

Supplemental Material

Supplemental material to: Assessment for residual disease after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension

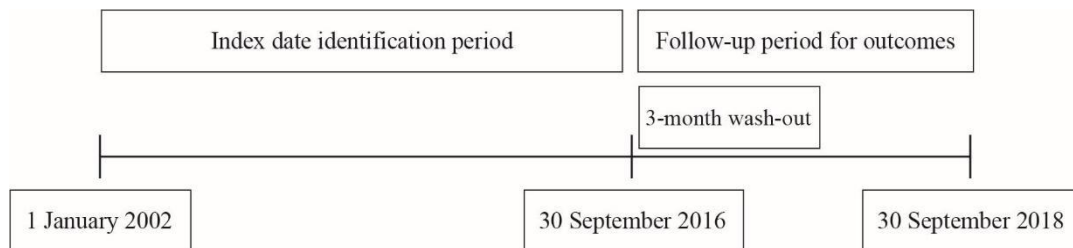


Figure S1 Study time frame.

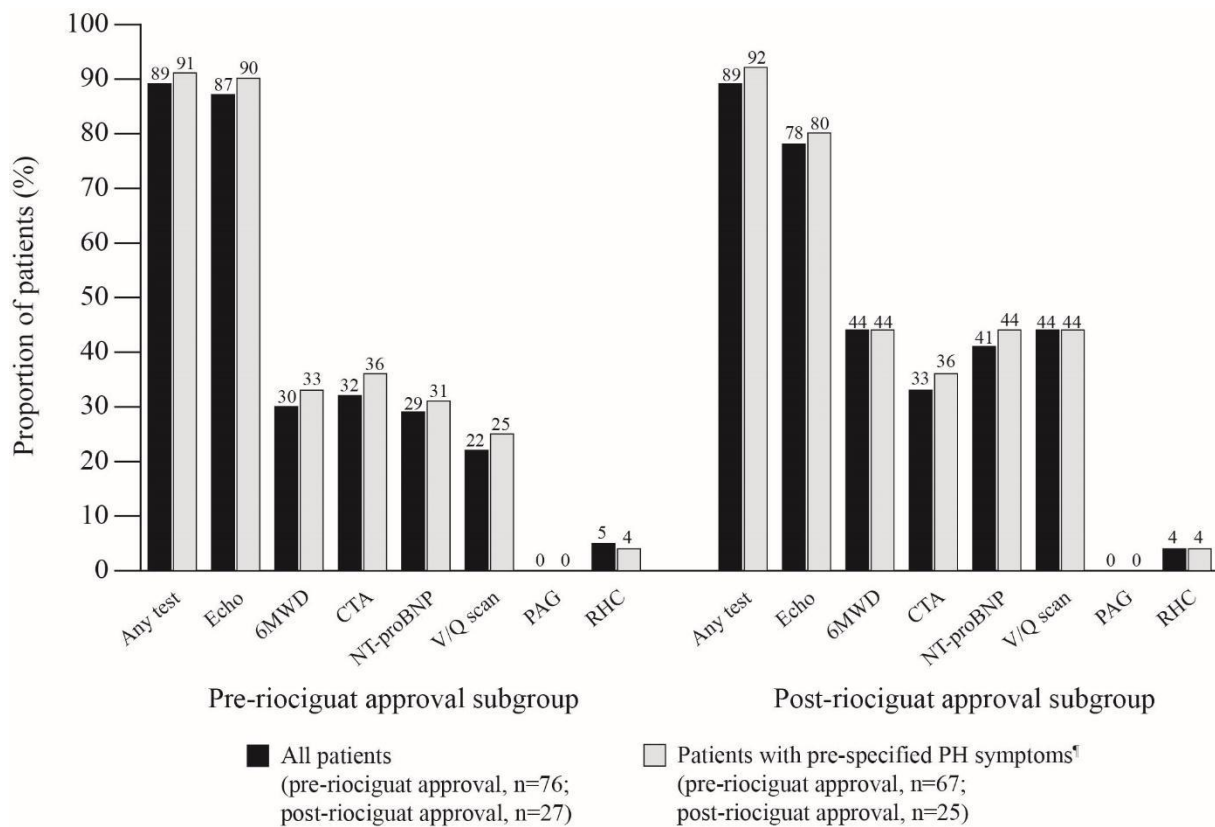


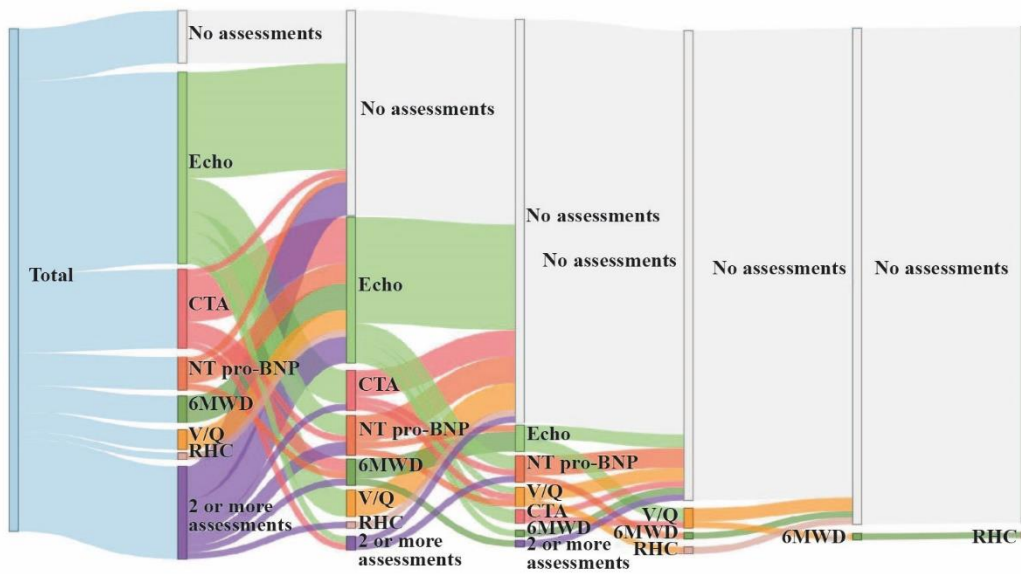
Figure S2 Rates of diagnostic assessment for all patients and patients with pre-specified residual PH symptoms in the per-protocol defined pre-riociguat[#] and post-riociguat approval subgroups.

[#]Including 21 patients in the pre-riociguat approval subgroup who underwent PEA prior to riociguat approval but had clinical data that spanned the post-riociguat approval date.

