Pulmonary Arterial Hypertension associated with Protein Kinase Inhibitors: A pharmacovigilance-pharmacodynamic study

SUPPLEMENTARY MATERIAL

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Appendix 1. Details of co-reported MedDRA term excluded from the analysis

-**cardiac disorders** (from MedDRA classification: Cardiac disorders SOC - Cardiac and vascular disorder congenital HGLT - Cardiac and vascular investigation HGLT).

- **pulmonary disorders** (respiratory and mediastinal neoplasms malignant and unspecified HGLT - bronchial disorders (excl neoplasms) HGLT - lower respiratory tract inflammatory and immunologic conditions HLT– parenchymal lung disorders HLT - pulmonary thrombotic and embolic conditions HLT - respiratory tract disorders NEC HLT – tumour embolism / tumour thrombosis PT) and

-**thrombotic disorders** (embolism and thrombosis HGLT).

Figure S1. Flow chart of PAH cases selection for analysis

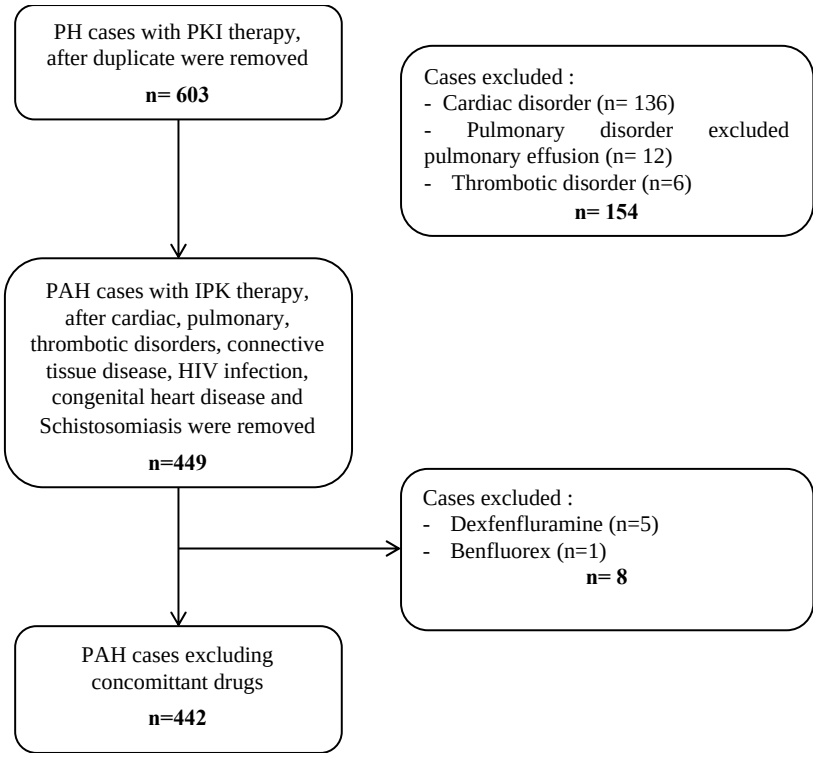
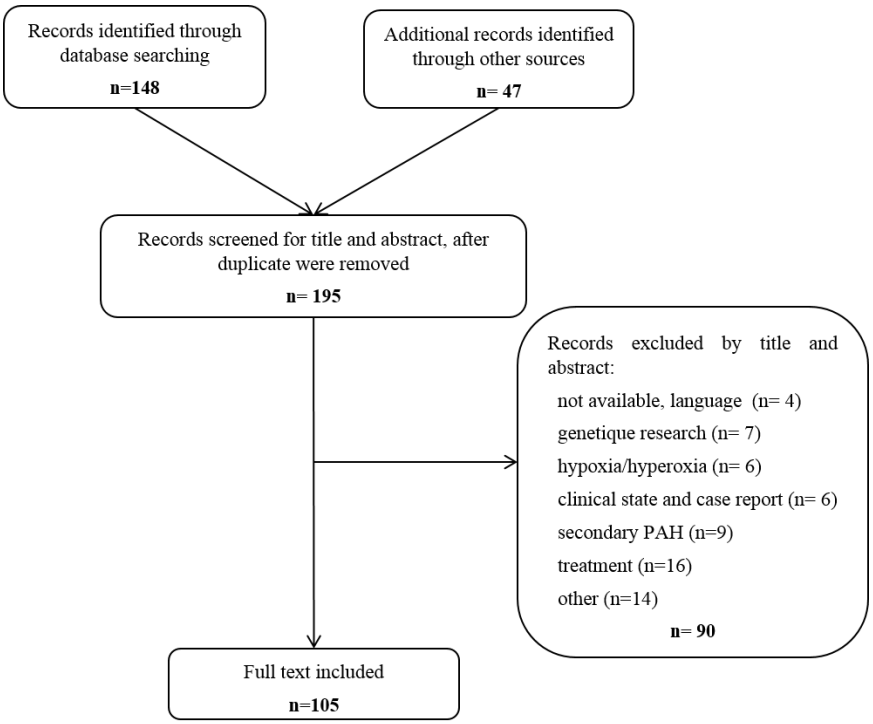


Figure S2. Flow chart of the literature review aiming to identify protein kinases involved in pulmonary function.



