.3, 31.0)	0.77 (0.47,1.28)	
Index Event								
IV diuretic < 3 months	46/399 (11.5)	8.7	16.5 (12.3, 22.1)	63/402 (15.7)	12.0	21.0 (16.2, 27.0)	0.72 (0.49,1.05)	0.134
Hospitalization < 3 months	303/1673 (18.1)	14.6	24.3 (21.7, 27.2)	300/1705 (17.6)	14.4	23.6 (21.0, 26.4)	1.01 (0.86,1.19)	
Hospitalization 3-6 Months	65/454 (14.3)	10.8	18.8 (14.6, 23.9)	78/417 (18.7)	14.1	26.3 (21.1, 32.5)	0.78 (0.56,1.08)	

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
eGFR at Baseline (mL/min/1.73 m²)								
≤30	66/259 (25.5)	21.1	37.1 (29.3, 46.2)	67/247 (27.1)	23.7	36.2 (28.8, 44.9)	0.90 (0.64,1.27)	0.695
>30 to ≤60	181/1054 (17.2)	13.3	23.2 (20.1, 26.6)	206/1064 (19.4)	15.2	25.7 (22.4, 29.4)	0.87 (0.71,1.07)	
>60	156/1161 (13.4)	10.6	17.0 (14.5, 20.0)	159/1174 (13.5)	10.7	18.8 (16.0, 22.0)	0.99 (0.79,1.24)	
NHYA Class at Baseline								
Class I/II	169/1478 (11.4)	8.8	16.1 (13.8, 18.8)	196/1499 (13.1)	10.2	18.9 (16.3, 21.8)	0.87 (0.71,1.06)	0.433
Class III/IV	244/1045 (23.3)	19.1	30.1 (26.7, 33.9)	244/1024 (23.8)	19.7	30.4 (26.9, 34.2)	0.97 (0.81,1.15)	
Use of Sacubitril/Valsartan at Baseline								
Yes	50/360 (13.9)	12.0	23.2 (16.8, 31.5)	64/371 (17.3)	15.3	26.6 (20.4, 34.4)	0.80 (0.55,1.15)	0.403
No	361/2161 (16.7)	13.0	21.8 (19.7, 24.2)	376/2148 (17.5)	13.7	23.3 (21.0, 25.7)	0.94 (0.82,1.09)	
NT-proBNP at Baseline by Quartiles (pg/mL)								
Q1 (≤1556)	34/599 (5.7)	4.1	8.9 (6.1, 12.7)	47/604 (7.8)	5.6	10.3 (7.5, 14.1)	0.73 (0.47,1.14)	0.052
Q2 (1556 - 2816)	64/613 (10.4)	7.6	14.5 (11.2, 18.6)	78/589 (13.2)	10.1	18.8 (14.9, 23.6)	0.76 (0.55,1.06)	
Q3 (2816 - 5314)	92/586 (15.7)	12.5	21.3 (17.3, 26.1)	115/613 (18.8)	15.3	26.0 (21.7, 30.9)	0.83 (0.63,1.09)	
Q4 (>5314)	208/616 (33.8)	32.0	44.5 (39.5, 49.9)	169/585 (28.9)	27.1	38.7 (33.3, 44.6)	1.16 (0.95,1.42)	
Ejection Fraction at Screening								
<35%	306/1725 (17.7)	14.1	23.3 (20.8, 26.0)	326/1741 (18.7)	15.3	24.8 (22.3, 27.6)	0.92 (0.79,1.08)	0.909
≥35%	106/791 (13.4)	10.4	19.3 (15.8, 23.4)	113/779 (14.5)	11.0	20.8 (17.2, 25.1)	0.94 (0.72,1.23)	
Ejection Fraction at Screening								
<40%	358/2158 (16.6)	13.1	22.1 (19.9, 24.5)	384/2158 (17.8)	14.3	24.1 (21.8, 26.6)	0.92 (0.80,1.06)	0.718
≥40%	54/358 (15.1)	11.7	21.7 (16.3, 28.6)	55/362 (15.2)	11.8	20.7 (15.8, 26.9)	0.99 (0.68,1.44)	

† Total subjects with an event / time at risk in years.

‡ Kaplan-Meier estimate and confidence interval at 2 years.

§ Hazard ratio (Vericiguat over Placebo), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.5 PH-41322/Table 14.2-32

表 2.7.3.7-25　副次評価項目（心不全による入院の初回発現までの期間）における部分集団解析（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
Gender								
Male	549/1921 (28.6)	27.2	36.2 (33.5, 39.0)	591/1921 (30.8)	30.2	39.0 (36.2, 42.0)	0.91 (0.81,1.02)	0.793
Female	142/605 (23.5)	21.9	31.7 (26.9, 37.0)	156/603 (25.9)	25.4	32.3 (27.7, 37.4)	0.88 (0.70,1.10)	
Age Group 1 (years)								
< 65	220/926 (23.8)	22.2	29.9 (26.3, 33.8)	279/947 (29.5)	29.2	36.6 (32.8, 40.7)	0.77 (0.65,0.92)	0.036
≥ 65	471/1600 (29.4)	28.1	37.9 (34.9, 41.1)	468/1577 (29.7)	29.0	37.9 (34.8, 41.3)	0.98 (0.86,1.11)	
Age Group 2 (years)								
< 75	446/1741 (25.6)	24.1	32.6 (29.9, 35.5)	516/1741 (29.6)	29.0	37.6 (34.7, 40.7)	0.84 (0.74,0.95)	0.045
≥ 75	245/785 (31.2)	30.1	40.4 (36.1, 45.1)	231/783 (29.5)	29.3	37.1 (32.8, 41.8)	1.05 (0.88,1.25)	
Race								
White	463/1621 (28.6)	25.5	35.8 (33.0, 38.8)	474/1618 (29.3)	27.2	36.2 (33.3, 39.2)	0.95 (0.84,1.08)	0.388
Asian	154/571 (27.0)	27.8	35.9 (30.6, 42.0)	172/561 (30.7)	32.8	40.5 (34.8, 46.7)	0.85 (0.69,1.06)	
Black	31/123 (25.2)	28.7	31.1 (22.4, 42.1)	37/126 (29.4)	32.5	42.0 (29.2, 57.7)	0.86 (0.54,1.39)	
Other	43/210 (20.5)	22.6	23.9 (18.0, 31.3)	64/219 (29.2)	33.6	38.1 (30.1, 47.4)	0.68 (0.46,1.00)	
Geographic Region								
Eastern Europe	216/848 (25.5)	23.4	32.7 (28.9, 36.9)	250/846 (29.6)	28.3	37.0 (33.0, 41.3)	0.84 (0.70,1.01)	0.282
Western Europe	149/443 (33.6)	29.5	40.4 (35.1, 46.2)	132/446 (29.6)	26.6	35.7 (30.6, 41.4)	1.11 (0.88,1.41)	
North America	94/281 (33.5)	31.1	40.4 (33.7, 47.8)	101/279 (36.2)	35.4	45.2 (37.9, 53.3)	0.89 (0.68,1.18)	
Latin and South America	62/362 (17.1)	17.3	22.5 (17.5, 28.5)	80/362 (22.1)	23.5	28.5 (22.9, 35.0)	0.75 (0.53,1.04)	
Asia Pacific	170/592 (28.7)	29.3	37.3 (32.1, 43.1)	184/591 (31.1)	32.5	40.0 (34.6, 45.9)	0.91 (0.74,1.12)	
Race in North America								
Black	22/62 (35.5)	38.8	38.8 (27.3, 53.0)	25/61 (41.0)	43.0	53.6 (37.2, 71.9)	0.91 (0.51,1.62)	0.936
Non-Black	72/219 (32.9)	29.3	40.4 (32.8, 48.9)	76/218 (34.9)	33.5	42.5 (34.8, 51.3)	0.89 (0.64,1.23)	
Index Event								
IV diuretic < 3 months	68/399 (17.0)	14.5	22.7 (17.8, 28.7)	92/402 (22.9)	20.2	31.1 (25.2, 37.9)	0.73 (0.53,1.00)	0.290
Hospitalization < 3 months	518/1673 (31.0)	30.8	39.6 (36.6, 42.7)	544/1705 (31.9)	33.0	39.8 (36.8, 42.9)	0.94 (0.84,1.06)	
Hospitalization 3-6 Months	105/454 (23.1)	20.2	29.8 (24.8, 35.5)	111/417 (26.6)	23.8	34.2 (28.6, 40.5)	0.86 (0.66,1.12)	

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
eGFR at Baseline (mL/min/1.73 m²)								
≤30	121/259 (46.7)	55.1	60.6 (51.9, 69.6)	101/247 (40.9)	48.7	51.4 (43.2, 60.1)	1.12 (0.86,1.46)	0.199
>30 to ≤60	307/1054 (29.1)	27.5	36.7 (33.1, 40.5)	351/1064 (33.0)	32.8	41.7 (37.9, 45.8)	0.85 (0.73,0.99)	
>60	251/1161 (21.6)	19.6	27.9 (24.7, 31.4)	283/1174 (24.1)	22.5	30.6 (27.3, 34.1)	0.88 (0.74,1.05)	
NHYA Class at Baseline								
Class I/II	363/1478 (24.6)	22.2	31.6 (28.6, 34.8)	377/1499 (25.2)	23.3	32.0 (29.0, 35.3)	0.96 (0.83,1.11)	0.204
Class III/IV	327/1045 (31.3)	31.7	40.2 (36.4, 44.1)	369/1024 (36.0)	38.8	45.4 (41.4, 49.6)	0.84 (0.72,0.97)	
Use of Sacubitril/Valsartan at Baseline								
Yes	111/360 (30.8)	32.9	42.4 (35.2, 50.5)	117/371 (31.5)	35.0	42.3 (35.2, 50.3)	0.95 (0.73,1.23)	0.642
No	577/2161 (26.7)	24.8	33.8 (31.3, 36.4)	629/2148 (29.3)	28.2	36.7 (34.1, 39.5)	0.89 (0.79,0.99)	
NT-proBNP at Baseline by Quartiles (pg/mL)								
Q1 (≤1556)	106/599 (17.7)	14.3	24.0 (19.9, 28.8)	142/604 (23.5)	19.6	31.3 (26.7, 36.5)	0.74 (0.57,0.95)	0.002
Q2 (1556 - 2816)	134/613 (21.9)	18.4	27.6 (23.5, 32.3)	156/589 (26.5)	24.4	33.5 (28.9, 38.7)	0.77 (0.61,0.97)	
Q3 (2816 - 5314)	166/586 (28.3)	27.7	35.1 (30.4, 40.2)	206/613 (33.6)	35.0	42.1 (37.0, 47.5)	0.80 (0.65,0.98)	
Q4 (>5314)	251/616 (40.7)	52.0	54.5 (48.8, 60.4)	209/585 (35.7)	44.0	45.3 (39.7, 51.4)	1.20 (1.00,1.44)	
Ejection Fraction at Screening								
<35%	494/1725 (28.6)	27.5	36.3 (33.4, 39.4)	543/1741 (31.2)	31.8	38.6 (35.7, 41.7)	0.88 (0.78,1.00)	0.503
≥35%	193/791 (24.4)	22.5	32.0 (28.1, 36.4)	201/779 (25.8)	23.4	34.3 (30.0, 39.0)	0.95 (0.78,1.16)	
Ejection Fraction at Screening								
<40%	602/2158 (27.9)	26.5	35.3 (32.8, 38.0)	659/2158 (30.5)	30.4	38.1 (35.4, 40.8)	0.88 (0.79,0.99)	0.339
≥40%	85/358 (23.7)	22.1	33.0 (26.8, 40.2)	85/362 (23.5)	21.2	32.8 (26.4, 40.2)	1.03 (0.77,1.40)	

† Total subjects with an event / time at risk in years.

‡ Kaplan-Meier estimate and confidence interval at 2 years.

§ Hazard ratio (Vericiguat over Placebo), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.5 PH-41322/Table 14.2-35

表 2.7.3.7-26 主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）における部分集団解析（標準治療薬 3 剤の使用、医療機器の使用、インデックスイベントから無作為割付けまでの期間、体重）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
Triple-Therapy (MRA + Beta Blocker + Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)) at Baseline								
Yes	466/1480 (31.5)	28.9	39.7 (36.5, 43.0)	545/1529 (35.6)	34.4	43.2 (40.1, 46.4)	0.85 (0.75,0.96)	0.264
No	428/1041 (41.1)	40.7	49.5 (45.8, 53.3)	426/990 (43.0)	43.4	52.5 (48.5, 56.6)	0.94 (0.82,1.08)	
Implantable Cardioverter Defibrillator Use at Baseline								
Yes	284/696 (40.8)	38.7	47.4 (43.1, 51.9)	328/703 (46.7)	47.0	54.1 (49.6, 58.7)	0.85 (0.72,0.99)	0.389
No	610/1825 (33.4)	31.6	42.4 (39.5, 45.4)	643/1816 (35.4)	34.5	44.0 (41.1, 47.1)	0.92 (0.82,1.03)	
Biventricular Pacemaker Use at Baseline								
Yes	139/370 (37.6)	35.7	44.5 (38.7, 50.9)	169/369 (45.8)	46.8	55.8 (49.5, 62.3)	0.80 (0.64,1.00)	0.268
No	755/2151 (35.1)	33.2	43.7 (41.0, 46.4)	802/2150 (37.3)	36.4	45.3 (42.7, 48.1)	0.92 (0.83,1.01)	
Time from the Most Recent HF Decompensation Event to Randomization								
HF Hospitalization within 1 Month	395/956 (41.3)	42.6	51.1 (47.0, 55.4)	407/998 (40.8)	42.4	48.6 (44.7, 52.6)	1.01 (0.88,1.16)	0.230
HF Hospitalization 1-2 Months	170/445 (38.2)	37.1	46.6 (41.0, 52.7)	194/433 (44.8)	48.1	51.8 (46.0, 58.0)	0.79 (0.64,0.97)	
HF Hospitalization 2-3 Months	95/272 (34.9)	32.3	42.8 (36.0, 50.4)	100/274 (36.5)	34.7	45.7 (38.4, 53.6)	0.94 (0.71,1.24)	
HF Hospitalization 3-6 Months	141/454 (31.1)	27.1	38.4 (33.0, 44.3)	151/417 (36.2)	32.4	46.3 (40.3, 52.7)	0.85 (0.67,1.07)	
IV diuretic for HF (without hospitalization) within 3 Months	96/399 (24.1)	20.5	30.9 (25.5, 37.1)	120/402 (29.9)	26.4	38.7 (32.6, 45.5)	0.78 (0.60,1.02)	
Body Weight (kg)								
< 60	140/410 (34.1)	33.6	44.8 (38.4, 51.8)	139/390 (35.6)	36.3	44.2 (38.1, 50.8)	0.94 (0.74,1.19)	0.877
≥ 60 to ≤ 90	539/1517 (35.5)	33.5	43.7 (40.6, 46.9)	561/1486 (37.8)	37.7	46.8 (43.4, 50.3)	0.90 (0.80,1.02)	
> 90	213/589 (36.2)	33.5	43.5 (38.7, 48.7)	263/630 (41.7)	38.5	48.2 (43.7, 53.0)	0.87 (0.73,1.04)	

† Total subjects with an event / time at risk in years.

‡ Kaplan-Meier estimate and confidence interval at 2 years.

§ Hazard ratio (Vericiguat over Placebo), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 40, Section 2_14.2.2 update

表 2.7.3.7-27　副次評価項目（CV 死までの期間）における部分集団解析（標準治療薬 3 剤の使用、医療機器の使用、インデックスイベントから無作為割付けまでの期間、体重）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
Triple-Therapy (MRA + Beta Blocker + Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)) at Baseline								
Yes	197/1480 (13.3)	10.3	17.9 (15.4, 20.7)	240/1529 (15.7)	12.5	21.6 (18.9, 24.5)	0.82 (0.68,0.99)	0.092
No	214/1041 (20.6)	16.5	27.3 (24.1, 31.0)	200/990 (20.2)	16.1	26.8 (23.3, 30.6)	1.03 (0.85,1.25)	
Implantable Cardioverter Defibrillator Use at Baseline								
Yes	116/696 (16.7)	12.3	21.7 (18.2, 25.9)	163/703 (23.2)	17.8	29.0 (25.0, 33.5)	0.69 (0.55,0.88)	0.004
No	295/1825 (16.2)	13.1	21.8 (19.4, 24.5)	277/1816 (15.3)	12.4	21.3 (18.9, 24.0)	1.06 (0.90,1.24)	
Biventricular Pacemaker Use at Baseline								
Yes	63/370 (17.0)	13.1	23.3 (18.1, 29.7)	92/369 (24.9)	20.3	31.6 (26.1, 38.0)	0.66 (0.48,0.91)	0.023
No	348/2151 (16.2)	12.8	21.6 (19.4, 23.9)	348/2150 (16.2)	12.9	22.3 (20.0, 24.8)	0.99 (0.85,1.15)	
Time from the Most Recent HF Decompensation Event to Randomization								
HF Hospitalization within 1 Month	172/956 (18.0)	14.7	24.4 (21.0, 28.2)	174/998 (17.4)	14.4	23.0 (19.7, 26.7)	1.02 (0.83,1.26)	0.404
HF Hospitalization 1-2 Months	85/445 (19.1)	15.4	23.7 (19.2, 29.1)	80/433 (18.5)	15.1	24.4 (19.4, 30.5)	1.01 (0.74,1.37)	
HF Hospitalization 2-3 Months	46/272 (16.9)	13.0	25.1 (18.7, 33.1)	46/274 (16.8)	13.3	24.5 (18.4, 32.1)	0.99 (0.66,1.49)	
HF Hospitalization 3-6 Months	65/454 (14.3)	10.8	18.8 (14.6, 23.9)	78/417 (18.7)	14.1	26.3 (21.1, 32.5)	0.78 (0.56,1.08)	
IV diuretic for HF (without hospitalization) within 3 Months	46/399 (11.5)	8.7	16.5 (12.3, 22.1)	63/402 (15.7)	12.0	21.0 (16.2, 27.0)	0.72 (0.49,1.05)	
Body Weight (kg)								
< 60	74/410 (18.0)	15.2	27.0 (21.3, 33.9)	64/390 (16.4)	13.7	22.1 (17.1, 28.2)	1.08 (0.78,1.52)	0.226
≥ 60 to ≤ 90	248/1517 (16.3)	12.9	22.1 (19.5, 25.0)	280/1486 (18.8)	15.6	26.0 (23.1, 29.3)	0.83 (0.70,0.99)	
> 90	88/589 (14.9)	11.2	18.8 (15.2, 23.0)	93/630 (14.8)	10.6	19.3 (15.8, 23.6)	1.05 (0.78,1.41)	

† Total subjects with an event / time at risk in years.

‡ Kaplan-Meier estimate and confidence interval at 2 years.

§ Hazard ratio (Vericiguat over Placebo), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 41, Section 2_14.2.2 update

表 2.7.3.7-28　副次評価項目（心不全による入院の初回発現までの期間）における部分集団解析（標準治療薬 3 剤の使用、医療機器の使用、インデックスイベントから無作為割付けまでの期間、体重）（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% †	KM% (95% CI) ‡	n/m (%)	Annual% †	KM% (95% CI) ‡	HR (95% CI) §	p-Value §
Triple-Therapy (MRA + Beta Blocker + Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)) at Baseline								
Yes	366/1480 (24.7)	22.7	32.3 (29.2, 35.6)	421/1529 (27.5)	26.6	34.5 (31.5, 37.7)	0.87 (0.76,1.00)	0.568
No	322/1041 (30.9)	30.6	38.7 (35.1, 42.6)	325/990 (32.8)	33.2	42.1 (38.0, 46.4)	0.92 (0.79,1.08)	
Implantable Cardioverter Defibrillator Use at Baseline								
Yes	251/696 (36.1)	34.2	41.9 (37.8, 46.4)	261/703 (37.1)	37.4	45.2 (40.7, 50.0)	0.94 (0.79,1.12)	0.496
No	437/1825 (23.9)	22.6	32.2 (29.4, 35.2)	485/1816 (26.7)	26.0	34.3 (31.5, 37.4)	0.87 (0.77,1.00)	
Biventricular Pacemaker Use at Baseline								
Yes	116/370 (31.4)	29.8	36.9 (31.5, 43.0)	131/369 (35.5)	36.3	46.3 (39.8, 53.4)	0.86 (0.67,1.11)	0.726
No	572/2151 (26.6)	25.2	34.6 (32.0, 37.3)	615/2150 (28.6)	27.9	35.9 (33.3, 38.7)	0.91 (0.81,1.01)	
Time from the Most Recent HF Decompensation Event to Randomization								
HF Hospitalization within 1 Month	312/956 (32.6)	33.6	41.7 (37.7, 45.9)	323/998 (32.4)	33.7	41.0 (37.0, 45.2)	1.00 (0.86,1.17)	0.201
HF Hospitalization 1-2 Months	128/445 (28.8)	27.9	38.1 (32.4, 44.5)	148/433 (34.2)	36.9	41.2 (35.6, 47.3)	0.78 (0.62,0.99)	
HF Hospitalization 2-3 Months	78/272 (28.7)	26.5	34.6 (28.4, 41.8)	73/274 (26.6)	25.3	33.6 (27.1, 41.3)	1.05 (0.76,1.44)	
HF Hospitalization 3-6 Months	105/454 (23.1)	20.2	29.8 (24.8, 35.5)	111/417 (26.6)	23.8	34.2 (28.6, 40.5)	0.86 (0.66,1.12)	
IV diuretic for HF (without hospitalization) within 3 Months	68/399 (17.0)	14.5	22.7 (17.8, 28.7)	92/402 (22.9)	20.2	31.1 (25.2, 37.9)	0.73 (0.53,1.00)	
Body Weight (kg)								
< 60	97/410 (23.7)	23.3	32.1 (26.1, 39.1)	108/390 (27.7)	28.3	35.0 (29.3, 41.5)	0.84 (0.64,1.11)	0.694
≥ 60 to ≤ 90	414/1517 (27.3)	25.8	34.7 (31.7, 37.8)	415/1486 (27.9)	27.9	36.0 (32.7, 39.5)	0.94 (0.82,1.08)	
> 90	175/589 (29.7)	27.5	37.3 (32.5, 42.5)	217/630 (34.4)	31.7	41.4 (36.9, 46.3)	0.86 (0.71,1.05)	

† Total subjects with an event / time at risk in years.

‡ Kaplan-Meier estimate and confidence interval at 2 years.

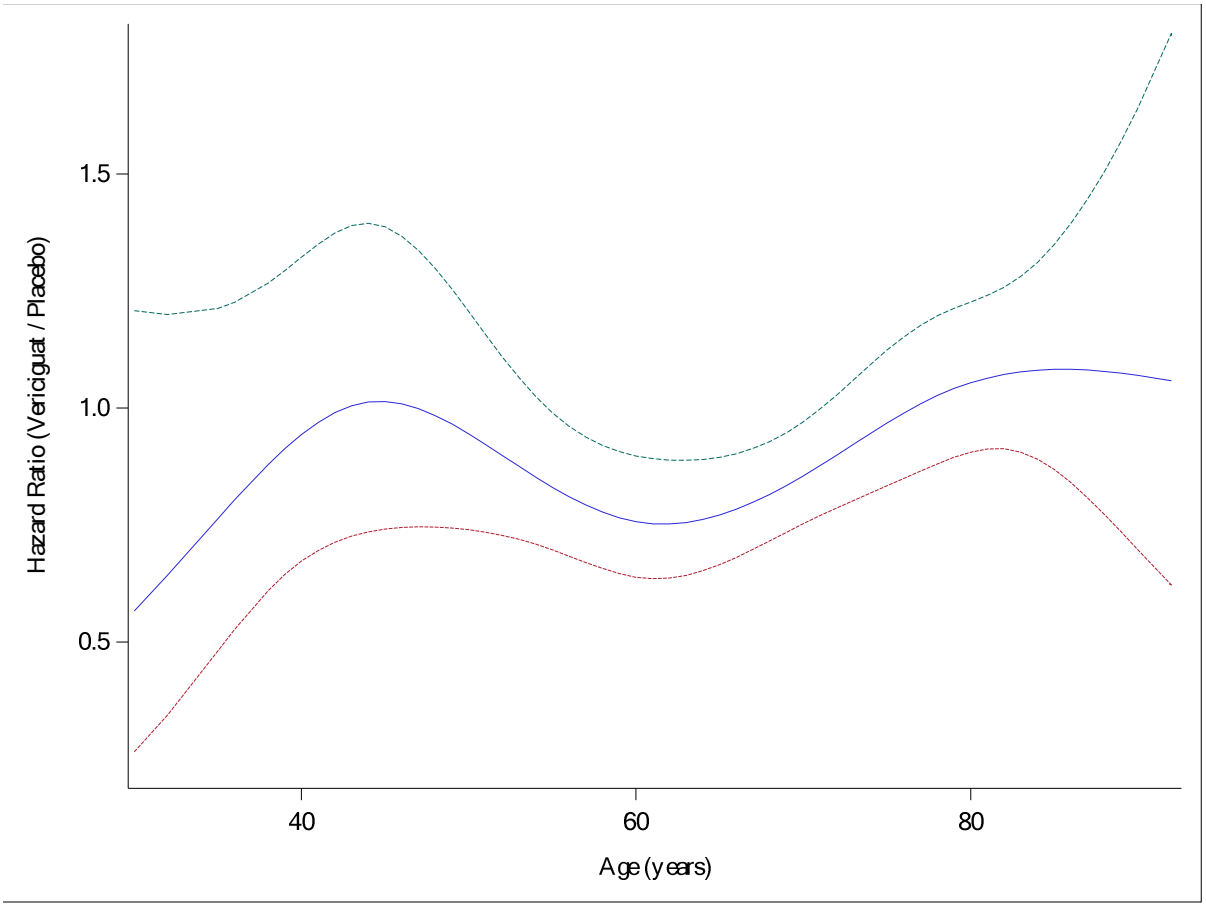
§ Hazard ratio (Vericiguat over Placebo), confidence interval, and p-Value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

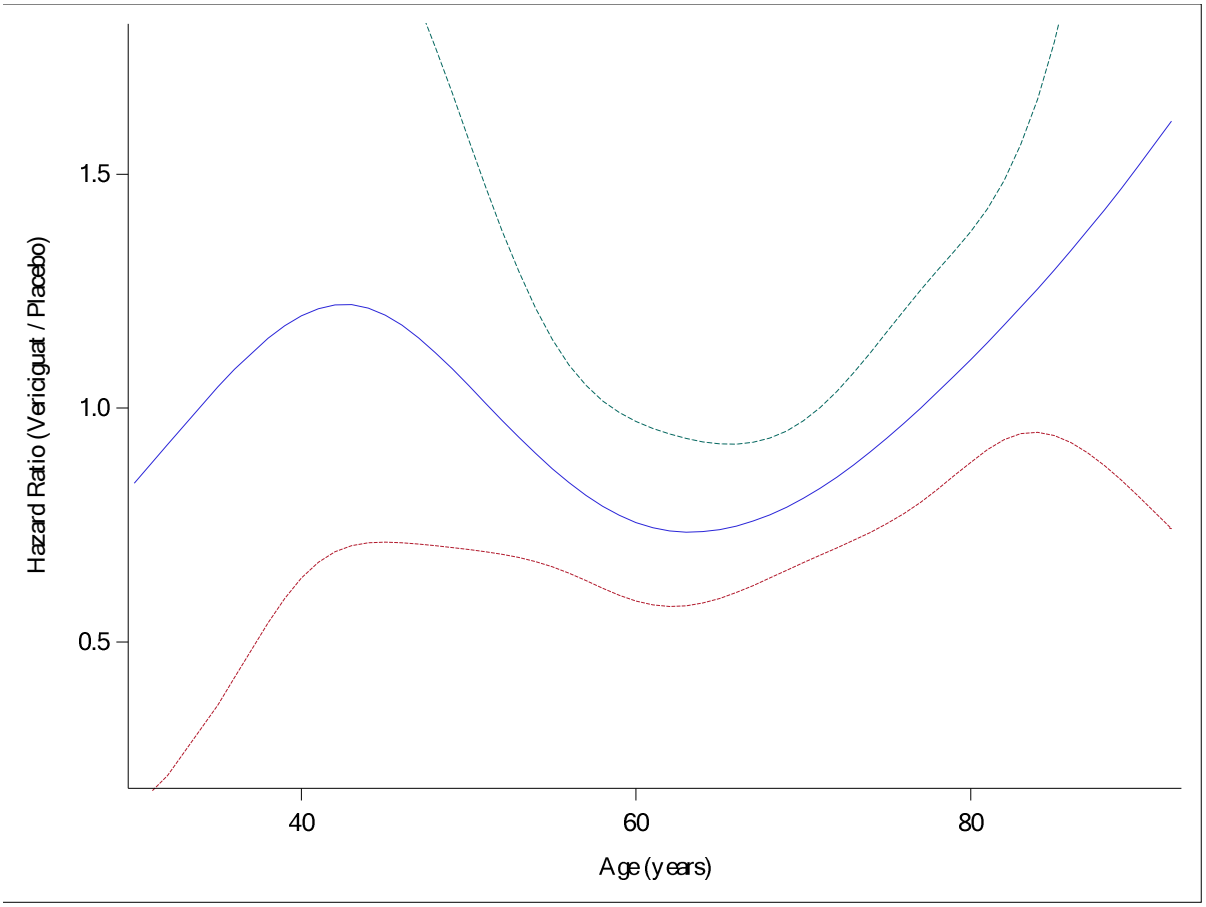
Source: 5.3.5.1.6 16493_Additional analysis/Table 42, Section 2_14.2.2 update

図 2.7.3.7-3　主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）におけるプラセボ群に対するハザード比と年齢との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



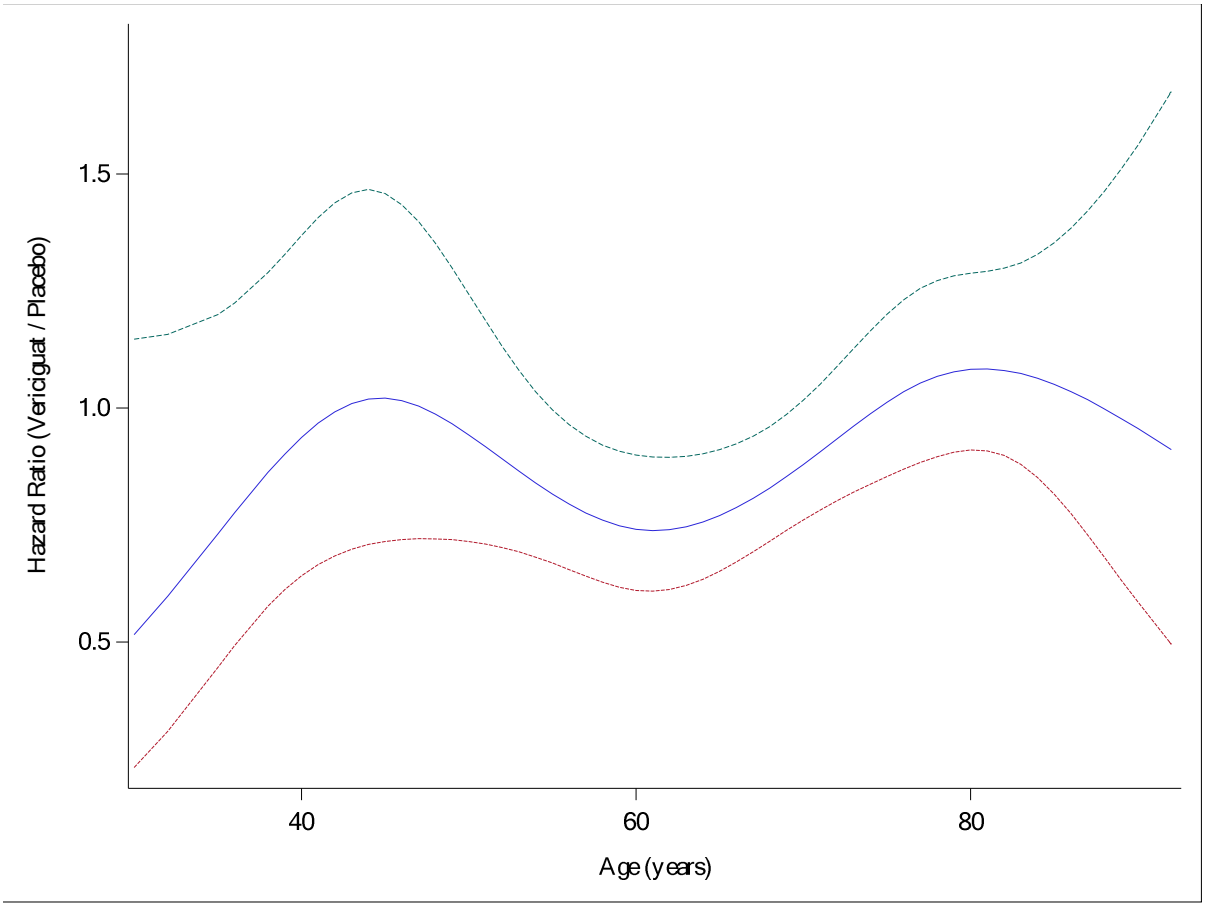
Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of age and their interactions with treatment.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Figure 4

図 2.7.3.7-4　副次評価項目（CV 死までの期間）におけるプラセボ群に対するハザード比と年齢との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



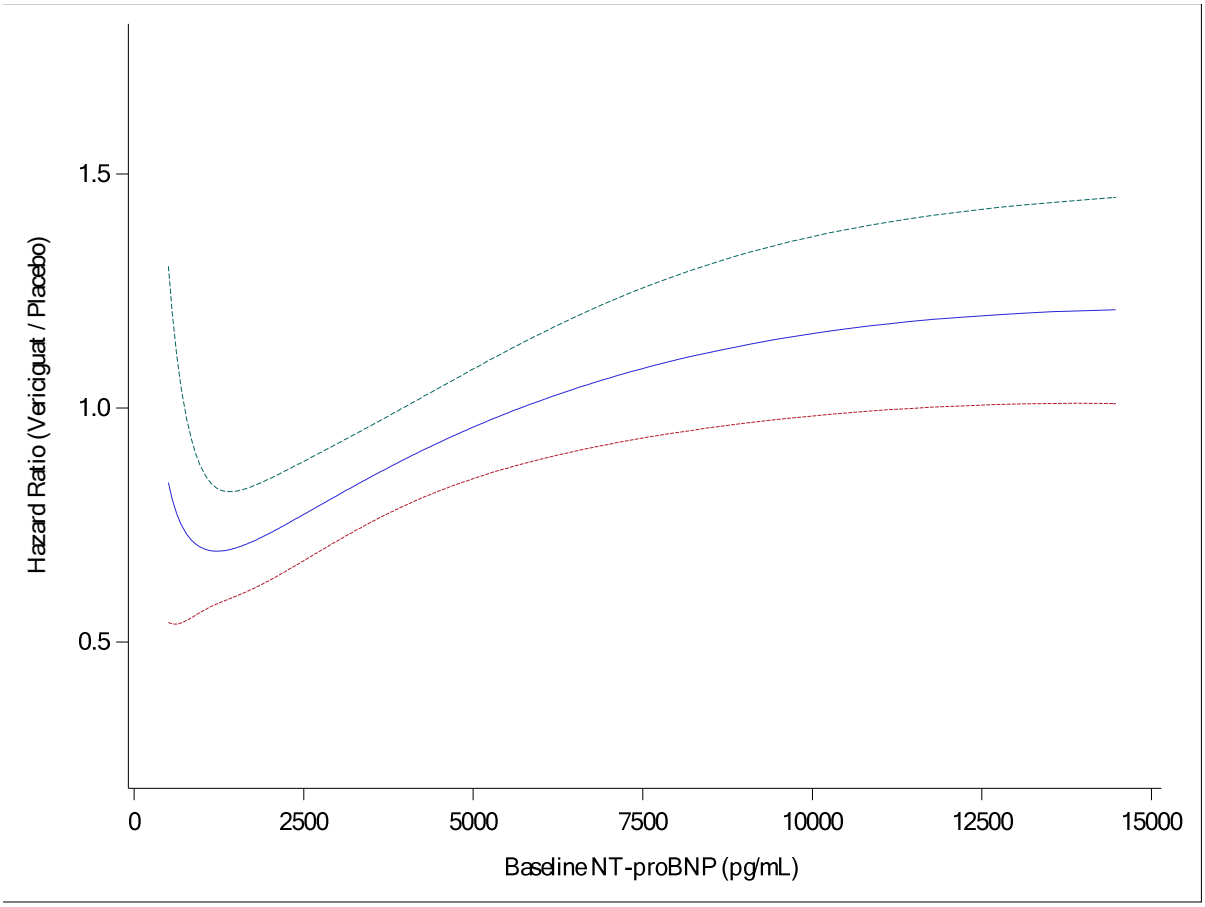
Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of age and their interactions with treatment.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Figure 6