[†]Syncope, malaise and fatigue, dyspnoea, haemoptysis, chest pain (unspecified), dizziness, gait abnormality, cardiomegaly, ascites and peripheral oedema.

6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PAG: pulmonary angiogram; PH: pulmonary hypertension; RHC: right heart catheterisation; V/Q: ventilation/perfusion.

a) Pre-riociguat approval subgroup



b) Post-riociguat approval subgroup

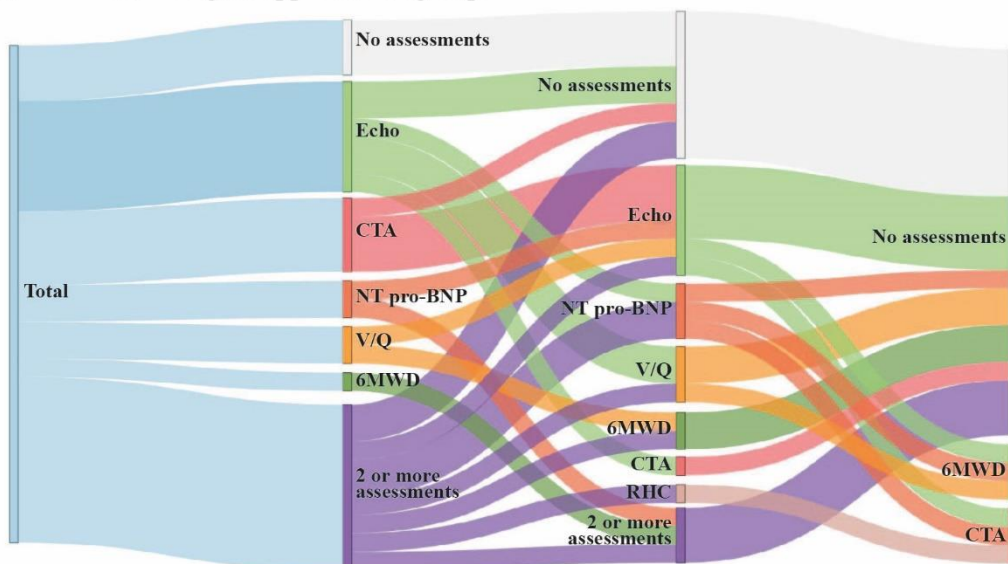


Figure S3 Sankey plots in the per-protocol determined patients in the per-protocol defined a)

pre-riociguat approval[#] (n=76) subgroup, and b) post-riociguat approval (n=27) subgroup.

