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Please cite this article as: Butler Oín, Ju S, Hoernig S, *et al*. Assessment for residual disease after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00572-2021).

Assessment for residual disease after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension

Concise title: Residual disease in CTEPH patients post-PEA

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Rates of residual PH symptoms are high after PEA but referral of patients with suspected persistent/recurrent CTEPH following PEA for CTEPH-specific diagnostic assessments is sub-optimal, highlighting potential gaps in CTEPH patient care post-PEA.

Plain language summary

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially fatal disease in which the blood vessels supplying the lungs become blocked. In many patients with CTEPH, the disease can be treated with surgery to remove the blockage. However, some of these

patients will still have symptoms. For these patients, the drug riociguat can be used to manage their symptoms. In this study we looked at medical insurance claims from 103 patients who had surgery for CTEPH in the USA to see how many of them still had PH-related symptoms after surgery, how often they went through diagnostic tests that are typically performed to diagnose CTEPH/PH, and what types of test were carried out. We also looked at whether patients had their surgery in the period of time before or after riociguat became available for doctors to prescribe. This meant that we could see if there was an increase in symptom testing after the new drug was approved, potentially due to increased awareness of the disease.

Most of the patients (89%) who had surgery for CTEPH still had symptoms three months after surgery. While most patients went through diagnostic tests that are typically performed to diagnose CTEPH/PH in the months after surgery, only 5% had a test called right heart catheterisation (RHC), the recommended test for CTEPH symptoms. In the period of time after riociguat became available for doctors to prescribe, patients were more likely to have had specific diagnostic tests for CTEPH symptoms, including RHC. Overall, our data show that many patients may not be tested fully for symptoms of CTEPH after they have had surgery. They also suggest that the approval of riociguat meant that healthcare professionals became more aware of the need to test patients for symptoms. It is important that healthcare professionals caring for patients with CTEPH realise that patients can continue to have symptoms after surgery. Regular testing of these patients can make sure that they get the best possible treatment.

Funding/Support

This study was funded by Bayer AG, Berlin, Germany and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Conflict of Interest Disclosures

O. Butler is an employee of Bayer AG. S. Ju was an employee of Bayer at the time of the study and is currently an employee of GlaxoSmithKline. S. Hoernig is an employee of Bayer AG. K. Vogtländer is an employee of Bayer AG. S. Bansilal is an employee of Bayer US. G.A. Heresi reports advisory board fees from Bayer Healthcare and Janssen Pharmaceuticals.

Author Contributions

O. Butler, S. Ju, S. Hoernig, K. Vogtländer, S. Bansilal, G.A. Heresi were involved in the concept and design of the study, analysis and interpretation of data, critical revision of the paper for important intellectual content, and gave final approval of the version to be published. S. Ju and K. Vogtländer were responsible for the statistical analysis. O. Butler supervised the study.

Keywords: Chronic thromboembolic pulmonary hypertension, CTEPH, PH, pulmonary endarterectomy, PEA.

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Abstract limit	250 words (either structured or not) [Currently 247]

Abstract

Objectives Pulmonary endarterectomy (PEA) is recommended for eligible patients with chronic thromboembolic pulmonary hypertension (CTEPH) and is potentially curative. However, persistent/recurrent CTEPH post-PEA can occur. Here we describe symptom and diagnostic assessment rates for residual disease post-PEA and longitudinal diagnostic patterns before and after riociguat approval for persistent/recurrent CTEPH after PEA.

Methods This US retrospective cohort study analysed MarketScan data (1 January 2002–30 September 2018) from patients who underwent PEA following a CTEPH/pulmonary hypertension (PH) claim with at least 730 days of continuous enrolment post-PEA. Data on pre-specified PH symptoms and the types and timings of diagnostic assessments were collected.

Results Of 103 patients (pre-riociguat approval, n=55; post-riociguat approval, n=48), residual PH symptoms more than 3 months after PEA were reported in 89% of patients. Overall, 89% of patients underwent 1 or more diagnostic tests (mean 4.6 tests/patient), most commonly echocardiography (84%), with only 5% of patients undergoing right heart catheterisation (RHC). In the post- *versus* pre-riociguat approval subgroup, assessments were more specific for CTEPH with an approximate 2-fold increase in 6-minute walking distance and *N*-terminal prohormone of brain natriuretic protein measurements and ventilation/perfusion scans, and a 4-fold increase in RHCs.

Conclusions Low RHC rates suggest that many patients with PH symptoms post-PEA are not being referred for full diagnostic work-up. Changes to longitudinal diagnostic patterns may indicate increased recognition of persistent/recurrent CTEPH post-PEA; however, there remains a need for greater awareness around the importance of continued follow-up for patients with residual PH symptoms post-PEA.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive form of pulmonary hypertension (PH) characterised by organised thromboembolic material and vascular remodelling due to defective angiogenesis, impaired fibrinolysis and endothelial dysfunction, leading to right ventricular failure and ultimately death [1-4]. CTEPH is a complication of 1 or more episodes of pulmonary embolism (PE) [3]; however, approximately 25% of patients do not present with a history of previous PE [5], although geographical differences have been noted in PE rates [4].

While the signs and symptoms of CTEPH are broadly similar to those of other forms of PH, such as pulmonary arterial hypertension, CTEPH is potentially curable with pulmonary endarterectomy (PEA) to remove the obstructive thrombofibrotic material [1]; however, up to 40% of patients are deemed inoperable or refuse surgery [6]. PEA is an intricate surgical technique requiring complex peri-procedural management and is therefore performed in specialised centres. It is associated with good outcomes, with low mortality rates reported in experienced centres, and improvements in haemodynamics and functional status [7, 8]. However, approximately one-third and up to one-half of patients may have some residual PH symptoms after surgery [7, 9], often the result of incomplete removal of proximal thrombotic material and/or small-vessel disease caused by vascular remodelling of the microscopic pulmonary arteries that is not amenable to PEA [2].

CTEPH is difficult to diagnose and remains an under-diagnosed condition [10]. The INFORM study (conducted 2010–2011) retrospectively analysed data from a claims database, and showed that 87% of patients had a claim for a PH-related symptom within 2 years following initial PE, but only 55% of patients had diagnostic procedural claims related to the identification of PH or CTEPH [11]. The INFORM study did not, however, investigate rates of persistent/recurrent CTEPH in the post-PEA setting.

Given the occurrence of persistent/recurrent CTEPH in patients undergoing PEA for CTEPH, we conducted a similar analysis to INFORM, to describe the number of diagnoses and symptoms related to PH, and the number of diagnostic tests used to assess the presence of CTEPH or PH symptoms in patients post-PEA to highlight any disconnect between patients showing signs of residual disease and receiving appropriate diagnostic assessments. During the data collection time period of this study (PEA conducted 2002–2016), the soluble guanylate cyclase stimulator riociguat was approved (October 2013 in the USA) as the first licensed medical therapy for use in patients with persistent/recurrent CTEPH after PEA [12]. Therefore, we also investigated whether the approval of riociguat and any concomitant changes in diagnostic options or disease awareness had an impact on the recognition of residual PH symptoms post-PEA.