図 2.7.3.7-5 副次評価項目（心不全による入院の初回発現までの期間）におけるプラセボ群に対するハザード比と年齢との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of age and their interactions with treatment.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Figure 8

図 2.7.3.7-6　主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）におけるプラセボ群に対するハザード比とベースラインの NT-proBNP 値との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

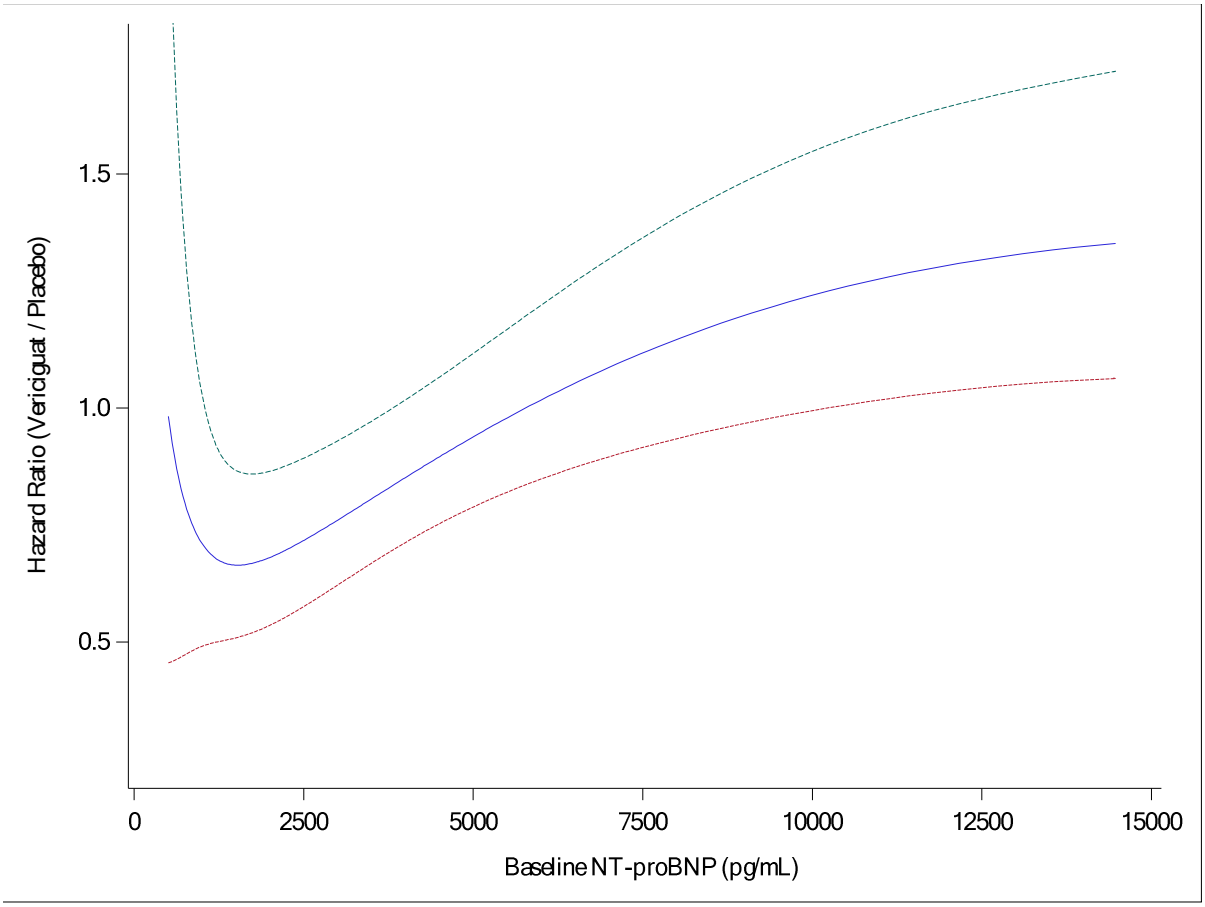


Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of baseline NT-proBNP and their interactions with treatment.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 5

図 2.7.3.7-7　副次評価項目（CV 死までの期間）におけるプラセボ群に対するハザード比とベースラインの NT-proBNP 値との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

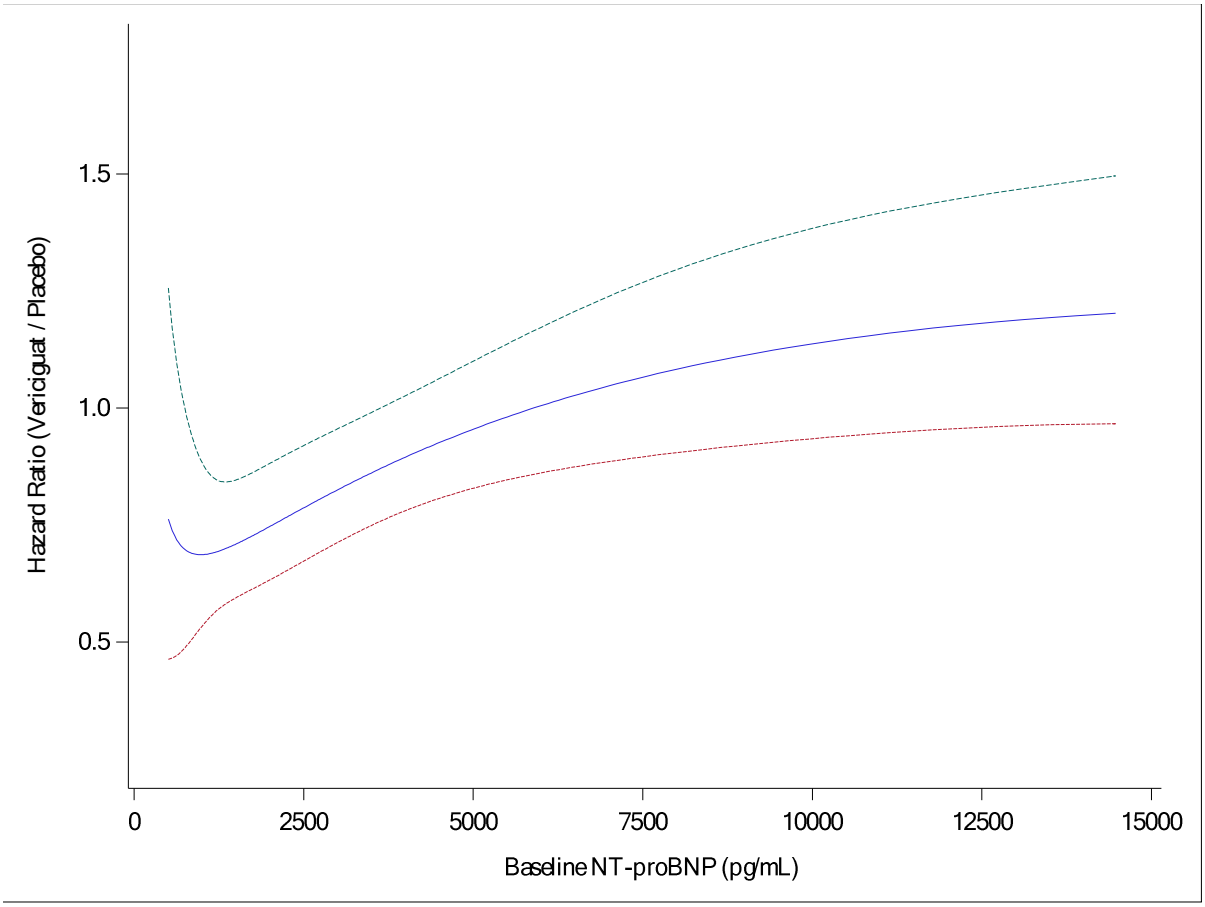


Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of baseline NT-proBNP and their interactions with treatment.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 7

図 2.7.3.7-8　副次評価項目（心不全による入院の初回発現までの期間）におけるプラセボ群に対するハザード比とベースラインの NT-proBNP 値との関連（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of baseline NT-proBNP and their interactions with treatment.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 9

表 2.7.3.7-29 ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の人口統計学的特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	599		604		1,203	
Gender						
Male	461	(77.0)	467	(77.3)	928	(77.1)
Female	138	(23.0)	137	(22.7)	275	(22.9)
Age (Years)						
≤50	73	(12.2)	80	(13.2)	153	(12.7)
51 to 60	126	(21.0)	125	(20.7)	251	(20.9)
61 to 70	197	(32.9)	194	(32.1)	391	(32.5)
71 to 80	149	(24.9)	153	(25.3)	302	(25.1)
≥81	54	(9.0)	52	(8.6)	106	(8.8)
Mean	64.9		64.7		64.8	
SD	12.3		12.1		12.2	
Median	66.0		66.0		66.0	
Range	24 to 92		24 to 94		24 to 94	
Race						
American Indian Or Alaska Native	6	(1.0)	6	(1.0)	12	(1.0)
Asian	147	(24.5)	137	(22.7)	284	(23.6)
Black	32	(5.3)	42	(7.0)	74	(6.2)
Multi-Racial	35	(5.8)	42	(7.0)	77	(6.4)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	2	(0.3)	3	(0.2)
Not Reported	1	(0.2)	0	(0.0)	1	(0.1)
White	377	(62.9)	375	(62.1)	752	(62.5)
Ethnicity						
Hispanic Or Latino	94	(15.7)	101	(16.7)	195	(16.2)
Not Hispanic Or Latino	489	(81.6)	490	(81.1)	979	(81.4)
Not Reported	8	(1.3)	4	(0.7)	12	(1.0)
Unknown	8	(1.3)	9	(1.5)	17	(1.4)
Geographic Region						
Eastern Europe	192	(32.1)	191	(31.6)	383	(31.8)
Western Europe	97	(16.2)	94	(15.6)	191	(15.9)
Asia Pacific	148	(24.7)	140	(23.2)	288	(23.9)
Latin and South America	78	(13.0)	90	(14.9)	168	(14.0)
North America	84	(14.0)	89	(14.7)	173	(14.4)
Race in North America						
Black	21	(3.5)	31	(5.1)	52	(4.3)
Non-Black	63	(10.5)	58	(9.6)	121	(10.1)
Outside North America	515	(86.0)	515	(85.3)	1,030	(85.6)

Source: 5.3.5.1.6 16493_Additional analysis/Table 1

表 2.7.3.7-30 ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の人口統計学的特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	613		589		1,202	
Gender						
Male	477	(77.8)	437	(74.2)	914	(76.0)
Female	136	(22.2)	152	(25.8)	288	(24.0)
Age (Years)						
≤50	56	(9.1)	66	(11.2)	122	(10.1)
51 to 60	111	(18.1)	99	(16.8)	210	(17.5)
61 to 70	193	(31.5)	175	(29.7)	368	(30.6)
71 to 80	178	(29.0)	197	(33.4)	375	(31.2)
≥81	75	(12.2)	52	(8.8)	127	(10.6)
Mean	67.0		66.2		66.6	
SD	11.9		12.0		11.9	
Median	68.0		68.0		68.0	
Range	24 to 93		27 to 92		24 to 93	
Race						
American Indian Or Alaska Native	3	(0.5)	7	(1.2)	10	(0.8)
Asian	127	(20.7)	142	(24.1)	269	(22.4)
Black	25	(4.1)	25	(4.2)	50	(4.2)
Multi-Racial	36	(5.9)	42	(7.1)	78	(6.5)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	2	(0.3)	3	(0.2)
White	421	(68.7)	371	(63.0)	792	(65.9)
Ethnicity						
Hispanic Or Latino	100	(16.3)	97	(16.5)	197	(16.4)
Not Hispanic Or Latino	493	(80.4)	485	(82.3)	978	(81.4)
Not Reported	15	(2.4)	4	(0.7)	19	(1.6)
Unknown	5	(0.8)	3	(0.5)	8	(0.7)
Geographic Region						
Eastern Europe	211	(34.4)	211	(35.8)	422	(35.1)
Western Europe	102	(16.6)	92	(15.6)	194	(16.1)
Asia Pacific	138	(22.5)	144	(24.4)	282	(23.5)
Latin and South America	88	(14.4)	86	(14.6)	174	(14.5)
North America	74	(12.1)	56	(9.5)	130	(10.8)
Race in North America						
Black	10	(1.6)	9	(1.5)	19	(1.6)
Non-Black	64	(10.4)	47	(8.0)	111	(9.2)
Outside North America	539	(87.9)	533	(90.5)	1,072	(89.2)

Source: 5.3.5.1.6 16493_Additional analysis/Table 2

表 2.7.3.7-31 ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の人口統計学的特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	586		613		1,199	
Gender						
Male	442	(75.4)	476	(77.7)	918	(76.6)
Female	144	(24.6)	137	(22.3)	281	(23.4)
Age (Years)						
≤50	48	(8.2)	41	(6.7)	89	(7.4)
51 to 60	98	(16.7)	96	(15.7)	194	(16.2)
61 to 70	164	(28.0)	177	(28.9)	341	(28.4)
71 to 80	185	(31.6)	205	(33.4)	390	(32.5)
≥81	91	(15.5)	94	(15.3)	185	(15.4)
Mean	68.1		68.9		68.5	
SD	12.1		11.8		12.0	
Median	70.0		70.0		70.0	
Range	25 to 94		23 to 97		23 to 97	
Race						
American Indian Or Alaska Native	7	(1.2)	7	(1.1)	14	(1.2)
Asian	159	(27.1)	139	(22.7)	298	(24.9)
Black	26	(4.4)	22	(3.6)	48	(4.0)
Multi-Racial	52	(8.9)	52	(8.5)	104	(8.7)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	4	(0.7)	5	(0.4)
White	341	(58.2)	389	(63.5)	730	(60.9)
Ethnicity						
Hispanic Or Latino	94	(16.0)	102	(16.6)	196	(16.3)
Not Hispanic Or Latino	478	(81.6)	497	(81.1)	975	(81.3)
Not Reported	5	(0.9)	9	(1.5)	14	(1.2)
Unknown	9	(1.5)	5	(0.8)	14	(1.2)
Geographic Region						
Eastern Europe	185	(31.6)	202	(33.0)	387	(32.3)
Western Europe	97	(16.6)	99	(16.2)	196	(16.3)
Asia Pacific	161	(27.5)	153	(25.0)	314	(26.2)
Latin and South America	86	(14.7)	97	(15.8)	183	(15.3)
North America	57	(9.7)	62	(10.1)	119	(9.9)
Race in North America						
Black	15	(2.6)	11	(1.8)	26	(2.2)
Non-Black	42	(7.2)	51	(8.3)	93	(7.8)
Outside North America	529	(90.3)	551	(89.9)	1,080	(90.1)

Source: 5.3.5.1.6 16493_Additional analysis/Table 3

表 2.7.3.7-32 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の人口統計学的特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	616		585		1,201	
Gender						
Male	458	(74.4)	428	(73.2)	886	(73.8)
Female	158	(25.6)	157	(26.8)	315	(26.2)
Age (Years)						
≤50	39	(6.3)	43	(7.4)	82	(6.8)
51 to 60	97	(15.7)	89	(15.2)	186	(15.5)
61 to 70	166	(26.9)	173	(29.6)	339	(28.2)
71 to 80	195	(31.7)	178	(30.4)	373	(31.1)
≥81	119	(19.3)	102	(17.4)	221	(18.4)
Mean	69.4		69.0		69.2	
SD	12.0		11.9		12.0	
Median	71.0		70.0		70.0	
Range	26 to 98		27 to 94		26 to 98	
Race						
American Indian Or Alaska Native	8	(1.3)	8	(1.4)	16	(1.3)
Asian	132	(21.4)	135	(23.1)	267	(22.2)
Black	31	(5.0)	29	(5.0)	60	(5.0)
Multi-Racial	55	(8.9)	42	(7.2)	97	(8.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	3	(0.5)	3	(0.2)
White	390	(63.3)	368	(62.9)	758	(63.1)
Ethnicity						
Hispanic Or Latino	111	(18.0)	90	(15.4)	201	(16.7)
Not Hispanic Or Latino	487	(79.1)	476	(81.4)	963	(80.2)
Not Reported	9	(1.5)	11	(1.9)	20	(1.7)
Unknown	9	(1.5)	8	(1.4)	17	(1.4)
Geographic Region						
Eastern Europe	217	(35.2)	193	(33.0)	410	(34.1)
Western Europe	116	(18.8)	111	(19.0)	227	(18.9)
Asia Pacific	135	(21.9)	142	(24.3)	277	(23.1)
Latin and South America	101	(16.4)	81	(13.8)	182	(15.2)
North America	47	(7.6)	58	(9.9)	105	(8.7)
Race in North America						
Black	10	(1.6)	7	(1.2)	17	(1.4)
Non-Black	37	(6.0)	51	(8.7)	88	(7.3)
Outside North America	569	(92.4)	527	(90.1)	1,096	(91.3)

Source: 5.3.5.1.6 16493_Additional analysis/Table 4

表 2.7.3.7-33 ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者のベースラインの疾患特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	599		604		1,203	
Height (cm)						
Subjects with data	598		599		1197	
Mean	168.5		168.8		168.6	
SD	9.6		9.6		9.6	
Median	169.0		169.0		169.0	
Range	138.0 to 202.0		136.0 to 195.6		136.0 to 202.0	
Weight (kg)						
Subjects with data	599		601		1200	
Mean	83.2		83.7		83.4	
SD	21.2		22.5		21.8	
Median	80.0		81.0		80.5	
Range	32.5 to 164.0		36.3 to 172.9		32.5 to 172.9	
Body Mass Index (kg/m^2)						
Subjects with data	598		598		1196	
Mean	29.1		29.2		29.1	
SD	6.1		6.6		6.3	
Median	28.1		28.2		28.1	
Range	14.2 to 54.2		15.8 to 63.0		14.2 to 63.0	
NT-proBNP at Randomization (pg/ml)						
Subjects with data	599		604		1203	
Mean	1001.5		971.0		986.2	
SD	376.2		383.7		380.1	
Median	1058.0		1023.0		1041.0	
Range	10.0 to 1554.0		70.0 to 1556.0		10.0 to 1556.0	
eGFR Category at Randomization ($mL/min/1.73\ m^2$)						
≤30	24	(4.0)	21	(3.5)	45	(3.7)
>30 to ≤60	221	(36.9)	193	(32.0)	414	(34.4)
>60	348	(58.1)	388	(64.2)	736	(61.2)
Missing	6	(1.0)	2	(0.3)	8	(0.7)
eGFR at Randomization ($mL/min/1.73\ m^2$)						
Subjects with data	593		602		1195	
Mean	68.6		72.0		70.3	
SD	27.2		27.9		27.6	
Median	65.3		69.2		67.6	
Range	18.6 to 202.4		11.1 to 226.8		11.1 to 226.8	
Index Event						
HF Hospitalization within 3 Months	379	(63.3)	374	(61.9)	753	(62.6)
HF Hospitalization 3-6 Months	95	(15.9)	99	(16.4)	194	(16.1)
IV diuretic for HF (without hospitalization) within 3 Months	125	(20.9)	131	(21.7)	256	(21.3)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Time of Primary Diagnosis of Heart Failure with Reduced Ejection Fraction to Randomization (Year)						
Subjects with data	599		604		1203	
Mean	4.5		4.8		4.7	
SD	5.2		5.0		5.1	
Median	2.7		3.0		2.9	
Range	0.0 to 42.8		0.0 to 29.7		0.0 to 42.8	
Time of Earliest Diagnosis of Heart Failure to Randomization (with or without Reduced Ejection Fraction) (Year)						
Subjects with data	599		604		1203	
Mean	5.0		5.2		5.1	
SD	5.6		5.2		5.4	
Median	3.3		3.3		3.3	
Range	0.0 to 43.2		0.0 to 29.7		0.0 to 43.2	
NYHA Class at Baseline						
NYHA Class I	0	(0.0)	1	(0.2)	1	(0.1)
NYHA Class II	417	(69.6)	412	(68.2)	829	(68.9)
NYHA Class III	178	(29.7)	185	(30.6)	363	(30.2)
NYHA Class IV	4	(0.7)	6	(1.0)	10	(0.8)
CCSA Class at Baseline						
No Angina	502	(83.8)	510	(84.4)	1,012	(84.1)
CCSA Class 1	51	(8.5)	53	(8.8)	104	(8.6)
CCSA Class 2	32	(5.3)	30	(5.0)	62	(5.2)
CCSA Class 3	14	(2.3)	11	(1.8)	25	(2.1)
Use of Sacubitril/Valsartan at Baseline						
Yes	83	(13.9)	88	(14.6)	171	(14.2)
No	516	(86.1)	516	(85.4)	1,032	(85.8)
History of Tobacco Use Assessed at Baseline						
Yes	373	(62.3)	377	(62.4)	750	(62.3)
No	226	(37.7)	227	(37.6)	453	(37.7)

NT-proBNP and creatinine for eGFR analyzed by central lab.
Source: 5.3.5.1.6 16493_Additional analysis/Table 5

表 2.7.3.7-34 ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者のベースラインの疾患特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	613		589		1,202	
Height (cm)						
Subjects with data	610		586		1196	
Mean	168.9		168.1		168.5	
SD	10.2		9.7		10.0	
Median	169.5		169.0		169.0	
Range	140.0 to 200.7		142.0 to 194.0		140.0 to 200.7	
Weight (kg)						
Subjects with data	613		587		1200	
Mean	82.4		80.8		81.6	
SD	21.7		21.1		21.4	
Median	79.9		78.5		79.0	
Range	40.7 to 181.6		39.2 to 195.0		39.2 to 195.0	
Body Mass Index (kg/m^2)						
Subjects with data	610		586		1196	
Mean	28.7		28.3		28.5	
SD	6.1		6.1		6.1	
Median	27.9		27.7		27.7	
Range	16.1 to 55.6		15.1 to 61.5		15.1 to 61.5	
NT-proBNP at Randomization (pg/ml)						
Subjects with data	613		589		1202	
Mean	2124.9		2168.6		2146.3	
SD	353.9		366.2		360.5	
Median	2074.0		2170.0		2119.5	
Range	1560.0 to 2816.0		1559.0 to 2816.0		1559.0 to 2816.0	
eGFR Category at Randomization ($mL/min/1.73\ m^2$)						
≤30	37	(6.0)	38	(6.5)	75	(6.2)
>30 to ≤60	246	(40.1)	229	(38.9)	475	(39.5)
>60	321	(52.4)	318	(54.0)	639	(53.2)
Missing	9	(1.5)	4	(0.7)	13	(1.1)
eGFR at Randomization ($mL/min/1.73\ m^2$)						
Subjects with data	604		585		1189	
Mean	65.3		65.9		65.6	
SD	25.8		26.6		26.2	
Median	61.5		63.1		62.2	
Range	15.2 to 180.0		13.7 to 218.7		13.7 to 218.7	
Index Event						
HF Hospitalization within 3 Months	372	(60.7)	382	(64.9)	754	(62.7)
HF Hospitalization 3-6 Months	138	(22.5)	110	(18.7)	248	(20.6)
IV diuretic for HF (without hospitalization) within 3 Months	103	(16.8)	97	(16.5)	200	(16.6)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Time of Primary Diagnosis of Heart Failure with Reduced Ejection Fraction to Randomization (Year)						
Subjects with data	613		589		1202	
Mean	4.9		4.9		4.9	
SD	5.6		5.6		5.6	
Median	3.1		2.9		3.0	
Range	0.0 to 40.6		0.0 to 32.7		0.0 to 40.6	
Time of Earliest Diagnosis of Heart Failure to Randomization (with or without Reduced Ejection Fraction) (Year)						
Subjects with data	613		589		1202	
Mean	5.3		5.3		5.3	
SD	5.8		5.7		5.8	
Median	3.4		3.4		3.4	
Range	0.0 to 40.6		0.0 to 33.1		0.0 to 40.6	
NYHA Class at Baseline						
NYHA Class II	393	(64.1)	365	(62.0)	758	(63.1)
NYHA Class III	216	(35.2)	220	(37.4)	436	(36.3)
NYHA Class IV	4	(0.7)	4	(0.7)	8	(0.7)
CCSA Class at Baseline						
No Angina	505	(82.4)	493	(83.7)	998	(83.0)
CCSA Class 1	72	(11.7)	50	(8.5)	122	(10.1)
CCSA Class 2	29	(4.7)	36	(6.1)	65	(5.4)
CCSA Class 3	7	(1.1)	10	(1.7)	17	(1.4)
Use of Sacubitril/Valsartan at Baseline						
Yes	94	(15.3)	88	(14.9)	182	(15.1)
No	519	(84.7)	501	(85.1)	1,020	(84.9)
History of Tobacco Use Assessed at Baseline						
Yes	348	(56.8)	352	(59.8)	700	(58.2)
No	265	(43.2)	237	(40.2)	502	(41.8)

NT-proBNP and creatinine for eGFR analyzed by central lab.
Source: 5.3.5.1.6 16493_Additional analysis/Table 6

表 2.7.3.7-35 ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者のベースラインの疾患特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	586		613		1,199	
Height (cm)						
Subjects with data	584		611		1195	
Mean	167.6		167.7		167.7	
SD	10.2		9.7		9.9	
Median	168.0		168.6		168.0	
Range	130.0 to 198.0		136.0 to 194.0		130.0 to 198.0	
Weight (kg)						
Subjects with data	585		613		1198	
Mean	75.4		77.6		76.5	
SD	18.5		19.1		18.8	
Median	74.0		75.0		74.7	
Range	35.9 to 163.0		34.6 to 184.2		34.6 to 184.2	
Body Mass Index (kg/m^2)						
Subjects with data	584		611		1195	
Mean	26.7		27.5		27.1	
SD	5.4		5.7		5.6	
Median	25.9		26.4		26.1	
Range	15.6 to 46.1		16.2 to 53.6		15.6 to 53.6	
NT-proBNP at Randomization (pg/ml)						
Subjects with data	586		613		1199	
Mean	3937.9		3886.7		3911.8	
SD	707.9		694.9		701.4	
Median	3852.0		3796.0		3819.0	
Range	2833.0 to 5310.0		2817.0 to 5314.0		2817.0 to 5314.0	
eGFR Category at Randomization ($mL/min/1.73\ m^2$)						
≤30	61	(10.4)	56	(9.1)	117	(9.8)
>30 to ≤60	257	(43.9)	293	(47.8)	550	(45.9)
>60	263	(44.9)	259	(42.3)	522	(43.5)
Missing	5	(0.9)	5	(0.8)	10	(0.8)
eGFR at Randomization ($mL/min/1.73\ m^2$)						
Subjects with data	581		608		1189	
Mean	60.1		58.2		59.1	
SD	26.0		24.8		25.4	
Median	55.4		54.1		54.7	
Range	15.3 to 221.2		17.1 to 206.1		15.3 to 221.2	
Index Event						
HF Hospitalization within 3 Months	397	(67.7)	427	(69.7)	824	(68.7)
HF Hospitalization 3-6 Months	99	(16.9)	96	(15.7)	195	(16.3)
IV diuretic for HF (without hospitalization) within 3 Months	90	(15.4)	90	(14.7)	180	(15.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Time of Primary Diagnosis of Heart Failure with Reduced Ejection Fraction to Randomization (Year)						
Subjects with data	586		613		1199	
Mean	4.8		4.7		4.8	
SD	5.6		5.3		5.4	
Median	2.9		2.9		2.9	
Range	0.0 to 39.0		0.1 to 48.4		0.0 to 48.4	
Time of Earliest Diagnosis of Heart Failure to Randomization (with or without Reduced Ejection Fraction) (Year)						
Subjects with data	586		613		1199	
Mean	5.1		5.2		5.2	
SD	5.6		5.8		5.7	
Median	3.1		3.2		3.2	
Range	0.0 to 39.0		0.1 to 48.4		0.0 to 48.4	
NYHA Class at Baseline						
NYHA Class II	329	(56.1)	369	(60.2)	698	(58.2)
NYHA Class III	247	(42.2)	237	(38.7)	484	(40.4)
NYHA Class IV	10	(1.7)	7	(1.1)	17	(1.4)
CCSA Class at Baseline						
No Angina	505	(86.2)	526	(85.8)	1,031	(86.0)
CCSA Class 1	37	(6.3)	48	(7.8)	85	(7.1)
CCSA Class 2	29	(4.9)	29	(4.7)	58	(4.8)
CCSA Class 3	14	(2.4)	10	(1.6)	24	(2.0)
CCSA Class 4	1	(0.2)	0	(0.0)	1	(0.1)
Use of Sacubitril/Valsartan at Baseline						
Yes	86	(14.7)	86	(14.0)	172	(14.3)
No	500	(85.3)	526	(85.8)	1,026	(85.6)
Missing	0	(0.0)	1	(0.2)	1	(0.1)
History of Tobacco Use Assessed at Baseline						
Yes	342	(58.4)	353	(57.6)	695	(58.0)
No	244	(41.6)	260	(42.4)	504	(42.0)

NT-proBNP and creatinine for eGFR analyzed by central lab.
Source: 5.3.5.1.6 16493_Additional analysis/Table 7

表 2.7.3.7-36 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者のベースラインの疾患特性（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	616		585		1,201	
Height (cm)						
Subjects with data	616		580		1196	
Mean	166.7		166.7		166.7	
SD	9.7		10.1		9.9	
Median	167.6		167.6		167.6	
Range	140.8 to 193.0		114.0 to 203.2		114.0 to 203.2	
Weight (kg)						
Subjects with data	616		582		1198	
Mean	73.4		73.9		73.6	
SD	17.5		18.7		18.1	
Median	72.1		71.5		72.0	
Range	32.7 to 149.3		34.2 to 187.2		32.7 to 187.2	
Body Mass Index (kg/m^2)						
Subjects with data	616		579		1195	
Mean	26.2		26.3		26.3	
SD	5.0		5.5		5.3	
Median	25.6		25.7		25.6	
Range	15.5 to 48.7		16.0 to 62.5		15.5 to 62.5	
NT-proBNP at Randomization (pg/ml)						
Subjects with data	616		585		1201	
Mean	11990.2		11867.5		11930.5	
SD	12214.8		8728.3		10655.8	
Median	8513.5		8866.0		8683.0	
Range	5319.0 to 175000.0		5326.0 to 86155.0		5319.0 to 175000.0	
eGFR Category at Randomization ($mL/min/1.73\ m^2$)						
≤30	124	(20.1)	117	(20.0)	241	(20.1)
>30 to ≤60	293	(47.6)	295	(50.4)	588	(49.0)
>60	197	(32.0)	170	(29.1)	367	(30.6)
Missing	2	(0.3)	3	(0.5)	5	(0.4)
eGFR at Randomization ($mL/min/1.73\ m^2$)						
Subjects with data	614		582		1196	
Mean	51.9		51.0		51.4	
SD	26.0		25.0		25.5	
Median	45.5		46.8		46.5	
Range	11.0 to 225.5		12.7 to 164.5		11.0 to 225.5	
Index Event						
HF Hospitalization within 3 Months	450	(73.1)	434	(74.2)	884	(73.6)
HF Hospitalization 3-6 Months	99	(16.1)	85	(14.5)	184	(15.3)
IV diuretic for HF (without hospitalization) within 3 Months	67	(10.9)	66	(11.3)	133	(11.1)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Time of Primary Diagnosis of Heart Failure with Reduced Ejection Fraction to Randomization (Year)						
Subjects with data	616		584		1200	
Mean	4.6		4.6		4.6	
SD	5.6		5.5		5.6	
Median	2.5		2.7		2.6	
Range	0.0 to 57.8		0.0 to 39.6		0.0 to 57.8	
Time of Earliest Diagnosis of Heart Failure to Randomization (with or without Reduced Ejection Fraction) (Year)						
Subjects with data	616		584		1200	
Mean	5.1		5.2		5.1	
SD	5.8		6.1		5.9	
Median	3.3		3.1		3.2	
Range	0.0 to 57.8		0.1 to 48.3		0.0 to 57.8	
NYHA Class at Baseline						
NYHA Class I	0	(0.0)	1	(0.2)	1	(0.1)
NYHA Class II	275	(44.6)	274	(46.8)	549	(45.7)
NYHA Class III	325	(52.8)	297	(50.8)	622	(51.8)
NYHA Class IV	16	(2.6)	13	(2.2)	29	(2.4)
CCSA Class at Baseline						
No Angina	538	(87.3)	501	(85.6)	1,039	(86.5)
CCSA Class 1	34	(5.5)	43	(7.4)	77	(6.4)
CCSA Class 2	28	(4.5)	23	(3.9)	51	(4.2)
CCSA Class 3	14	(2.3)	17	(2.9)	31	(2.6)
CCSA Class 4	2	(0.3)	1	(0.2)	3	(0.2)
Use of Sacubitril/Valsartan at Baseline						
Yes	74	(12.0)	85	(14.5)	159	(13.2)
No	542	(88.0)	500	(85.5)	1,042	(86.8)
History of Tobacco Use Assessed at Baseline						
Yes	346	(56.2)	326	(55.7)	672	(56.0)
No	270	(43.8)	259	(44.3)	529	(44.0)

NT-proBNP and creatinine for eGFR analyzed by central lab.
Source: 5.3.5.1.6 16493_Additional analysis/Table 8

表 2.7.3.7-37 ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者のインデックスイベントの要約（試験 16493、ITT 集団）

	Vericiguat	Placebo	Total
Subjects in population	599	604	1,203
Time from Index Event to Randomization (days)			
Subjects with data	594	598	1192
Mean	49.4	47.7	48.5
SD	46.06	50.68	48.42
Median	32.0	29.0	30.0
Range	2.0 to 343.0	2.0 to 621.0	2.0 to 621.0
Time from Index Event of HF Hospitalization (Admission Date) to Randomization (days)			
Subjects with data	472	470	942
Mean	54.0	51.3	52.7
SD	49.30	55.11	52.27
Median	34.0	29.0	31.0
Range	2.0 to 343.0	3.0 to 621.0	2.0 to 621.0
Time from Index Event of IV Diuretics Treatment to Randomization (days)			
Subjects with data	122	128	250
Mean	31.6	34.1	32.9
SD	23.09	24.99	24.07
Median	25.5	26.5	26.0
Range	2.0 to 91.0	2.0 to 105.0	2.0 to 105.0

Index events include heart failure hospitalization or IV diuretic treatment without hospitalization prior to randomization.
Source: 5.3.5.1.6 16493_Additional analysis/Table 9

表 2.7.3.7-38 ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者のインデックスイベントの要約（試験 16493、ITT 集団）

	Vericiguat	Placebo	Total
Subjects in population	613	589	1,202
Time from Index Event to Randomization (days)			
Subjects with data	604	585	1189
Mean	57.1	53.8	55.5
SD	50.02	48.85	49.45
Median	36.0	35.0	36.0
Range	2.0 to 217.0	2.0 to 350.0	2.0 to 350.0
Time from Index Event of HF Hospitalization (Admission Date) to Randomization (days)			
Subjects with data	506	491	997
Mean	63.0	57.8	60.4
SD	51.78	51.43	51.65
Median	44.5	39.0	42.0
Range	4.0 to 217.0	3.0 to 350.0	3.0 to 350.0
Time from Index Event of IV Diuretics Treatment to Randomization (days)			
Subjects with data	98	94	192
Mean	26.3	33.2	29.7
SD	21.37	23.18	22.49
Median	20.5	27.5	23.0
Range	2.0 to 90.0	2.0 to 93.0	2.0 to 93.0

Index events include heart failure hospitalization or IV diuretic treatment without hospitalization prior to randomization.
Source: 5.3.5.1.6 16493_Additional analysis/Table 10

表 2.7.3.7-39 ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者のインデックスイベントの要約（試験 16493、ITT 集団）

	Vericiguat	Placebo	Total
Subjects in population	586	613	1,199
Time from Index Event to Randomization (days)			
Subjects with data	581	606	1187
Mean	49.8	48.9	49.4
SD	44.87	44.08	44.45
Median	32.0	32.0	32.0
Range	2.0 to 197.0	2.0 to 245.0	2.0 to 245.0
Time from Index Event of HF Hospitalization (Admission Date) to Randomization (days)			
Subjects with data	493	522	1015
Mean	51.2	51.9	51.6
SD	46.95	45.79	46.33
Median	32.0	34.5	32.0
Range	2.0 to 197.0	2.0 to 245.0	2.0 to 245.0
Time from Index Event of IV Diuretics Treatment to Randomization (days)			
Subjects with data	88	84	172
Mean	42.0	30.6	36.4
SD	29.79	24.59	27.90
Median	40.5	23.0	29.0
Range	2.0 to 180.0	2.0 to 91.0	2.0 to 180.0

Index events include heart failure hospitalization or IV diuretic treatment without hospitalization prior to randomization.
Source: 5.3.5.1.6 16493_Additional analysis/Table 11

表 2.7.3.7-40 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者のインデックスイベントの要約（試験 16493、ITT 集団）