[#]Including 21 patients in the pre-riociguat approval subgroup who underwent PEA prior to riociguat approval but had clinical data that spanned the post-riociguat approval date.

The thickness of the bars indicates higher level of use of a particular diagnostic pathway.

Nodes describing the simultaneous occurrences of 2 or more assessments were collapsed into a single node.

6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PEA: pulmonary endarterectomy; RHC: right heart catheterisation; V/Q: ventilation/perfusion.

Table S1 Coding used to assess claims

PH	
ICD-9-CM codes for PH	<ul style="list-style-type: none">● 416.0 (Primary PH)● 416.8 (Other chronic pulmonary heart diseases)
ICD-10-CM codes for PH	<ul style="list-style-type: none">● I27.0 (Primary PH)● I27.2 (Other secondary pulmonary hypertension)
CTEPH	
ICD-10-CM codes for CTEPH	<ul style="list-style-type: none">● I27.24 (CTEPH)
PEA	
CPT code for PEA	<ul style="list-style-type: none">● 33916 (PEA, with or without embolectomy, with cardiopulmonary bypass)● 33910 (Pulmonary artery embolectomy, with cardiopulmonary bypass)
ICD-9-CM code for PEA	<ul style="list-style-type: none">● 38.15 (Endarterectomy, other thoracic vessels)
ICD-10-PCS codes for PEA	<ul style="list-style-type: none">● 02CP0ZZ (Extirpation of matter from pulmonary trunk, open approach)● 02CQ0ZZ (Extirpation of matter from right pulmonary artery, open approach)● 02CR0ZZ (Extirpation of matter from left pulmonary artery, open approach)

CM: clinical modification; CPT: current procedure terminology; CTEPH: chronic thromboembolic pulmonary hypertension; ICD-9/-10: 9th and 10th revisions of the International Classification of Diseases; PCS: procedure coding system; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

Table S2 Coding used to assess PH symptoms

PH symptoms	ICD-9-CM codes	ICD-10-CM codes
Syncope	● 780.2	● R55
Malaise and fatigue	● 780.7	● R53.81 (Other malaise) ● R53.82 (Chronic fatigue) ● R53.83 (Chronic fatigue)
Dyspnoea	● 786.0	● R06.00 (Dyspnoea, unspecified) ● R06.01 (Orthopnoea) ● R06.02 (Shortness of breath) ● R06.09 (Other forms of dyspnoea)
Haemoptysis	● 786.3	● R04.2
Chest pain, unspecified	● 786.5	● R07.82 (Intercostal pain) ● R07.81 (Pleurodynia) ● R07.1 (Chest pain on breathing) ● R07.2 (Precordial pain) ● R07.89 (Other chest pain) ● R07.9 (Chest pain, unspecified)
Dizziness/vertigo, not otherwise specified	● 780.4	● R42
Gait abnormality	● 781.2	● R26.0 (Ataxic gait) ● R26.1 (Paralytic gait) ● R26.89 (Other abnormalities of gait and mobility) ● R26.9 (Unspecified abnormalities of gait and mobility)
Cardiomegaly	● 429.3	● I51.7
Ascites	● 789.3	● R19.06 (Epigastric swelling, mass or lump) ● R19.07 (Generalised intra-abdominal and pelvic swelling, mass and lump) ● R19.04 (Left lower quadrant abdominal swelling, mass and lump) ● R19.05 (Periumbilical swelling, mass or lump) ● R19.09 (Other intra-abdominal and pelvic swelling, mass and lump) ● R19.02 (Left upper quadrant abdominal swelling, mass and lump) ● R19.03 (Right lower quadrant abdominal swelling, mass and lump) ● R19.00 (Intraabdominal and pelvic swelling, mass and lump, unspecified site) ● R19.01 (Right upper quadrant abdominal swelling, mass and lump)
Peripheral oedema	● 782.3	● R60.0 (Localised oedema) ● R60.1 (Generalised oedema) ● R60.9 (Oedema, unspecified)

ICD-9/-10-CM: 9th and 10th revisions of the International Classification of Diseases Clinical
Modification; PH: pulmonary hypertension.