Methods

Study design

This retrospective cohort study analysed data from the MarketScan Commercial Claims and Encounters Database and Medicare Supplemental and Coordination of Benefits Database (Truven Health Analytics). MarketScan captures longitudinal, individual-level administrative claims data, including inpatient and outpatient claims, outpatient prescription claims, clinical utilisation records and healthcare expenditures, from patients in the USA. All data collected in this study were de-identified to comply with data protection regulations and compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. Additional informed consent or institutional review board/ethical approval was not required. Patients were identified with specified inclusion/exclusion criteria between 1 January 2002 and 30 September 2016 (inclusive), with a follow-up period of up to 2 years following the index date until 30 September 2018 (supplemental figure S1). Adult patients aged 18 years or over who underwent PEA following a claim of PH or CTEPH with at least 730 days of continuous enrolment post-PEA were eligible for inclusion in the study. The index event was defined as the first claim related to PEA in eligible patients with a prior history of a claim of PH or CTEPH. Claims arising in the 3 months after PEA were excluded to account for symptoms resulting from the PEA index event or from immediate post-operative haemodynamic measurements. Claims were assessed based on codes from the 9th and 10th revisions of the International Classification of Diseases (ICD) and the current procedure terminology (CPT) for PH, CTEPH and PEA, as described in supplemental table S1.

Variables and endpoints

Claims were assessed for 10 pre-specified PH symptoms: syncope, malaise and fatigue, dyspnoea, haemoptysis, chest pain (unspecified), dizziness, gait abnormality, cardiomegaly, ascites and peripheral oedema. Claims were also assessed for the following 7 diagnostic tests: echocardiogram, computed tomography angiogram (CTA), pulmonary angiogram (PAG), right heart catheterisation (RHC), ventilation/perfusion (V/Q) scan, 6-minute walking distance (6MWD) and measurement of *N*-terminal prohormone of brain natriuretic protein (NT-proBNP) levels. ICD and CPT codes for PH symptoms and diagnostic tests are shown in supplemental table S2 and table S3, respectively.

Endpoints assessed were the number and percentage of patients who underwent diagnostic assessments and/or had residual PH symptoms after the index date, after a 3-month wash-out period post-PEA. Thus, symptoms and diagnostic procedures occurring during the first 3 months post-PEA were excluded from the primary analysis to rule out symptoms arising from the PEA index event or during the immediate post-operative period. The number of diagnostic assessments and days from the index date to the earliest diagnostic assessment were also evaluated.

For the pre-specified time trends analysis, patients who underwent PEA between 1 January 2002 and 30 September 2013 (inclusive) were included in the pre-riociguat approval subgroup, and patients who underwent PEA between 1 October 2013 and 30 September 2016 (inclusive) were included in the post-riociguat approval subgroup. Subsequently, it was noted that, for those patients who underwent PEA after 30 September 2011, the 730-day follow-up period included both the pre- and post-riociguat approval periods; consequently, *post hoc* these patients were excluded from the pre-riociguat approval subgroup and were incorporated into the post-riociguat approval subgroup.

Statistical methods

All analyses were descriptive in nature and no formal hypothesis testing was conducted. Univariate statistics were used to describe the study population for categorical and continuous variables. Rates of diagnostic assessments were performed in the overall population and in a subgroup of patients with at least 1 of 10 pre-specified PH symptoms, as described above, excluding a wash-out period of the first 3 months. Sensitivity analyses were conducted to assess the rate of these events without a wash-out period, or with 1- and 7-day wash-out periods.

Diagnostic assessment pathways were visualised using Sankey plots, calculated with R Studio version 3.6.3; only the first record for each assessment was used to construct the plots. Tests occurring on the same day were included in the same node of a pathway to provide an overview of the preferred assessment patterns.

No imputation of missing data was performed, and data analysis was conducted using SAS version 9.4 by using the SAS Macro algorithms developed by Bayer Global Data Analytics group.

Results

Study cohort

Of 182 286 926 patients in the MarketScan database, 103 met the analysis inclusion criteria (figure 1). Of 76 patients originally assigned to the pre-riociguat approval group (per-protocol), 21 patients were reassigned *post hoc* to the post-riociguat approval subgroup as their follow-up occurred after riociguat approval. Consequently, there were 55 patients in the pre-riociguat approval subgroup and 48 patients in the post-riociguat approval subgroups (figure 1).

In the overall population, mean age was 55.6 years and 59% of patients were male (table 1). Age and the Charlson comorbidity index score were similar in the *post hoc* defined pre-riociguat and post-riociguat approval subgroups, although there was a higher proportion of males (71% *versus* 49%) in the post- *versus* pre-riociguat approval subgroup (table 1). The demographic and clinical characteristics data for patients in the per-protocol pre- and post-approval subgroups are summarised in supplemental table S4.

Residual symptoms of PH

Residual PH symptoms more than 3 months after PEA were reported in 92 patients (89%) in the overall cohort. The most common PH symptoms reported across the overall and *post hoc* pre- and post-riociguat approval groups were dyspnoea (range: 60–73%) and chest pain (unspecified) (range: 31–35%). Full details of PH symptoms relative to tests undertaken for the overall cohort and subgroups are provided in supplemental table S5. Rates of residual PH symptoms and diagnostic assessments occurring in the 2-year follow-up period, with varying exclusion periods, are shown in supplemental table S6.

Rates of diagnostic assessment

In total, 89% of patients (n=92) underwent 1 or more of the 7 pre-specified tests for residual disease after PEA with a mean (standard deviation [SD]) of 4.6 (3.8) diagnostic tests per patient (table 2). The mean (SD) time from PEA (index date) to the first diagnostic test (after the 3-month wash-out period) was 183 (100) days (table 2). Equivalent data for patients in the per-protocol pre- and post-riociguat approval subgroups are summarised in supplemental table S7. The majority of patients with PH symptoms (n=92) underwent at least 1 diagnostic assessment after the 3-month post-PEA wash-out period (n=84, 91%), with the most common assessment being echocardiography (n=80, 87%) (supplemental table S5).

The most commonly performed assessment was echocardiography, which was undertaken in 84% of patients (n=87) with approximately one-third of all patients receiving CTA (32%; n=33) or a V/Q scan (28%; n=29) or being assessed for NT-proBNP levels (32%; n=33) or 6MWD (34%; n=35) (figure 2a). Only 5% of patients (n=5) underwent RHC, and a PAG was not obtained for any patient. Echocardiography and 6MWD tended to be assessed first with a mean (SD) of 222 (128) and 221 (148) days post-PEA, respectively, with RHC assessed last at 410 (249) days post-PEA (table 2).