	Vericiguat	Placebo	Total
Subjects in population	616	585	1,201
Time from Index Event to Randomization (days)			
Subjects with data	611	581	1192
Mean	46.7	48.4	47.5
SD	42.14	44.18	43.13
Median	31.0	31.0	31.0
Range	2.0 to 198.0	2.0 to 253.0	2.0 to 253.0
Time from Index Event of HF Hospitalization (Admission Date) to Randomization (days)			
Subjects with data	548	519	1067
Mean	48.5	50.6	49.5
SD	43.55	45.69	44.60
Median	31.5	34.0	32.0
Range	2.0 to 198.0	2.0 to 253.0	2.0 to 253.0
Time from Index Event of IV Diuretics Treatment to Randomization (days)			
Subjects with data	63	62	125
Mean	30.8	29.8	30.3
SD	21.19	20.78	20.91
Median	29.0	27.0	28.0
Range	2.0 to 74.0	3.0 to 89.0	2.0 to 89.0

Index events include heart failure hospitalization or IV diuretic treatment without hospitalization prior to randomization.
Source: 5.3.5.1.6 16493_Additional analysis/Table 12

表 2.7.3.7-41 ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の入院状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	599		604		1,203	
Subjects Randomized while Hospitalized						
No	550	(91.8)	539	(89.2)	1,089	(90.5)
Yes	49	(8.2)	65	(10.8)	114	(9.5)
Time from Admission to Randomization (Days)						
Subjects with data	49		65		114	
Mean	8.6		7.9		8.2	
SD	4.55		4.83		4.71	
Median	8.0		7.0		7.0	
Range	2.0 to 25.0		3.0 to 28.0		2.0 to 28.0	
Time from Randomization to Discharge (Days)						
Subjects with data	49		65		114	
Mean	2.2		1.8		2.0	
SD	2.42		1.90		2.14	
Median	1.0		1.0		1.0	
Range	1.0 to 13.0		1.0 to 14.0		1.0 to 14.0	

Source: 5.3.5.1.6 16493_Additional analysis/Table 13

表 2.7.3.7-42 ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の入院状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	613		589		1,202	
Subjects Randomized while Hospitalized						
No	560	(91.4)	545	(92.5)	1,105	(91.9)
Yes	53	(8.6)	44	(7.5)	97	(8.1)
Time from Admission to Randomization (Days)						
Subjects with data	53		44		97	
Mean	10.3		9.6		10.0	
SD	7.18		6.70		6.94	
Median	8.0		7.5		8.0	
Range	1.0 to 36.0		3.0 to 34.0		1.0 to 36.0	
Time from Randomization to Discharge (Days)						
Subjects with data	53		44		97	
Mean	1.9		3.2		2.5	
SD	1.84		3.37		2.72	
Median	1.0		1.5		1.0	
Range	1.0 to 11.0		1.0 to 17.0		1.0 to 17.0	

Source: 5.3.5.1.6 16493_Additional analysis/Table 14

表 2.7.3.7-43 ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の入院状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	586		613		1,199	
Subjects Randomized while Hospitalized						
No	499	(85.2)	556	(90.7)	1,055	(88.0)
Yes	87	(14.8)	57	(9.3)	144	(12.0)
Time from Admission to Randomization (Days)						
Subjects with data	87		57		144	
Mean	9.0		10.5		9.6	
SD	5.20		8.60		6.77	
Median	8.0		9.0		8.0	
Range	1.0 to 28.0		1.0 to 60.0		1.0 to 60.0	
Time from Randomization to Discharge (Days)						
Subjects with data	87		57		144	
Mean	3.2		3.7		3.4	
SD	7.40		4.90		6.52	
Median	1.0		1.0		1.0	
Range	1.0 to 65.0		1.0 to 21.0		1.0 to 65.0	

Source: 5.3.5.1.6 16493_Additional analysis/Table 15

表 2.7.3.7-44 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の入院状況（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	616		585		1,201	
Subjects Randomized while Hospitalized						
No	525	(85.2)	498	(85.1)	1,023	(85.2)
Yes	91	(14.8)	87	(14.9)	178	(14.8)
Time from Admission to Randomization (Days)						
Subjects with data	91		87		178	
Mean	9.8		10.0		9.9	
SD	7.15		5.60		6.42	
Median	8.0		9.0		8.0	
Range	1.0 to 48.0		1.0 to 29.0		1.0 to 48.0	
Time from Randomization to Discharge (Days)						
Subjects with data	91		87		178	
Mean	3.4		5.3		4.3	
SD	4.05		19.94		14.23	
Median	2.0		2.0		2.0	
Range	1.0 to 22.0		1.0 to 186.0		1.0 to 186.0	

Source: 5.3.5.1.6 16493_Additional analysis/Table 16

表 2.7.3.7-45 ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者のスクリーニング時の eGFR 及び LVEF（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	599		604		1,203	
eGFR at Screening (mL/min/1.73 m^2)						
Subjects with data	597		604		1201	
Mean	63.7		67.0		65.4	
SD	20.90		22.32		21.68	
Median	60.0		64.0		61.0	
Range	19.0 to 160.0		15.0 to 149.2		15.0 to 160.0	
eGFR Category at Screening (mL/min/1.73 m^2)						
≥15 to ≤30	24	(4.0)	19	(3.1)	43	(3.6)
>30 to ≤60	298	(49.7)	244	(40.4)	542	(45.1)
>60	275	(45.9)	341	(56.5)	616	(51.2)
Missing	2	(0.3)	0	(0.0)	2	(0.2)
Ejection Fraction (%) Recorded at Screening						
Subjects with data	596		604		1200	
Mean	30.6		30.2		30.4	
SD	8.10		7.92		8.01	
Median	30.0		30.0		30.0	
Range	10.0 to 44.0		10.0 to 44.0		10.0 to 44.0	
Ejection Fraction (%) Category Recorded at Screening						
<30%	241	(40.2)	254	(42.1)	495	(41.1)
≥30% to <35%	119	(19.9)	142	(23.5)	261	(21.7)
≥35% to <40%	129	(21.5)	111	(18.4)	240	(20.0)
≥40% to ≤45%	107	(17.9)	97	(16.1)	204	(17.0)
Missing	3	(0.5)	0	(0.0)	3	(0.2)

Source: 5.3.5.1.6 16493_Additional analysis/Table 17

表 2.7.3.7-46　ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者のスクリーニング時の eGFR 及び LVEF（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	613		589		1,202	
eGFR at Screening (mL/min/1.73 m^2)						
Subjects with data	613		589		1202	
Mean	61.0		62.2		61.6	
SD	22.28		22.93		22.60	
Median	60.0		60.0		60.0	
Range	16.0 to 143.1		16.0 to 150.0		16.0 to 150.0	
eGFR Category at Screening (mL/min/1.73 m^2)						
≥15 to ≤30	39	(6.4)	37	(6.3)	76	(6.3)
>30 to ≤60	300	(48.9)	273	(46.3)	573	(47.7)
>60	274	(44.7)	279	(47.4)	553	(46.0)
Ejection Fraction (%) Recorded at Screening						
Subjects with data	612		587		1199	
Mean	29.6		29.2		29.4	
SD	8.18		8.45		8.31	
Median	30.0		30.0		30.0	
Range	6.0 to 44.0		5.0 to 45.0		5.0 to 45.0	
Ejection Fraction (%) Category Recorded at Screening						
<30%	280	(45.7)	286	(48.6)	566	(47.1)
≥30% to <35%	128	(20.9)	101	(17.1)	229	(19.1)
≥35% to <40%	112	(18.3)	107	(18.2)	219	(18.2)
≥40% to ≤45%	92	(15.0)	93	(15.8)	185	(15.4)
Missing	1	(0.2)	2	(0.3)	3	(0.2)

Source: 5.3.5.1.6 16493_Additional analysis/Table 18

表 2.7.3.7-47　ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者のスクリーニング時の eGFR 及び LVEF（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	586		613		1,199	
eGFR at Screening (mL/min/1.73 m^2)						
Subjects with data	583		613		1196	
Mean	56.4		55.2		55.8	
SD	21.85		20.56		21.20	
Median	55.0		53.0		54.0	
Range	16.0 to 139.0		17.0 to 142.7		16.0 to 142.7	
eGFR Category at Screening (mL/min/1.73 m^2)						
≥15 to ≤30	60	(10.2)	60	(9.8)	120	(10.0)
>30 to ≤60	303	(51.7)	361	(58.9)	664	(55.4)
>60	220	(37.5)	192	(31.3)	412	(34.4)
Missing	3	(0.5)	0	(0.0)	3	(0.3)
Ejection Fraction (%) Recorded at Screening						
Subjects with data	586		612		1198	
Mean	28.9		28.6		28.8	
SD	8.08		8.32		8.20	
Median	30.0		28.0		29.0	
Range	10.0 to 44.0		5.0 to 44.0		5.0 to 44.0	
Ejection Fraction (%) Category Recorded at Screening						
<30%	287	(49.0)	319	(52.0)	606	(50.5)
≥30% to <35%	132	(22.5)	106	(17.3)	238	(19.8)
≥35% to <40%	92	(15.7)	95	(15.5)	187	(15.6)
≥40% to ≤45%	75	(12.8)	92	(15.0)	167	(13.9)
Missing	0	(0.0)	1	(0.2)	1	(0.1)

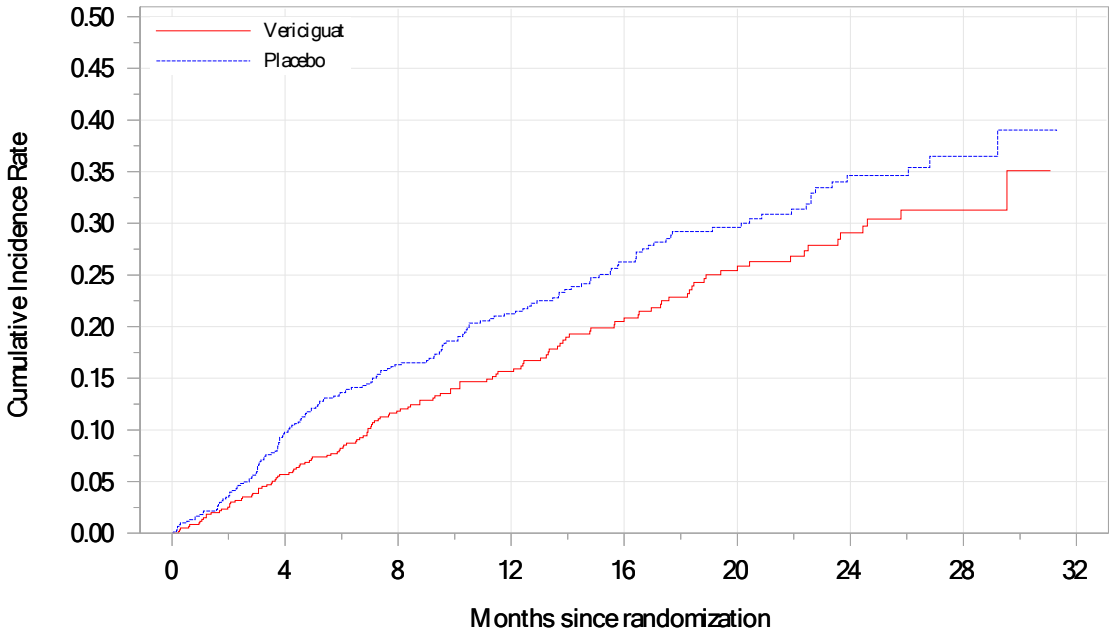
Source: 5.3.5.1.6 16493_Additional analysis/Table 19

表 2.7.3.7-48 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者のスクリーニング時の eGFR 及び LVEF（試験 16493、ITT 集団）

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	616		585		1,201	
eGFR at Screening (mL/min/1.73 m^2)						
Subjects with data	616		583		1199	
Mean	49.3		49.8		49.5	
SD	21.37		24.19		22.77	
Median	46.0		45.0		45.2	
Range	15.0 to 134.1		15.0 to 195.2		15.0 to 195.2	
eGFR Category at Screening (mL/min/1.73 m^2)						
≥15 to ≤30	123	(20.0)	124	(21.2)	247	(20.6)
>30 to ≤60	334	(54.2)	319	(54.5)	653	(54.4)
>60	159	(25.8)	140	(23.9)	299	(24.9)
Missing	0	(0.0)	2	(0.3)	2	(0.2)
Ejection Fraction (%) Recorded at Screening						
Subjects with data	612		585		1197	
Mean	27.2		27.2		27.2	
SD	8.25		8.38		8.31	
Median	27.0		26.0		27.0	
Range	8.0 to 45.0		8.0 to 45.0		8.0 to 45.0	
Ejection Fraction (%) Category Recorded at Screening						
<30%	351	(57.0)	351	(60.0)	702	(58.5)
≥30% to <35%	116	(18.8)	91	(15.6)	207	(17.2)
≥35% to <40%	81	(13.1)	82	(14.0)	163	(13.6)
≥40% to ≤45%	64	(10.4)	61	(10.4)	125	(10.4)
Missing	4	(0.6)	0	(0.0)	4	(0.3)

Source: 5.3.5.1.6 16493_Additional analysis/Table 20

図 2.7.3.7-9　ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	599	563	450	326	247	176	112	46	0
Placebo	604	543	434	324	239	172	106	45	0

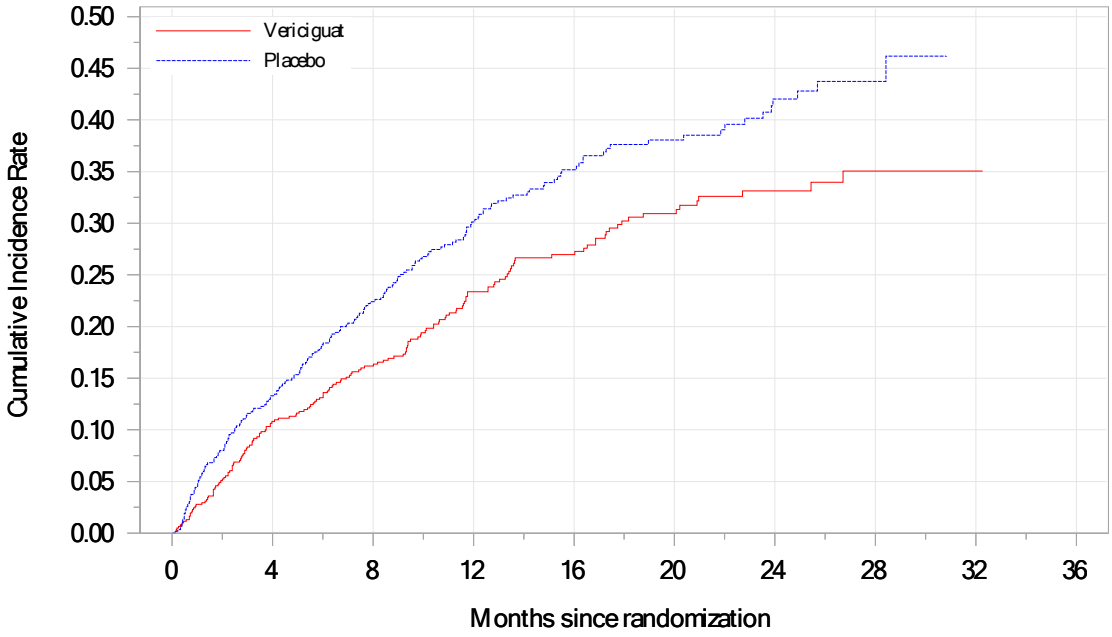
Cumulative number of events up to the time point

Vericiguat	0	34	69	86	103	117	124	127	128
Placebo	0	59	97	120	138	148	158	160	161

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 10

図 2.7.3.7-10　ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	613	544	451	326	234	175	105	34	1	0
Placebo	589	509	399	280	194	131	90	29	0	0

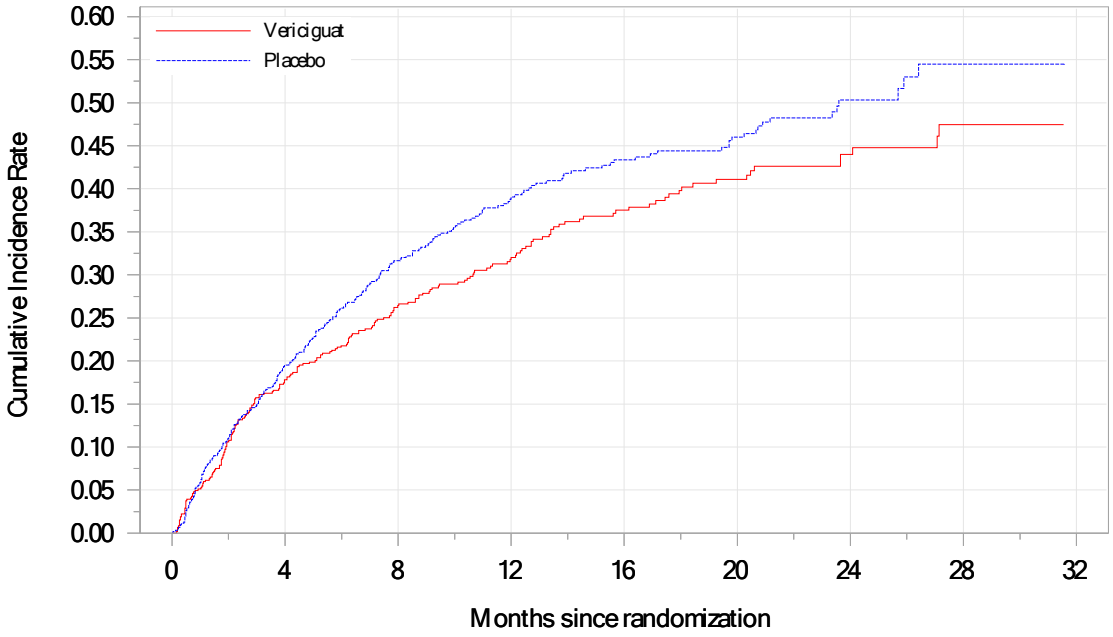
Cumulative number of events up to the time point

Vericiguat	0	66	98	132	146	158	163	165	165	165
Placebo	0	78	130	165	183	191	198	200	201	201

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 11

図 2.7.3.7-11　ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	586	479	367	267	177	121	73	25	0
Placebo	613	488	359	235	171	132	65	15	0

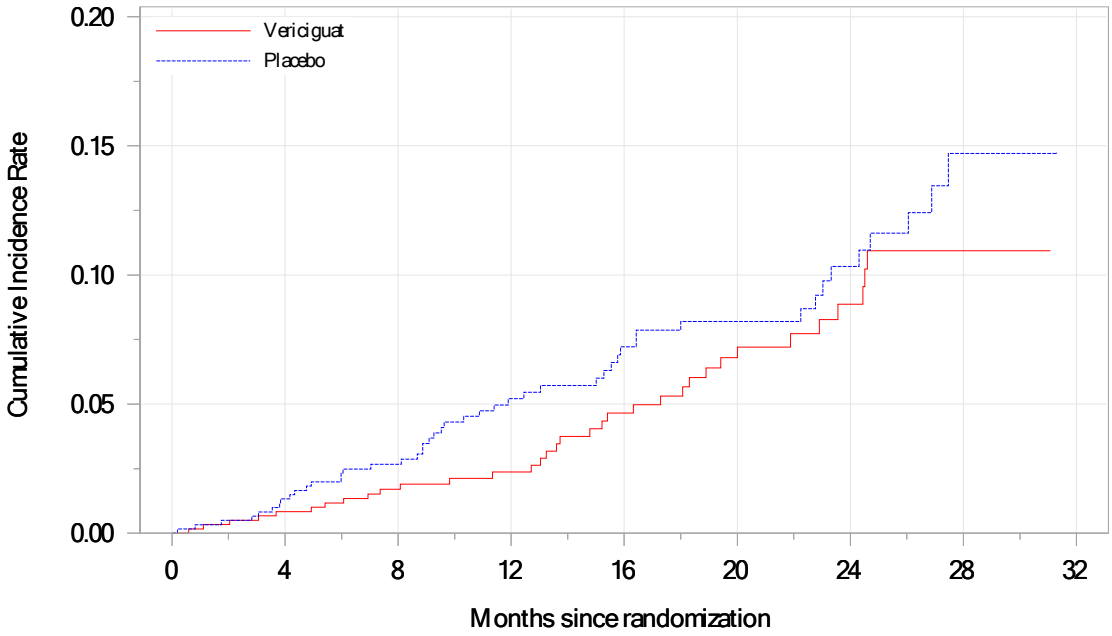
Cumulative number of events up to the time point

Vericiguat	0	104	152	177	196	205	210	213	213
Placebo	0	119	190	224	239	246	254	257	257

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 12

図 2.7.3.7-12　ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の副次評価項目（CV 死までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	599	593	506	387	299	222	142	59	0
Placebo	604	596	507	391	301	226	146	58	0

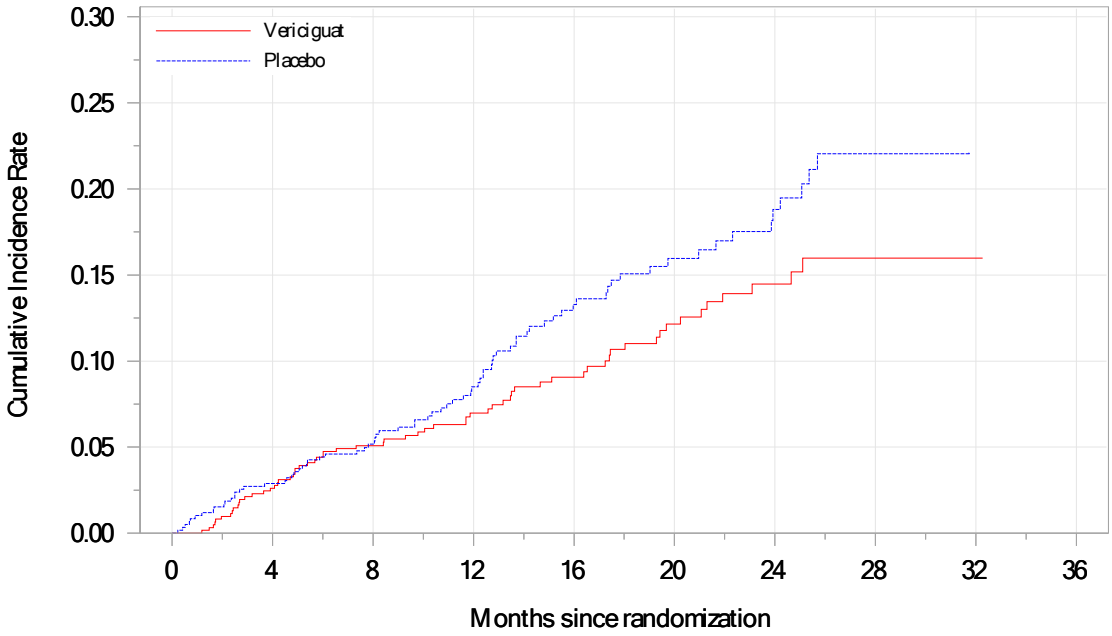
Cumulative number of events up to the time point

Vericiguat	0	5	10	13	21	27	31	34	34
Placebo	0	8	16	28	35	38	42	47	47

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 14

図 2.7.3.7-13　ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の副次評価項目（CV 死までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	613	595	514	396	296	223	135	47	1	0
Placebo	589	570	488	365	261	176	123	40	0	0

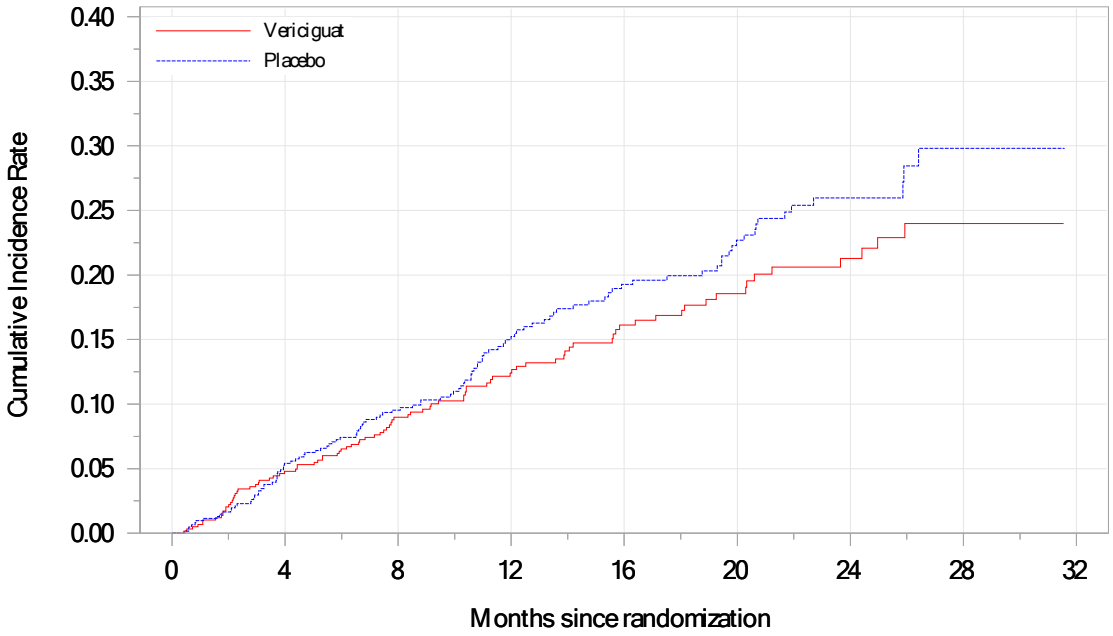
Cumulative number of events up to the time point

Vericiguat	0	16	31	40	48	57	62	64	64	64
Placebo	0	17	30	45	62	69	74	78	78	78

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 15

図 2.7.3.7-14　ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の副次評価項目（CV 死までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	586	554	454	335	235	171	106	41	0
Placebo	613	573	471	329	245	191	105	29	0

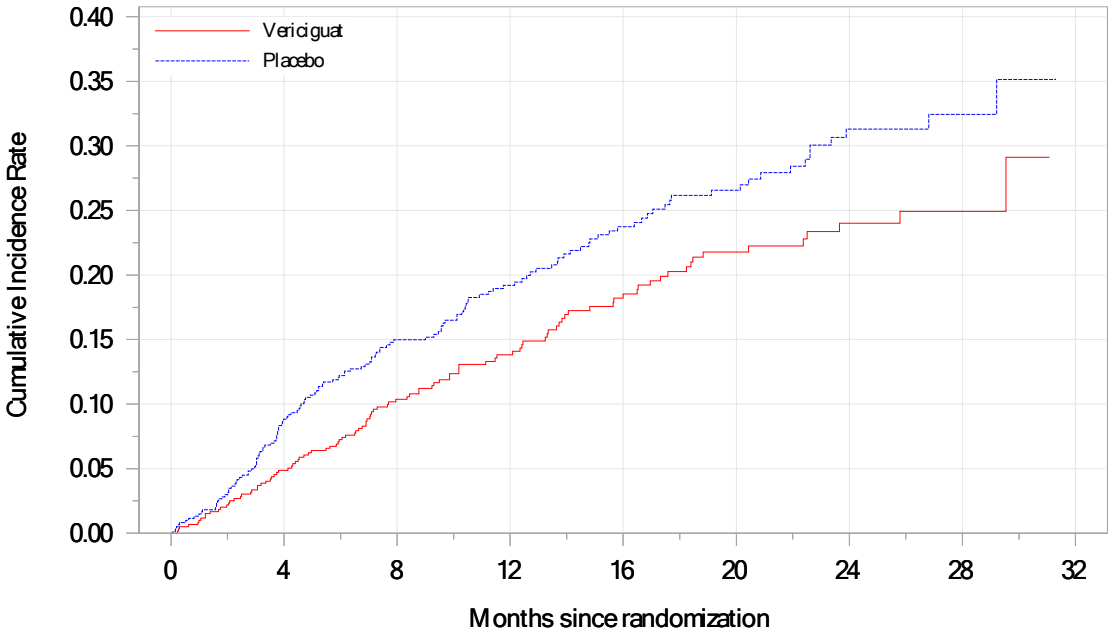
Cumulative number of events up to the time point

Vericiguat	0	28	51	66	78	84	89	92	92
Placebo	0	33	57	82	96	105	112	115	115

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 16

図 2.7.3.7-15　ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の副次評価項目（心不全による入院の初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	599	563	450	326	247	176	112	46	0
Placebo	604	542	433	323	238	171	105	45	0

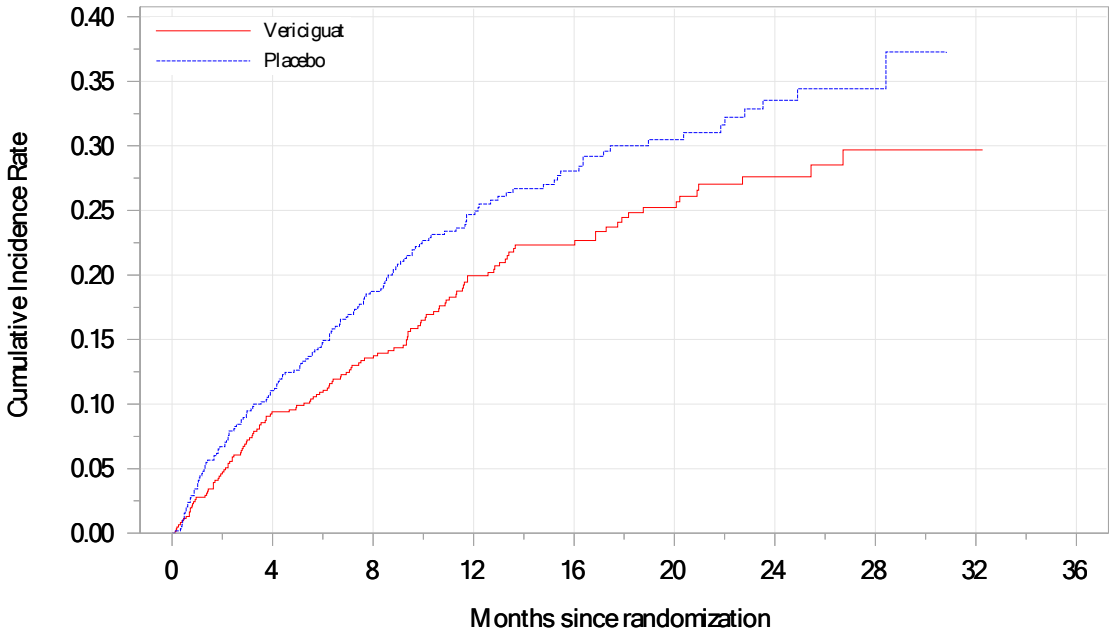
Cumulative number of events up to the time point

Vericiguat	0	29	60	75	90	100	104	105	106
Placebo	0	53	88	107	123	131	140	141	142

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 18

図 2.7.3.7-16　ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の副次評価項目（心不全による入院の初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	613	543	450	325	233	175	105	34	1	0
Placebo	589	509	399	280	194	131	90	29	0	0

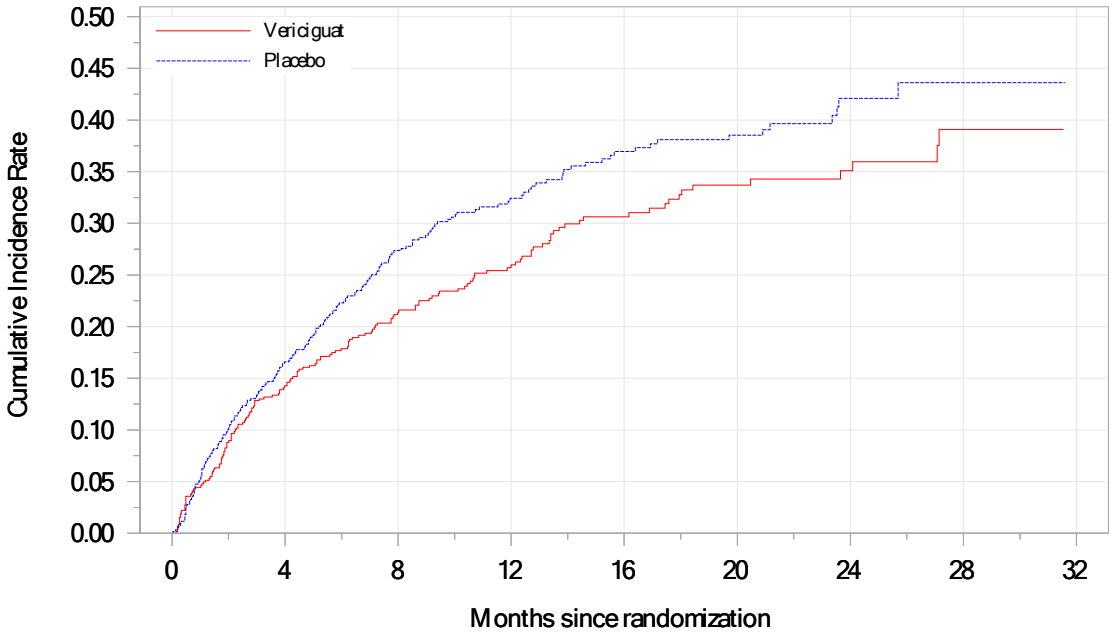
Cumulative number of events up to the time point

Vericiguat	0	57	81	110	119	127	132	134	134	134
Placebo	0	64	106	132	143	149	154	155	156	156

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 19

図 2.7.3.7-17　ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の副次評価項目（心不全による入院の初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	586	479	367	267	177	121	73	25	0
Placebo	613	488	359	235	171	132	65	15	0

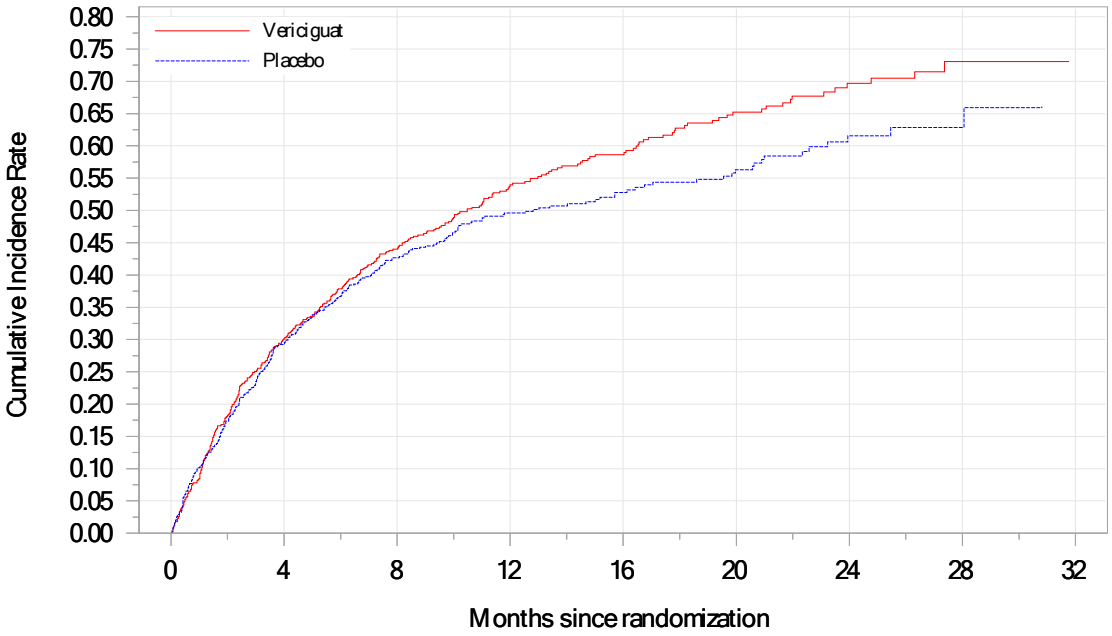
Cumulative number of events up to the time point

Vericiguat	0	82	120	139	154	161	163	166	166
Placebo	0	100	160	182	196	200	205	206	206

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 20

図 2.7.3.7-18　ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の主要評価項目（CV 死又は心不全による入院の複合エンドポイントの初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	616	417	286	187	129	80	43	15	0
Placebo	585	403	279	196	125	87	40	13	0