Table S3 Coding used to assess diagnostic tests

	CPT/ICD/HCPCS/Procedure Code Modifier
V/Q scan	
Pulmonary perfusion imaging	● 78580
Pulmonary ventilation (<i>e.g.</i> aerosol or gas) and perfusion imaging	● 78582
Pulmonary perfusion with vent single breath	● 78584
Pulmonary perfusion with wash-out, with or without single breath	● Diagnostic test
Pulmonary ventilation imaging	● 78586
Pulmonary ventilation multiple projections	● 78587
Pulmonary perfusion imaging, particulate, with ventilation imaging, aerosol, 1 or multiple projection	● 7858
Echocardiogram	
Echocardiogram transthoracic, real-time, 2D, with or without M-mode, complete, spectral and colour flow Doppler	● 93306
Echocardiogram transthoracic, real-time, 2D, with or without M-mode recording, complete	● 93307
Echocardiogram transthoracic, real-time, 2D, with or without M-mode recording, follow-up/limited	● 93308
Doppler echocardiogram, pulse wave with spectral display	● 93320
Doppler echocardiogram, colour flow velocity mapping	● 93325
Diagnostic ultrasound of heart (ICD-9-PCS code)	● 8872
Diagnostic ultrasound of heart (ICD-10-PCS code)	<ul style="list-style-type: none"> ● B24.4ZZZ (Ultrasonography of right heart) ● B24.DZZ4 (Ultrasonography of paediatric heart, transoesophageal) ● B24.DYZZ (Ultrasonography of paediatric heart using other contrast) ● B24.4ZZ4 (Ultrasonography of right heart, transoesophageal) ● B24.DZZZ (Ultrasonography of paediatric heart) ● B24.5ZZ4 (Ultrasonography of left heart, transoesophageal) ● B24.6ZZ4 (Ultrasonography of right and left heart, transoesophageal) ● B24.5YZZ (Ultrasonography of left heart using other contrast) ● B24.4YZZ (Ultrasonography of right heart)

	<ul style="list-style-type: none"> ● using other contrast) ● B24.5ZZZ (Ultrasonography of left heart) ● B24.6ZZZ (Ultrasonography of right and left heart) ● B24.6YZZ (Ultrasonography of right and left heart using other contrast)
Doppler echocardiogram, pulse wave with spectral follow-up/limited studies	● 93321
Agitated saline echocardiogram	
Unlisted therapeutic, prophylactic or diagnostic intravenous or intra-arterial injection or infusion	● 96379
<i>PLUS</i>	
Sterile water, saline and/or dextrose, diluent/flush, 10 mL	● A4216
<i>PLUS</i>	
Echocardiogram	● See codes listed above for echocardiogram
<i>OR</i>	
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study	● 93308
<i>PLUS</i>	
Sterile water, saline and/or dextrose, diluent/flush, 10 mL	● A4216
<i>OR</i>	
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study	● 93308
<i>PLUS</i>	
Infusion, normal saline solution, 250 cc	● J7050
<i>OR</i>	
Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug	● 96374
<i>PLUS</i>	
Distinct procedural service	● Modifier-59
<i>PLUS</i>	
Echocardiogram	● See codes listed above for echocardiogram
CT scan	
Computed tomography, thorax; with contrast material(s)	● 71260
Computed tomography, thorax; with and without contrast material(s)	● 71270
Computed tomography angiography, thorax; with and without contrast material(s)	● 71275
RHC	

Right heart catheterisation	● 93501
Combined right and left heart cardiac catheterisation (ICD-9-PCS code)	● 3723
Combined right and left heart cardiac catheterisation (ICD-10-PCS code)	● 4A0.20N8 (Measurement of cardiac sampling and pressure, bilateral, open approach) ● 4A0.23N8 (Measurement of cardiac sampling and pressure, bilateral, percutaneous approach)
Right heart cardiac catheterisation (ICD-9-PCS code)	● 3721
Right heart cardiac catheterisation (ICD-10-PCS code)	● 4A0.20N6 (Measurement of cardiac sampling and pressure, right heart, open approach) ● 4A0.23N6 (Measurement of cardiac sampling and pressure, right heart, percutaneous approach)
Insertion flow directed catheter for monitoring	● 93503
Pulmonary angiogram	
Angiography pulmonary, unilateral, selective, radiological supervision and interpretation	● 75741
Angiography pulmonary, bilateral, selective, radiological supervision and interpretation	● 75743
Angiography pulmonary, non-selective, catheter/venous injection, radiological supervision and interpretation	● 75746
NT-proBNP	
Assay of natriuretic peptide	● 83880
6MWD	
Pulmonary stress testing; simple	● 94620
Exercise test for bronchospasm, including pre- and post-spirometry, electrocardiographic recording(s) and pulse oximetry	● 94617
Pulmonary stress testing (<i>e.g.</i> 6-minute walk test), including measurement of heart rate, oximetry and oxygen titration	● 94618