Appendix 2. Selected protein kinases and most relevant references.

Target involved in pulmonary pathophysiology	Sources
ALK1 Activin receptor-like kinase-1	(Star et al., 2010) ; (Girerd et al., 2017) ; (Gore et al., 2014)
ALK5 transforming growth factor-β1 (TGFβ1)	(Tojais et al., 2017) (Upton and Morrell, 2013)
AMPKa1 (AMP-activated protein kinase)	(Ibe et al., 2013) (Omura et al., 2016)
AMPKa2	(Ibe et al., 2013)
BMPR-1 = ALK6	(Chida et al., 2012)
BMPR-2	(Tojais et al., 2017)
B-Raf (Rapidly Accelerated Fibrosarcoma)	(Awad et al., 2016)
C-Raf = Raf1	(Hopper et al., 2015)
DDR1 Discoidin domain receptor	(Sakamoto et al., 2001)
EIF2AK4 eukaryotic translation initiation factor 2 alpha kinase 4	(Tenorio et al., 2015) (Eichstaedt et al., 2016) (Best et al., 2017)
ERB-b1 = EGFR = Her1	(Dahal et al., 2010)
ERB-b2 = HER2	(Dahal et al., 2010)
focal adhesion kinase FAK	(Paulin et al., 2014)
FGFR1	(Zheng et al., 2015) (Kim, 2014) (Izikki et al., 2009)
FGFR2	(Schermuly et al., 2011)
IGF-1R (insulin like growth factor)	(Sun et al., 2016) (Baumgart et al., 2017) (Dewachter et al., 2014)
JAK 1	(Lachmann et al., 2017)

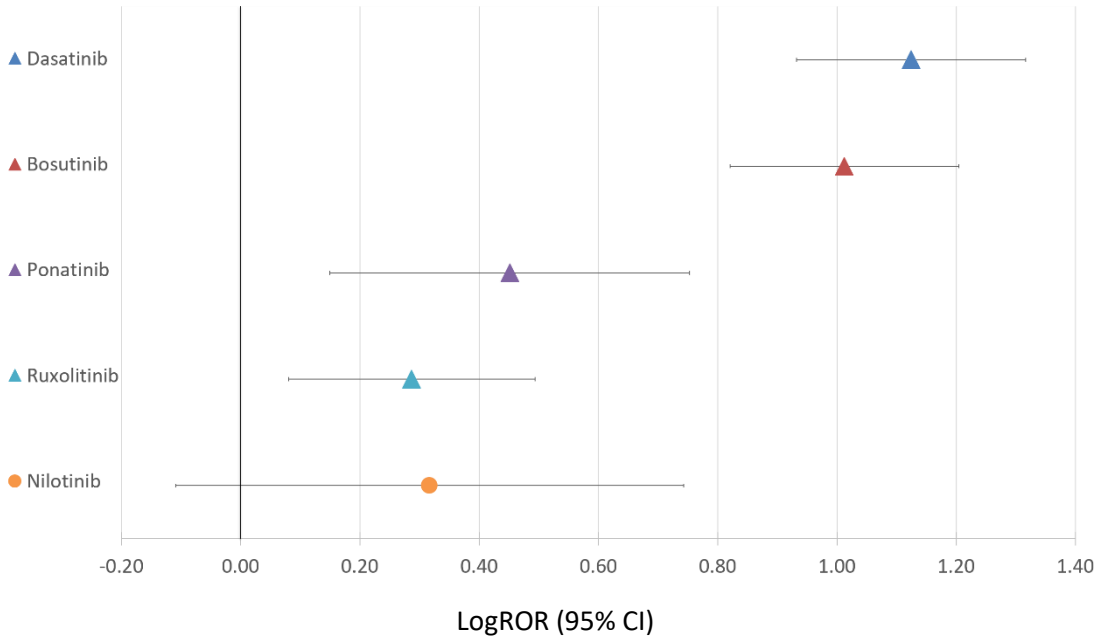
JAK2	(Mattar et al., 2016)
JNK1/2 (c-Jun N-terminal kinase) = mitogen-activated protein kinase 9	(Wilson et al., 2015) (Das et al., 2016)
c-kit = KIT **stem cell growth factor receptor (SCFR)**	(Montani et al., 2014) (Farha et al., 2014)
Lck Leukocyte C-terminal Src kinase	(Andruska et al., 2017)
lyn	(Pullamsetti et al., 2012a)
c MET = HGF	(Schermuly et al., 2011)
PDGFRα	(Berghausen et al., 2013) (Schermuly, 2005)
PDGFRβ	(Cai et al., 2017) (Weatherald et al., 2017)
PKG cGMP-dependent protein kinase	(Patel et al., 2014)
ROCK-2	(Shimizu et al., 2013)
Tyrosine-protein kinase c-Src	(Guignabert et al., 2016)
TEC	(de Lavallade et al., 2008)
TEK receptor tyrosine kinase TIE2	(Guignabert et al., 2016)
VEGFR-1	(Derrett-Smith et al., 2013)
VEGFR-2	(Nicolls et al., 2012)
VEGFR-3	(Hwangbo et al., 2017)
c-yes	(Pullamsetti et al., 2012b)