The results of the wash-out period sensitivity analysis are shown in supplemental table S6. Of note, 71% of the patients with residual PH symptoms underwent RHC assessment when no wash-out period post-PEA was applied, with the percentage dropping to 36% when a wash-out of 1 day after PEA was applied, and further to 9% with a wash-out of 1 week and 5% with the pre-specified 3-month wash-out of the primary analysis.

An overview of assessment pathways followed for all patients is shown in a Sankey plot in figure 3a.

Diagnostic assessment in the pre- versus post-riociguat approval subgroups

In the pre- and post-riociguat approval subgroups, 87% (n=48) and 92% (n=44) of patients underwent 1 or more of the pre-specified diagnostic assessments with a mean (SD) number of tests of 3.8 (2.3) and 5.4 (4.8), respectively (figure 2b; table 2). The mean (SD) time to first test was 197 (118) days pre-riociguat approval and 167 (76) days post-riociguat approval (table 2). For patients with pre-specified PH symptoms, 90% (n=43) and 93% (n=41) underwent 1 or more of the pre-specified diagnostic assessments in the pre- and post-riociguat approval subgroups, respectively (supplemental table S5). These findings are similar to the subgroups defined per-protocol (supplemental figure S2 and table S8) where 91% (n=61) and 92% (n=23) of patients in the pre- and post-riociguat approval subgroups, respectively, underwent 1 or more of the pre-specified diagnostic assessments.

Use of echocardiography, the most commonly used assessment, occurred at a similar rate in the *post hoc* pre- and post-riociguat approval subgroups (85% [n=47] and 83% [n=40], respectively; figure 2b). Numerical differences were observed between subgroups for the use of 6MWD, V/Q scans and measurement of NT-proBNP levels with approximately twice as many patients undergoing these diagnostic tests in the post- *versus* pre-riociguat approval subgroup (figure 2b). The proportion of patients undergoing RHC also increased from 2% (n=1) in the pre-riociguat approval subgroup to 8% (n=4) in the post-riociguat approval subgroup, although the patient numbers were very low. No differences between pre- and post-riociguat approval subgroups were observed for the use of CTA (in 31% [n=17] and 33% [n=16] of patients, respectively). Overall, similar but less marked differences between the subgroups for diagnostic assessment utilisation were also observed in the per-protocol determined subgroups (supplemental figure S2 and table S8).

In the pre-riociguat approval subgroup, when not considering RHC due to the small number of patients undergoing this procedure, the earliest assessments performed were 6MWD (mean

[SD] time to first test: 174 [101] days) followed by echocardiography (223 [122] days) and CTA (224 [128] days), while in the post-riociguat approval subgroup, the earliest assessments were measurement of NT-proBNP levels (205 [107] days) then echocardiography (221 [136] days) (table 2).

Increased use of diagnostic methodologies that are more specific for CTEPH was observed in the post- *versus* pre-riociguat approval subgroup when comparing the Sankey plots (figure 3b and c). Similar findings but with less marked subgroup differences were also observed in the per-protocol determined subgroups (supplemental figure S3a and b).

Discussion

In this retrospective cohort study, based on the format of the INFORM study [11], analysing MarketScan data from a 2-year period in patients who had undergone PEA following a claim of PH or CTEPH, rates of residual PH symptoms were high. Overall, 89% of patients had residual PH symptoms more than 3 months after PEA, most commonly dyspnoea reported in 66% of patients. Rates of diagnostic assessment that occurred more than 3 months after PEA were also high, with 89% and 91% of all patients and those experiencing residual PH symptoms, respectively, undergoing 1 or more assessment.

The majority (84%) of patients underwent echocardiography with approximately one-third of patients receiving CTA, a V/Q scan and/or an assessment of 6MWD or NT-proBNP levels. The percentage of patients with residual PH symptoms who underwent RHC assessment was substantially reduced when a post-PEA wash-out period was applied, suggesting that the vast majority of patients who underwent RHC did so during the immediate post-operative period. This sensitivity analysis highlighted the importance of applying a 3-month wash-out period to ensure that the assessments occurred in response to subsequent residual symptoms of PH rather than the PEA index event. Overall rates of RHC were low, although they increased from 2% to 8% in the period post-riociguat approval, suggesting relatively few patients reporting residual PH symptoms were referred for full diagnostic work-up despite European Society of Cardiology and the European Respiratory Society guidelines recommending at least 1 haemodynamic assessment 6–12 months after PEA [1]. The results of this study therefore suggest that the diagnostic follow-up of patients with residual PH symptoms post-PEA is sub-optimal, indicating a need for increased awareness of the importance of continued management for patients with CTEPH-related symptoms following surgery.

In the longitudinal analysis of diagnostic pathways, our data suggested that there were implied differences in the assessment time and proportion of diagnostic tools used to assess patients

post-PEA in the time periods before and after the approval of riociguat. Prior to riociguat approval, 6MWD assessments, echocardiography and CTA were among the earliest assessments provided, whereas post-riociguat approval the earliest assessments were measurement of NT-proBNP and echocardiography. When assessing the diagnostic pathway Sankey plots after an initial echocardiogram, most patients in the pre-riociguat approval subgroup received CTA or assessment of NT-proBNP whereas most patients received CTA or a V/Q scan in the post-riociguat approval subgroup. In the post-riociguat approval subgroup, a higher proportion of patients underwent many of the diagnostic tests, with twice as many patients undergoing a V/Q scan and assessment of 6MWD and NT-proBNP levels. These data may suggest an increased awareness of specific CTEPH diagnostic procedures following the introduction of riociguat, which possibly reflects changes in the treatment landscape.

Limitations should be noted when assessing these data, including the small number of patients included in the analysis due to the limited number of eligible patients, particularly in the pre- and post-riociguat sub-analysis groups. It is also possible that co-morbidities may have been responsible for the pre-specified symptoms in some patients. The use of diagnostic codes for PH may mean that some patients without CTEPH may have been included in the analysis, potentially resulting in an overestimation of the CTEPH population. The PH diagnostic code used as the CTEPH diagnostic code was only implemented on 1 October 2017, towards the end of our study. However, the combination of a code related to PH/CTEPH with a code related to PEA likely meant that the study population reflected the patients of interest. Two-component code-based algorithms have been demonstrated to have a higher positive predictive value than single-component algorithms for the identification of CTEPH [13]. The number of patients with confirmed residual CTEPH diagnoses by specific procedures and their continuation to further workup could also not be established due to limitations of the MarketScan database but may be useful to investigate in future using data from clinical

practice and CTEPH registries. Furthermore, the MarketScan database is a convenience sample that may not represent the wider population of patients with CTEPH; for example, the database is skewed towards southern states of the USA [14, 15] and only includes patients with commercial insurance coverage. However, it should be noted that our data do reflect a diverse geographical and demographic US population due to the size and breadth of the MarketScan database. They may not, however, reflect other countries with different healthcare systems or reimbursement practices for diagnostic tests and treatments. It may be valuable for future studies, without the geographical limitations of the MarketScan database, to investigate whether differences in rates of symptoms or diagnostic assessments are impacted by a patient's location and distance from an expert centre for PEA. Finally, the temporal analysis with respect to riociguat approval may have missed other changes in the medical treatment landscape which could have influenced findings.