2D: 2-dimensional; 6MWD: 6-minute walking distance; CPT: current procedure terminology;

CT: computed tomography; HCPCS: healthcare common procedure coding system; ICD-9/-

10: 9th and 10th revisions of the International Classification of Diseases; NT-proBNP: N-

terminal prohormone of brain natriuretic protein; PCS: procedure coding system; RHC: right heart catheterisation; V/Q: ventilation/perfusion.

Table S4 Per-protocol population demographic and clinical characteristics

	Pre-riociguat approval[#] (n=76)	Post-riociguat approval (n=27)
Age (years), mean (SD)	56.0 (14.5)	54.3 (14.0)
Sex, n (%)		
Male	42 (55)	19 (70)
Female	34 (45)	8 (30)
Duration of follow-up (days), mean (SD)	1824.4 (978.8)	985.5 (246.0)
Charlson comorbidity index, mean (SD) [¶]	1.7 (1.8)	2.1 (1.6)

[#]Including 21 patients in the pre-riociguat approval subgroup who underwent PEA prior to riociguat approval but had clinical data that spanned the post-riociguat approval date.

[¶]Identified within less than or equal to 12 months prior to the index date and excluding the category of “chronic pulmonary disease”.

PEA: pulmonary endarterectomy; SD: standard deviation.

[#]*Post hoc* analysis including the 21 patients whose post-PEA observation period overlapped with the period following riociguat approval in the USA.

6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PAG: pulmonary angiogram; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; RHC: right heart catheterisation; V/Q: ventilation/perfusion.

Table S6 Rates of residual PH symptoms and diagnostic assessments occurring in the 2 years post-PEA applying wash-out periods of 0 days, 1 day and 7 days