Appendix 3. Results of ROR sensitivity analysis, standardizing on time on the market.

Sensitivity analysis were performed to compare the proportion of PAH reported for each PKI with the proportion of PAH reported for all other PKI.

We performed an analysis using only reported cases from the first six years after the FDA approval. A positive disproportionality signal was found for dasatinib with a ROR of 13.32 (8.56; 20.72), bosutinib 10.30 (6.63; 16.00), ponatinib 2.83 (1.41; 5.66), ruxolitinib 1.94 (1.20; 3.12) and nilotinib 2.07 (0.78; 5.53). Logarithmic value are represented in Figure S3.

Figure S3. Disproportionality signal of PAH induced by PKI six years after FDA approval versus all medication in pharmacovigilance database. ROR and 95% CI were log transformed.



Appendix 4. Results of correlations sensitivity analysis standardizing on time on the market, including only PKI with more the 3 PAH cases and using affinity data from Davis et al.

Target	6 year after approval		More than 3 cases		Affinity data from Davis et al.	
	r	p-value	r	p-value	r	p-value
ALK1	0.47	0.079	**0.9**	**0.0058**	0.54	0.036
ALK5	0.42	0.12	**0.98**	**0.000069**	0.4	0.14
AMPKa1	-0.17	0.55	-0.26	0.57	-0.18	0.53
AMPKa2	-0.2	0.47	-0.3	0.52	-0.18	0.51
B_Raf	0.37	0.17	0.68	0.093	0.43	0.11
BMPR_1	0.3	0.28	0.85	0.015	0.56	0.031
BMPR_2	0.2	0.47	-0.12	0.8	0.095	0.74
c_yes	**0.84**	**0.000079**	**0.87**	**0.0011**	**0.82**	**0.00018**
c-src	**0.89**	**0.000007**	**0.9**	**0.0054**	**0.86**	**0.000042**
DDR1	0.48	0.068	0.66	0.11	0.47	0.075
EIF2K4	0.2	0.47	0.31	0.5	0.16	0.56
ERB_b1	0.053	0.85	0.044	0.93	0.052	0.85
FAK	0.084	0.76	-0.046	0.92	-0.0045	0.99
FGFR1	-0.2	0.48	0.0069	0.99	-0.17	0.54
FGFR2	-0.091	0.75	0.29	0.53	-0.044	0.88
HER2	-0.012	0.97	0.012	0.98	0.027	0.92
HGF	-0.2	0.47	-0.0081	0.99	-0.2	0.48
IGF_1R	-0.22	0.44	-0.3	0.52	-0.19	0.49
JAK1	-0.21	0.46	-0.31	0.49	-0.17	0.55
JAK2	0.014	0.96	-0.041	0.93	0.046	0.87
JNK1	-0.2	0.48	-0.2	0.67	-0.17	0.55
JNK2	-0.31	0.26	-0.41	0.37	-0.32	0.25
KIT	0.3	0.28	0.44	0.32	0.33	0.23
Lck	**0.84**	**0.00016**	0.86	0.028	**0.78**	**0.00057**
Lyn	**0.83**	**0.00012**	0.83	0.02	**0.8**	**0.00036**
PDGFRalfa	0.22	0.44	0.44	0.32	0.29	0.29
PDGFRbeta	0.25	0.38	0.39	0.39	0.27	0.32
PKG	-0.14	0.63	-0.15	0.75	NA	NA
RAF1	0.33	0.22	0.85	0.016	0.37	0.18
ROCK_2	0.038	0.89	-0.19	0.68	-0.02	0.94
TEC	**0.77**	**0.00082**	**0.96**	**0.00069**	**0.88**	**0.000015**
TIE2	-0.22	0.43	-0.056	0.91	-0.25	0.36

VEGFR_1	-0.32	0.24	-0.26	0.58	-0.32	0.24
VEGFR_2	-0.29	0.29	-0.26	0.58	-0.29	0.29
VEGFR_3	-0.37	0.18	-0.39	0.39	-0.37	0.18

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