Conclusions

To conclude, low rates of RHC suggest that many patients showing signs or symptoms associated with persistent/recurrent CTEPH following PEA surgery are not being referred for full diagnostic work-up. An increase in the use of specific diagnostic tests to assess persistent/recurrent CTEPH after PEA may indicate that awareness of CTEPH and understanding of disease diagnosis has increased in recent years, possibly due to the influence of an evolving treatment landscape following the approval of new medical therapies. Further research into real-world treatment patterns for persistent/recurrent CTEPH after PEA may increase awareness of undiagnosed and untreated residual disease, help healthcare professionals to recognise the potential gaps in care and raise awareness of the need for follow-up and screening for persistent/recurrent CTEPH after PEA.

Acknowledgements

Medical writing assistance was provided by Johanna Barry, PhD, and Rachael Powis, PhD, at Adelphi Communications Ltd (Bollington, UK), funded by Bayer AG (Berlin, Germany) in accordance with Good Publications Practice.

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Figure Legends

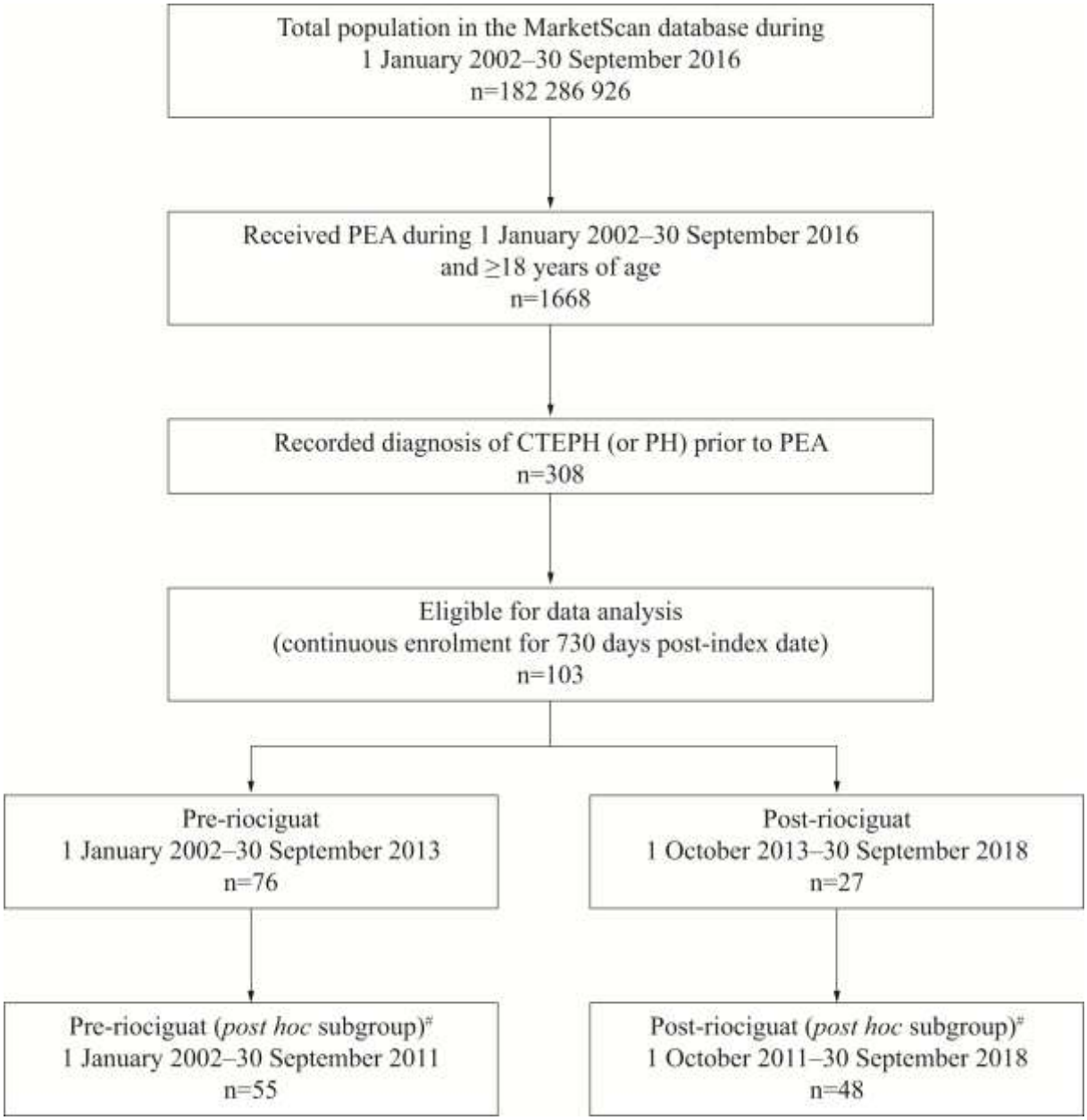


FIGURE 1 Flowchart of patient selection.

#*Post hoc* defined subgroups, whereby 21 patients whose PEA surgery occurred before the approval of riociguat in the USA but whose observation period extended beyond the riociguat

approval date were reassigned from the pre-riociguat approval subgroup to the post-riociguat approval subgroup.

A recorded diagnosis of CTEPH (or PH) was not available in the MarketScan database for 1360 of the 1668 patients identified who underwent PEA.

CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

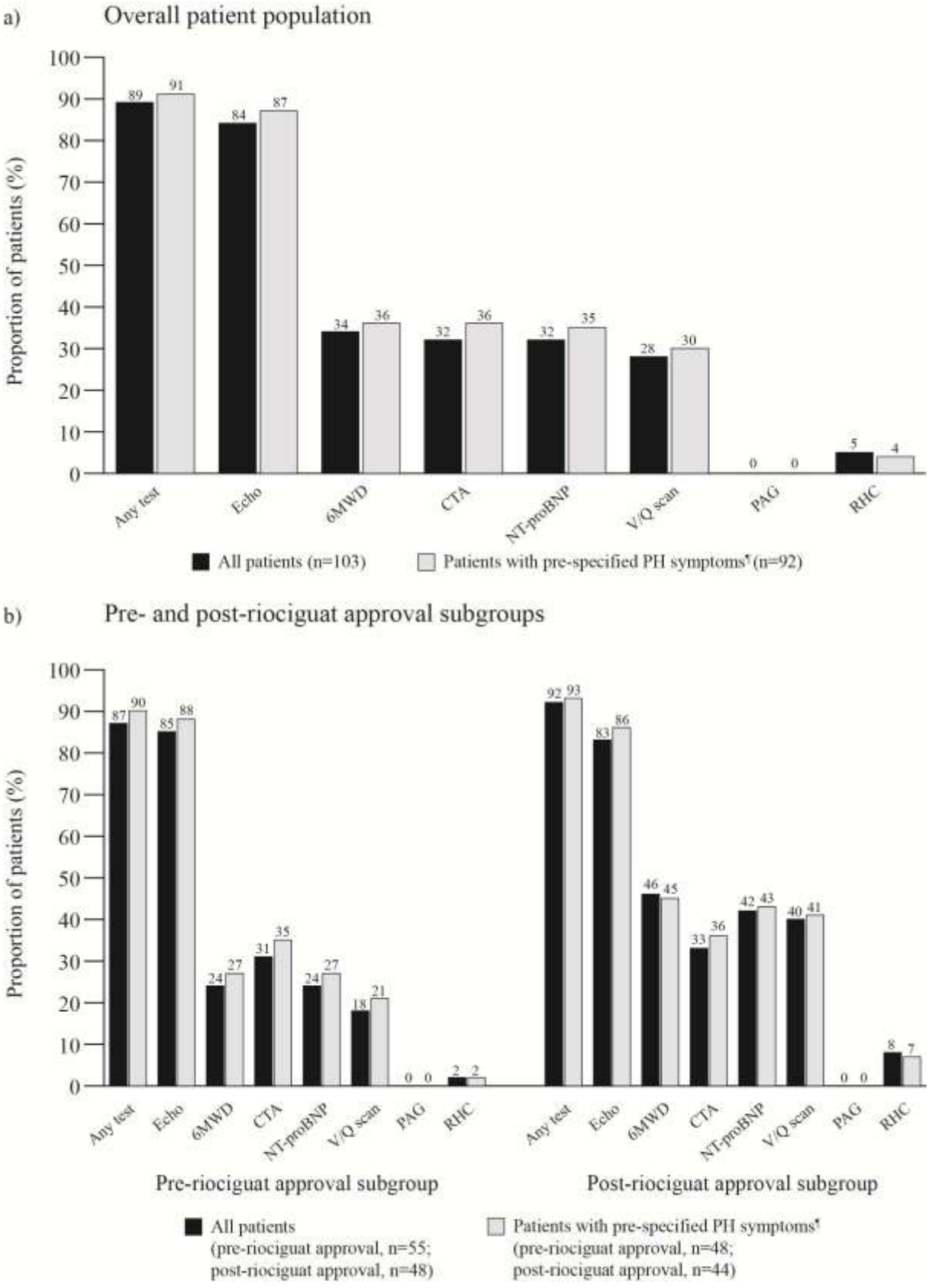

a)
Overall patient population
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
89
91
84
87
34
36
32
36
32
35
28
30
0
0
5
4
Any test
Echo
6MWD
CTA
NT-proBNP
V/Q scan
PAG
RHC
All patients (n=103)
Patients with pre-specified PH symptoms¶ (n=92)
b)
Pre- and post-riociguat approval subgroups
Proportion of patients (%)
87
90
85
88
24
27
31
35
24
27
18
21
0
0
2
2
92
93
83
86
46
45
33
36
42
43
40
41
0
0
8
7
Any test
Echo
6MWD
CTA
NT-proBNP
V/Q scan
PAG
RHC
Pre-riociguat approval subgroup
Post-riociguat approval subgroup
All patients
(pre-riociguat approval, n=55;
post-riociguat approval, n=48)
Patients with pre-specified PH symptoms¶
(pre-riociguat approval, n=48;
post-riociguat approval, n=44)

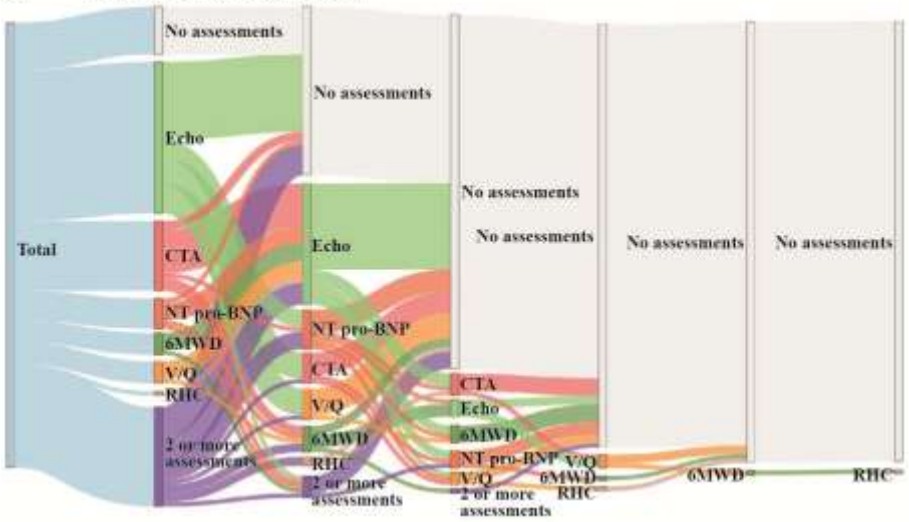
FIGURE 2 Rates of diagnostic assessment 2 years post-PEA for all patients and patients with pre-specified residual PH symptoms a) in the overall population, b) in the *post hoc* defined pre- and post-riociguat approval[#] subgroups.

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

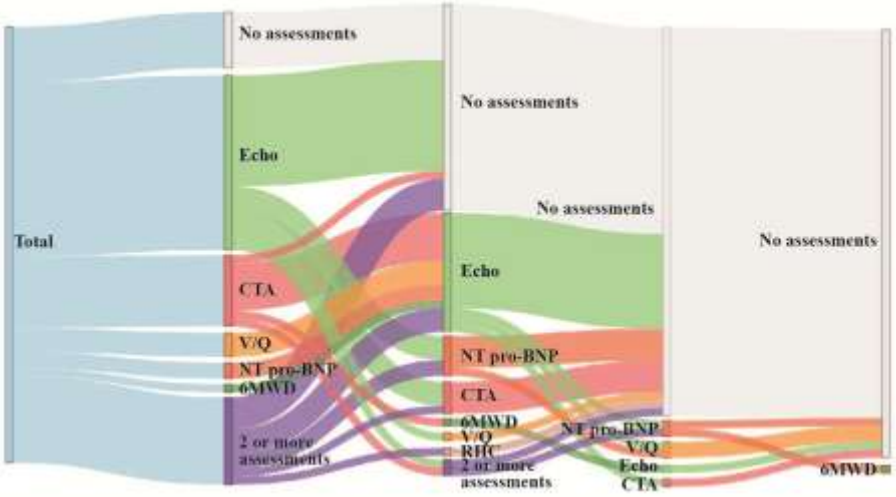
[¶]Syncope, malaise and fatigue, dyspnoea, haemoptysis, chest pain (unspecified), dizziness, gait abnormality, cardiomegaly, ascites and peripheral oedema.