n (%)	Total	Any test	Echo	6MWD	CTA	NT-proBNP	V/Q scan	PAG	RHC
No wash-out period									
Total	103	101 (98)	100 (97)	51 (50)	46 (45)	37 (36)	44 (43)	5 (5)	72 (70)
Any PH symptom	101	99 (98)	98 (97)	51 (50)	46 (46)	37 (37)	44 (44)	5 (5)	72 (71)
Dyspnoea	84	84 (100)	83 (99)	46 (55)	42 (50)	35 (42)	37 (44)	5 (6)	63 (75)
Chest pain, unspecified	51	49 (96)	48 (94)	26 (51)	26 (51)	20 (39)	21 (41)	1 (2)	34 (67)
Cardiomegaly	58	58 (100)	58 (100)	31 (53)	27 (47)	22 (38)	30 (52)	2 (3)	45 (78)
Malaise and fatigue	30	30 (100)	30 (100)	16 (53)	17 (57)	14 (47)	11 (37)	1 (3)	19 (63)
Peripheral oedema	27	26 (96)	26 (96)	11 (41)	14 (52)	10 (37)	10 (37)	1 (4)	21 (78)
Dizziness	13	12 (92)	12 (92)	3 (23)	5 (38)	2 (15)	5 (38)	0	6 (46)
Syncope	12	11 (92)	11 (92)	4 (33)	5 (42)	5 (42)	5 (42)	0	8 (67)
Haemoptysis	7	7 (100)	7 (100)	5 (71)	4 (57)	4 (57)	4 (57)	1 (14)	5 (71)
Ascites	4	4 (100)	4 (100)	3 (75)	1 (25)	2 (50)	2 (50)	0	4 (100)
Gait abnormality	3	3 (100)	3 (100)	0	3 (100)	1 (33)	1 (33)	0	1 (33)
1-day wash-out period									
Total	103	100 (97)	97 (94)	51 (50)	44 (43)	36 (35)	44 (43)	5 (5)	36 (35)
Any PH symptom	101	98 (97)	95 (94)	51 (50)	44 (44)	36 (36)	44 (44)	5 (5)	36 (36)
Dyspnoea	84	83 (99)	80 (95)	46 (55)	40 (48)	34 (40)	37 (44)	5 (6)	33 (39)
Chest pain, unspecified	49	46 (94)	45 (92)	25 (51)	24 (49)	18 (37)	21 (43)	1 (2)	16 (33)
Cardiomegaly	57	57 (100)	56 (98)	31 (54)	26 (46)	21 (37)	30 (53)	2 (4)	24 (42)
Malaise and fatigue	30	30 (100)	30 (100)	16 (53)	15 (50)	14 (47)	11 (37)	1 (3)	11 (37)
Peripheral oedema	27	26 (96)	26 (96)	11 (41)	14 (52)	10 (37)	10 (37)	1 (4)	13 (48)
Dizziness	13	12 (92)	12 (92)	3 (23)	5 (38)	2 (15)	5 (38)	0	2 (15)
Syncope	12	10 (83)	10 (83)	4 (33)	5 (42)	5 (42)	5 (42)	0	6 (50)
Haemoptysis	7	7 (100)	7 (100)	5 (71)	4 (57)	4 (57)	4 (57)	1 (14)	2 (29)
Ascites	4	4 (100)	4 (100)	3 (75)	1 (25)	2 (50)	2 (50)	0	2 (50)
Gait abnormality	3	3 (100)	2 (67)	0	3 (100)	0	1 (33)	0	0
7-day wash-out period									
Total	103	97 (94)	95 (92)	50 (49)	40 (39)	36 (35)	40 (39)	1 (1)	9 (9)
Any PH symptom	99	93 (94)	92 (93)	50 (51)	40 (40)	35 (35)	40 (40)	1 (1)	9 (9)
Dyspnoea	80	77 (96)	76 (95)	45 (56)	36 (45)	33 (41)	35 (44)	1 (1)	7 (9)
Chest pain, unspecified	45	42 (93)	42 (93)	23 (51)	23 (51)	16 (36)	20 (44)	1 (2)	4 (9)
Cardiomegaly	51	49 (96)	49 (96)	28 (55)	23 (45)	20 (39)	26 (51)	0	5 (10)
Malaise and fatigue	29	28 (97)	28 (97)	16 (55)	13 (45)	14 (48)	10 (34)	0	1 (3)
Peripheral oedema	26	25 (96)	25 (96)	11 (42)	11 (42)	10 (38)	9 (35)	0	3 (12)
Dizziness	13	12 (92)	12 (92)	3 (23)	5 (38)	2 (15)	5 (38)	0	0
Syncope	10	9 (90)	9 (90)	4 (40)	4 (40)	5 (50)	4 (40)	0	0
Haemoptysis	6	6 (100)	6 (100)	4 (67)	4 (67)	3 (50)	3 (50)	1 (17)	1 (17)
Ascites	4	4 (100)	4 (100)	3 (75)	1 (25)	2 (50)	2 (50)	0	0
Gait abnormality	3	3 (100)	2 (67)	0	3 (100)	0	1 (33)	0	0

6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PAG: pulmonary angiogram; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; RHC: right heart catheterisation; V/Q: ventilation/perfusion.

Table S7 Number of tests and days to earliest diagnostic test after PEA in the per-protocol defined pre-riociguat approval[#] and post-riociguat approval subgroups undergoing PEA

Diagnostic test	Pre-riociguat approval [#] (n=76)			Post-riociguat approval (n=27)		
	n (%)	Number of tests after PEA (mean [SD])	Number of days to first test (mean [SD])	n (%)	Number of tests after PEA (mean [SD])	Number of days to first test (mean [SD])
Any test	68 (89)	4.6 (3.5)	185.4 (106.8)	24 (89)	4.7 (4.6)	175.2 (81.2)
Echo	66 (87)	2.4 (1.1)	220.2 (120.7)	21 (78)	2.4 (1.5)	226.7 (152.2)
6MWD	23 (30)	3.1 (1.7)	190.5 (127.1)	12 (44)	2.4 (1.1)	280.8 (170.6)
CTA	24 (32)	2.0 (2.2)	201.9 (114.7)	9 (33)	1.3 (0.7)	350.2 (213.5)
NT-proBNP	22 (29)	3.2 (3.3)	250.0 (162.6)	11 (41)	3.8 (5.2)	208.7 (103.8)
V/Q scan	17 (22)	1.6 (0.8)	336.9 (198.3)	12 (44)	1.3 (0.7)	228.0 (152.3)
RHC	4 (5)	2.5 (3.0)	341.3 (225.6)	1 (4)	2.0 (NA)	685.0 (NA)