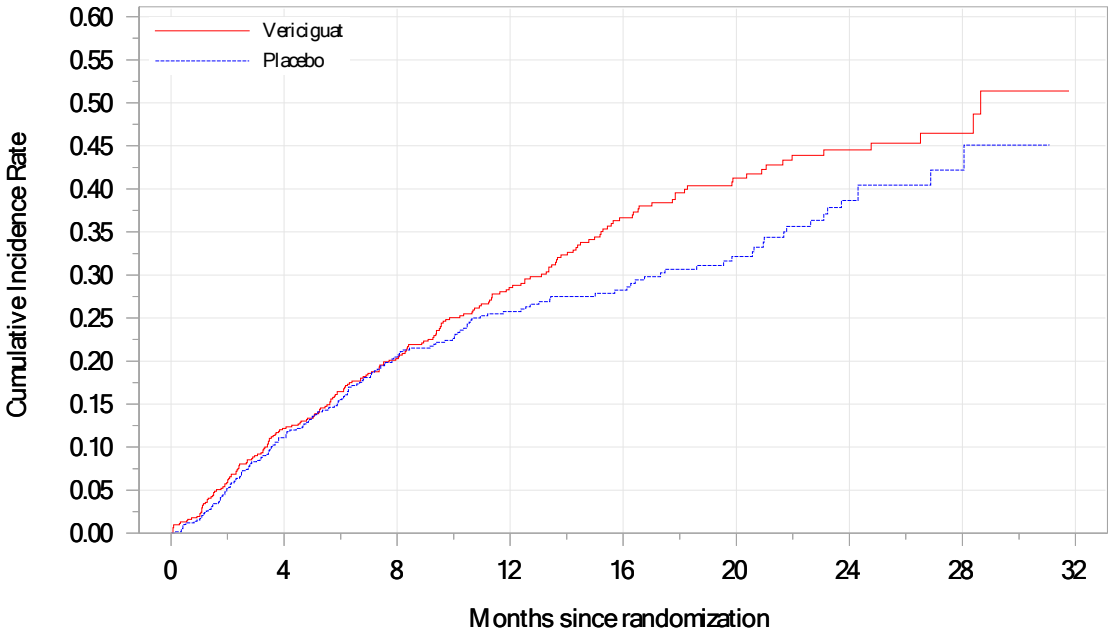
Cumulative number of events up to the time point

Vericiguat	0	183	263	309	326	344	352	355	355
Placebo	0	169	243	274	284	292	300	301	302

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 13

図 2.7.3.7-19　ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の副次評価項目（CV 死までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	616	523	405	287	189	130	79	30	0
Placebo	585	505	379	276	186	131	71	22	0

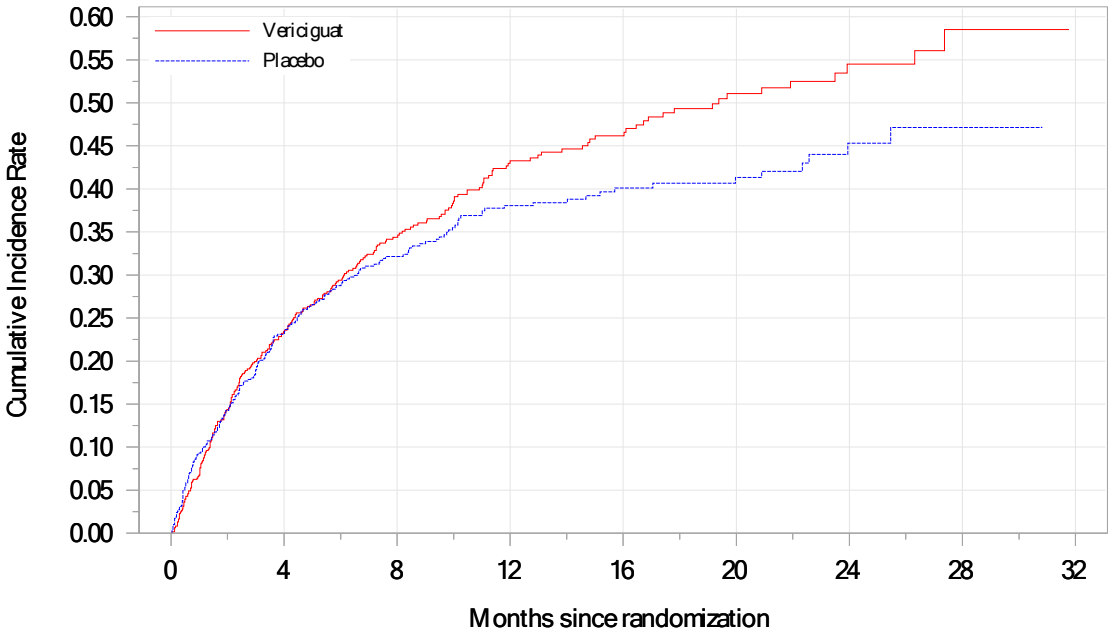
Cumulative number of events up to the time point

Vericiguat	0	74	120	158	186	198	204	206	208
Placebo	0	64	115	138	146	155	165	168	169

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 17

図 2.7.3.7-20　ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の副次評価項目（心不全による入院の初回発現までの期間）の Kaplan-Meier 曲線（試験 16493、ITT 集団、主解析のカットオフまでのデータ）



Number of subjects at risk

Vericiguat	616	417	286	187	129	80	43	15	0
Placebo	585	403	279	196	125	87	40	13	0

Cumulative number of events up to the time point

Vericiguat	0	137	193	227	235	245	249	251	251
Placebo	0	130	175	197	202	204	208	209	209

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Figure 21

表 2.7.3.7-49　ベースラインの NT-proBNP 値が Q1（1,556pg/mL 以下）の被験者の NT-proBNP 値（pg/mL）の推移（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

Visit	Treatment	Baseline			Value			Change from Baseline		
		N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	599	1001.5 (376.2)	1058.0 [733.0, 1322.0]						
	Placebo	604	971.0 (383.7)	1023.0 [675.5, 1293.0]						
Week 16	Vericiguat	534	1000.7 (375.9)	1055.0 [733.0, 1323.0]	534	1184.8 (1567.5)	861.0 [462.0, 1381.0]	534	184.1 (1534.3)	-68.5 [-405.0, 311.0]
	Placebo	556	960.3 (386.2)	1014.5 [659.5, 1286.0]	556	1190.9 (1501.3)	908.0 [506.0, 1451.5]	556	230.5 (1431.4)	7.5 [-295.0, 401.0]
Week 32	Vericiguat	458	998.2 (381.0)	1057.5 [731.0, 1317.0]	458	1121.1 (1190.3)	817.0 [434.0, 1432.0]	458	122.9 (1156.3)	-72.0 [-445.0, 347.0]
	Placebo	460	960.5 (387.2)	1013.0 [661.0, 1288.0]	460	1193.9 (1348.4)	836.5 [444.0, 1485.0]	460	233.4 (1281.2)	-40.0 [-357.5, 371.5]
Week 48	Vericiguat	347	1021.0 (381.7)	1091.0 [748.0, 1348.0]	347	1149.9 (1119.9)	840.0 [406.0, 1552.0]	347	128.9 (1057.9)	-96.0 [-467.0, 464.0]
	Placebo	362	960.0 (385.8)	1011.0 [665.0, 1277.0]	362	1204.2 (1308.3)	852.5 [408.0, 1545.0]	362	244.2 (1246.6)	-20.0 [-397.0, 477.0]
Week 96	Vericiguat	133	1068.4 (361.7)	1154.0 [817.0, 1360.0]	133	1461.5 (3721.5)	740.0 [381.0, 1537.0]	133	393.1 (3675.4)	-174.0 [-635.0, 457.0]
	Placebo	135	913.2 (410.0)	957.0 [560.0, 1255.0]	135	1358.9 (1531.6)	909.0 [449.0, 1616.0]	135	445.7 (1459.2)	-3.0 [-222.0, 656.0]
Week 144	Vericiguat	1	1080.0 (0.0)	1080.0 [1080.0, 1080.0]	1	635.0 (0.0)	635.0 [635.0, 635.0]	1	-445.0 (0.0)	-445.0 [-445.0, -445.0]
	Placebo	1	846.0 (0.0)	846.0 [846.0, 846.0]	1	1133.0 (0.0)	1133.0 [1133.0, 1133.0]	1	287.0 (0.0)	287.0 [287.0, 287.0]

For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and the specific timepoint.
SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.
Based on data up to the primary completion date (18Jun2019).
Source: 5.3.5.1.6 16493_Additional analysis/Table 47

表 2.7.3.7-50　ベースラインの NT-proBNP 値が Q2（1,556pg/mL 超 2,816pg/mL 以下）の被験者の NT-proBNP 値（pg/mL）の推移（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

		Baseline			Value			Change from Baseline		
Visit	Treatment	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	613	2124.9 (353.9)	2074.0 [1826.0, 2421.0]						
	Placebo	589	2168.6 (366.2)	2170.0 [1851.0, 2472.0]						
Week 16	Vericiguat	542	2121.5 (354.6)	2070.5 [1824.0, 2414.0]	542	2010.4 (1623.6)	1626.5 [1078.0, 2480.0]	542	-111.1 (1619.8)	-446.5 [-985.0, 311.0]
	Placebo	523	2162.5 (364.1)	2174.0 [1843.0, 2463.0]	523	2376.2 (2036.0)	1869.0 [1249.0, 2843.0]	523	213.7 (1972.8)	-170.0 [-874.0, 684.0]
Week 32	Vericiguat	475	2127.6 (358.9)	2072.0 [1824.0, 2437.0]	475	2041.7 (2008.0)	1596.0 [984.0, 2381.0]	475	-85.9 (1991.8)	-462.0 [-1136.0, 371.0]
	Placebo	441	2170.1 (361.5)	2177.0 [1858.0, 2466.0]	441	2415.9 (2418.3)	1801.0 [1005.0, 2837.0]	441	245.8 (2383.7)	-316.0 [-1095.0, 631.0]
Week 48	Vericiguat	370	2118.4 (351.1)	2056.0 [1828.0, 2412.0]	370	2159.9 (3248.7)	1533.5 [889.0, 2408.0]	370	41.5 (3251.2)	-565.0 [-1169.0, 400.0]
	Placebo	328	2168.4 (359.3)	2174.0 [1865.5, 2464.0]	328	2468.5 (2733.2)	1859.0 [1019.5, 2935.0]	328	300.1 (2718.8)	-224.5 [-1148.5, 702.5]
Week 96	Vericiguat	125	2077.0 (325.7)	2008.0 [1828.0, 2352.0]	125	2544.7 (4437.9)	1468.0 [937.0, 2464.0]	125	467.7 (4395.8)	-547.0 [-1045.0, 496.0]
	Placebo	110	2135.1 (358.5)	2126.0 [1828.0, 2428.0]	110	2126.7 (2086.6)	1749.0 [611.0, 2816.0]	110	-8.5 (2101.9)	-330.5 [-1573.0, 739.0]
Week 144	Vericiguat	1	2068.0 (0.0)	2068.0 [2068.0, 2068.0]	1	5098.0 (0.0)	5098.0 [5098.0, 5098.0]	1	3030.0 (0.0)	3030.0 [3030.0, 3030.0]
	Placebo	0			0			0		

For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and the specific timepoint.

SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 48

表 2.7.3.7-51　ベースラインの NT-proBNP 値が Q3（2,816pg/mL 超 5,314pg/mL 以下）の被験者の NT-proBNP 値（pg/mL）の推移（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

Visit	Treatment	Baseline			Value			Change from Baseline		
		N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	586	3937.9 (707.9)	3852.0 [3336.0, 4508.0]						
	Placebo	613	3886.7 (694.9)	3796.0 [3306.0, 4437.0]						
Week 16	Vericiguat	496	3931.6 (709.4)	3828.0 [3337.0, 4521.0]	496	3407.1 (2682.1)	2850.5 [1681.0, 4171.5]	496	-524.5 (2654.1)	-1042.5 [-2100.5, 320.0]
	Placebo	529	3891.5 (682.3)	3804.0 [3322.0, 4426.0]	529	4078.9 (3914.4)	3199.0 [1939.0, 4886.0]	529	187.4 (3848.5)	-571.0 [-1818.0, 1028.0]
Week 32	Vericiguat	401	3929.8 (722.3)	3819.0 [3321.0, 4541.0]	401	3505.1 (3496.6)	2605.0 [1539.0, 4262.0]	401	-424.8 (3432.0)	-1202.0 [-2327.0, 388.0]
	Placebo	432	3869.9 (684.1)	3766.5 [3301.0, 4391.0]	432	4002.3 (4198.4)	2833.5 [1748.0, 4778.0]	432	132.4 (4087.6)	-768.5 [-2110.0, 799.5]
Week 48	Vericiguat	294	3940.7 (710.3)	3859.0 [3346.0, 4541.0]	294	3244.7 (4077.5)	2469.0 [1281.0, 3982.0]	294	-696.0 (4139.1)	-1521.0 [-2589.0, 29.0]
	Placebo	299	3886.6 (701.6)	3785.0 [3284.0, 4457.0]	299	4220.3 (4942.6)	3005.0 [1703.0, 4817.0]	299	333.7 (4852.5)	-757.0 [-2090.0, 1044.0]
Week 96	Vericiguat	93	3950.5 (735.8)	3756.0 [3387.0, 4553.0]	93	3433.3 (5094.5)	2059.0 [1047.0, 3992.0]	93	-517.2 (5153.5)	-1679.0 [-2880.0, 39.0]
	Placebo	99	3917.8 (716.9)	3837.0 [3322.0, 4540.0]	99	3607.8 (3146.6)	2708.0 [1531.0, 5119.0]	99	-310.0 (3202.1)	-1078.0 [-2272.0, 1207.0]

For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and the specific timepoint.

SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 49

表 2.7.3.7-52 ベースラインの NT-proBNP 値が Q4（5,314pg/mL 超）の被験者の NT-proBNP 値（pg/mL）の推移（試験 16493、ITT 集団、主解析のカットオフまでのデータ）

Visit	Treatment	Baseline			Value			Change from Baseline		
		N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]	N	Mean (SD)	Median [Q1, Q3]
Baseline	Vericiguat	616	11990.2 (12214.8)	8513.5 [6679.0, 13628.5]						
	Placebo	585	11867.5 (8728.3)	8866.0 [6534.0, 13607.0]						
Week 16	Vericiguat	475	11266.5 (10170.1)	8261.0 [6536.0, 13053.0]	475	8953.1 (12836.6)	5851.0 [3530.0, 10162.0]	475	-2313.4 (14580.9)	-2808.0 [-5611.0, 373.0]
	Placebo	445	11108.4 (7493.8)	8455.0 [6367.0, 13234.0]	445	9199.5 (9715.5)	6722.0 [3683.0, 10871.0]	445	-1908.9 (9130.0)	-2135.0 [-5467.0, 1181.0]
Week 32	Vericiguat	355	11271.9 (11062.8)	8173.0 [6419.0, 13040.0]	355	8609.1 (11193.5)	5308.0 [2729.0, 10242.0]	355	-2662.9 (14045.9)	-3269.0 [-6520.0, 698.0]
	Placebo	332	11082.1 (7930.7)	8260.0 [6319.5, 13001.0]	332	9068.6 (9788.8)	5953.0 [3215.5, 10908.0]	332	-2013.4 (10065.4)	-2561.0 [-6364.5, 958.5]
Week 48	Vericiguat	242	11199.9 (12448.4)	8130.0 [6313.0, 13190.0]	242	7728.3 (9203.8)	5096.0 [2618.0, 8915.0]	242	-3471.6 (14755.8)	-3458.5 [-6864.0, -60.0]
	Placebo	238	10635.6 (6849.8)	8479.0 [6318.0, 12163.0]	238	7225.4 (8058.5)	4648.0 [2368.0, 8886.0]	238	-3410.2 (8298.9)	-3619.5 [-6826.0, 258.0]
Week 96	Vericiguat	70	11495.4 (20345.0)	7605.0 [6007.0, 11015.0]	70	7252.2 (7781.1)	4418.0 [2153.0, 12046.0]	70	-4243.2 (18716.0)	-3355.5 [-5336.0, 54.0]
	Placebo	62	8904.9 (5094.0)	6800.0 [6052.0, 9994.0]	62	7724.6 (10056.4)	4608.5 [1855.0, 7659.0]	62	-1180.3 (8771.0)	-2649.5 [-5853.0, 1070.0]

For baseline and at the respective time point, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and the specific timepoint.

SD=Standard deviation, Q1= the first quartile, Q3=the third quartile.

Based on data up to the primary completion date (18Jun2019).

Source: 5.3.5.1.6 16493_Additional analysis/Table 50

2.7.3.7.2　　日本人死亡例の叙述

Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
Non-CV Death	Sepsis	敗血症		Day 455
SAE	Interstitial lung disease	間質性肺疾患	Severe	Day 400
Discontinuation of Study Medication Due to AE	Interstitial lung disease	間質性肺疾患	Severe	Day 400

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 4 years, 10 months, 27 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Back pain; Hypertension; Insomnia; Cardiac failure; Hyperlipidaemia; Diabetes mellitus; Hyperuricaemia; Atrial fibrillation; Chronic hepatitis; Gallbladder polyp; Hepatic steatosis; Atrioventricular block complete; Atrial flutter; Sleep apnoea syndrome; Ventricular tachycardia; Gastrooesophageal reflux disease; Chronic gastritis; Large intestine polyp; Gastrointestinal submucosal tumour; Diabetic nephropathy; Echocardiogram; Renal cyst
History of Medical/ Surgical Procedures	Cardiac resynchronisation therapy

Concomitant Medications at Randomization	apixaban, candesartan cilexetil, brotizolam, atorvastatin calcium, amiodarone hydrochloride, mosapride citrate, esomeprazole magnesium, teneligliptin hydrobromide, spironolactone, ursodeoxycholic acid, mexiletine hydrochloride, febuxostat, mitiglinide calcium, bisoprolol fumarate, furosemide, tolvaptan, azosemide, insulin glargine biosimilar 1

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-20	627 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
-20	44 %		
1		NYHA CLASS II	51.7 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 65 日～第 88 日、第 274 日～第 298 日及び第 345 日～第 367 日に心不全のため入院した。

第 358 日～第 379 日に気管支炎（非重篤な有害事象）が発現した。

息切れ及び軽度の脛骨前浮腫が 2 日間発現した後、第 402 日に間質性肺疾患（発現日は第 400 日）のため入院した。SO_2は 84%であり、酸素療法が開始された。臨床検査の結果、Krebs von den Lungen-6 抗原、LDH、BNP、CRP 及び白血球の増加、並びに HGB 及び HCT の減少が認められた。胸部 X 線及び CT 検査により間質性肺疾患が確認された。第 404 日に胸部 X 線検査で悪化（詳細不明）が認められ、第 405 日に非侵襲的換気療法が開始された。間質性肺疾患のため治験薬の投与は中止された。最終投与日は第 406 日であった。第 407 日に挿管し、機械的換気が行われた。塩酸モルヒネ、ミダゾラム、ロクロニウム臭化物、パラセタモール、フロセミド、プレドニゾロン、メチルプレドニゾロンコハク酸エステルナトリウム、セフトリアキソンナトリウム及びシベレスタットナトリウムが投与された。第 407 日～第 414 日に胸部 X 線検査で改善（詳細不明）が認められた。第 416 日に胸部 CT 検査で悪化（詳細不明）が認められた。第 417 日に細菌性肺炎（非重篤な有害事象）と診断され、レボフロキサシンが投与された。胸部 X 線検査で急性肺水腫（非重篤な有害事象）が認められたが、約 5 時間後に消失した。トルバプタンが治療薬に追加された。ステロイド治療は継続した。第 428 日に気管切開が行われた。第 429 日に胸部 X 線検査で悪化（詳細不明）が認められた。第 434 日に胸部 X 線検査で改善（詳細不明）が認められた。第 438 日に胸部 X 線検査で肺炎陰影の悪化が認められた。第 439 日から第 454 日までの複数の胸部 X 線検査では、被験者の状態は悪化と改善を繰り返した。第 454 日にメロペネム三水和物が投与された。第 455 日に被験者は敗血症により死亡した（目撃者ありと報告された）。治験責任（分担）医師より、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、間質性肺疾患及び細菌性肺炎の転帰は未回復であった。

治験責任（分担）医師により、間質性肺疾患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	31	placebo	0	1
32	112	placebo	0	1
113	168	placebo	0	1
169	203	placebo	0	1
204	204	placebo	0	0
205	216	placebo	0	1
217	219	placebo	0	0
220	231	placebo	0	1
232	245	placebo	0	1
246	246	placebo	0	0
247	259	placebo	0	1
260	260	placebo	0	1
261	262	placebo	0	0
263	288	placebo	0	1
289	289	placebo	0	0
290	294	placebo	0	1
295	307	placebo	0	1
308	308	placebo	0	0
309	315	placebo	0	1

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
316	327	placebo	0	1
328	328	placebo	0	0
329	336	placebo	0	1
337	337	placebo	0	0
338	341	placebo	0	1
342	343	placebo	0	0
344	347	placebo	0	1
348	348	placebo	0	0
349	365	placebo	0	1
366	369	placebo	0	1
370	371	placebo	0	0
372	377	placebo	0	1
378	378	placebo	0	0
379	389	placebo	0	1
390	391	placebo	0	0
392	393	placebo	0	1
394	394	placebo	0	0
395	405	placebo	0	1
406	406	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-14	125	77	83	
1	126	78	72	8[redacted]9
1	117	65	75	
15	117	66	74	8[redacted].2
32	124	74	79	8[redacted].9
64	121	73	81	8[redacted].2
113	116	70	76	7[redacted].6
141	113	68	74	
169	86	52	73	
204	92	55	75	
232	94	58	69	8[redacted].3
260	108	72	75	
295	101	55	69	8[redacted].2
316	110	68	75	
344	103	73	69	9[redacted].2
366	103	66	70	

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	35	32	14.193	89
113	38	33	5.814	87
232	30	29	8.208	57

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
344	32	34	6.84	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
-20	112.268(H)
1	123.76
113	159.12(H)
232	150.28(H)
344	176.8(H)

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

Table 5. Potential Study Endpoints

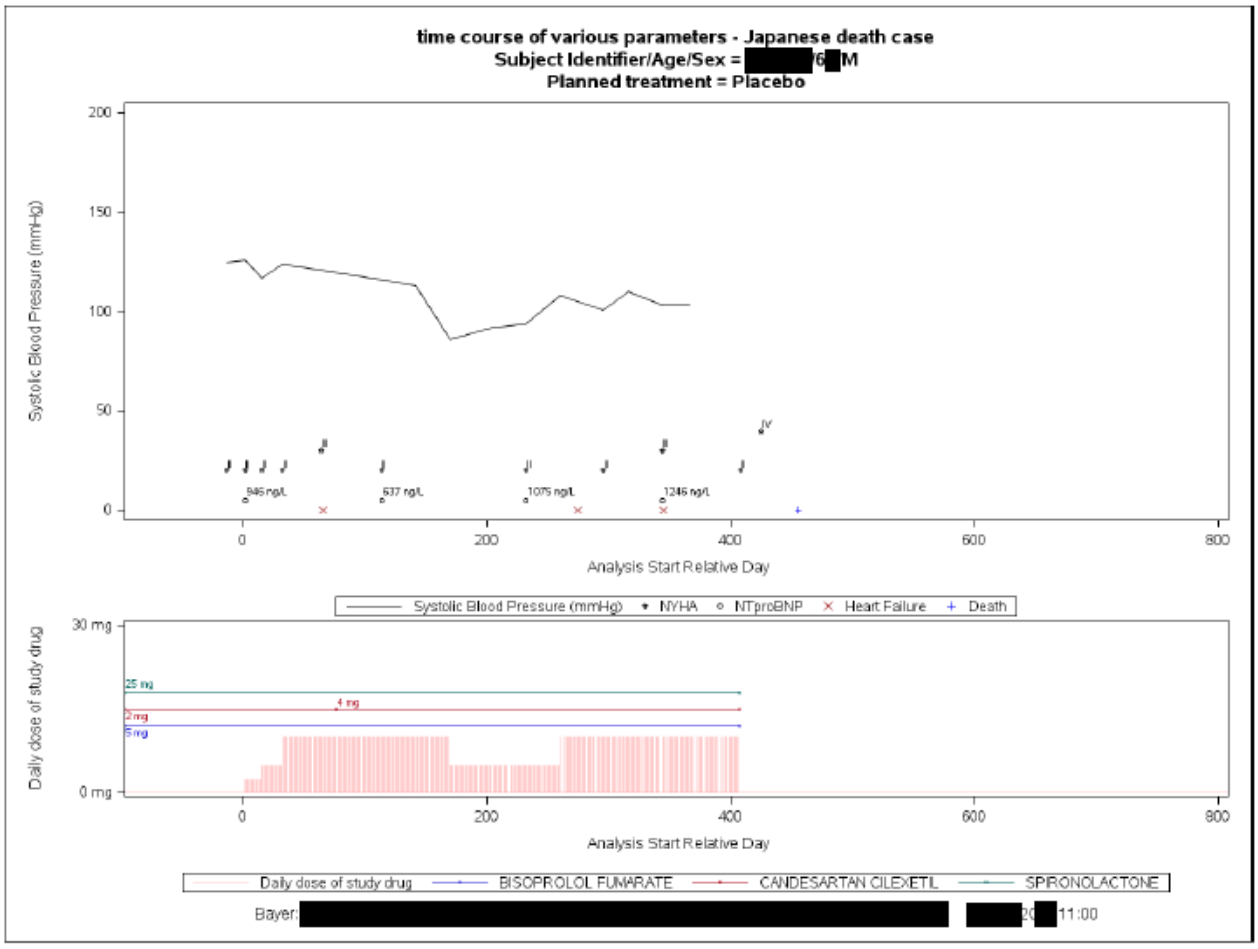
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
57		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
65	88	Heart Failure	Hospitalization	Heart Failure
274	298	Heart Failure	Hospitalization	Heart Failure
316		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
344		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
345	367	Heart Failure	Hospitalization	Heart Failure
455		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]/6[redacted]M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
946 ng/L
637 ng/L
1075 ng/L
1246 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
25 mg
4 mg
2 mg
5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
CANDESARTAN CILEXETIL
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	Cardiac failure	心不全		Day 235
SAE	Hyperkalaemia	高カリウム血症	Severe	Day 133

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 1 year, 4 months prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Diabetes mellitus; Hypertension; Diabetic retinopathy; Chronic kidney disease; Tinea pedis; Cardiac failure chronic; Hyperuricaemia; Hyperkalaemia; Diabetic nephropathy; Anaemia; Hyperlipidaemia
History of Medical/ Surgical Procedures	Vitrectomy; Lens extraction

Concomitant Medications at Randomization	teneligliptin hydrobromide, carvedilol, spironolactone, calcium polystyrene sulfonate, pitavastatin calcium, nifedipine, furosemide, lansoprazole, allopurinol, sodium bicarbonate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-8		214.1 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
-103	35 %		
1		NYHA CLASS II	17.7 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高カリウム血症があった。

第 134 日に高カリウム血症の悪化（発現日は第 133 日）のため入院したが、症状や心調律異常は認められなかった。高カリウム血症はスピロノラクトンに関連するものであり、スピロノラクトンによる心不全に対する治療は中止された。ポリスチレンスルホン酸カルシウムの投与が継続され、フロセミド、グルコン酸カルシウム、ヒトインスリン、グルコース及び重炭酸ナトリウムも投与された。第 138 日に高カリウム血症は消失し、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。

被験者は第 192 日～第 225 日に心不全のため他院へ入院した。入院時に治験薬を持参しておらず、治験薬の最終投与日は第 191 日であった。

第 235 日目に被験者は心不全のため死亡した（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。剖検は実施されず、追加情報は報告されなかった。

治験責任（分担）医師により、高カリウム血症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	41	MK-1242	10	1
42	42	MK-1242	10	0
43	56	MK-1242	10	1
57	119	MK-1242	10	1
120	147	MK-1242	10	1
148	190	MK-1242	10	1
191	191	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	168	89	81	9[redacted]4
1	168	89	81	
1	133	72	89	
15	117	64	82	9[redacted]
29	127	66	84	9[redacted]3
57	192	108	76	10[redacted].5
120	124	73	89	9[redacted].65
148	129	68	86	9[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	14	14	4.617	79
120	15	17	<2.565	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
-8	318.24(H)

Study Day	CREAT µmol/L
1	327.08(H)
120	344.76(H)
133	418.132(H)

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

Table 5. Potential Study Endpoints

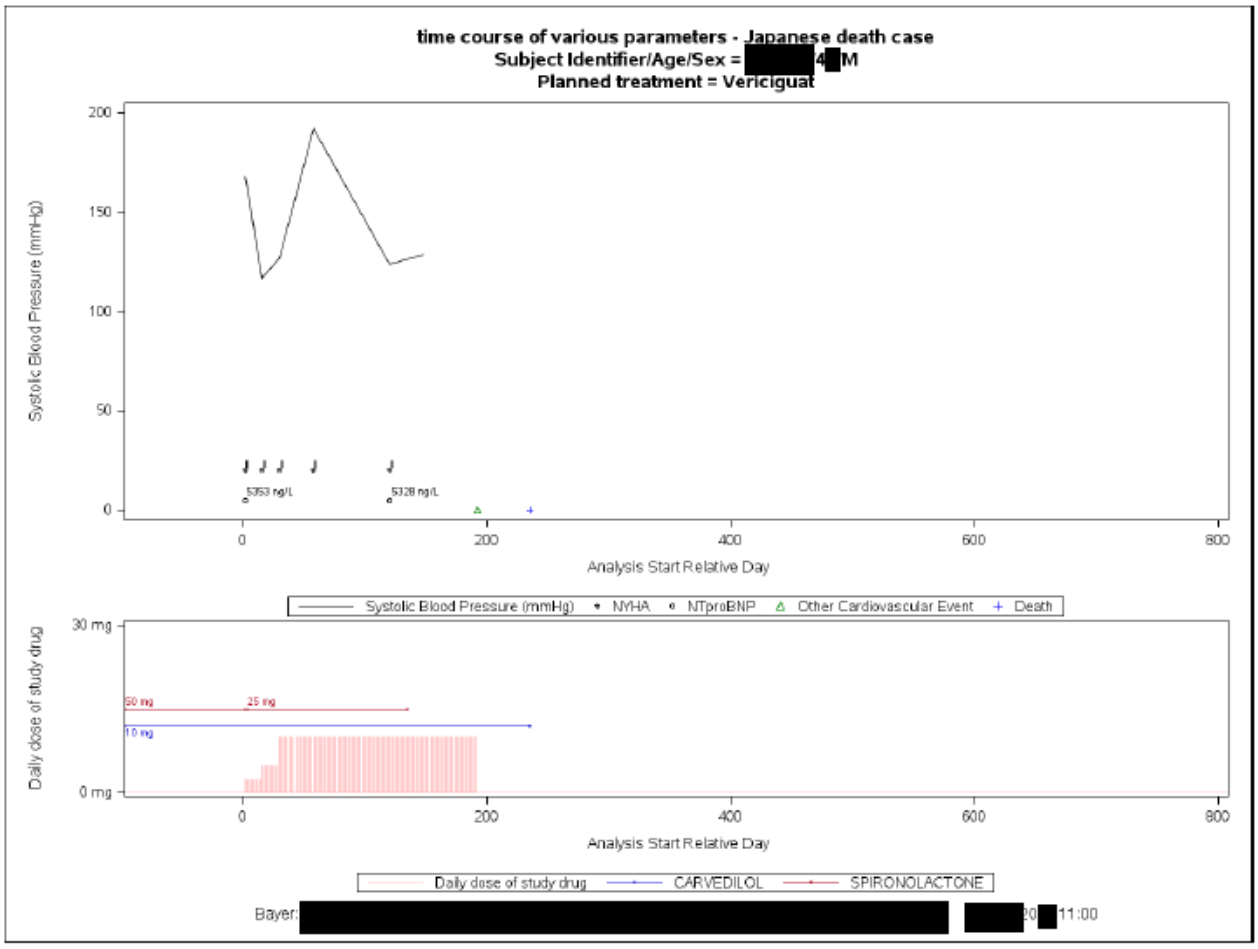
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
192	225	Heart Failure	Hospitalization	Other Cardiovascular Event
235		Heart Failure	Death	Undetermined Cause Of Death

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]4[redacted]M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
5353 ng/L
5328 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
5.0 mg
2.5 mg
1.0 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	Cardiac failure	心不全		Day 279
SAE	Pneumonia	肺炎	Severe	Day 202
SAE	Pseudomembranous colitis	偽膜性大腸炎	Severe	Day 214
SAE	Pseudomembranous colitis	偽膜性大腸炎	Severe	Day 229
SAE	Cardiac failure	心不全	Severe	Day 244

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

Primary Diagnosis	Subject was initially diagnosed with heart failure approximately 7 years prior to first dose of study medication. Subject was diagnosed with heart failure with reduced ejection fraction approximately 5 months, 20 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Gastrointestinal disorder; Ventricular extrasystoles; Osteoporosis; Hypertension; Glaucoma; Atrial flutter; Cardiac failure chronic; Atrial fibrillation; Atrial tachycardia; Anaemia; Gastric cancer; Haemorrhoids; Back pain; Rhabdomyolysis; Cataract; Pseudomembranous colitis; Cystitis
History of Medical/ Surgical Procedures	Tricuspid valve repair; Mitral valve repair; Aortic valve replacement; Cardiac resynchronisation therapy

Concomitant Medications at Randomization	amiodarone hydrochloride, bisoprolol, rivaroxaban, ferrous sulfate, losartan potassium, rebamipide, etizolam, rabeprazole sodium, latanoprost, fluticasone propionate, bacillus mesentericus;clostridium butyricum;enterococcus faecalis, furosemide, magnesium oxide, cefpodoxime proxetil

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-21		679.7 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
-70	38 %		
1		NYHA CLASS II	43.4 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、本試験組入れと同年の偽膜性大腸炎及び膀胱炎があった。

第 148 日に心不全の増悪（非重篤な有害事象）が発現し、第 149 日に心房粗動の悪化のため入院し、除細動を受けた。フロセミド、ニフェカラント塩酸塩及びアミオダロン塩酸塩が投与された。第 162 日に心不全の増悪は消失し、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 202 日に心不全及び肺炎のため入院し、発熱及び CRP 増加が認められた。CT 及び胸部 X 線検査の結果、心嚢液貯留及び心拡大が認められた。フロセミド、セフトリアキソンナトリウム及びアジスロマイシンが投与された。心不全治療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 201 日であった。第 214 日に発熱及び胃痛を伴う偽膜性大腸炎と診断された。メトロニダゾール、パラセタモール、*Enterococcus faecalis* 及び *Bifidobacterium bifidum* が投与された。第 227 日に肺炎及び偽膜性大腸炎は消失し、被験者は退院し、帰宅した。

第 229 日に被験者は偽膜性大腸炎のため入院し、上腹部痛、下痢及び発熱が認められ、便培養は陽性であった。*Clostridium butyricum*、セフトリアキソンナトリウム、メトロニダゾール、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、アスパラギン酸カリウム及びバンコマイシン塩酸塩が投与された。第 244 日に呼吸困難を伴う心不全の増悪が認められた。第 245 日に胸部 X 線検査で胸水及び心拡大が認められた。フロセミド、トルバプタン、ドブタミン塩酸塩、メロペネム及びカンレノ酸カリウムが投与された。第 270 日に胸部 X 線検査で肺炎、胸水及び心拡大が認められた。第 279 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）。剖検は実施されなかった。死亡時に、偽膜性大腸炎の転帰は未回復であった。

治験責任（分担）医師により、心不全、肺炎及び偽膜性大腸炎（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	placebo	0	1
2	14	placebo	0	1
15	28	placebo	0	1
29	49	placebo	0	1
50	105	placebo	0	1
106	200	placebo	0	1
201	201	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-21	102	58	75	
1	108	52	76	4[redacted].5
1	98	52	75	4[redacted].5
15	113	60	75	4[redacted]
29	112	62	75	4[redacted].5
50	100	60	75	4[redacted]
106	122	65	77	4[redacted]
227	107	53	74	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	10	25	7.353	92
106	9(L)	27	2.907	110
227	15	34	3.762	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
-21	103.428(H)
1	106.08
106	114.92
227	88.4