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

a) Overall patient population



b) Pre-riociguat approval subgroup



c) Post-riociguat approval subgroup

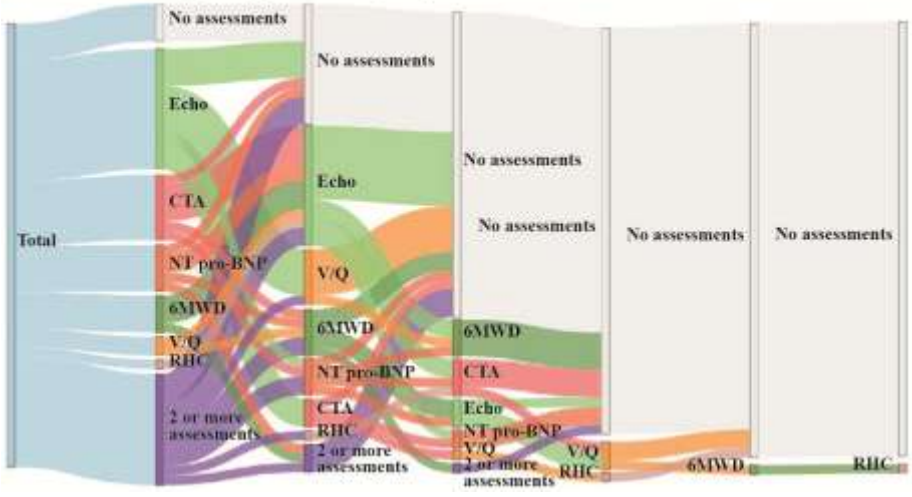


FIGURE 3 Sankey plots illustrating diagnostic pathways a) in the overall patient population (n=103), b) in the *post hoc* defined pre-riociguat approval subgroup (n=55), c) in the post-riociguat approval[#] (n=48) subgroup.

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

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 1 Demographic and clinical characteristics in the overall population and in the subgroups defined *post hoc* according to completion of clinical assessment either pre- or post-riociguat[#] approval

	Total (n=103)	**Pre-riociguat approval (n=55)**	**Post-riociguat approval[#] (n=48)**
Age (years), mean (SD)	55.6 (14.3)	57.9 (14.7)	52.9 (13.5)
Sex, n (%)			
Male	61 (59)	27 (49)	34 (71)
Female	42 (41)	28 (51)	14 (29)
Duration of follow-up (days), mean (SD)	1604.5 (925.9)	1922.5 (1082.7)	1240.1 (509.6)
Charlson comorbidity index,[¶] mean (SD)	1.8 (1.7)	1.6 (1.8)	2.0 (1.6)

[#]*Post hoc* defined subgroups, whereby 21 patients whose PEA surgery occurred before the approval of riociguat in the USA but whose observation period extended beyond the riociguat approval date were reassigned from the pre-riociguat approval subgroup to the post-riociguat approval subgroup.

[¶]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.

TABLE 2 Number of tests and days to the first diagnostic test after PEA in the overall population, and in the *post hoc* defined pre-riociguat approval and post-riociguat approval[#] subgroups

	Total population (n=103)			**Pre-riociguat approval (n=55)**			**Post-riociguat approval[#] (n=48)**		
Diagnostic test	**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])**	**n (%)**	**Number of tests after PEA (mean [SD])**	**Number of days to first test (mean [SD])**
Any test	92 (89)	4.6 (3.8)	182.7 (100.4)	48 (87)	3.8 (2.3)	196.9 (117.8)	44 (92)	5.4 (4.8)	167.3 (75.6)
Echo	87 (84)	2.4 (1.2)	221.7 (128.1)	47 (85)	2.4 (1.2)	222.6 (122.1)	40 (83)	2.4 (1.2)	220.7 (136.4)
6MWD	35 (34)	2.9 (1.5)	221.4 (147.5)	13 (24)	2.8 (1.7)	174.2 (101.4)	22 (46)	2.9 (1.4)	249.4 (164.8)
CTA	33 (32)	1.8 (1.9)	242.3 (159.2)	17 (31)	2.2 (2.6)	223.9 (127.7)	16 (33)	1.4 (0.7)	261.9 (189.5)
NT-proBNP	33 (32)	3.4 (3.9)	236.2 (145.3)	13 (24)	1.8 (1.3)	283.7 (185.1)	20 (42)	4.5 (4.7)	205.4 (106.7)
V/Q scan	29 (28)	1.5 (0.7)	291.8 (185.9)	10 (18)	1.6 (0.5)	287.0 (202.6)	19 (40)	1.4 (0.8)	294.4 (182.3)
PAG	0	0	0	0	0	0	0	0	0
RHC	5 (5)	2.4 (2.6)	410.0 (248.6)	1 (2)	1.0 (NA)	133.0 (NA)	4 (8)	2.8 (2.9)	479.3 (224.5)

[#]*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; NA: not available; NT-proBNP: *N*-terminal prohormone of brain natriuretic protein; PAG: pulmonary angiogram; PEA: pulmonary endarterectomy; RHC: right heart catheterisation; SD: standard deviation; V/Q: ventilation/perfusion.

Supplemental Material

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

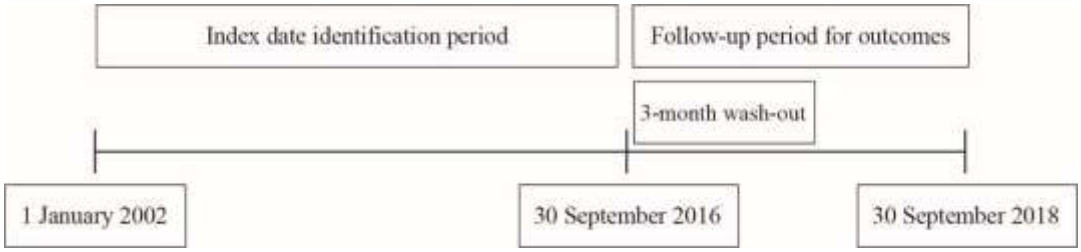


Figure S1 Study time frame.