[#]Including 21 patients in the pre-riociguat approval subgroup who underwent PEA prior to riociguat approval but had clinical data that spanned the post-riociguat approval date. 6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NA: not available; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PEA: pulmonary endarterectomy; RHC: right heart catheterisation; SD: standard deviation; V/Q: ventilation/perfusion.

Table S8 Rates of diagnostic assessment in patients with residual PH symptoms undergoing PEA in the per-protocol defined pre-riociguat approval[#] and post-riociguat approval subgroups

n (%)	Total	Any test	Echo	6MWD	CTA	NT-proBNP	V/Q scan	PAG	RHC
Diagnostic assessment in patients with residual PH symptoms undergoing PEA (pre-riociguat approval subgroup)[#]									
Any PH symptom	67	61 (91)	60 (90)	22 (33)	24 (36)	21 (31)	17 (25)	0	3 (4)
Dyspnoea	51	49 (96)	48 (94)	22 (43)	20 (39)	20 (39)	15 (29)	0	3 (6)
Chest pain, unspecified	24	22 (92)	22 (92)	4 (17)	12 (50)	6 (25)	8 (33)	0	1 (4)
Cardiomegaly	17	16 (94)	16 (94)	5 (29)	9 (53)	3 (18)	7 (41)	0	2 (12)
Malaise and fatigue	12	11 (92)	11 (92)	5 (42)	4 (33)	7 (58)	1 (8)	0	0
Peripheral oedema	13	11 (85)	11 (85)	5 (38)	5 (38)	6 (46)	2 (15)	0	1 (8)
Dizziness	7	7 (100)	7 (100)	0	3 (43)	2 (29)	1 (14)	0	0
Syncope	2	2 (100)	2 (100)	1 (50)	1 (50)	1 (50)	1 (50)	0	0
Haemoptysis	4	4 (100)	4 (100)	2 (50)	2 (50)	1 (25)	1 (25)	0	1 (25)
Ascites	3	3 (100)	3 (100)	2 (67)	1 (33)	1 (33)	0	0	0
Gait abnormality	2	2 (100)	2 (100)	0	2 (100)	0	1 (50)	0	0
Diagnostic assessment in patients with residual PH symptoms undergoing PEA (post-riociguat approval subgroup)									
Any PH symptom	25	23 (92)	20 (80)	11 (44)	9 (36)	11 (44)	11 (44)	0	1 (4)
Dyspnoea	17	17 (100)	16 (94)	9 (53)	7 (41)	11 (65)	8 (47)	0	1 (6)
Chest pain, unspecified	10	10 (100)	9 (90)	5 (50)	7 (70)	6 (60)	3 (30)	0	1 (10)
Cardiomegaly	10	9 (90)	9 (90)	3 (30)	4 (40)	3 (30)	4 (40)	0	0
Malaise and fatigue	8	7 (88)	7 (88)	5 (63)	3 (38)	4 (50)	4 (50)	0	1 (13)
Peripheral oedema	4	4 (100)	3 (75)	2 (50)	1 (25)	1 (25)	2 (50)	0	0
Dizziness	3	3 (100)	2 (67)	1 (33)	1 (33)	0	2 (67)	0	0
Syncope	5	5 (100)	5 (100)	3 (60)	2 (40)	3 (60)	2 (40)	0	0
Haemoptysis	0	0	0	0	0	0	0	0	0
Ascites	1	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)	0	0
Gait abnormality	0	0	0	0	0	0	0	0	0

[#]Including 21 patients in the pre-riociguat approval subgroup who underwent PEA prior to riociguat approval but had clinical data that spanned the post-riociguat approval date. 6MWD: 6-minute walking distance; CTA: computed tomography angiogram; Echo: echocardiogram; NT-

proBNP: *N*-terminal prohormone of brain natriuretic protein; PAG: pulmonary angiogram; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; RHC: right heart catheterisation; V/Q: ventilation/perfusion.