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

Table 5. Potential Study Endpoints

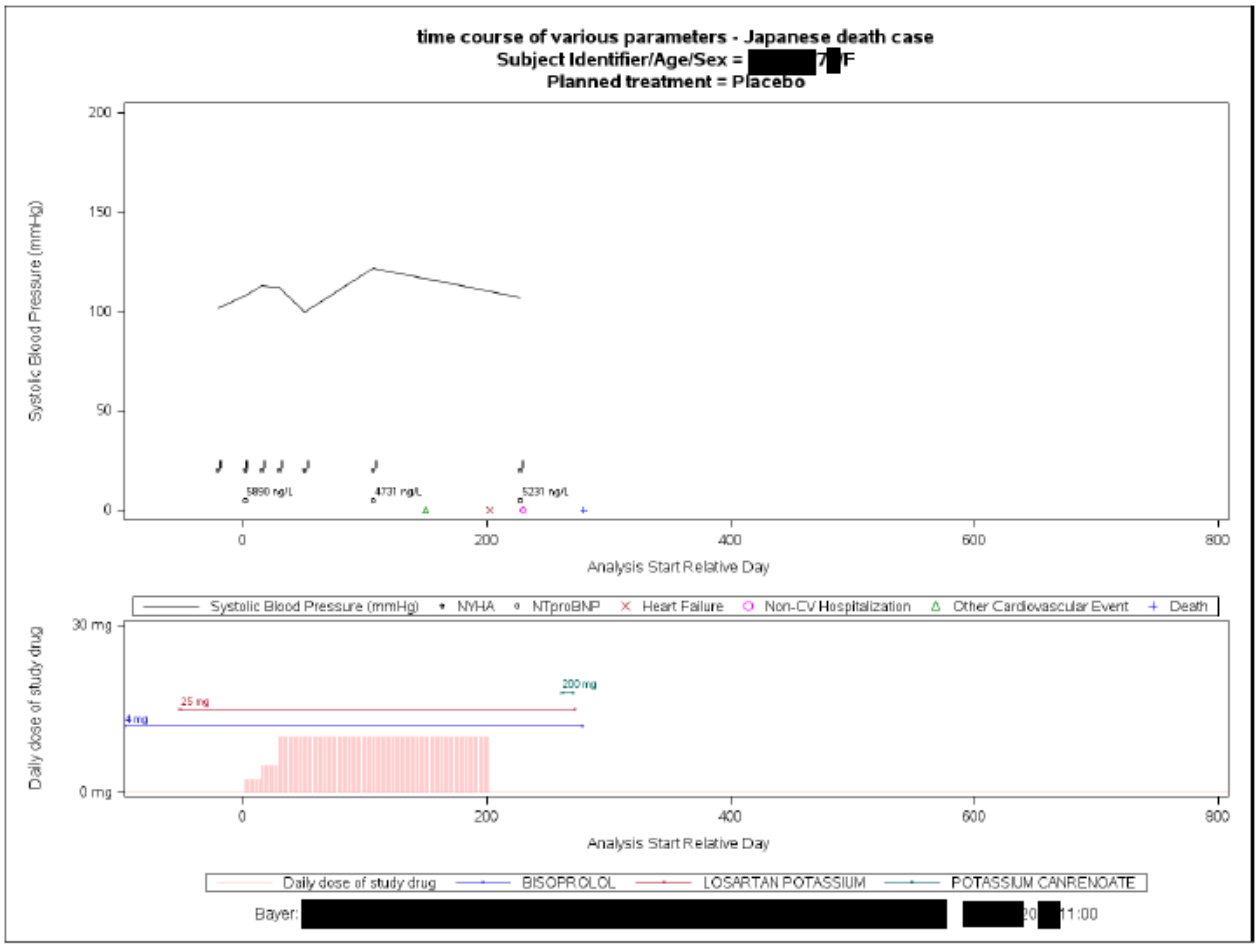
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
149	162	Other Cardiovascular Event	Hospitalization	Other Cardiovascular Event
202	227	Heart Failure	Hospitalization	Heart Failure
229	279	Non-CV Hospitalization	Hospitalization	Non-CV Hospitalization
279		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]F
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
5890 ng/L
4731 ng/L
5231 ng/L
0
200
400
600
800
Analysis Start Relative Day
Systolic Blood Pressure (mmHg)
NYHA
NTproBNP
Heart Failure
Non-CV Hospitalization
Other Cardiovascular Event
Death
Daily dose of study drug
30 mg
0 mg
25 mg
4 mg
200 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL
LOSARTAN POTASSIUM
POTASSIUM CANRENOATE
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 341
Discontinuation of Study Medication Due to Other Reason	Withdrawal by Subject			Day 50

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 3 years, 1 month, 14 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; Coronary artery disease; Myocardial infarction; Angina pectoris; Chronic kidney disease; Diabetic retinopathy; Diabetic neuropathy; Hyperuricaemia; Chronic gastritis; Hyperlipidaemia; Hypertension; Peripheral arterial occlusive disease; Atrial tachycardia; Echocardiogram; Constipation; Back pain; Insomnia
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Coronary artery bypass; Mitral valve replacement

Concomitant Medications at Randomization	linagliptin, acetylsalicylic acid, lansoprazole, pimobendan, mitiglinide calcium, trichlormethiazide, insulin aspart;insulin degludec, bisoprolol fumarate, warfarin potassium, perindopril erbumine, febuxostat, tolvaptan, magnesium oxide, loxoprofen sodium, azosemide, rosuvastatin calcium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-14	1682 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
-42	28 %		
1		NYHA CLASS III	34.4 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:

被験者の同意撤回により治験薬の投与が中止された。最終投与日は第 50 日であった。

被験者は、第 50 日～第 58 日、第 64 日～第 71 日及び第 96 日～第 187 日に心不全のため入院した。

第 316 日に被験者は心不全のため入院し、ピモベンダン、トリクロルメチアジド、ビソプロロールフマル酸塩、ペリンドプリルエルブミン、トルバプタン、アゾセミド、ロスバスタチンカルシウム及びフロセミドの投与が継続された。第 341 日に被験者は心不全のため死亡した。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	placebo	0	1
2	15	placebo	0	1
16	29	placebo	0	1
30	49	placebo	0	1
50	50	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-14	109	69	77	
1	107	64	70	5[redacted].6
1	98	57	69	
15	111	64	73	5[redacted]
29	104	65	117	5[redacted].3
43	98	54	67	5[redacted].6
50	99	53	70	6[redacted].4
78	99	59	72	6[redacted].8
81	105	60	81	6[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	17	23	20.349(H)	207(H)
81	26	35	23.94(H)	256(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	163.54(H)
1	176.8(H)
81	194.48(H)

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

Table 5. Potential Study Endpoints

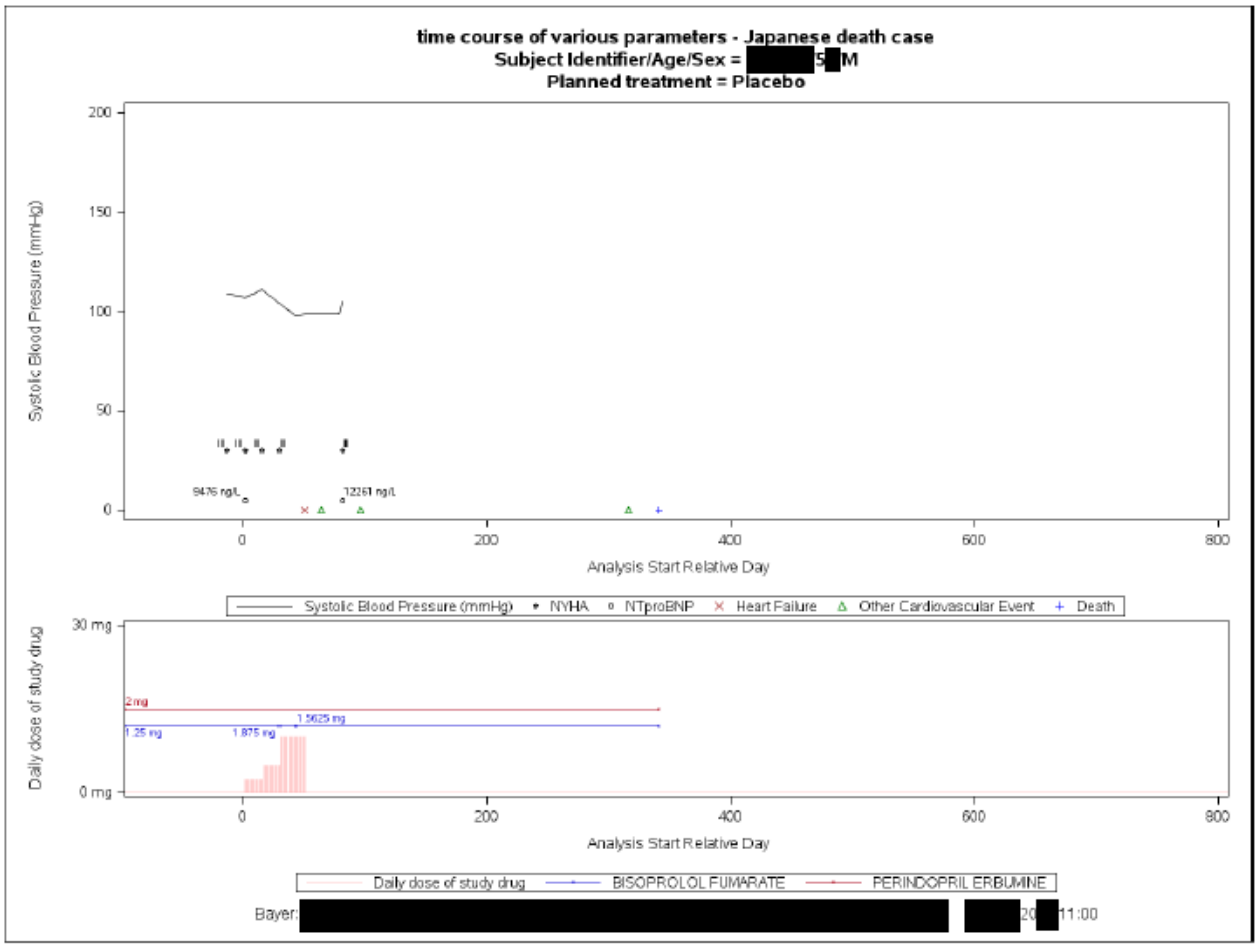
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
37		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
50	58	Heart Failure	Hospitalization	Heart Failure
63		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
64	71	Heart Failure	Hospitalization	Other Cardiovascular Event
78		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
96	187	Heart Failure	Hospitalization	Other Cardiovascular Event
316	341	Heart Failure	Hospitalization	Other Cardiovascular Event
341		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] 5[redacted] M
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
9476 ng/L
12261 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
2 mg
1.5625 mg
1.25 mg
1.875 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
PERINDOPRIL ERBUMINE
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	Pneumonia	肺炎		Day 743
SAE	Renal failure	腎不全	Severe	Day 392
SAE	Pneumonia	肺炎	Severe	Day 720

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

Primary Diagnosis	Subject was initially diagnosed with heart failure approximately 7 years prior to first dose of study medication. Subject was diagnosed with heart failure with reduced ejection fraction approximately 3 months, 29 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Hypertension; Lumbar spinal stenosis; Atrial fibrillation; Chronic kidney disease; Insomnia; Glucose tolerance impaired; Sinus node dysfunction; Cardiac failure; Coronary artery disease; Myocardial infarction; Hyperlipidaemia; Anaemia; Sleep apnoea syndrome; Rhabdomyolysis; Hyperuricaemia; Hypothyroidism; Echocardiogram; Peripheral arterial occlusive disease
History of Medical/ Surgical Procedures	Implantable defibrillator insertion; Coronary artery bypass; Vascular operation; Percutaneous coronary intervention

Concomitant Medications at Randomization	acetylsalicylic acid, benfotiamine;cyanocobalamin;pyridoxine hydrochloride, tocopheryl nicotinate, zolpidem tartrate, vonoprazan fumarate, furosemide, prasugrel hydrochloride, mecobalamin, febuxostat, bisoprolol fumarate, bepridil hydrochloride monohydrate, warfarin potassium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-15	735 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
-16	41 %		
1		NYHA CLASS II	25 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 7 年前から慢性腎臓病があった。

被験者は第16日～第21日に不整脈のため入院した。

第392日に腎不全の悪化、心不全の増悪（非重篤な有害事象）及びペースメーカー原性不整脈（非重篤な有害事象）が発現した。心電図検査で心房頻脈（非重篤な有害事象）、胸部X線検査で胸水及び肺うっ血が認められた。同日、心臓ペースメーカーの調整が行われ、フロセミドの投与及び腎代替療法が行われた。第399日に腎不全の悪化のため治験薬の投与が中断され、第401日に10mgで再開された。第406日に心不全の増悪は消失した。第455日に心房頻脈及びペースメーカー原性不整脈は消失した。腎不全の悪化の転帰は未回復であった。

第720日に被験者は心不全のため入院し、肺炎と診断され、貧血の悪化（非重篤な有害事象）、悪液質（非重篤な有害事象）及びINR増加（非重篤な有害事象）が発現した。胸部X線検査で肺うっ血、胸水、及び肺炎の存在を示す局所網状影が認められた。心エコーで両心房拡大、肺高血圧症及び胸水が認められた。酸素吸入が行われ、フロセミド、スピロノラクトン、ビソプロロールフマル酸塩、トルバプタン、アンピシリンナトリウム／スルバクタムナトリウム、ピペラシリンナトリウム／タゾバクタム、グルコース、グルコース／アミノ酸NOS（not otherwise specified）／電解質NOS／チアミン塩酸塩、塩化ナトリウム、塩化カリウム、アスコルビン酸／ビオチン／シアノコバラミン／エルゴカルシフェロール／葉酸／ニコチンアミド／パンテノール／フィトメナジオン／ピリドキシン塩酸塩／レチノールパルミチン酸エステル／リボフラビンリン酸エステルナトリウム／チアミン、硫酸銅／塩化第二鉄／塩化マンガン／ヨウ化カリウム／硫酸亜鉛、ヒトアルブミン及び赤血球が投与された。第721日に低カリウム血症（非重篤な有害事象）が発現し、塩化カリウムが投与された。第724日に機械的換気（非侵襲的陽圧）が行われた。第727日に低カリウム血症は消失した。継続している腎不全の悪化に対して、第729日～第741日にダルベポエチンアルファの投与及び腎代替療法が行われた。透析離脱まで治験薬の投与は中断されたが、その後再開されず、最終投与日は第729日であった。第730日に胸部CT検査で胸水及び肺水腫が引き続き認められ、メロペネム、クリンダマイシンリン酸エステル及びメチルプレドニゾロンコハク酸エステルナトリウムによる治療が行われた。非重篤な有害事象として、フィブリンDダイマー増加（第732日）、肝機能異常（第733日）、末梢性浮腫（第737日）及び高カリウム血症（第740日）も発現した。第741日に胸部CT検査で胸水、肺水腫、肺気腫を伴うすりガラス陰影が認められ、間質性肺炎が疑われた。緩和ケアが開始された。第743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）。剖検は実施されなかった。死亡時に、貧血、悪液質、INR増加、フィブリンDダイマー増加、肝機能異常、末梢性浮腫及び高カリウム血症の転帰は未回復であった。

治験責任（分担）医師により、肺炎及び腎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	16	MK-1242	2.5	1
17	29	MK-1242	5	1
30	52	MK-1242	10	1
53	82	MK-1242	10	1
83	83	MK-1242	10	0
84	113	MK-1242	10	1
114	142	MK-1242	10	1
143	143	MK-1242	10	0
144	172	MK-1242	10	1
173	173	MK-1242	10	0
174	202	MK-1242	10	1
203	203	MK-1242	10	0

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
204	232	MK-1242	10	1
233	308	MK-1242	10	1
309	309	MK-1242	10	0
310	337	MK-1242	10	1
338	399	MK-1242	10	1
400	400	MK-1242	10	0
401	426	MK-1242	10	1
427	427	MK-1242	10	0
428	455	MK-1242	10	1
456	515	MK-1242	10	1
516	516	MK-1242	10	0
517	533	MK-1242	10	1
534	534	MK-1242	10	0
535	567	MK-1242	10	1
568	592	MK-1242	10	1
593	593	MK-1242	10	0
594	619	MK-1242	10	1
620	679	MK-1242	10	1
680	728	MK-1242	10	1
729	729	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	120	65	70	5[redacted].1
1	120	65	70	
1	125	64	70	
16	148	74	70	5[redacted].3
29	139	66	70	5[redacted].8
52	128	62	70	5[redacted].7
113	127	72	70	5[redacted].5
134	143	65	70	5[redacted].4
183	140	69	70	5[redacted].5
232	147	75	70	5[redacted]
281	128	70	70	5[redacted].5
337	160	76	70	5[redacted].6
357	132	60	72	5[redacted].5
371	144	60	71	5[redacted].5
392	123	60	70	5[redacted].5
406	120	60	75	5[redacted].8
455	132	69	75	5[redacted].7
511	144	72	76	5[redacted].3
521	139	70	74	5[redacted]
546	128	63	72	5[redacted].2
567	136	69	72	5[redacted].4
591	143	69	76	5[redacted].4
619	122	69	67	5[redacted].4
647	121	66	66	5[redacted].6

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
679	140	70	76	5[redacted].1
700	111	54	77	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	17	30	5.13	118(H)
10	36	79(H)		
16	80(H)	103(H)		
20	34	46(H)		
52		30		
113	15	27	3.762	113
232	17	38	4.959	98
337	26	48(H)	6.498	103
679	20	32	12.141	136(H)
733	65(H)	215(H)		
734	71(H)	187(H)		
735	53(H)	125(H)		
736	249(H)	683(H)		
737	256(H)	481(H)		
738	190(H)	201(H)		
739	192(H)	255(H)		
740	147(H)	163(H)		
741	121(H)	105(H)		
742	84(H)	72(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
-7	200.668(H)
1	221(H)
113	229.84(H)
232	212.16(H)
337	203.32(H)
392	228.956(H)
406	233.376(H)
546	249.288(H)
567	239.564(H)
679	282.88(H)
720	293.488(H)
721	297.908(H)
722	306.748(H)
724	342.108(H)
725	374.816(H)

Study Day	CREAT µmol/L
727	342.108(H)
729	346.528(H)
730	253.708(H)
731	299.676(H)
732	345.644(H)
733	384.54(H)
734	411.06(H)
735	307.632(H)
736	373.932(H)
737	299.676(H)
738	351.832(H)
739	257.244(H)
740	298.792(H)
741	342.992(H)
742	297.908(H)

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

Table 5. Potential Study Endpoints

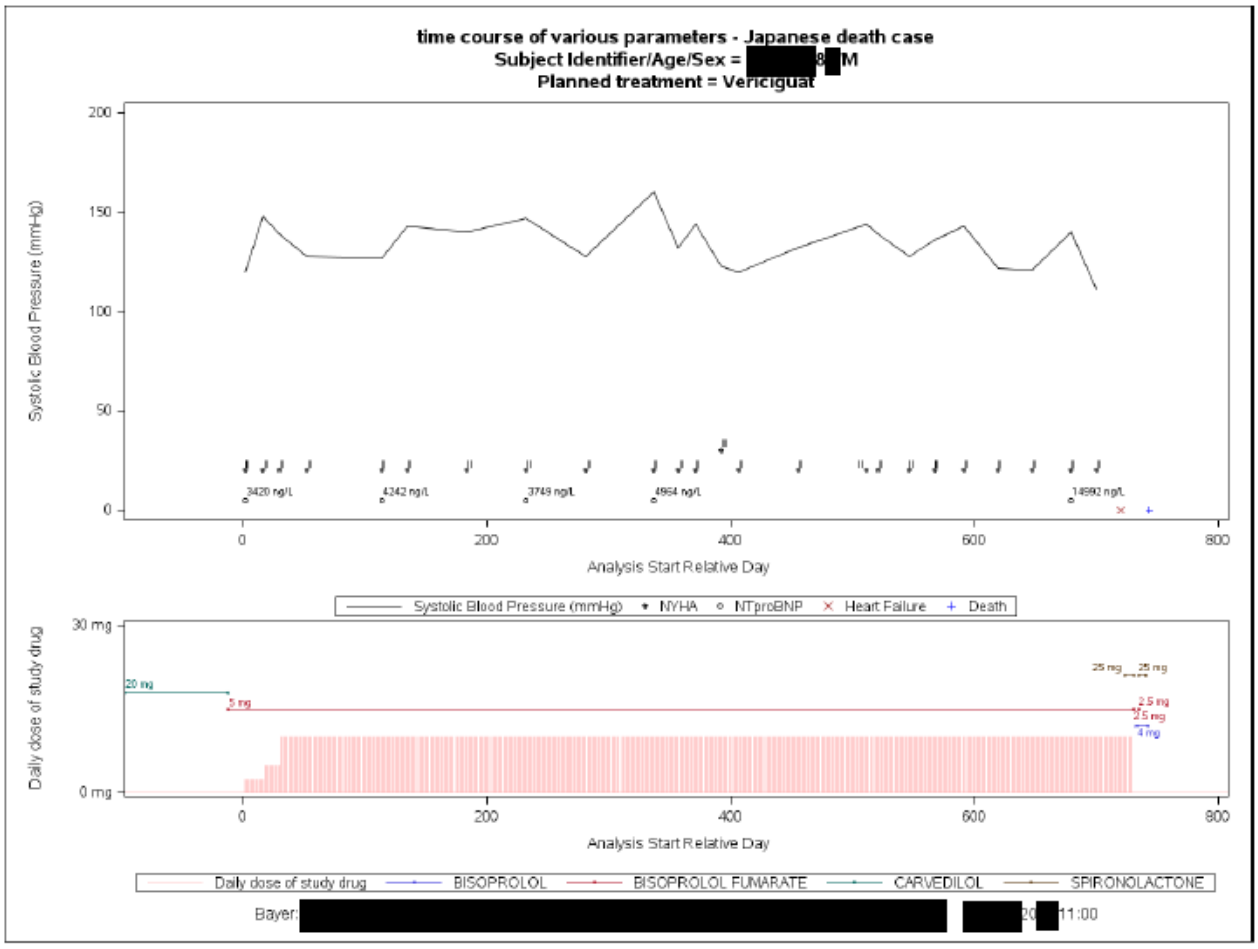
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
16	21	Other Cardiovascular Event	Hospitalization	Not Hospitalized
392		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
720	743	Heart Failure	Hospitalization	Heart Failure
743		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 M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
3420 ng/L
4242 ng/L
3749 ng/L
4984 ng/L
14992 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
20 mg
5 mg
25 mg
25 mg
2.5 mg
2.5 mg
4 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL
BISOPROLOL FUMARATE
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)
Non-CV Death	Pneumonia bacterial	細菌性肺炎		Day 211
SAE	Urinary tract infection	尿路感染	Severe	Day 122
SAE	Hyperglycaemia	高血糖	Severe	Day 125
SAE	Pneumonia bacterial	細菌性肺炎	Severe	Day 196
SAE	Fungaemia	真菌血症	Severe	Day 196

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 1 year, 9 months, 7 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Hyperlipidaemia; Diabetes mellitus; Hypertension; Coronary artery disease; Myocardial infarction; Cerebrovascular accident; Bundle branch block right; Sleep apnoea syndrome; Osteomyelitis; Constipation; Ventricular tachycardia; Anaemia; Peripheral arterial occlusive disease; Chronic kidney disease; Hyperuricaemia; Pneumonia
History of Medical/ Surgical Procedures	Cardiac pacemaker insertion; Percutaneous coronary intervention; Coronary artery bypass; Continuous positive airway pressure

Concomitant Medications at Randomization	pitavastatin calcium, insulin glargine, acetylsalicylic acid, lansoprazole, tolvaptan, furosemide, carvedilol, enalapril maleate, insulin lispro

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-30	652 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	31 %		
1		NYHA CLASS II	59.9 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、本試験組入れの約 30 年間前から糖尿病があった。

第 122 日に発熱を伴う尿路感染が発現した。第 125 日に被験者は尿路感染のため入院し、高血糖が認めら

れた。入院時に一過性の頻脈、心拍数 81bpm、呼吸数増加及び疲労が認められた。血液及び尿培養は陽性であった。尿路感染のため治験薬の投与は中断され、第 127 日目に 2.5mg で再開された。インスリンリスプロ、インスリングラルギン、セフトリアキソンナトリウム、ピペラシリンナトリウム／タゾバクタムナトリウムが投与された。第 132 日に心不全の増悪（非重篤な有害事象）が認められ、フロセミド、トルバプタン及びアゾセミドが投与された。第 148 日に尿路感染及び高血糖は消失し、被験者は退院し、帰宅した。心不全は未回復であった。

第 196 日に発熱及び頭部ふらふら感が発現した後、被験者は細菌性肺炎及び真菌血症のため入院した。褥瘡性潰瘍（非重篤な有害事象）も発現した。胸部 CT 及び胸部 X 線検査で肺野のすりガラス陰影が認められた。血液培養は陽性であった。第 197 日に心房細動（非重篤な有害事象）が発現し、ヘパリンナトリウムが投与された。第 196 日に真菌血症のため治験薬の投与が中断され、第 198 日に 2.5mg で再開されたが、内服薬の経口投与が困難となり第 200 日に治験薬の最終投与が行われた。第 201 日に強直性痙攣（非重篤な有害事象、30 分間持続）及び急性腎障害（非重篤な有害事象）が発現した。胸部 CT 検査ですりガラス陰影の増悪及び急性呼吸窮迫症候群が認められた。パラセタモール、スピロノラクトン、フロセミドナトリウム、カンレノ酸カリウム、グルコース／塩化ナトリウム／乳酸ナトリウム、アンピシリンナトリウム／スルバクタムナトリウム、ヒトインスリン、塩化カルシウム二水和物／グルコース／塩化カリウム／酢酸ナトリウム／塩化ナトリウム、グアイアズレン、エドキサバントシル酸塩水和物、インスリンリスプロ、ピペラシリンナトリウム／タゾバクタムナトリウム、正常ヒト免疫グロブリン、インスリングラルギン、フルコナゾール、アミノ酸 NOS／電解質 NOS／グルコース／チアミン塩酸塩、レボフロキサシン、アンホテリシン b リポソーム、アゾセミド、ノルエピネフリン、ホスフルコナゾール、トルバプタン、センノシド a+b 及びモルヒネ塩酸塩が投与された。第 202 日に低血圧（非重篤な有害事象）が発現した。収縮期血圧は 60mmHg で、症状は報告されなかった。第 211 日に被験者は細菌性肺炎のため死亡した（目撃者ありと報告された）。剖検が実施されたが、結果は報告されなかった。褥瘡性潰瘍、心房細動、急性腎障害及び低血圧の転帰は未回復であった。

治験責任（分担）医師により、尿路感染、高血糖、細菌性肺炎及び真菌血症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	2.5	1
30	42	MK-1242	2.5	1
43	43	MK-1242	2.5	0
44	91	MK-1242	2.5	1
92	123	MK-1242	2.5	1
124	124	MK-1242	2.5	0
125	126	MK-1242	2.5	0
127	148	MK-1242	2.5	1
149	195	MK-1242	2.5	1
196	197	MK-1242	2.5	0
198	199	MK-1242	2.5	1
200	200	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	121	66	74	5[redacted]
1	121	66	74	
1	121	70	64	
15	97	58	67	6[redacted].6
29	112	70	70	6[redacted].7
56	103	63	68	6[redacted].6
91	96	55	60	5[redacted]
126	119	59	64	5[redacted].3
127	142	78	74	5[redacted].9
139	92	54	64	5[redacted].2
148	115	71	68	5[redacted].2
161	101	49	60	5[redacted]
189	97	64	60	6[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	7(L)	9(L)	3.42	94
125			18.81	
126	20	32	6.84	159(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	91.936
1	106.08
125	119.34(H)
126	150.28(H)
126	140.556(H)
147	120.224(H)
157	136.136(H)
196	110.5(H)
197	115.804(H)
198	137.02(H)
199	153.816(H)
200	171.496(H)
201	212.16(H)
202	198.016(H)
203	230.724(H)
204	231.608(H)
205	272.272(H)
209	366.86(H)

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

Table 5. Potential Study Endpoints

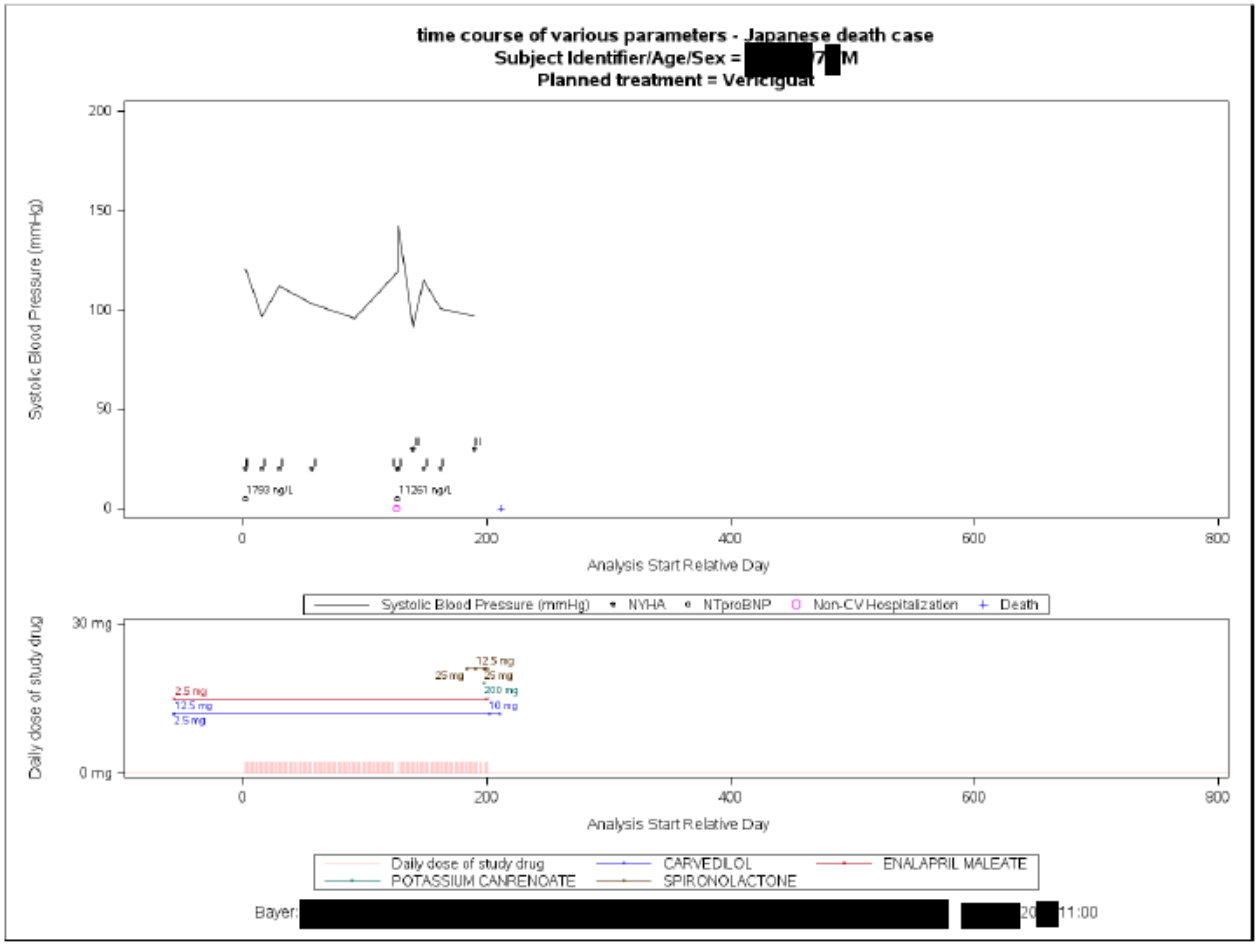
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
15		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
125	148	Non-CV Hospitalization	Hospitalization	Non-CV Hospitalization
211		Non-CV Event	Death	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)
CV Death	Cardiac failure	心不全		Day 81
Event of Clinical Interest	Liver function test abnormal	肝機能検査異常	Mild	Day 81

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 15 years, 4 months, 10 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Cerebrovascular accident; Insomnia; Myocardial infarction; Hypertension; Atrial fibrillation; Peripheral arterial occlusive disease; Coronary artery disease; Angina pectoris; Constipation; Hyperuricaemia; Back pain; Osteoporosis; Spinal osteoarthritis; Glaucoma; Cataract; Tinea pedis; Seasonal allergy; Urticaria; Pneumonia; Nephrolithiasis; Hepatic steatosis; Benign prostatic hyperplasia; Echocardiogram
History of Medical/ Surgical Procedures	Coronary artery bypass; Implantable defibrillator insertion; Percutaneous coronary intervention

Concomitant Medications at Randomization	enalapril maleate, torasemide, digoxin, loxoprofen sodium, magnesium oxide, olopatadine hydrochloride, carvedilol, nizatidine, zolpidem tartrate, allopurinol, warfarin, pimobendan, bepridil hydrochloride monohydrate, zopiclone, acetylsalicylic acid, prasugrel hydrochloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-21	755 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
-43	20 %		
1		NYHA CLASS II	58.6 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 1 年前から脂肪肝があった。

被験者は第 11 日～第 53 日に不整脈のため入院した。

第 61 日に被験者は心不全のため入院し、フロセミド及びトルバプタンが投与された。第 63 日に肝機能検査値異常（非重篤な有害事象）が発現した。胸部 X 線及び心エコー像は正常であった。第 67 日に悪心（非重篤な有害事象、30 分間持続）が発現した。悪心に対してドンペリドンが投与された。第 75 日に肝機能検査値異常は消失した。第 80 日に治験薬の最終投与が行われた。第 81 日に肝機能検査値異常（非重篤な有害事象）が再度発現した。第 81 日に心不全の増悪による致死的な心房細動が発現し、被験者は心不全のため死亡した（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、肝機能検査値異常の転帰は未回復であった。

治験責任（分担）医師により、肝機能検査値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	15	MK-1242	2.5	1
16	29	MK-1242	2.5	1
30	79	MK-1242	2.5	1
80	80	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	104	66	74	5[redacted]9
1	104	66	74	
1	117	67	68	
16	90	64	79	5[redacted]6
30	99	63	76	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	17	24	11.457	99
63	86(H)	66(H)	30.78(H)	299
67	47(H)	30	34.2(H)	316
75	30	52(H)	27.36(H)	407(H)
76	24	32	29.07(H)	269
78	22	37	29.07(H)	273
81	190(H)	321(H)	59.85(H)	271

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	98.124(H)
1	106.08

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

Table 5. Potential Study Endpoints

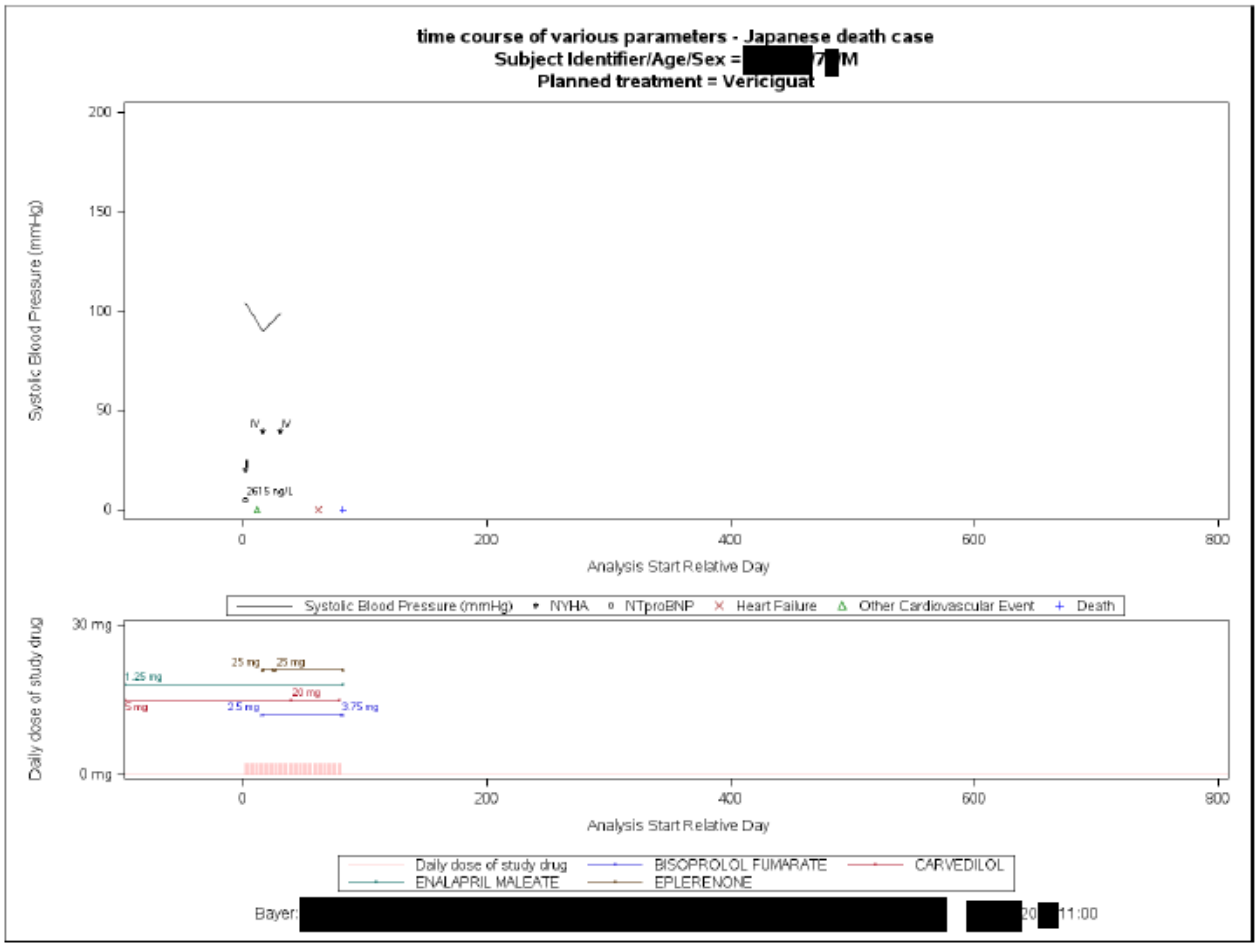
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
11	53	Other Cardiovascular Event	Hospitalization	Other Cardiovascular Event
61	81	Heart Failure	Hospitalization	Heart Failure
81		Heart Failure	Death	Heart Failure