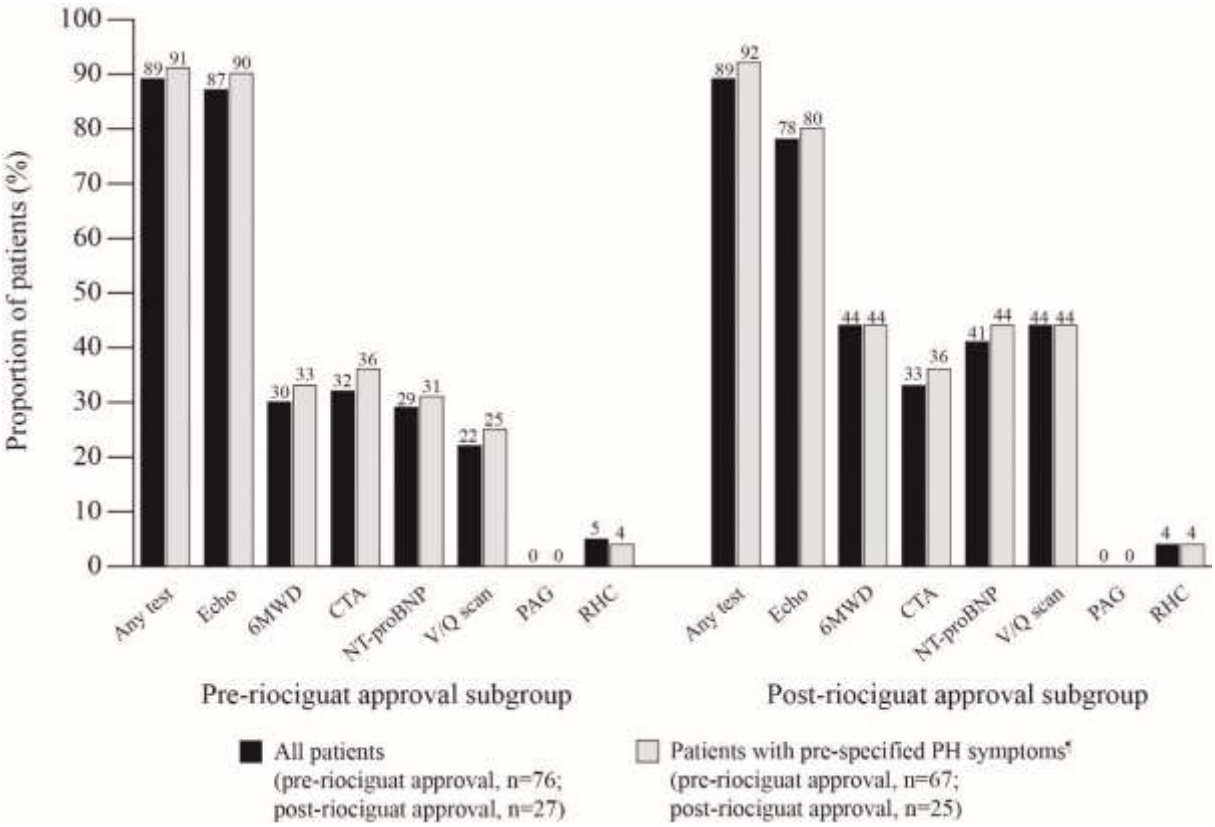


Figure S2 Rates of diagnostic assessment for all patients and patients with pre-specified residual PH symptoms in the per-protocol defined pre-riociguat[#] and post-riociguat approval subgroups.

[#]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.

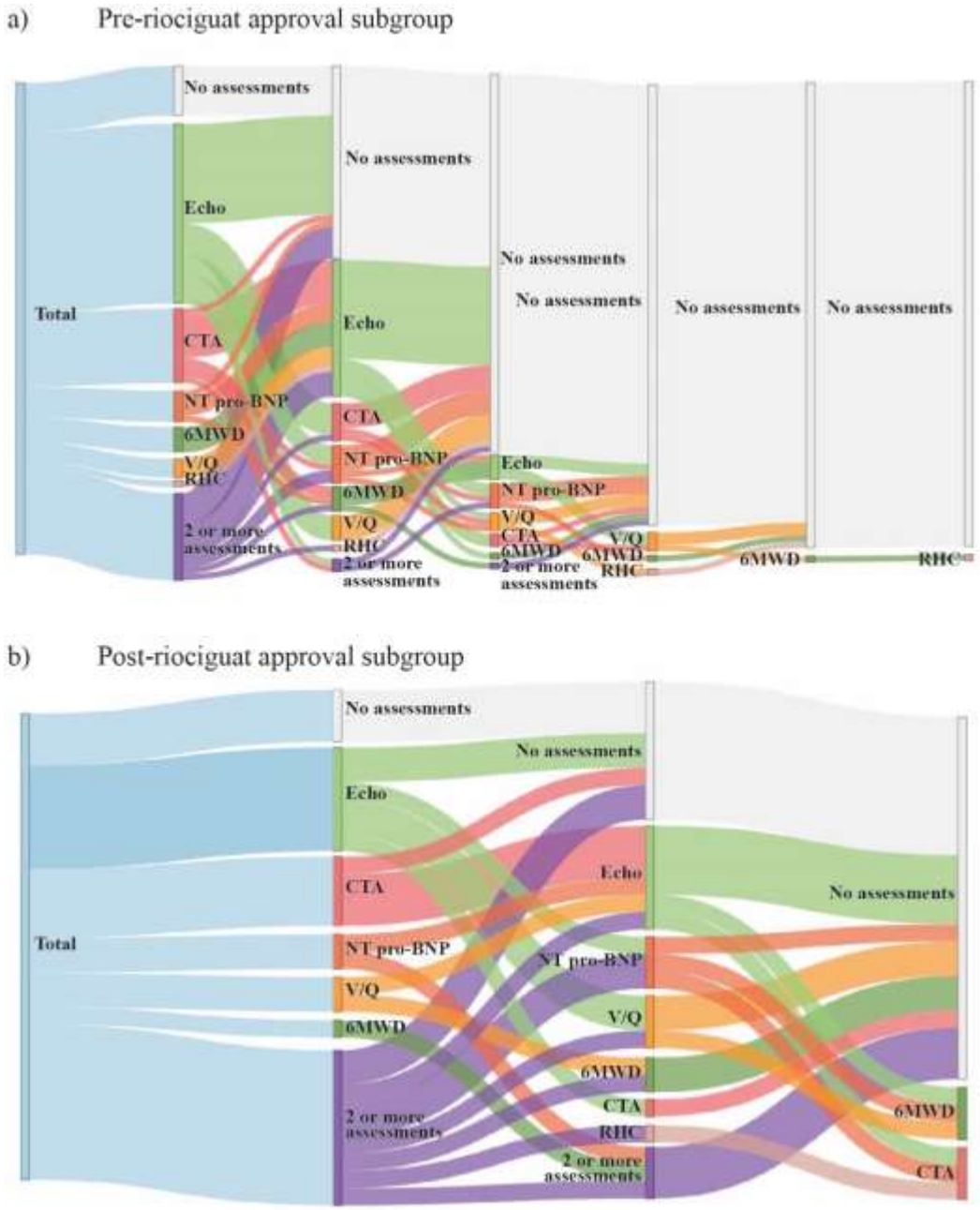


Figure S3 Sankey plots in the per-protocol determined patients in the per-protocol defined a) pre-riociguat approval[#] (n=76) subgroup, and b) post-riociguat approval (n=27) subgroup.