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 93

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 379 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Appendicitis, Bacteraemia, Conjunctivitis, Coronary artery disease, Echocardiogram, Myocardial infarction, Anaemia, Angina pectoris, Blood albumin decreased, Constipation, Diabetes mellitus, Hyperlipidaemia, Hypertension, Insomnia, Oral candidiasis, Sarcopenia, Seasonal allergy
History of Medical/ Surgical Procedures	Coronary artery bypass, Percutaneous coronary intervention

Concomitant Medications at Randomization	clopidogrel bisulfate, lansoprazole, clostridium butyricum, azosemide, carvedilol, perindopril erbumine, amiodarone hydrochloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-8	513.7 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	23 %		
1		NYHA CLASS II	93.7 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 64 日に心不全のため入院した。心不全の治療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 63 日であった。入院中、第 64 日に肺炎（非重篤な有害事象）、第 91 日に多臓器機能不全症候群（非重篤な有害事象）が発現した。その後、被験者は第 93 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。剖検は実施されなかった。死亡時に、多臓器機能不全症候群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	10	MK-1242	2.5	1
11	22	MK-1242	2.5	1
23	62	MK-1242	2.5	1
63	63	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	101	58	77	
1	101	58	77	3[redacted].6
1	93	58	69	
10	91	58	83	3[redacted].4
22	94	53	78	3[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	7(L)	13	8.379	81
91	739	1584(H)	-	1131(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	70.72

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

Table 5. Potential Study Endpoints

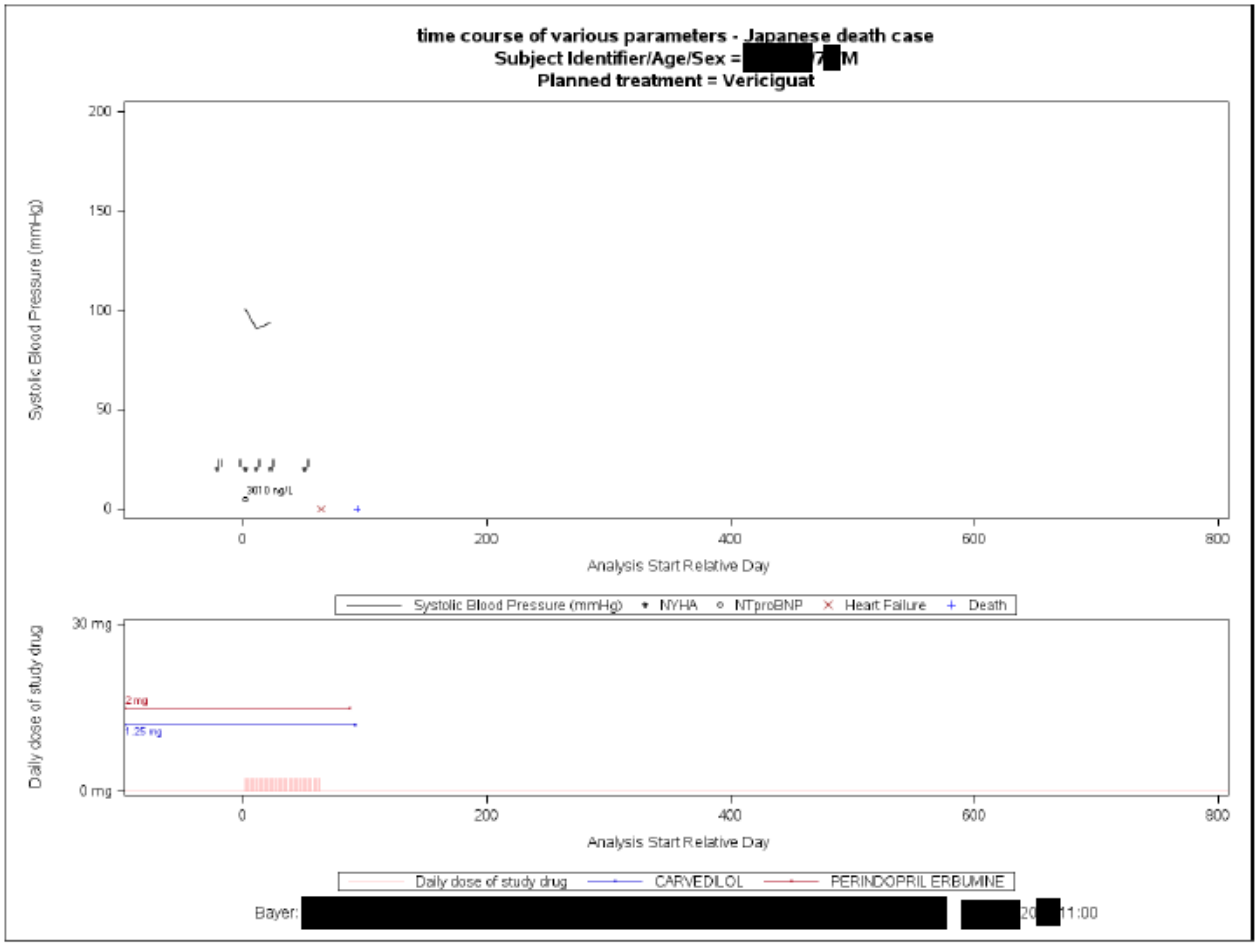
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
64	93	Heart Failure	Hospitalization	Heart Failure
93		Heart Failure	Death	Heart Failure

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 371
SAE	Pubis fracture	恥骨骨折	Severe	Day 42
SAE	Tuberculous pleurisy	結核性胸膜炎	Severe	Day 232
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 273

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 12 years, 10 months, 10 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; Cataract; Retinal tear; Congestive cardiomyopathy; Chronic kidney disease; Constipation; Hyperuricaemia; Anaemia; Dry eye; Senile pruritus; Echocardiogram
History of Medical/ Surgical Procedures	Mitral valve repair; Tricuspid valve repair; Adaptive servo-ventilation

Concomitant Medications at Randomization	pregabalin, magnesium oxide, esomeprazole magnesium, allopurinol, pimobendan, tolvaptan, furosemide, enalapril maleate, mexiletine hydrochloride, warfarin, ferrous sodium citrate, carvedilol, tocopheryl acetate, hyaluronate sodium, pirenoxine, mucopolysaccharide polysulfuric acid ester, trichlormethiazide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1		556.3 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
-29	42 %		
1		NYHA CLASS II	38.4 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:

第 42 日に被験者は転倒後の恥骨骨折のため入院し、安静及び保存的治療を受けた。低血圧及び失神は認

められなかった。第 46 日に心不全の増悪（非重篤な有害事象）と診断され、第 50 日に消失した。第 53 日に尿路感染（非重篤な有害事象）と診断された。プレガバリン、ワルファリン、ワルファリンカリウム、酸化マグネシウム、アロプリノール、メキシレチン塩酸塩、トリクロルメチアジド、カルペリチド、ポリスチレンスルホン酸ナトリウム、クエン酸第一鉄ナトリウム、カルベジロール、エソメプラゾールマグネシウム、イミダプリル塩酸塩、セフカペンピボキシル塩酸塩、ピコスルファートナトリウム、トルバプタン、センノシド a+b、炭酸水素ナトリウム／無水リン酸二水素ナトリウム、ベタメタゾン吉草酸エステル／ゲンタマイシン硫酸塩、及びムコ多糖体多硫酸エステルが投与された。第 59 日に尿路感染は消失し、第 80 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 85 日に恥骨骨折は消失した。

第 106 日に胸部 X 線検査で胸水が認められ、第 107 日に被験者は心不全のため入院した。第 122 日に心臓カテーテルが実施され、第 129 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 149 日に骨髄異形成症候群（非重篤な有害事象）と診断され、赤血球輸血を複数回受けた。

第 239 日に被験者は呼吸困難の発現後に結核性胸膜炎（発現日は第 232 日）のため入院した。胸部 X 線検査で胸水が認められ、第 239 日及び第 241 日に胸腔吸引が実施され、悪性腫瘍の所見は認められなかった。第 241 日に不眠症（非重篤な有害事象）が認められた。第 246 日に縦隔鏡検査で結核性胸膜炎の病理所見が認められ、1010mL の胸腔ドレナージが行われた。第 267 日に皮膚擦過傷（非重篤な有害事象）が発現した。第 268 日に心不全の増悪（非重篤な有害事象）が認められた。第 273 日にミオクローヌス（非重篤な有害事象）が発現した。酸素、ヘパリンナトリウム、グルコース、グリセリン、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、カルバゾクロムスルホン酸ナトリウム、トラネキサム酸、ミダゾラム、パラセタモール、イソニアジド、リファンピシン、エタンブトール二塩酸塩、ドブタミン塩酸塩、リン酸ピリドキサール、ビサコジル、ワルファリン、フロセミドナトリウム、センノシド a+b、酸化マグネシウム及びブロチゾラムが投与された。治験責任（分担）医師の判断により治験薬の投与が中止された。最終投与日は第 273 日であった。第 291 日にミオクローヌスは消失した。第 295 日に心不全の増悪は回復し、被験者は退院し、長期療養施設に入所した。

第 371 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）。剖検は実施されなかった。死亡時に、骨髄異形成症候群、結核性胸膜炎、不眠症及び皮膚擦過傷の転帰は不明と報告された。

治験責任（分担）医師により、恥骨骨折及び結核性胸膜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	14	MK-1242	2.5	1
15	24	MK-1242	5	1
25	25	MK-1242	5	0
26	28	MK-1242	5	1
29	62	MK-1242	10	1
63	105	MK-1242	10	1
106	224	MK-1242	10	1
225	272	MK-1242	10	1
273	273	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	109	50	50	5[redacted].1
1	109	50	50	
1	113	57	70	
15	117	63	75	5[redacted].6
29	113	57	69	5[redacted].2
63	106	37	40	5[redacted].5
106	107	42	44	5[redacted].1
225	108	44	51	5[redacted].7
274	102	45	68	5[redacted].2
289	102	48	76	5[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	16	30	17.1	198(H)
106	9(L)	17	18.468	225(H)
225	7(L)	17	12.996	131(H)
274	6(L)	22	13.167	135(H)
289	11	18	8.208	123(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	141.44(H)
1	150.28(H)
106	141.44(H)
225	203.32(H)
274	159.12(H)
289	132.6(H)

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

Table 5. Potential Study Endpoints

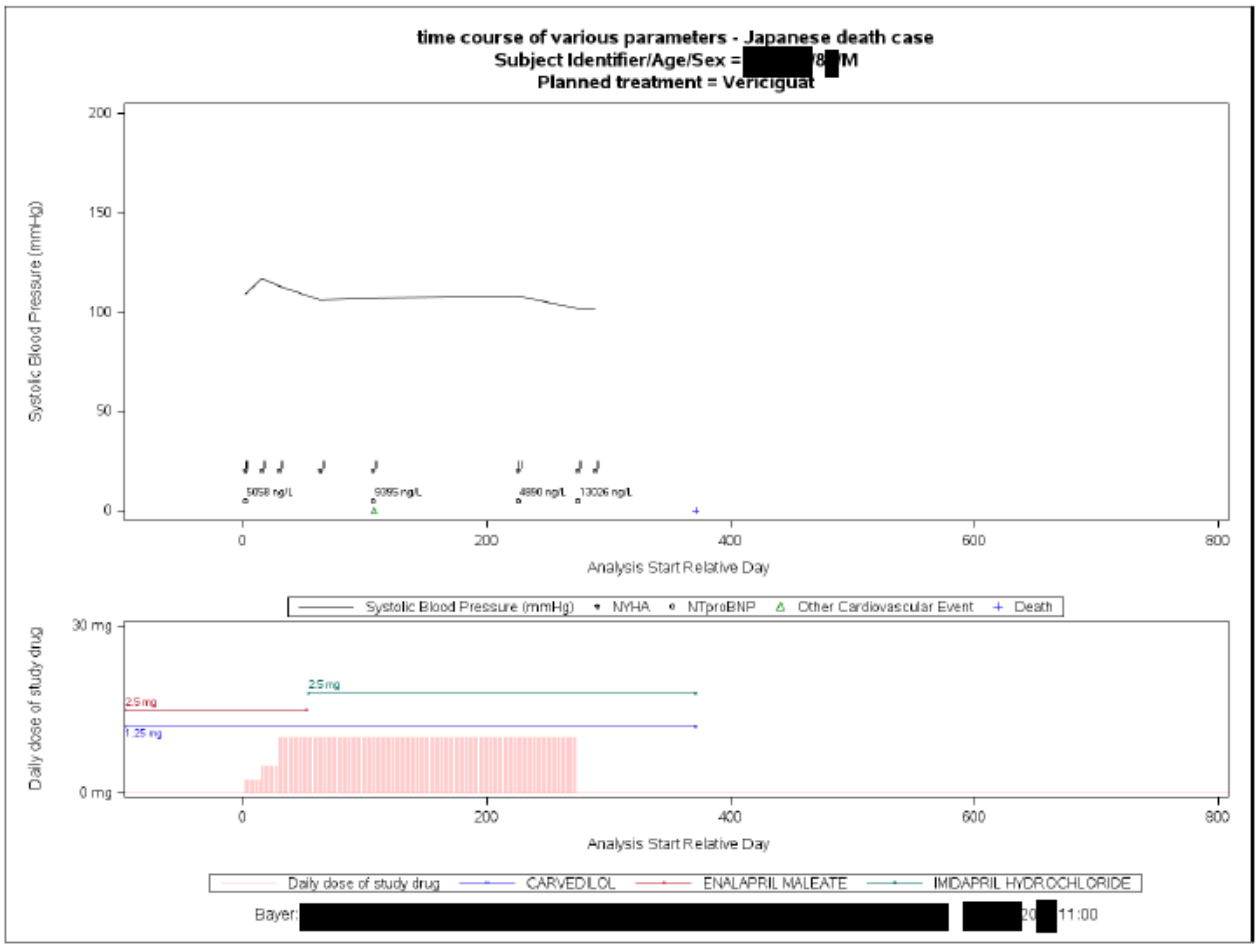
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
107	129	Heart Failure	Hospitalization	Other Cardiovascular Event
371		Heart Failure	Death	Undetermined Cause Of Death

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.



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 fibrillation	心室細動		Day 355
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 240

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

Primary Diagnosis	Subject was initially diagnosed with heart failure approximately 2 years prior to first dose of study medication. Subject was diagnosed with heart failure with reduced ejection fraction approximately 5 months, 7 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Hyperlipidaemia; Hypertension; Myocardial infarction; Angina pectoris; Diabetes mellitus; Lumbar spinal stenosis; Intervertebral disc protrusion; Osteoarthritis; Cardiac failure; Anaemia; Bundle branch block left; Coronary artery disease; Echocardiogram; Atrioventricular block first degree; Left atrial enlargement; Left ventricular enlargement; Mitral valve incompetence; Hyperuricaemia
History of Medical/ Surgical Procedures	Coronary artery bypass; Percutaneous coronary intervention

Concomitant Medications at Randomization	pregabalin, famotidine, spironolactone, metformin hydrochloride, clopidogrel, rosuvastatin, carvedilol, liraglutide, furosemide, hyaluronate sodium, mepivacaine hydrochloride, loxoprofen sodium, tramadol hydrochloride

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-12	452 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
-12	26 %		
1		NYHA CLASS II	55.2 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 243 日に被験者は脳卒中のため入院し、誤嚥性肺炎（非重篤な有害事象）、褥瘡性潰瘍（非重篤な有害事象）及び右腋窩の創傷（非重篤な有害事象）と診断された。心電図検査で、左脚ブロックと心房細動

（非重篤な有害事象）が認められ、心室性期外収縮（非重篤な有害事象）と診断された。頭部 CT 検査で橋に低吸収が認められた。頭部 MRI 及び血管造影で橋出血及び左小脳半球梗塞の疑いが認められた。頚部血管造影で左総頚動脈狭窄の疑いが認められた。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た。最終投与日は第 240 日であった。第 244 日に肝機能検査値が上昇し、肝機能異常（非重篤な有害事象）と診断された。第 247 日に心エコー検査で僧帽弁及び三尖弁に中等度の逆流が認められ、胸部 X 線検査で胸水が認められた。第 250 日に胸部 X 線検査で浸潤影が認められた。第 267 日に心エコー検査で左室壁の運動低下が認められた。第 284 日に腹部 CT 検査で肝うっ血が認められた。第 290 日に心電図検査で心房細動が認められ、心エコー検査で高度の運動低下が認められた。酸素、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、ヒトインスリン、ジルチアゼム塩酸塩、パラセタモール、システイン／グリシン／グリチルリジン酸、エダラボン、ヒドロキソコバラミン酢酸塩／ピリドキシン塩酸塩／チアミンジスルフィド、オメプラゾール、アンピシリンナトリウム／スルバクタムナトリウム、スルファジアジン銀、ロスバスタチン、ポビドンヨード、ピコスルファートナトリウム、*Clostridium butyricum*、アルギン酸ナトリウム、ボノプラザンフマル酸塩、ドブタミン塩酸塩、塩化カリウム、グルコン酸カリウム、インスリングラルギン後続 1、テネリグリプチン臭化水素酸塩水和物、塩化ナトリウム、ヒトアルブミン及びトルバプタンが投与された。フロセミドが増量された。第 324 日に被験者は試験を完了した。入院中に心室細動が発現し、第 355 日に心室細動のため死亡した（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、誤嚥性肺炎、褥瘡性潰瘍、心房細動、心室性期外収縮及び肝機能異常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	15	MK-1242	2.5	1
16	29	MK-1242	5	1
30	50	MK-1242	10	1
51	99	MK-1242	10	1
100	148	MK-1242	10	1
149	204	MK-1242	10	1
205	239	MK-1242	10	1
240	240	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	109	67	71	7[redacted].6
1	109	67	71	
1	111	67	75	
15	112	65	78	7[redacted]
29	118	63	80	7[redacted]
50	132	64	83	8[redacted]
99	120	65	83	7[redacted].9
148	122	67	66	7[redacted].7
204	140	69	81	7[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	19	30	15.903	79
99	15	23	12.996	72
204	15	24	9.747	76
244	54(H)	122(H)	32.49(H)	352(H)
259	22	27	11.115	96

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	119.34(H)
1	114.92
99	88.4
204	88.4
259	53.04(L)

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

Table 5. Potential Study Endpoints

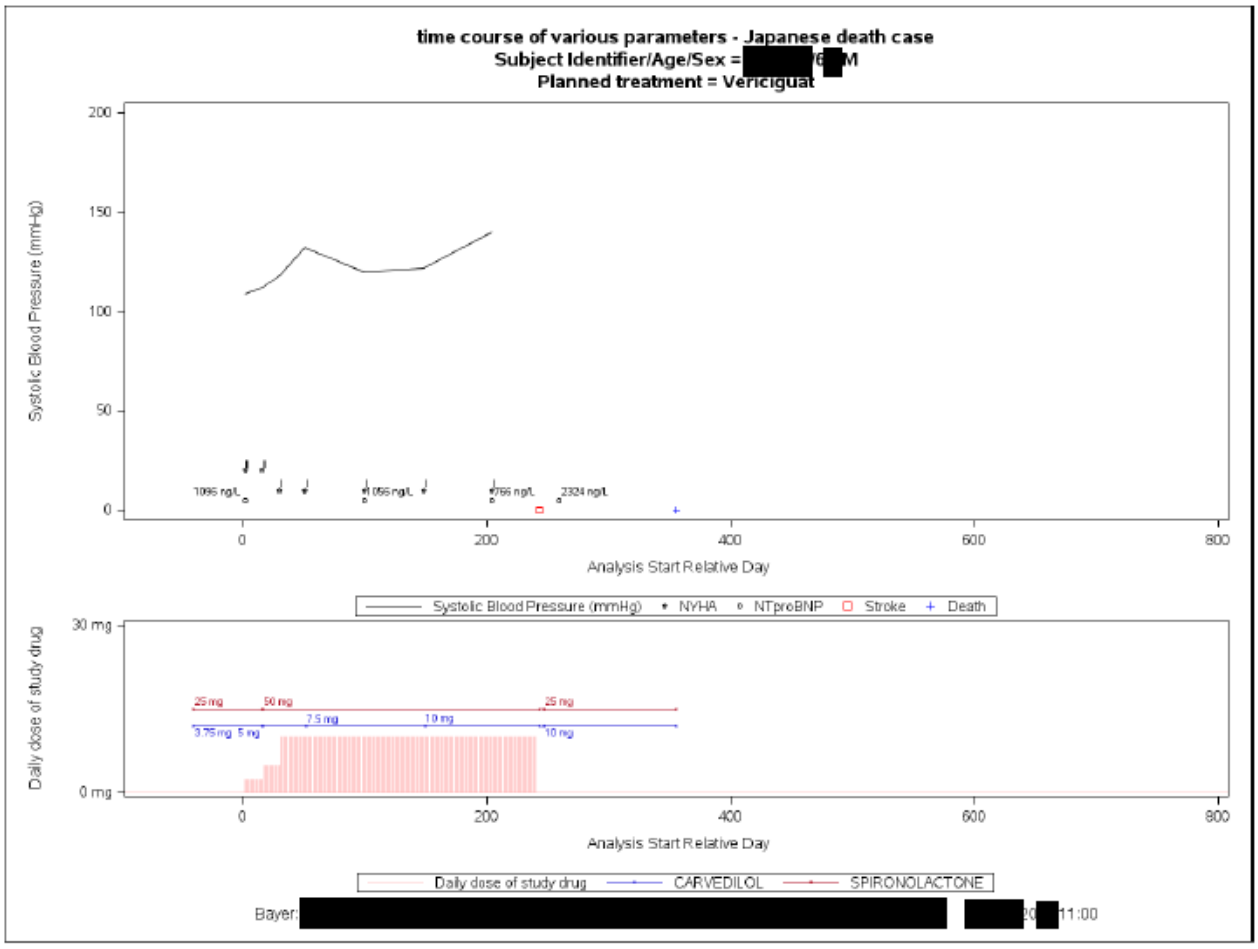
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
243	355	Stroke	Hospitalization	Stroke
355		Sudden Cardiac Death	Death	Stroke

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
1096 ng/L
1056 ng/L
1766 ng/L
2324 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
0 mg
25 mg
50 mg
25 mg
3.75 mg
5 mg
7.5 mg
10 mg
10 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	心不全		Day 188

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

Primary Diagnosis	Subject was diagnosed with heart failure with reduced ejection fraction 97 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Constipation, Echocardiogram, Pneumonia aspiration, Atrial fibrillation, Cardiac failure, Chronic kidney disease, Coronary artery disease, Diabetes mellitus, Diabetic retinopathy, Hyperlipidaemia, Hypertension, Large intestine polyp, Left atrial enlargement, Left ventricular enlargement, Myocardial infarction, Pleural effusion, Sleep apnoea syndrome, Tinea pedis
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	atorvastatin, empagliflozin, sitagliptin phosphate, lansoprazole, acetylsalicylic acid, edoxaban tosilate, white soft paraffin, tolvaptan, enalapril maleate, azosemide, carvedilol, furosemide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	2845 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
-28	26 %		
1		NYHA CLASS II	38.4 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:

第 15 日に低血圧（非重篤な有害事象）が発現し、治験薬の投与は中断された。その後、再開されず、治験薬の最終投与日は第 15 日であった。

家族より連絡があり、被験者は、第 188 日に心不全のため死亡したことが判明した。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。

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	15	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-14	82	52	99	
1	100	60	101	5[redacted]
1	104	59	101	
15	81	48	99	5[redacted]
29	93	52	98	5[redacted].7
50	107	58	94	6[redacted]
99	107	64	104	6[redacted].3
141	108	70	97	5[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	54(H)	25	8.208	125(H)
99	29	23	7.866	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	158.236(H)
1	159.12(H)
99	212.16(H)

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

Table 5. Potential Study Endpoints

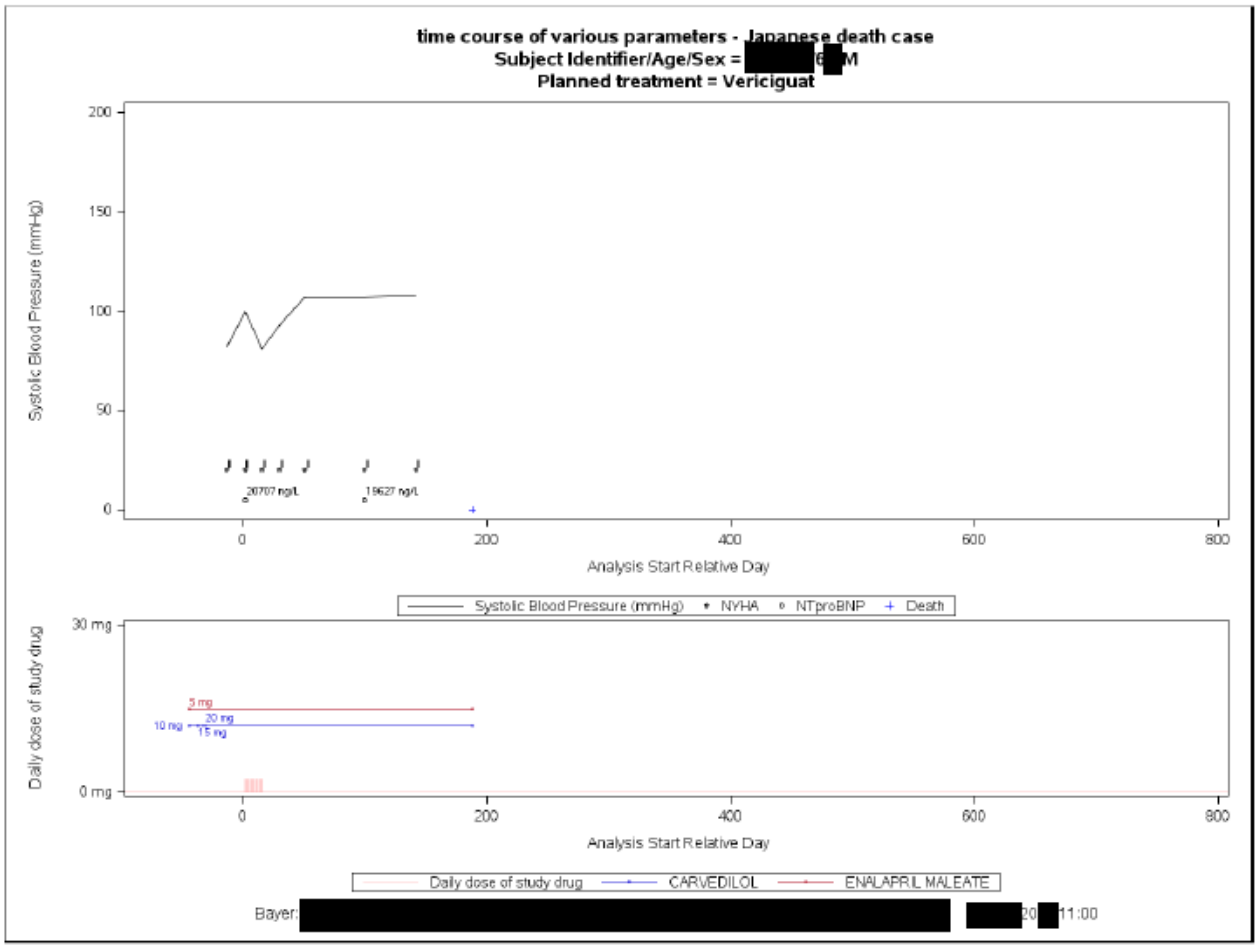
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
188		Heart Failure	Death	Undetermined Cause Of Death

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.



Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
Non-CV Death	Ventricular arrhythmia	心室性不整脈		Day 311
SAE	Diabetes mellitus	糖尿病	Severe	Day 55
SAE	Diabetes mellitus	糖尿病	Severe	Day 216
SAE	Chronic obstructive pulmonary disease	慢性閉塞性肺疾患	Severe	Day 288
SAE	Large intestinal ulcer haemorrhage	出血性大腸潰瘍	Severe	Day 299
SAE	Large intestinal stenosis	大腸狭窄	Severe	Day 309
Event of Clinical Interest	Syncope	失神	Moderate	Day 284
Event of Clinical Interest	Syncope	失神	Moderate	Day 299
Event of Clinical Interest	Hypotension	低血圧	Moderate	Day 309

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 months, 25 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Cerebrovascular accident; Arrhythmia; Chronic obstructive pulmonary disease; Peripheral arterial occlusive disease; Hypertension; Hypertonic bladder; Benign prostatic hyperplasia; Diabetes mellitus; Hyperlipidaemia; Coronary artery disease; Angina pectoris; Chronic kidney disease; Anaemia; Atrial fibrillation; Pemphigoid; Tricuspid valve incompetence; Mitral valve incompetence; Hyperuricaemia; Echocardiogram; Decubitus ulcer; Osteoporosis; Hepatic function abnormal; Skin injury
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	acetylsalicylic acid, rosuvastatin calcium, amlodipine besilate;telmisartan, esomeprazole magnesium, limaprost alfadex, azosemide, spironolactone, amiodarone hydrochloride, mirabegron, miglitol, prednisolone, warfarin potassium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-16	719 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
-82	34 %		

Study Day	LVEF*	NYHA Class*	eGFR
1		NYHA CLASS II	41.5 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 33 年前から慢性閉塞性肺疾患が、約 6 年前から糖尿病があった。

第 27 日に肝機能異常の悪化（非重篤な有害事象）と診断された。第 55 日に低血糖症（非重篤な有害事象、15 分間持続）が発現し、被験者は糖尿病の悪化のため入院した。ミグリトールの投与は継続され、ヒトインスリンの投与及び食事療法・運動療法が実施された。第 60 日に糖尿病の悪化は回復し、被験者は退院し、帰宅した。第 76 日に徐脈（非重篤な有害事象）が発現した。

第 233 日に被験者は徴候及び症状を伴わない糖尿病の悪化（発現日は第 216 日）のため入院し、ステロイド誘発性高血糖（非重篤な有害事象）と診断された。ミグリトール、ヒトインスリン及びインスリングラルギンが投与された。第 255 日に糖尿病の悪化は回復し、被験者は退院し、帰宅した。

第 284 日に失神（非重篤な有害事象、30 秒間持続）が発現した。被験者は病院で検査を受けた。血圧は 133/47mmHg、胸部 X 線検査、心エコー検査及び頭部 CT 検査の結果に臨床的に重要な所見は認められなかった。塩化カルシウム二水和物／グルコース／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 287 日に小腸炎（非重篤な有害事象）が発現し、グルコース／塩化ナトリウム／乳酸ナトリウム、レボフロキサシン及び *Bifidobacterium bifidum* が投与された。第 289 日に被験者は慢性閉塞性肺疾患の悪化（発現日は第 288 日）のため入院し、誤嚥性肺炎（非重篤な有害事象）及びプロトロンビン時間延長（非重篤な有害事象）が認められた。セフトリアキソンナトリウム、サルブタモール硫酸塩、プレドニゾロン、ブロムヘキシン塩酸塩、塩化ナトリウム、アンピシリンナトリウム／スルバクタムナトリウム、イプラトロピウム臭化物水和物及び 23 価肺炎球菌多糖体ワクチンが投与された。第 299 日に出血性大腸潰瘍及び失神（非重篤な有害事象、10 秒間持続）が発現した。血圧は 117／70mmHg であった。赤血球、血漿及びピコスルファートナトリウムが投与され、絶食療法が行われた。出血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 298 日であった。第 300 日に上部消化管内視鏡検査で異常は認められず、結腸内視鏡検査で横行結腸に出血が認められた。非重篤な有害事象として、第 301 日に心室性期外収縮、第 306 日に大腸ポリープ及び痔核、第 307 日に心房粗動が認められた。第 309 日に大腸狭窄、及び倦怠感を伴う低血圧（非重篤な有害事象）が発現した。収縮期血圧は約 70～80mmHg であった。直腸鏡検査で多数の鮮血便が認められ、大腸内視鏡検査で結腸の出血及び大腸狭窄が認められた。血漿、カルバゾクロムスルホン酸ナトリウム、トラネキサム酸、第Ⅱ因子（プロトロンビン）／第Ⅸ因子／第Ⅶ因子（プロコンバーチン）／第Ⅹ因子（スチュアート・プロワー因子）／プロテイン C（凝固阻害薬）／プロテイン S、オメプラゾール、メナテトレノン、赤血球及びヒトアルブミンが投与された。スピロノラクトン、アムロジピンベシル酸塩／テルミサルタン、及びアゾセミドは中止された。第 311 日に心停止となり、直流カルディオバージョンが行われたが、被験者は心室性不整脈のため死亡した（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。死亡時の転帰は、徐脈、高血糖、小腸炎、慢性閉塞性肺疾患、誤嚥性肺炎、プロトロンビン時間延長、大腸潰瘍出血、心室性期外収縮、大腸ポリープ、痔核、心房粗動、大腸狭窄及び低血圧は未回復であり、肝機能異常は軽快であった。

治験責任（分担）医師により、糖尿病（両事象）、慢性閉塞性肺疾患、出血性大腸潰瘍、大腸狭窄、失神

（両事象）及び低血圧は、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	12	placebo	0	1
13	26	placebo	0	1
27	118	placebo	0	1
119	167	placebo	0	1
168	168	placebo	0	0
169	216	placebo	0	1
217	257	placebo	0	1
258	258	placebo	0	0
259	289	placebo	0	1
290	290	placebo	0	0
291	297	placebo	0	1
298	298	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	134	69	59	5[redacted].5
1	134	69	59	
1	139	76	57	
13	132	66	65	5[redacted].4
27	132	71	62	5[redacted].6
55	136	49	66	5[redacted].8
118	104	58	71	4[redacted].9
216	138	66	73	5[redacted].9
307	105	44	47	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	108(H)	73(H)	4.617	63
118	72(H)	39	4.446	51
216	63(H)	37	5.985	54

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	129.064(H)
1	141.44(H)
118	221(H)

Study Day	CREAT µmol/L
216	159.12(H)

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

Table 5. Potential Study Endpoints

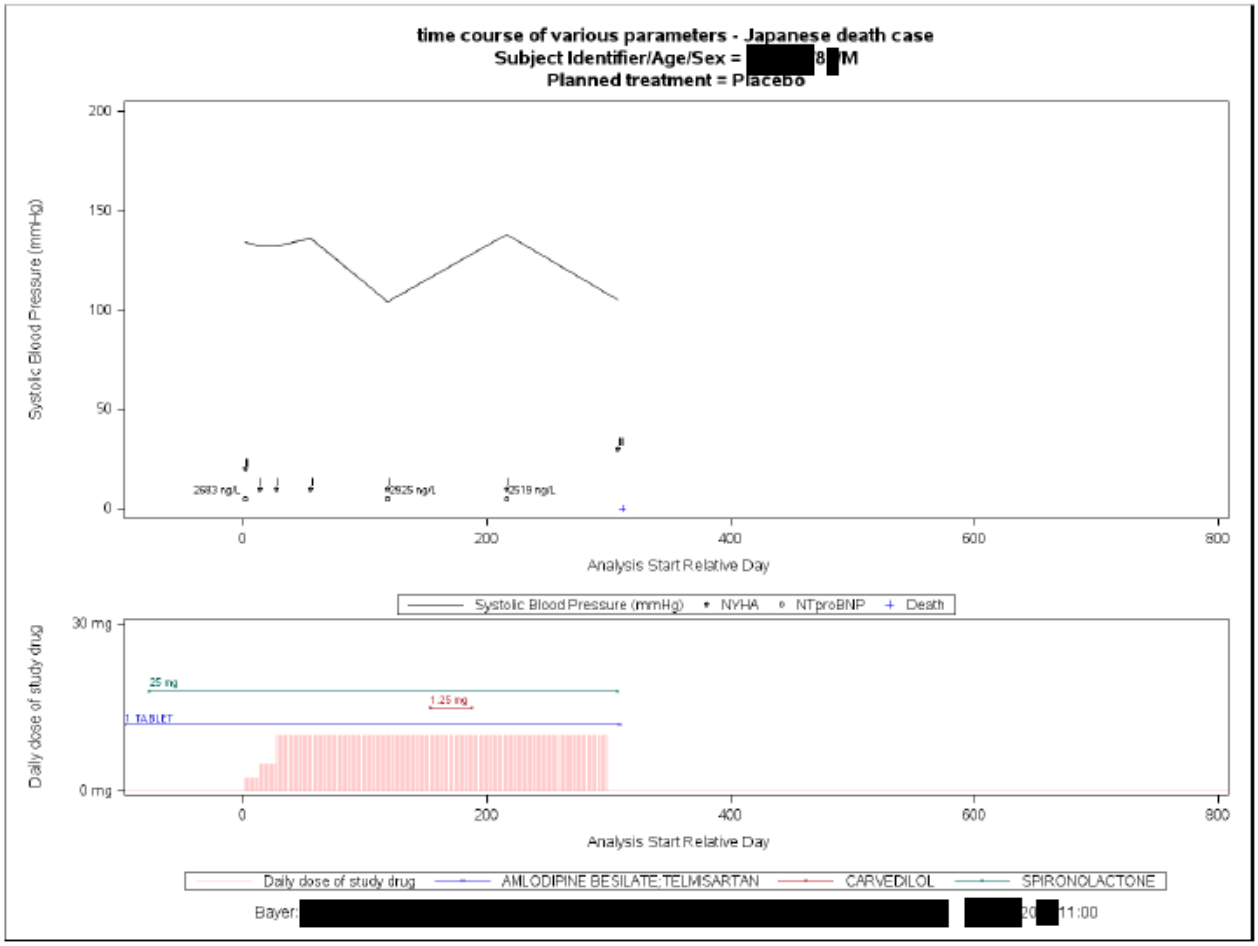
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
311		Sudden Cardiac Death	Death	Non-CV Event

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 72
SAE	Pneumonia	肺炎	Severe	Day 67
Event of Clinical Interest	Hepatic function abnormal	肝機能異常	Moderate	Day 72

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 9 years, 2 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	Coronary artery disease; Angina pectoris; Myocardial infarction; Hyperlipidaemia; Hypertension; Diabetes mellitus; Cardiac failure; Constipation; Anaemia; Sleep apnoea syndrome; Atypical mycobacterial infection; Atrioventricular block complete; Diabetic nephropathy; Back pain; Mitral valve incompetence; Pulmonary valve incompetence; Chronic kidney disease; Atrial fibrillation; Eczema asteatotic; Intervertebral disc protrusion; Tricuspid valve incompetence; Atrioventricular block first degree; Atrioventricular block second degree; Atrial flutter; Hyperuricaemia; Arthritis; Congestive cardiomyopathy; Upper respiratory tract infection; Echocardiogram; Nasopharyngitis
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Cardiac resynchronisation therapy; Implantable defibrillator insertion

Concomitant Medications at Randomization	linagliptin, amiodarone, carvedilol, perindopril erbumine, glimepiride, febuxostat, rabeprazole sodium, azosemide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	588 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
-21	22 %		
1		NYHA CLASS II	35.6 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:

第 36 日に被験者は心不全のため入院した。胸部 X 線検査で肺うっ血及び胸水が認められ、酸素、ヘパリ

ンナトリウム、フロセミド、カルペリチド及びトルバプタンが投与された。第 38 日に胸部不快感（非重篤な有害事象）が発現し、ニトログリセリンが投与された。第 39 日に胸部不快感は消失し、第 48 日に被験者は退院し、帰宅した。

第 71 日に被験者は疲労を伴う肺炎（発現日は第 67 日）のため入院し、心不全の増悪（非重篤な有害事象）と診断された。胸部 X 線検査で肺炎及び心拡大が認められ、フロセミドナトリウム、メロペネム、酸素、パラセタモール及びクラリスロマイシンが投与された。第 72 日に意識不明の状態で発見され、エピネフリンが投与された。心肺蘇生中に血液が採取され、臨床検査で肝機能異常（非重篤な有害事象）が認められた。同日、被験者は肺炎のため死亡した（目撃者ありと報告された）。剖検は実施されなかった。心不全の増悪及び肝機能異常の転帰は未回復であった。治験薬の最終投与日は第 71 日であった。

治験責任（分担）医師により、肺炎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	15	MK-1242	2.5	1
16	29	MK-1242	2.5	1
30	70	MK-1242	2.5	1
71	71	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	113	63	71	5[redacted]65
1	113	63	71	
1	108	76	81	
15	97	68	70	5[redacted].6
29	105	73	75	5[redacted].95

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	21	36	6.669	109
72	4315(H)	12490(H)	56.088(H)	373(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	154.7(H)
1	167.96(H)

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

Table 5. Potential Study Endpoints

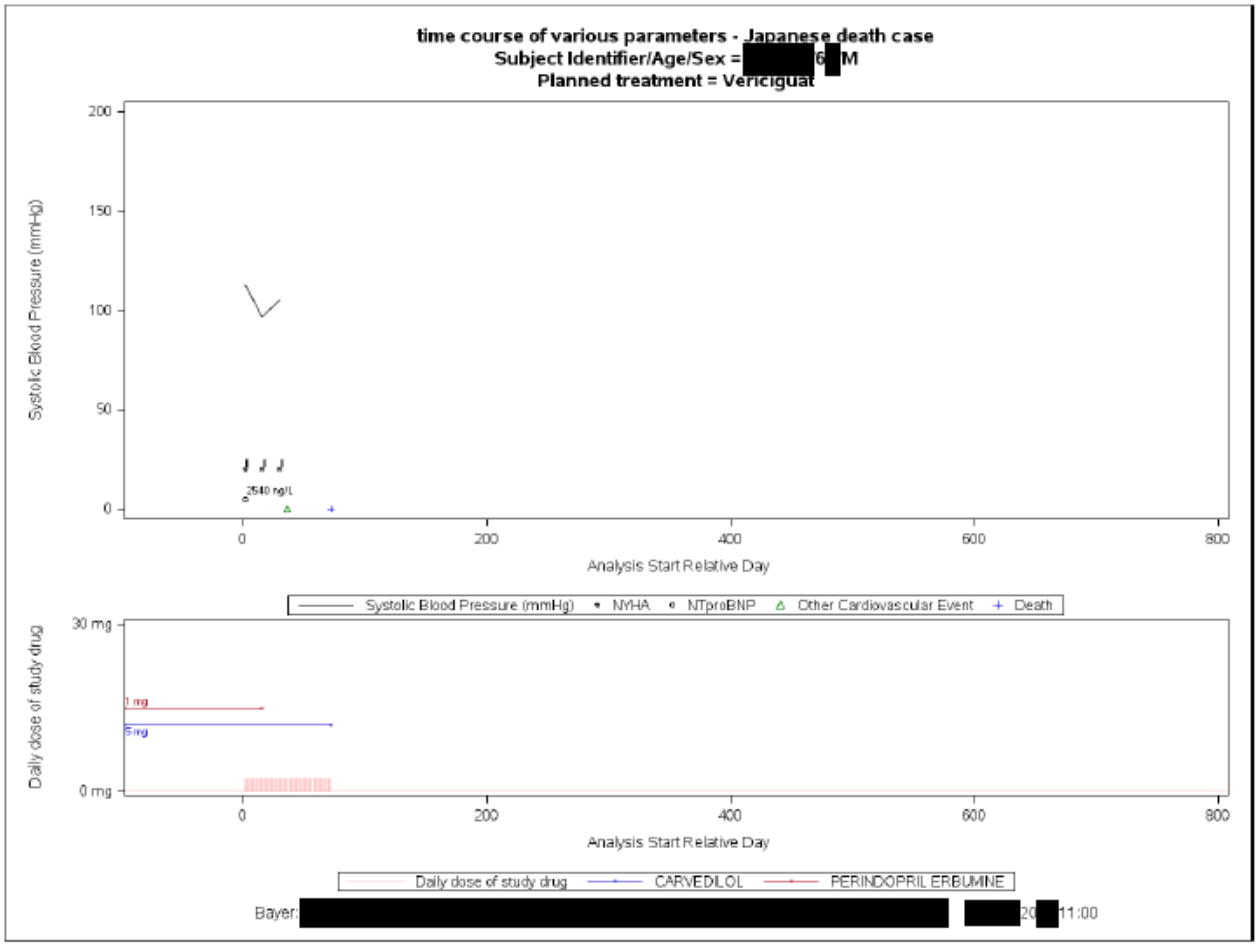
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
29		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
34		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
36	48	Heart Failure	Hospitalization	Other Cardiovascular Event
71	72	Non-CV Hospitalization	Hospitalization	Not Hospitalized
72		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: Matching Placebo + 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 199
SAE	Infectious pleural effusion	感染性胸水	Severe	Day 184

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 years, 11 months, 9 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; Angina pectoris; Diabetes mellitus; Myocardial infarction; Coronary artery disease; Hyperlipidaemia; Peripheral arterial occlusive disease; Hyperuricaemia; Dementia; Diabetic retinopathy; Tinea pedis; Nasopharyngitis; Fibula fracture; Eczema asteatotic; Atrial fibrillation
History of Medical/ Surgical Procedures	Coronary artery bypass

Concomitant Medications at Randomization	furosemide, losartan potassium, rosuvastatin calcium, acetylsalicylic acid;lansoprazole, tolvaptan, terbinafine hydrochloride, urea, insulin aspart, teneligliptin hydrobromide, febuxostat, bisoprolol fumarate, chlorphenamine maleate;dihydrocodeine phosphate;methylephedrine hydrochloride-dl, eplerenone, insulin glargine, mucopolysaccharide polysulfuric acid ester, guaiazulene, pimobendan

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-7	884 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	30 %		
1		NYHA CLASS III	34.1 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:

被験者は第 99 日～第 117 日に心不全のため入院した。

第 162 日に被験者は心不全のため入院し、胸部 X 線検査で胸水の増加、肺動脈のうっ血及び心拡大が認め

られた。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、及びドブタミン塩酸塩が投与され、フロセミドの投与は継続された。不眠症（非重篤な有害事象）と診断され、第 164 日に便秘（非重篤な有害事象）が発現した。第 171 日に褥瘡性潰瘍（非重篤な有害事象）が発現した。第 174 日～第 184 日に胸腔ドレーンが留置され、大量の胸水が除去された。第 184 日、呼吸困難の発現後に感染性胸水と診断された。胸部 X 線検査で膿胸が認められた。胸水は漿液性に変化しており、胸水培養は陽性であった。膿胸の原因は胸水ドレナージのための胸腔チューブの挿入であった。アンピシリンナトリウム／スルバクタムナトリウム及びピペラシリンナトリウム／タゾバクタムナトリウムが投与された。第 187 日に臨床検査でクレアチニンの増加が認められ、慢性腎臓病の悪化（非重篤な有害事象）と診断された。第 188 日に別の胸腔ドレーンが挿入され、少量の膿性液体が排出された。第 192 日に低血糖（非重篤な有害事象）が発現した。トリクロルメチアジド、スボレキサント、ラメルテオン、ルビプロストン、ポビドンヨード、酸化亜鉛、エスゾピクロン、ヘパリンナトリウム、グルコース／塩化ナトリウム／乳酸ナトリウム、グルコース、モルヒネ塩酸塩が投与された。第 199 日に意識レベルの低下が認められ、被験者は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、感染性胸水、不眠症、便秘、褥瘡性潰瘍、慢性腎臓病の悪化及び低血糖の転帰は未回復であった。心不全の治療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 170 日であった。

治験責任（分担）医師により、感染性胸水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	13	placebo	0	1
14	22	placebo	0	0
23	63	placebo	0	0
64	82	placebo	0	1
83	99	placebo	0	1
100	116	placebo	0	1
117	169	placebo	0	1
170	170	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	101	48	70	6[redacted].5
1	101	48	70	
1	92	51	75	
13	87	53	79	6[redacted].9
22	86	52	76	6[redacted].2
64	90	49	83	6[redacted].1
82	92	45	85	6[redacted].3
99	92	51	92	7[redacted].4
116	93	56	85	5[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	15	17	10.089	138(H)
99	19	34	12.825	119(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
-7	166.192(H)
1	167.96(H)
99	176.8(H)
187	252.824(H)

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

Table 5. Potential Study Endpoints

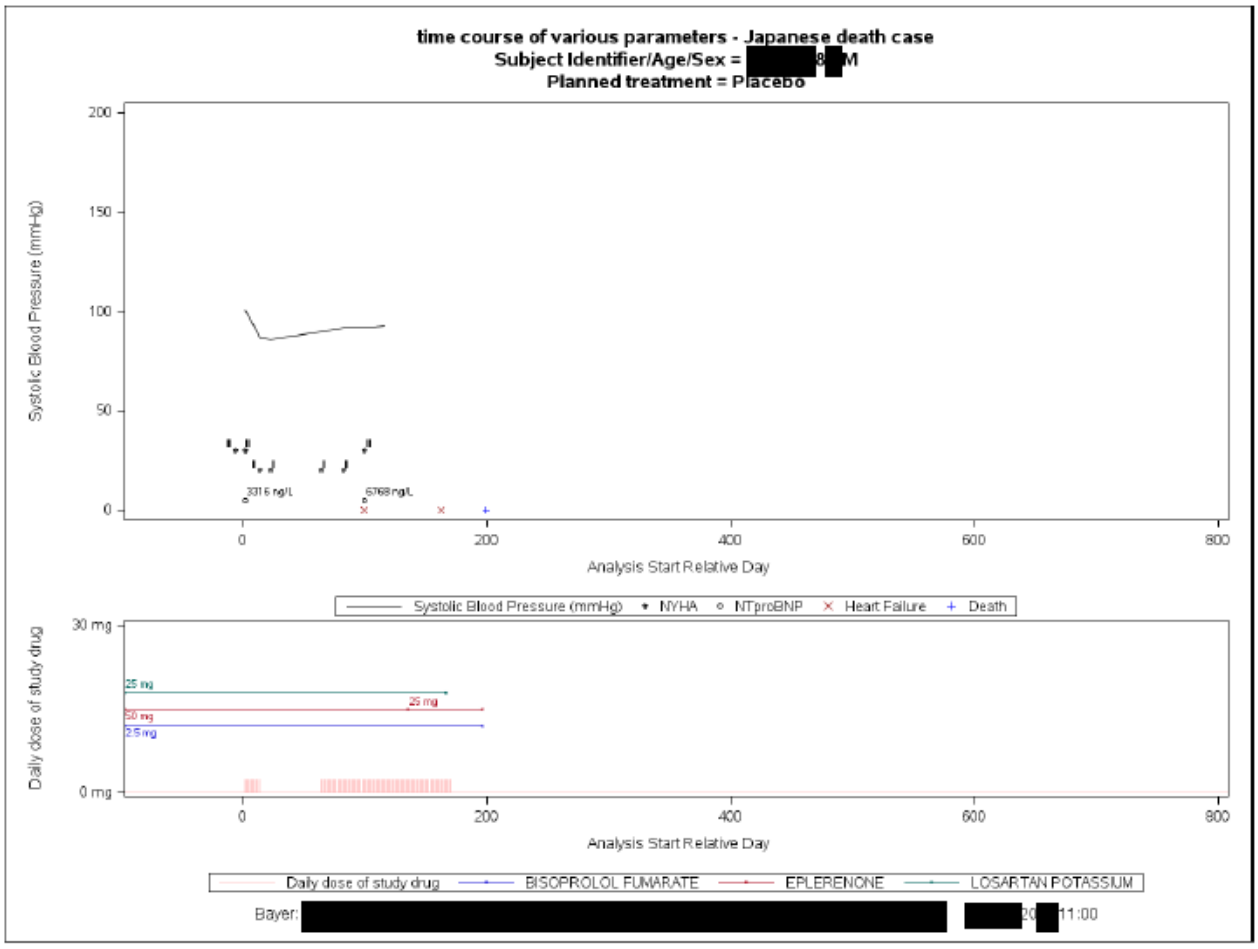
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
99	117	Heart Failure	Hospitalization	Heart Failure
162	199	Heart Failure	Hospitalization	Heart Failure
199		Heart Failure	Death	Heart Failure

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]
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
3315 ng/L
5768 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
25 mg
25 mg
50 mg
2.5 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
EPLERENONE
LOSARTAN POTASSIUM
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 237
SAE	Anaemia	貧血	Severe	Day 120
SAE	Colon cancer	結腸癌	Severe	Day 127
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 150
Event of Clinical Interest	Syncope	失神	Mild	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 1 year, 12 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Chronic gastritis; Dental caries; Headache; Hypertension; Aortic valve incompetence; Cardiac failure chronic; Atrial fibrillation; Lumbar spinal stenosis; Insomnia; Anaemia
History of Medical/ Surgical Procedures	None

Concomitant Medications at Randomization	edoxaban tosilate, amiodarone hydrochloride, carvedilol, nifedipine, olmesartan medoxomil, etizolam, zolpidem tartrate, furosemide, diclofenac sodium, limaprost alfadex, pregabalin, paracetamol, cinnamomum cassia bark;ephedra spp. herb;glycyrrhiza spp. root;paeonia lactiflora root;pueraria lobata root;zingiber officinale rhizome;ziziphus jujuba var. inermis fruit, acetylsalicylic acid;caffeine;paracetamol, bromhexine hydrochloride;carbocisteine

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
-91	40 %		
1		NYHA CLASS II	64.4 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 3 ヵ月前から貧血があった。

第 120 日に被験者は貧血の悪化のため入院し、朝から浮動性めまいがあったと報告した。病院での待機中に失神（非重篤な有害事象、3 分間持続）が発現し、塩化ナトリウムが投与された。血圧は 70／42mmHg、心拍数は 57bpm であった。また、胃潰瘍（非重篤な有害事象）と診断され、上部消化管内視鏡検査で確認され、23 時間後に消失した。濃厚赤血球、含糖酸化鉄、エソメプラゾールマグネシウム、クエン酸鉄ナトリウムが投与された。第 124 日に便秘（非重篤な有害事象）が発現し、センノシド a+b の投与後、第 125 日に消失した。第 127 日に結腸鏡検査で S 状結腸癌及び大腸腺腫が認められ、進行結腸癌と診断された。被験者は 1 ヵ月前にタール便があったこと、癌の病歴がないことも報告した。治験責任（分担）医師により、結腸癌は出血性病変ではなく、貧血の悪化と関連なしと判断された。センノシド a+b が投与された。被験者は結腸癌に対する外科的治療を拒否し、第 130 日に退院し、帰宅した。

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 150 日であった。第 169 日に貧血の悪化は消失した。

第 219 日に被験者は進行結腸癌のため入院し、第 220 日に大腸腺腫のポリープ切除術を受けた。第 221 日に退院し、帰宅した。

第 237 日に被験者は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。剖検の有無は不明であった。死亡時に、結腸癌の転帰は未回復であった。

治験責任（分担）医師により、貧血、結腸癌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	15	MK-1242	2.5	1
16	18	MK-1242	2.5	1
19	36	MK-1242	2.5	0
37	50	MK-1242	2.5	0
51	56	MK-1242	2.5	1
57	57	MK-1242	2.5	0
58	64	MK-1242	2.5	1
65	71	MK-1242	2.5	1
72	72	MK-1242	2.5	0
73	78	MK-1242	2.5	1
79	83	MK-1242	5	1
84	86	MK-1242	5	0
87	92	MK-1242	5	1
93	110	MK-1242	5	1
111	114	MK-1242	5	0
115	120	MK-1242	5	1
121	126	MK-1242	5	1
127	130	MK-1242	10	1
131	146	MK-1242	10	0
147	149	MK-1242	10	1
150	150	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	107	58	77	7[redacted]2
1	107	58	77	
1	120	68	76	
15	95	57	76	7[redacted]6
36	89	50	60	6[redacted]9
50	119	59	69	7[redacted]
64	99	55	80	6[redacted]8
78	106	55	82	7[redacted]
92	98	56	79	7[redacted]2
120				6[redacted]5
126	115	60	79	
150	106	59	82	6[redacted]7
169	119	63	88	6[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	6(L)	15	6.669	41(L)
120	6(L)	20	4.275	33(L)
169	8(L)	19	6.498	62

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	83.98
1	97.24
120	79.56
169	79.56

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

Table 5. Hemoglobin and Hematocrit Laboratory Values

Study Day	HGB g/L	HCT %
1	113(L)	35.2(L)
120	75(L)	23.6(L)
120	76(L)	
128	106(L)	33.6(L)
169	146	46.7
169	148	45.2

A = abnormal; H = high; HCT = hematocrit; HGB = hemoglobin; L = low.

Table 6. Potential Study Endpoints

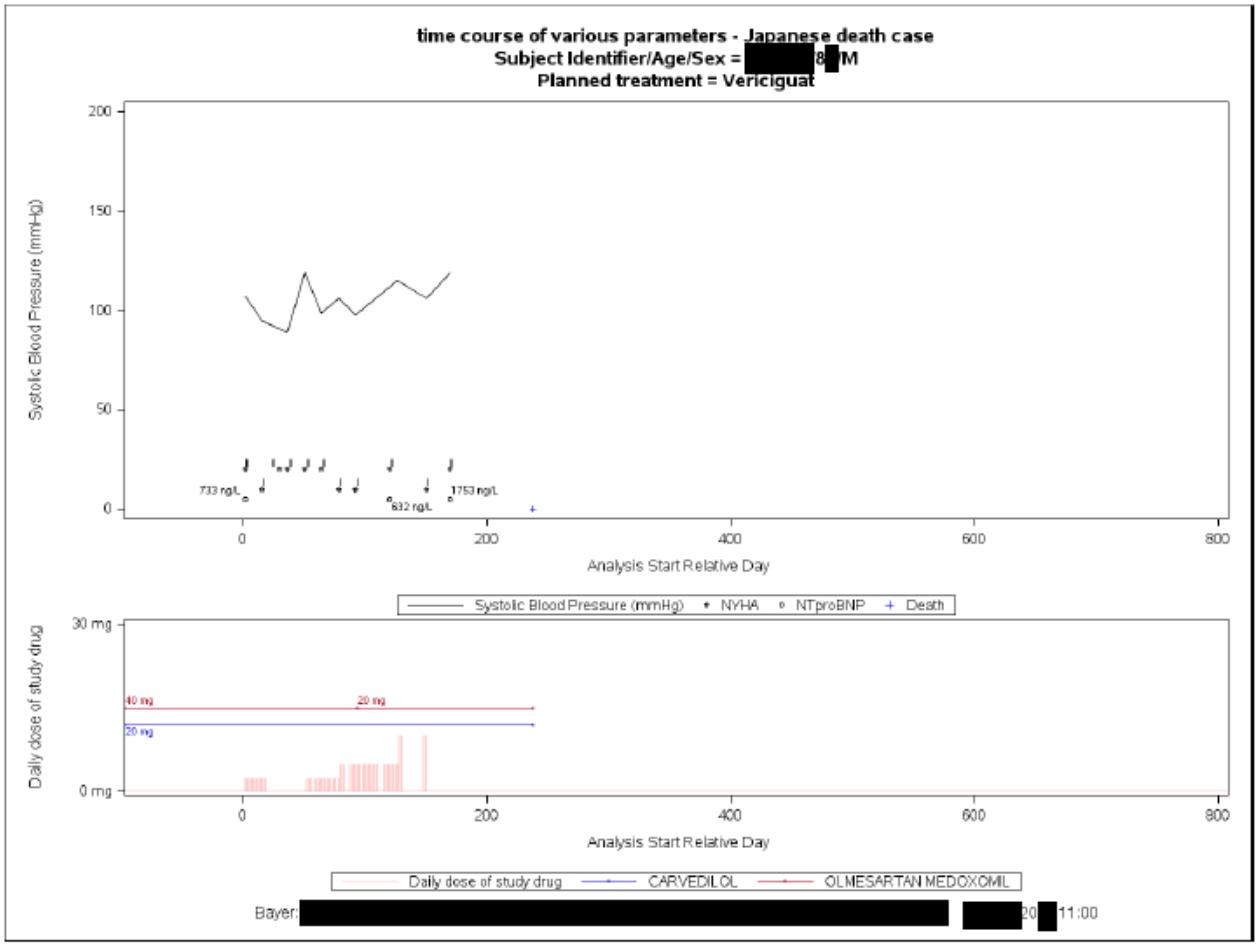
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
237		Heart Failure	Death	Undetermined Cause Of Death

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.



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 789
SAE	Cardiac failure	心不全	Moderate	Day 668
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 487
Event of Clinical Interest	Hypotension	低血圧	Mild	Day 482
Event of Clinical Interest	Hypotension	低血圧	Mild	Day 501

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, 8 months, 23 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Glaucoma; Insomnia; Hyperuricaemia; Coronary artery disease; Myocardial infarction; Diabetes mellitus; Hypertension; Hyperlipidaemia; Hypothyroidism; Constipation; Atrial fibrillation; Atrial flutter; Chronic kidney disease; Echocardiogram
History of Medical/ Surgical Procedures	Percutaneous coronary intervention; Implantable defibrillator insertion; Cardiac resynchronisation therapy

Concomitant Medications at Randomization	levothyroxine sodium, magnesium oxide, atorvastatin, sennoside a+b, etizolam, ramelteon, pimobendan, indapamide, digoxin, apixaban, teneligliptin hydrobromide, acetylsalicylic acid;lansoprazole, furosemide, febuxostat, gliclazide, bisoprolol fumarate, trichlormethiazide, bimatoprost, cyanocobalamin, hyaluronate sodium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
1	639 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
-84	34 %		
1		NYHA CLASS III	45.9 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 244 日～第 286 日に心不全のため、第 414 日～第 420 日に観察のため入院した。

第 473 日に被験者は心不全のため入院した。第 481 日に脱水（非重篤な有害事象）が発現した。第 482 日に脱水のため、浮動性めまいを伴う低血圧（非重篤な有害事象）が発現した。血圧は 73／42mmHg であった。フロセミド及びスピロノラクトンの投与は中止され、エナラプリルマレイン酸塩及びドブタミン塩酸塩が投与された。第 483 日に低血圧は消失した（症状なし）。血圧は 81／45mmHg であった。第 487 日に脱水は消失し、低血圧（非重篤な有害事象）が発現した。症状及び血圧は報告されなかった。低血圧のため治験薬の投与は中断された。その後、治験責任（分担）医師の判断により治験薬の投与は中止され、最終投与日は第 487 日であった。第 493 日に被験者は退院し、帰宅した。

第 498 日に被験者は心不全のため入院し、フロセミドが投与された。第 499 日に胸部 X 線検査で肺うっ血が認められ、心臓カテーテルが実施された。第 500 日に低血圧は消失した。第 501 日目に非重篤な有害事象として、頭部ふらふら感を伴う起立性の低血圧（非重篤な有害事象）と診断された。収縮期血圧は 60～90mmHg、拡張期血圧は 40～60mmHg であった（測定日不明）。第 517 日に被験者は退院し、帰宅した。低血圧の転帰は未回復であった。

被験者は第 530 日～第 555 日、第 610 日～第 619 日、第 626 日～第 636 日に心不全のため入院した。

第 668 日に労作時呼吸困難及び肺うっ血が発現し、心不全の増悪と診断された。胸部 X 線検査で右胸水が認められた。第 673 日に被験者は心不全のため入院し、フロセミドが投与された。胸部 X 線検査でわずかに改善が認められた。第 678 日に胸部 X 線検査で肺うっ血が認められた。第 680 日に腹部膨満（非重篤な有害事象）と診断され、ジメチコンが投与された。第 683 日に心不全の増悪は回復し、被験者は退院し、帰宅した。腹部膨満の転帰は未回復であった。

被験者は第 697 日～第 711 日及び第 739 日～第 789 日に心不全のため入院した。第 789 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。

治験責任（分担）医師により、低血圧（両事象）及び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	14	MK-1242	2.5	1
15	28	MK-1242	5	1
29	244	MK-1242	10	1
245	247	MK-1242	5	0
248	325	MK-1242	5	1
326	386	MK-1242	10	1
387	387	MK-1242	10	0
388	451	MK-1242	10	1
452	470	MK-1242	10	1
471	471	MK-1242	10	0
472	487	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	119	75	94	5[redacted]4
1	119	75	94	
1	104	63	91	
15	119	67	83	5[redacted].3
29	110	69	91	5[redacted].9
57	111	71	84	6[redacted].3
106	102	59	83	5[redacted].7
211	110	62	84	5[redacted].5
248	103	71	81	
266	99	66	80	
295	99	63	87	
325	104	68	83	5[redacted].7
353	101	63	82	6[redacted].1
451	101	60	80	6[redacted]
488	91	62	86	
570	87	54	88	6[redacted].7
668	92	54	62	6[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	19	20	14.706	113
106	18	21	9.063	94
211	30	26	12.996	99
325	20	22	13.338	93
668	17	17	10.431	96

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	122.876(H)
1	132.6(H)
106	185.64(H)
211	185.64(H)
325	194.48(H)
668	212.16(H)

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

Table 5. Potential Study Endpoints

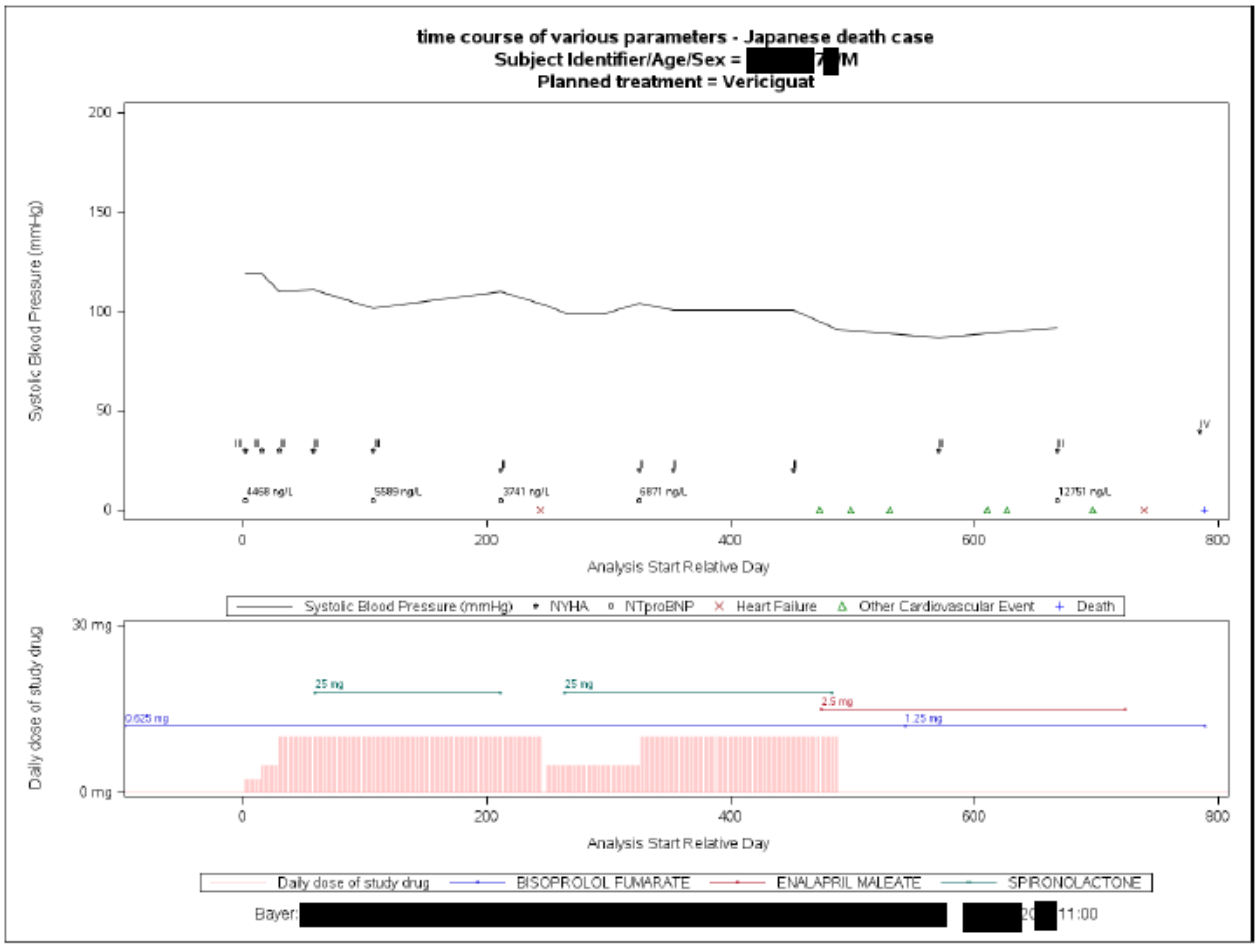
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
57		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
244	286	Heart Failure	Hospitalization	Heart Failure
295		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
473	493	Heart Failure	Hospitalization	Other Cardiovascular Event
498	517	Heart Failure	Hospitalization	Other Cardiovascular Event
528		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Does not meet criteria
530	555	Heart Failure	Hospitalization	Other Cardiovascular Event
570		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
591		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
610	619	Heart Failure	Hospitalization	Other Cardiovascular Event
626	636	Heart Failure	Hospitalization	Other Cardiovascular Event
668		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
673	683	Heart Failure	Hospitalization	Not Hospitalized
697	711	Heart Failure	Hospitalization	Other Cardiovascular Event
739	789	Heart Failure	Hospitalization	Heart Failure
789		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
4468 ng/L
5589 ng/L
3741 ng/L
6871 ng/L
12751 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
0 mg
25 mg
25 mg
2.5 mg
1.25 mg
0.625 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
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	心肺停止		Day 495

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 625 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure 3 to 6 months prior to randomization.