[#]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	• 416.0 (Primary PH) • 416.8 (Other chronic pulmonary heart diseases)
ICD-10-CM codes for PH	• I27.0 (Primary PH) • I27.2 (Other secondary pulmonary hypertension)
CTEPH	
ICD-10-CM codes for CTEPH	• I27.24 (CTEPH)
PEA	
CPT code for PEA	• 33916 (PEA, with or without embolectomy, with cardiopulmonary bypass) • 33910 (Pulmonary artery embolectomy, with cardiopulmonary bypass)
ICD-9-CM code for PEA	• 38.15 (Endarterectomy, other thoracic vessels)
ICD-10-PCS codes for PEA	• 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 (*e.g.* 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)	• 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

	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 *PLUS* Sterile water, saline and/or dextrose, diluent/flush, 10 mL *PLUS* Echocardiogram	● 96379 ● A4216 ● See codes listed above for echocardiogram
OR	
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study *PLUS* Sterile water, saline and/or dextrose, diluent/flush, 10 mL	● 93308 ● A4216
OR	
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study *PLUS* Infusion, normal saline solution, 250 cc	● 93308 ● J7050
OR	
Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug *PLUS* Distinct procedural service *PLUS* Echocardiogram	● 96374 ● Modifier-59 ● 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 (*e.g.* 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.

Table S5 Rates of residual PH symptoms and diagnostic assessments in the overall population, pre-riociguat and post-riociguat approval subgroups

n (%)	Total	Any test	Echo	6MWD	CTA	NT-proBNP	V/Q scan	PAG	RHC
Diagnostic assessment rates in patients with residual PH symptoms (overall population)									
Total	**103**	**92 (89)**	**87 (84)**	**35 (34)**	**33 (32)**	**33 (32)**	**29 (28)**	**0**	**5 (5)**
Any PH symptom	**92**	**84 (91)**	**80 (87)**	**33 (36)**	**33 (36)**	**32 (35)**	**28 (30)**	**0**	**4 (4)**
Dyspnoea	68	66 (97)	64 (94)	31 (46)	27 (40)	31 (46)	23 (34)	0	4 (6)
Chest pain, unspecified	34	32 (94)	31 (91)	9 (26)	19 (56)	12 (35)	11 (32)	0	2 (6)
Cardiomegaly	27	25 (93)	25 (93)	8 (30)	13 (48)	6 (22)	11 (41)	0	2 (7)
Malaise and fatigue	20	18 (90)	18 (90)	10 (50)	7 (35)	11 (55)	5 (25)	0	1 (5)
Peripheral oedema	17	15 (88)	14 (82)	7 (41)	6 (35)	7 (41)	4 (24)	0	1 (6)
Dizziness	10	10 (100)	9 (90)	1 (10)	4 (40)	2 (20)	3 (30)	0	0
Syncope	7	7 (100)	7 (100)	4 (57)	3 (43)	4 (57)	3 (43)	0	0
Haemoptysis	4	4 (100)	4 (100)	2 (50)	2 (50)	1 (25)	1 (25)	0	1 (25)
Ascites	4	4 (100)	4 (100)	3 (75)	1 (25)	2 (50)	1 (25)	0	0
Gait abnormality	2	2 (100)	2 (100)	0	2 (100)	0	1 (50)	0	0
Diagnostic assessment rates in patients with residual PH symptoms (pre-riociguat approval subgroup)									
Total	**55**	**48 (87)**	**47 (85)**	**13 (24)**	**17 (31)**	**13 (24)**	**10 (18)**	**0**	**1 (2)**
Any PH symptom	**48**	**43 (90)**	**42 (88)**	**13 (27)**	**17 (35)**	**13 (27)**	**10 (21)**	**0**	**1 (2)**
Dyspnoea	33	31 (94)	30 (91)	13 (39)	13 (39)	12 (36)	8 (24)	0	1 (3)
Chest pain, unspecified	19	17 (89)	17 (89)	2 (11)	9 (47)	4 (21)	5 (26)	0	0
Cardiomegaly	9	8 (89)	8 (89)	1 (11)	5 (56)	0	2 (22)	0	0
Malaise and fatigue	8	8 (100)	8 (100)	3 (38)	2 (25)	5 (63)	0	0	0
Peripheral oedema	9	8 (89)	8 (89)	3 (33)	3 (33)	4 (44)	0	0	0
Dizziness	5	5 (100)	5 (100)	0	2 (40)	2 (40)	0	0	0
Syncope	0	0	0	0	0	0	0	0	0
Haemoptysis	2	2 (100)	2 (100)	0	1 (50)	0	0	0	0
Ascites	1	1 (100)	1 (100)	0	1 (100)	0	0	0	0
Gait abnormality	2	2 (100)	2 (100)	0	2 (100)	0	1 (50)	0	0
Diagnostic assessment rates in patients with residual PH symptoms (post-riociguat approval subgroup)[#]									
Total	**48**	**44 (92)**	**40 (83)**	**22 (46)**	**16 (33)**	**20 (42)**	**19 (40)**	**0**	**4 (8)**
Any PH symptom	**44**	**41 (93)**	**38 (86)**	**20 (45)**	**16 (36)**	**19 (43)**	**18 (41)**	**0**	**3 (7)**
Dyspnoea	35	35 (100)	34 (97)	18 (51)	14 (40)	19 (54)	15 (43)	0	3 (9)
Chest pain, unspecified	15	15 (100)	14 (93)	7 (47)	10 (67)	8 (53)	6 (40)	0	2 (13)
Cardiomegaly	18	17 (94)	17 (94)	7 (39)	8 (44)	6 (33)	9 (50)	0	2 (11)
Malaise and fatigue	12	10 (83)	10 (83)	7 (58)	5 (42)	6 (50)	5 (42)	0	1 (8)
Peripheral oedema	8	7 (88)	6 (75)	4 (50)	3 (38)	3 (38)	4 (50)	0	1 (13)
Dizziness	5	5 (100)	4 (80)	1 (20)	2 (40)	0	3 (60)	0	0
Syncope	7	7 (100)	7 (100)	4 (57)	3 (43)	4 (57)	3 (43)	0	0
Haemoptysis	2	2 (100)	2 (100)	2 (100)	1 (50)	1 (50)	1 (50)	0	1 (50)
Ascites	3	3 (100)	3 (100)	3 (100)	0	2 (67)	1 (33)	0	0
Gait abnormality	0	0	0	0	0	0	0	0	0

[#]*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

	Pre-riociguat approval[#] (n=76)			Post-riociguat approval (n=27)		
Diagnostic test	**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.