Medical History	Constipation, Coronary artery disease, Diabetes mellitus, Hyperlipidaemia, Hypertension, Mitral valve incompetence, Subclavian artery stenosis, Echocardiogram,
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	sennoside a+b, acetylsalicylic acid, candesartan cilexetil, clopidogrel bisulfate, esomeprazole magnesium, glimepiride, miglitol, mexiletine hydrochloride, furosemide, insulin aspart;insulin degludec, trelagliptin succinate, bisoprolol fumarate, magnesium oxide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-21	506 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
-21	45 %		
1		NYHA CLASS II	38.9 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 2 日～第 20 日、第 67 日～第 90 日に心不全のため入院した。

第 495 日に心肺停止の状態で発見され、死亡に至った。治験責任（分担）医師は、「心肺停止であり直接的な原因が不明なことから現時点では因果関係なし」とし、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 495 日であった。

治験期間中、非重篤な有害事象として、第 2 日に肺炎、第 3 日に高尿酸血症、第 60 日に上咽頭炎、第 150 日に貧血、第 171 日に浮動性めまい、第 229 日に上咽頭炎、第 338 日に口腔内痛が発現した。死亡時

に、貧血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	2	placebo	0	1
3	15	placebo	0	0
16	29	placebo	0	1
30	67	placebo	0	1
68	84	placebo	0	0
85	101	placebo	0	1
102	115	placebo	0	1
116	141	placebo	0	1
142	145	placebo	0	0
146	171	placebo	0	1
172	201	placebo	0	1
202	204	placebo	0	0
205	232	placebo	0	1
233	346	placebo	0	1
347	403	placebo	0	1
404	406	placebo	0	0
407	465	placebo	0	1
466	495	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-21	137	70	69	
1	126	54	101	6[redacted]2
1	124	64	88	
16	112	52	72	5[redacted].2
29	103	51	76	5[redacted].4
67	115	61	67	5[redacted].5
84	108	56	62	
101	112	56	88	5[redacted].9
115	109	51	76	
171	123	55	61	
204	118	53	76	5[redacted].8
232	108	56	82	5[redacted].3
346	133	58	84	5[redacted].8
465	121	53	73	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	12	18	7.866	82
101	19	23	7.695	80
232	19	29	5.13	83
346	23	28	4.104	79

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	106.964(H)
1	150.28(H)
101	123.76
232	141.44(H)
346	123.76

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

Table 5. Potential Study Endpoints

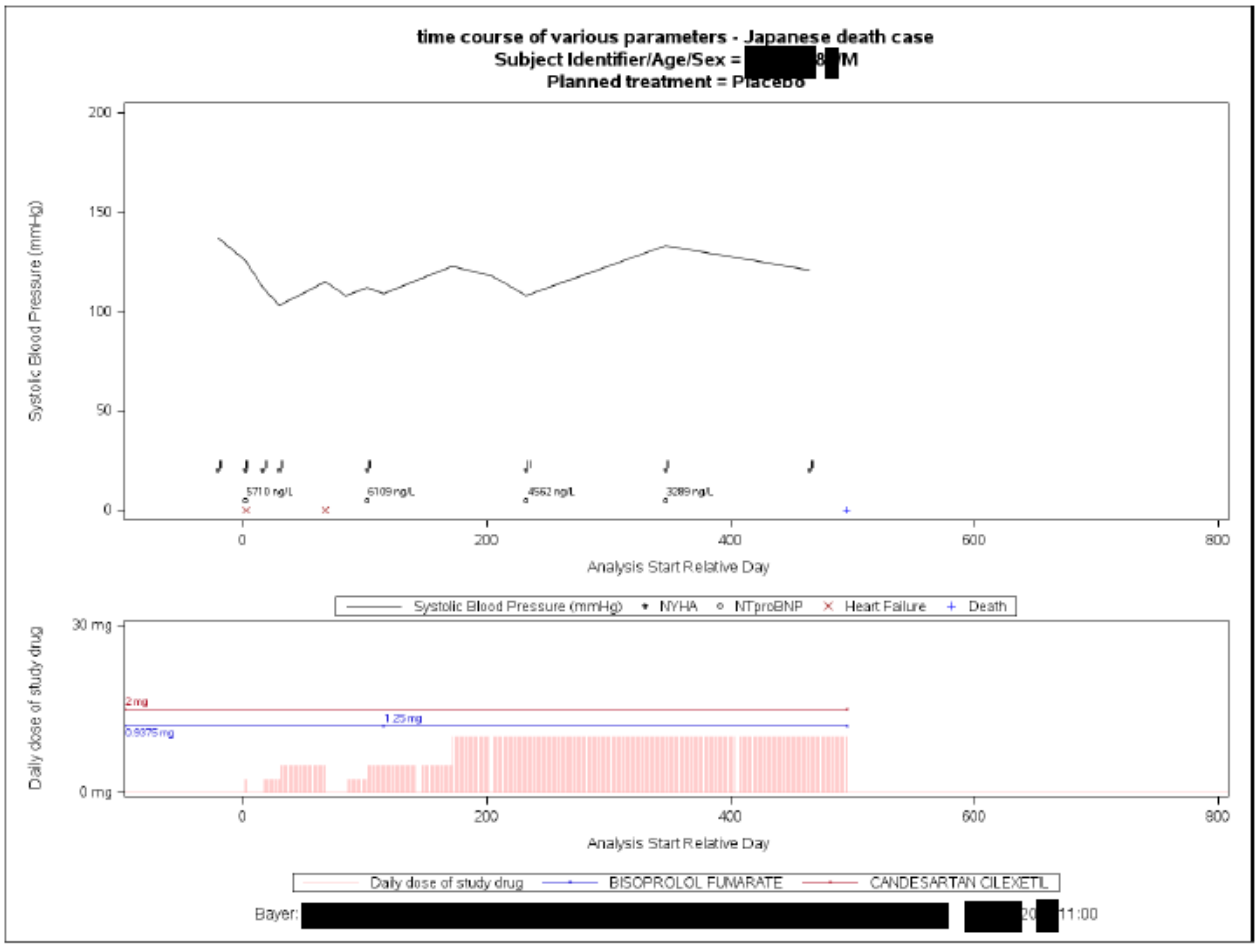
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
2	20	Heart Failure	Hospitalization	Heart Failure
67	90	Heart Failure	Hospitalization	Heart Failure
129		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
495		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]
Planned treatment = Placebo
Systolic Blood Pressure (mmHg)
200
150
100
50
0
5710 ng/L
6109 ng/L
4562 ng/L
3289 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
2 mg
1.25 mg
0.9375 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
CANDESARTAN CILEXETIL
Bayer: [redacted]

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 377
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 344

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 10 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	Hyperlipidaemia; Hypertension; Aortic aneurysm; Hyperuricaemia; Hypoacusis; Insomnia; Constipation; Aortic stenosis; Sleep apnoea syndrome; Anaemia; Mitral valve incompetence; Chronic kidney disease; Artery dissection; Pneumonia; Echocardiogram; Cerebrovascular accident
History of Medical/ Surgical Procedures	None

Concomitant Medications at Randomization	pravastatin sodium, rabeprazole sodium, zolpidem tartrate, acetylsalicylic acid, carvedilol, telmisartan, sennoside a+b, febuxostat, furosemide

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-19	1267 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	37 %		
1		NYHA CLASS II	56.9 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 64 日～第 117 日及び第 295 日～第 313 日に心不全の増悪のため入院した。

第 344 日に被験者は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は中止され、最終投与日は同日であった。胸部 X 線検査では、第 344 日に肺うっ血、第 350 日に浸潤影の悪化が認められ、第 359 日には変化なしであった。第 350 日に血液量減少症（非重篤な有害事象）が発現した。アズレ

ンスルホン酸ナトリウム、アスコルビン酸／ビオチン／カルシウム／炭水化物 NOS／塩素／コリン／クロム／銅／脂肪 NOS／葉酸／フルクトオリゴ糖／鉄／レボカルニチン／マグネシウム／マンガン／モリブデン／ニコチン酸／パントテン酸、フロセミド、ヒトアルブミン、ゾルピデム酒石酸塩、パラセタモール及びヒドロキシジンが投与された。第 367 日に血液量減少症は消失し、心電図検査では特記すべき変化は認められなかった（詳細不明）。第 377 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、治験薬は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	17	MK-1242	2.5	1
18	31	MK-1242	5	1
32	115	MK-1242	5	0
116	218	MK-1242	2.5	1
219	295	MK-1242	2.5	1
296	332	MK-1242	2.5	0
333	344	MK-1242	2.5	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-19	114	64	73	
1	122	56	50	5[redacted].5
1	116	57	44	
17	115	59	48	6[redacted].1
31	81	42	43	6[redacted].6
64	114	57	44	
114	88	62	57	4[redacted].8
115	101	58	60	
129	92	52	63	5[redacted].3
143	102	46	53	
218	97	46	47	5[redacted].8
295	95	51	61	5[redacted].5
332	99	60	62	4[redacted].5
344	94	52	61	
367	93	51	62	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	15	21	4.959	82
87	155(H)	241(H)		
101	30	21		
114	13	17	4.617	76
218	5(L)	12	4.788	65
332	7(L)	16	12.483	66

Study Day	ALT IU/L	AST IU/L	BILI µmol/L	ALP IU/L
367	10	16	11.799	53

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
-19	118.456(H)
1	106.08
114	167.96(H)
218	114.92
332	141.44(H)
367	97.24

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

Table 5. Potential Study Endpoints

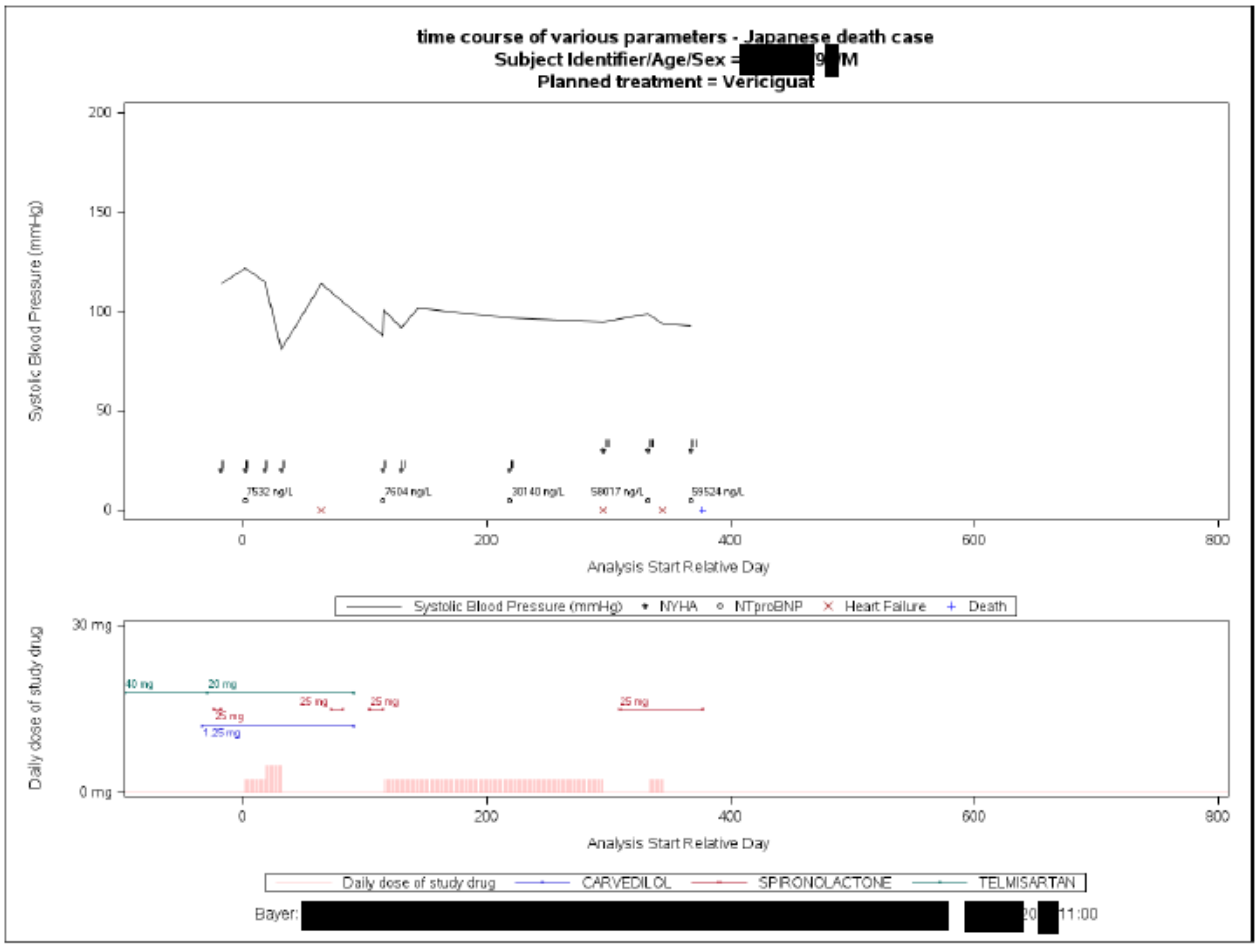
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
17		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
64	117	Heart Failure	Hospitalization	Heart Failure
295	313	Heart Failure	Hospitalization	Heart Failure
332		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
344	377	Heart Failure	Hospitalization	Heart Failure
377		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]9 M
Planned treatment = Vericiguat
Systolic Blood Pressure (mmHg)
200
150
100
50
0
7532 ng/L
7604 ng/L
30140 ng/L
58017 ng/L
59524 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
40 mg
20 mg
25 mg
25 mg
25 mg
25 mg
1.25 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
CARVEDILOL
SPIRONOLACTONE
TELMISARTAN
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 387
Discontinuation of Study Medication Due to Other Reason	Physician Decision			Day 373
Event of Clinical Interest	Hepatic function abnormal	肝機能異常	Moderate	Day 372

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 5 years, 1 month, 12 days prior to first dose of study medication.
Index Event	IV diuretic for heart failure within 3 months of randomization.

Medical History	Coronary artery disease; Hypertension; Alcoholic liver disease; Diabetes mellitus; Angina pectoris; Hyperlipidaemia; Hyperuricaemia; Cataract; Retinal haemorrhage; Echocardiogram; Atrial fibrillation
History of Medical/ Surgical Procedures	Coronary artery bypass; Percutaneous coronary intervention

Concomitant Medications at Randomization	sitagliptin phosphate, rosuvastatin calcium, spironolactone, furosemide, acetylsalicylic acid;lansoprazole, febuxostat, trichlormethiazide, glimepiride, bisoprolol fumarate, edoxaban tosilate

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-21	843 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
-35	35 %		
1		NYHA CLASS II	49.3 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:

被験者の病歴には、本試験組入れの約 10 年前からアルコール性肝疾患があった。

第 372 日に心不全の増悪及び呼吸困難が認められた。臨床検査の結果、BNP、AST、ALT 及び総ビリルビンの上昇が認められ、肝機能異常（非重篤な有害事象）及び胆石症（非重篤な有害事象）と診断された。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 373 日であった。第 374 日、持続性の呼吸困難の発現後に、被験者は心不全のため入院した。同日に出血性素因（非重篤な有害事象）が発現した。ドブタミン塩酸塩、トルバプタン及びフロセミドが投与された。第 376 日に譫妄（非重篤な有害事象）及び感染（非重篤な有害事象）が発現した。セフジニル、ハロペリドール、塩酸リドカイン、ゾピクロン、ラメルテオン、ヒドロキシジン及び塩酸ペンタゾシンが投与された。第 378 日に徐脈（非重篤な有害事象）及び血圧低下（非重篤な有害事象、測定値不明）が発現し、ノルエピネフリンが投与された。第 387 日に被験者は病院で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、肝機能異常、胆石症、出血性素因、譫妄、感染、血圧低下及び徐脈の転帰は未回復であった。

治験責任（分担）医師により、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	placebo	0	1
2	16	placebo	0	1
17	44	placebo	0	1
45	50	placebo	0	0
51	78	placebo	0	1
79	92	placebo	0	1
93	93	placebo	0	0
94	106	placebo	0	1
107	161	placebo	0	1
162	172	placebo	0	0
173	227	placebo	0	1
228	286	placebo	0	1
287	291	placebo	0	0
292	351	placebo	0	1
352	361	placebo	0	1
362	364	placebo	0	0
365	373	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-21	134	70	75	
1	135	80	78	5[redacted].7
1	118	71	70	
16	135	85	90	5[redacted].9
31	121	80	72	5[redacted].1
78	129	82	64	
106	119	70	75	5[redacted]
227	105	72	70	5[redacted].9
351	108	58	95	5[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	23	27	13.167	51
106	12	21	9.576	51
227	24	30	14.193	50
351	9(L)	18	14.535	70
372	781(H)	2584(H)	63.27(H)	243
374	460(H)	478(H)	27.36(H)	234

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	111.384(H)
1	123.76
106	114.92
227	114.92
351	106.08

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

Table 5. Potential Study Endpoints

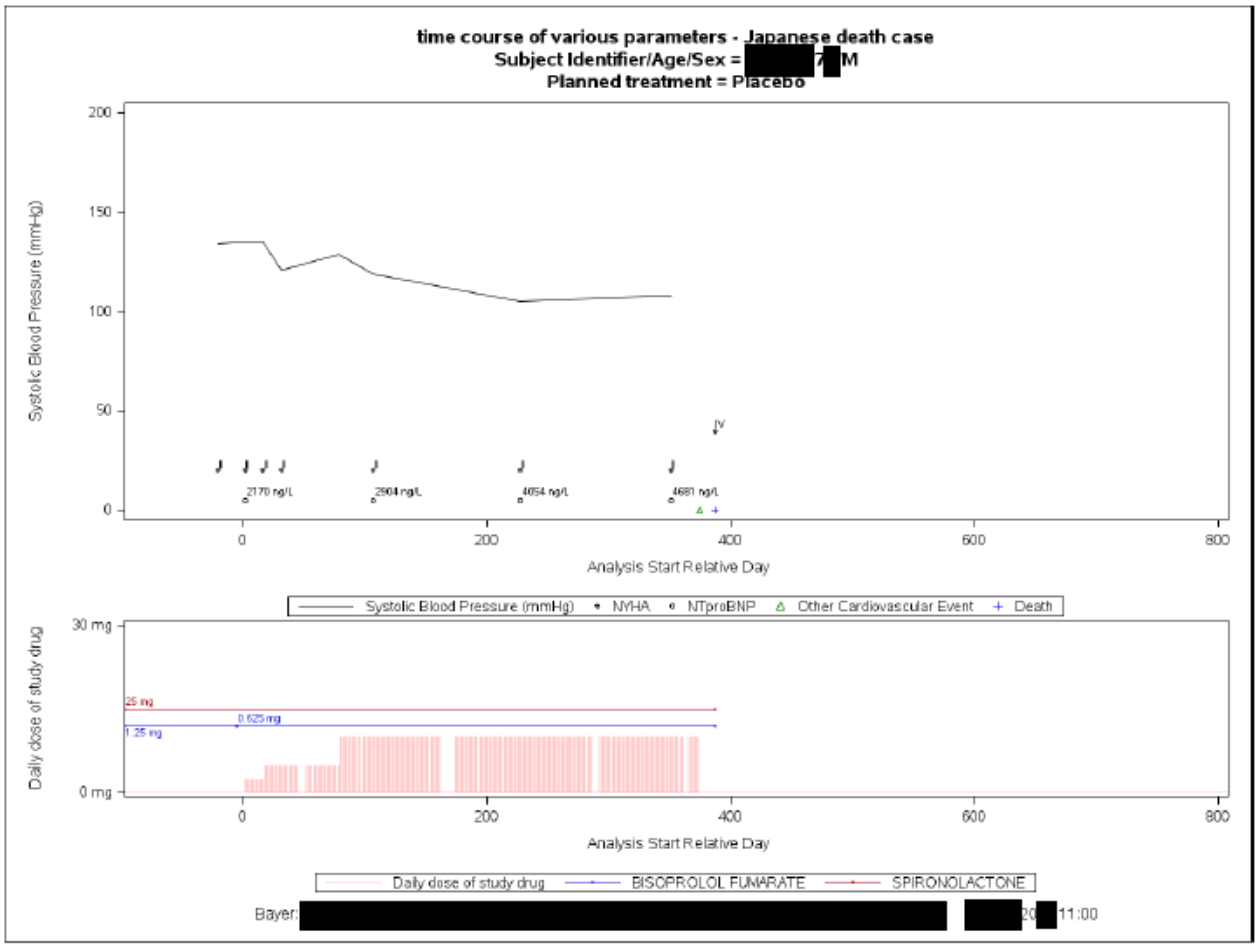
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
372		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
374	387	Heart Failure	Hospitalization	Other Cardiovascular Event
387		Heart Failure	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
2170 ng/L
2904 ng/L
4054 ng/L
4681 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
0.625 mg
1.25 mg
0 mg
0
200
400
600
800
Analysis Start Relative Day
Daily dose of study drug
BISOPROLOL FUMARATE
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	Marasmus	マラスムス		Day 754
SAE	Anaemia	貧血	Severe	Day 467
Discontinuation of Study Medication Due to Other Reason	Withdrawal by Subject			Day 648

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 2 years, 11 months, 22 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Tinea infection; Hypertension; Atrial fibrillation; Chronic kidney disease; Hyperuricaemia; Dermatitis contact; Cardiac imaging procedure
History of Medical/ Surgical Procedures	None

Concomitant Medications at Randomization	furosemide, febuxostat, esomeprazole magnesium, telmisartan, guaiazulene, calcium polystyrene sulfonate, warfarin

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-15	852 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
-14	43 %		
1		NYHA CLASS III	28.3 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:

第 463 日、浴室で転倒した後に右上肢の挫傷（非重篤な有害事象）が認められ、絆創膏で治療した。第 475 日に被験者は貧血（発現日は第 467 日）のため入院した。右上肢の皮下出血及び腫脹が認められ、赤血球 2 単位が投与された。第 476 日に貧血は消失し、被験者は退院し、帰宅した。第 518 日～第 531 日に両上肢に挫傷（非重篤な有害事象）が発現し、第 537 日に右上肢の挫傷は消失した。

被験者の同意撤回のため治験薬の投与は中止され、最終投与日は第 648 日であった。

第 728 日に被験者は全身衰弱のため入院し、第 754 日にマラスムス（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。

治験責任（分担）医師により、貧血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
28	53	MK-1242	5	1
54	109	MK-1242	10	1
110	161	MK-1242	10	1
162	162	MK-1242	10	0
163	214	MK-1242	10	1
215	321	MK-1242	10	1
322	438	MK-1242	10	1
439	536	MK-1242	10	1
537	648	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
-1	117	66	74	
1	106	60	70	5[redacted].4
1	104	60	79	
12	113	70	96	5[redacted].2
28	124	72	89	5[redacted]
54	145	86	93	5[redacted].5
75	122	68	83	5[redacted].2
110	114	71	93	5[redacted].2
215	125	73	81	5[redacted].4
322	100	52	73	6[redacted].5
439	130	65	69	5[redacted].5
537	144	74	82	5[redacted].1
649	111	55	64	5[redacted]
663	97	42	63	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	15	24	14.022	99
110	8(L)	11	30.267(H)	77
215	35	64(H)	29.925(H)	144(H)
322	27	47(H)	24.111(H)	117(H)
649	16	29	20.007(H)	101
663	14	29	17.613	107

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
-3	177.684(H)
1	194.48(H)
110	238.68(H)
215	212.16(H)
322	212.16(H)
649	212.16(H)
663	203.32(H)

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

Table 5. Hemoglobin and Hematocrit Laboratory Values

Study Day	HGB g/L	HCT %
1	118(L)	37.4
110	118(L)	37.4
215	108(L)	33.7(L)
322	88(L)	27.8(L)
467	65(L)	
476	89(L)	
502	106(L)	
649	98(L)	29.8(L)
663	96(L)	29.7(L)

A = abnormal; H = high; HCT = hematocrit; HGB = hemoglobin; L = low.

Table 6. Potential Study Endpoints

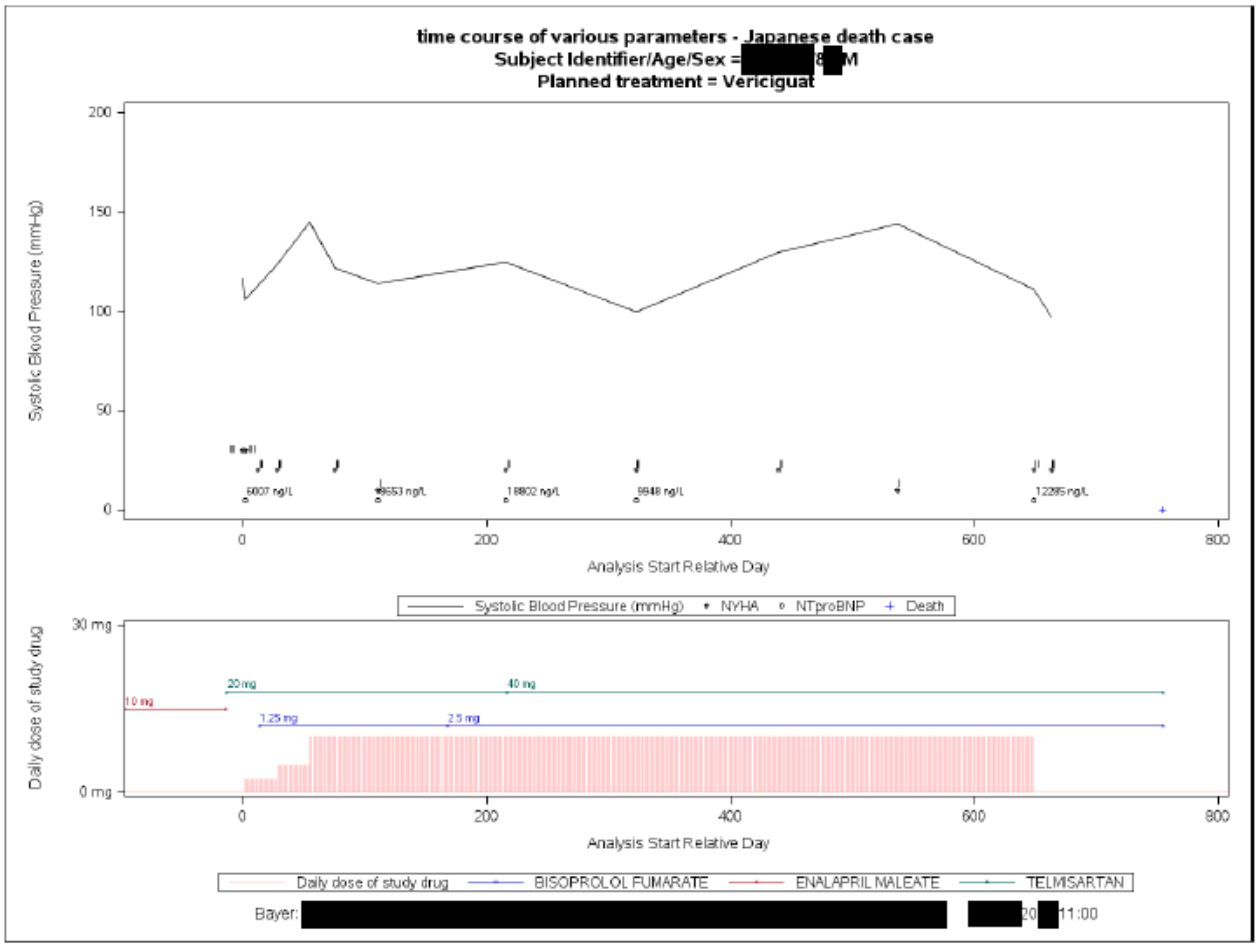
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
754		Non-CV Event	Death	Undetermined Cause Of Death

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.



Subject Number: [redacted]

Treatment Arm: Matching Placebo + Standard HF therapy

Event Type	Preferred Term		Severity	Study Day (relative to treatment)
CV Death	Subarachnoid haemorrhage	くも膜下出血		Day 693
SAE	Chronic kidney disease	慢性腎臓病	Severe	Day 15
SAE	Constipation	便秘	Severe	Day 665
SAE	Gastrooesophageal reflux disease	胃食道逆流性疾患	Severe	Day 671
SAE	Hyperkalaemia	高カリウム血症	Severe	Day 690
SAE	Subarachnoid haemorrhage	くも膜下出血	Severe	Day 691

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, 1 month, 8 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; Myocardial infarction; Cerebrovascular accident; Vertebral artery dissection; Anaemia; Peripheral arterial occlusive disease; Femoral neck fracture; Cholecystitis; Constipation; Chronic kidney disease; Cardiac imaging procedure
History of Medical/ Surgical Procedures	Coronary artery bypass; Percutaneous coronary intervention

Concomitant Medications at Randomization	levoglutamide;sodium gualenate, glibenclamide, clopidogrel bisulfate, spironolactone, ifenprodil tartrate, magnesium oxide, azelnidipine;olmesartan medoxomil, linagliptin, azosemide, acetylsalicylic acid, rosuvastatin calcium

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-14	305 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
-189	44 %		
1		NYHA CLASS II	29.4 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 1 年前から慢性腎臓病及び便秘があった。

第 15 日に慢性腎臓病の悪化と診断された。

第 665 日に腹部膨満感を伴う便秘の悪化、第 666 日に腰痛（非重篤な有害事象）が認められた。第 669 日に腹部 X 線及び CT 検査で、腸管内に大量の便及びガスが認められた。パラセタモール、ルビプロストン、センノシド a+b 及びグリセロールが投与された。便塞栓除去及び浣腸が行われたが、排便はなかった。第 671 日に被験者は便秘の悪化のため入院し、食欲低下を伴う胃食道逆流症及び十二指腸炎（非重篤な有害事象）が認められた。追加治療として、エロビキシバット、アミノ酸 NOS／グルコース／電解質 NOS／塩酸チアミン、クエン酸マグネシウム及びピコスルファートナトリウムが投与された。第 675 日に大腸内視鏡検査で臨床的に重要な所見は認められなかった。第 676 日に便秘の悪化は消失し、被験者は退院し、帰宅した。腰痛及び十二指腸炎の転帰は未回復であった。

第 679 日に被験者は胃食道逆流症のため入院した。腹部 X 線検査で消化管に大量のガスが認められたが、イレウスではなかった。第 681 日に上部消化管内視鏡検査で、胃食道逆流症及び十二指腸炎が認められた。グリセロール、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、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、グルコース／塩化ナトリウム、ボノプラザンフマル酸塩及びメトクロプラミドが投与された。第 687 日に被験者は退院して帰宅し、胃食道逆流症の転帰は軽快であった。

第 690 日に被験者は高カリウム血症と、BUN 及び血清クレアチニンの上昇並びに eGFR の低下を伴う慢性腎臓病の悪化のため入院した。徐脈（非重篤な有害事象）及び誤嚥性肺炎（非重篤な有害事象）が認められた。血圧低下（測定値の報告なし）、尿量減少及び悪心も認められた。持続的血液ろ過透析が行われ、スボレキサント、メトクロプラミド、ハロペリドール、ペンタゾシン、アトロピン、ヘパリンナトリウム、リドカイン及び酸素が投与された。慢性腎臓病の悪化及び高カリウム血症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 689 日であった。第 691 日に徐脈は消失し、血圧上昇（200／104mmHg）、意識レベル低下及び足の硬直が認められた。頭部 CT 検査でくも膜下出血及び水頭症、脳 MRI 検査でくも膜下出血が認められ、水頭症（非重篤な有害事象）と診断された。ニトログリセリン、ニカルジピン塩酸塩、カルバゾクロムスルホン酸ナトリウム、トラネキサム酸、アンピシリンナトリウム／スルバクタムナトリウムが投与された。第 693 日に被験者はくも膜下出血のため死亡した（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、慢性腎臓病の悪化、腰痛、十二指腸炎、高カリウム血症、誤嚥性肺炎及び水頭症の転帰は未回復であった。

治験責任（分担）医師により、くも膜下出血、慢性腎臓病、便秘、胃食道逆流症及び高カリウム血症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	66	placebo	0	1
67	67	placebo	0	0
68	105	placebo	0	1
106	217	placebo	0	1
218	275	placebo	0	1

Dose Start Day	Dose End Day	Study Treatment	Dose per Administration mg	Number of Daily Doses
276	277	placebo	0	0
278	336	placebo	0	1
337	441	placebo	0	1
442	539	placebo	0	1
540	637	placebo	0	1
638	688	placebo	0	1
689	689	placebo	0	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	162	56	62	6[redacted]05
1	162	56	62	
1	159	56	63	
15	151	56	94	6[redacted]8
29	156	53	67	6[redacted]8
50	168	58	68	6[redacted]5
106	166	58	70	6[redacted]8
218	189	62	74	6[redacted]1
337	186	63	70	6[redacted]8
442	166	59	67	6[redacted]5
540	186	72	71	6[redacted]4
638	185	77	86	6[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	15	18	4.788	72
106	16	21	5.985	71
218	17	25	5.985	67
337	23	23	6.498	67
638	33	32	4.959	62

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	149.396(H)
1	194.48(H)
106	185.64(H)
218	132.6(H)
337	167.96(H)
638	194.48(H)
671	355.368(H)

Study Day	CREAT µmol/L
690	660.348(H)
691	344.76(H)
692	487.084(H)

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

Table 5. Potential Study Endpoints

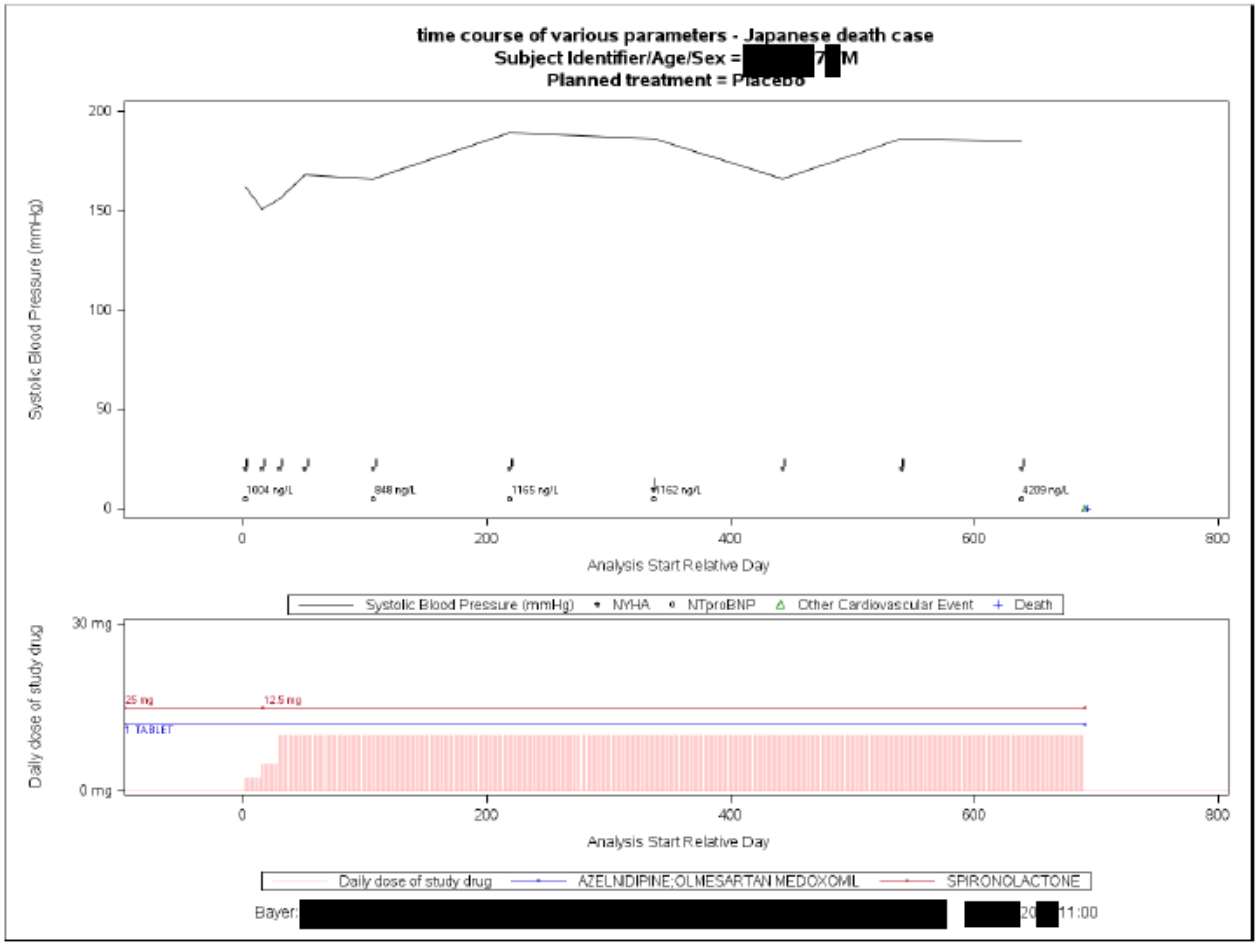
Event Start Day*	Event End Day*	Investigator-Reported Potential Endpoint Category	Event Type	CEC Adjudication Outcome†
690	693	Non-CV Hospitalization	Hospitalization	Other Cardiovascular Event
693		Non-CV Event	Death	Stroke

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	Pneumonia	肺炎		Day 641
SAE	Chronic kidney disease	慢性腎臓病	Severe	Day 257
Discontinuation of Study Medication Due to AE	Chronic kidney disease	慢性腎臓病	Severe	Day 257

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 3 years, 4 months, 10 days prior to first dose of study medication.
Index Event	Hospitalization for heart failure within 0 to 3 months of randomization.

Medical History	Insomnia; Osteoporosis; Lymphoma; Hyperlipidaemia; Hypertension; Asthma; Constipation; Chronic kidney disease; Coronary artery disease; Angina pectoris; Hyperuricaemia; Gastrooesophageal reflux disease; Hypothyroidism; Dementia; Conjunctivitis; Dry skin; Transient ischaemic attack; Echocardiogram
History of Medical/ Surgical Procedures	Percutaneous coronary intervention

Concomitant Medications at Randomization	spironolactone, furosemide, brotizolam, acetylsalicylic acid, sennoside a+b, fluvastatin sodium, montelukast sodium, febuxostat, rabeprazole sodium, magnesium oxide, levothyroxine sodium, carvedilol, pimobendan, mucopolysaccharide polysulfuric acid ester, dextromethorphan hydrobromide, tolvaptan, bisacodyl

Historical Natriuretic Peptide Labs

Study Day	BNP*	NT-proBNP*
-14	403 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
-41	20 %		
1		NYHA CLASS II	26.7 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 6 年前から慢性腎臓病があった。

被験者は第 183 日～第 198 日及び第 211 日～第 247 日に心不全のため入院した。

第 257 日に被験者は心不全のため入院した。クレアチニン値の上昇が認められ、慢性腎臓病の悪化と診断された。浮腫及び顕著な体重増加が認められた。グルコン酸カリウム及びフロセミドが投与された。第 266 日に腎性貧血（非重篤な有害事象）と診断され、ダルベポエチンアルファが投与された。第 273 日に慢性腎臓病のため治験薬の投与が中止された。最終投与日は同日であった。第 281 日に透析が行われた。第 282 日に腎性貧血は消失した。第 344 日に被験者は退院し、高度看護施設に入所した。

第 641 日に被験者は肺炎のため死亡した。剖検は実施されず、追加情報は報告されなかった。死亡時に、慢性腎臓病の転帰は軽快であった。

治験責任（分担）医師により、慢性腎臓病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	185	MK-1242	10	1
186	186	MK-1242	10	2
187	187	MK-1242	10	0
188	272	MK-1242	10	1
273	273	MK-1242	10	1

Table 2. Vital Signs

Study Day	Systolic mm Hg	Diastolic mm Hg	Heart Rate bpm	Weight kg
1	115	59	81	5[redacted]7
1	115	59	81	
1	113	56	78	
15	118	56	76	5[redacted].5
29	108	62	92	5[redacted].3
57	111	61	85	5[redacted].2
85	106	55	86	5[redacted].4
106	118	66	75	5[redacted].1
134	118	53	77	5[redacted].2
155	114	46	65	5[redacted].5
183	113	50	60	5[redacted].3
204	108	54	75	5[redacted].1
211	107	49	89	5[redacted]
311	98	54	63	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	14	23	8.892	105
57	59(H)	59(H)		2713(H)
106	11	19	6.498	129(H)
134	14	25		277
211	13	17	5.985	93
311	20	24	7.866	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
1	140.556(H)
1	159.12(H)
106	194.48(H)
211	212.16(H)
257	277.576(H)
280	606.424(H)
291	715.156(H)
301	481.78(H)
311	380.12(H)
311	371.28(H)
337	410.176(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†
183	198	Heart Failure	Hospitalization	Heart Failure
204		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
211	247	Heart Failure	Hospitalization	Heart Failure
255		Urgent Heart Failure Clinic Visit	Urgent Heart Failure Visit	Urgent Heart Failure Clinic Visit
257	344	Heart Failure	Hospitalization	Heart Failure
641		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.