

Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study

Authors: David Zisman¹, Sandeep Sahay², Debabrata Bandyopadhyay³, Amro Al-Astal⁴, Meredith Broderick⁵, Danielle Caudell Stamper⁶, Hunter Champion⁷, Maral DerSarkissian⁸, Matthew Hunsucker⁹, Dasom Lee⁵, Kevin Maher⁵, Andrew Nelsen⁵, Raj Parikh¹⁰, Franck Rahaghi⁵, Abhijit Raval¹¹, Claire M. Thrasher⁵, Tejaswini Kulkarni¹², Oksana A. Shlobin¹³, David G. Kiely¹⁴, Steven Nathan¹³, Mary Beth Scholand¹⁵

¹Division of Pulmonary Medicine, Cleveland Clinic Florida, Weston, FL; ²Division of Pulmonary, Critical Care and Sleep Medicine, Houston Methodist Hospital, Houston, TX; ³Center for Advanced Lung Disease and Lung Transplant Program, Tampa General Hospital, FL; ⁴Internal Medicine and Pulmonology, Marshall University Joan C. Edwards School of Medicine, Huntington, WV; ⁵United Therapeutics Corporation, Research Triangle Park, NC; ⁶Medpace, Cincinnati, OH; ⁷Southeastern Cardiology, Columbus, GA; ⁸Analysis Group, Los Angeles, CA; ⁹Pulmonary and Critical Care Medicine, LeBauer Healthcare, Greensboro, NC; ¹⁰Department of Pulmonary Critical Care Medicine, Hartford Hospital, Hartford, CT; ¹¹Internal Medicine, Pulmonary Disease & Critical Care, AnMed Pulmonary And Sleep Medicine, Anderson, SC; ¹²Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL; ¹³Advanced Lung Disease and Transplant Program, Inova Schar Heart and Vascular Institute, Inova Fairfax Hospital, Falls Church, VA; ¹⁴Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, UK and NIHR Biomedical Research Centre, Sheffield; ¹⁵Department of Medicine, University of Utah, Salt Lake City, UT.

Corresponding author: David Zisman (zismand@ccf.org).

Table S1. Site-level institutional review board (IRB) approvals.

Site ID	Investigator	IRB Type	IRB Name	Approval #
008	Swaminathan, A	Local	Duke Health	Pro00113444
015	Crossno, P	Local	Intermountain Health	1052528
026	Sears, S	Local	Legacy Research Institute	2090
028	Belloli, E	Central	Advarra	Pro00068420
030	Veeraraghavan, S	Central	Advarra	Pro00068420
035	Nathan, S	Central	Advarra	Pro00068420
049	Sahay, S	Central	Advarra	Pro00068420
050	Estrada Anzueto, R	Central	Advarra	Pro00068420
053	Jablonski, R	Local	Loyola University	216698051723
072	Zisman, D	Local	Cleveland Clinic	24-158
099	Weaver, E	Central	Advarra	Pro00068420
107	Parikh, R	Central	Advarra	Pro00068420
188	Smith, S	Local	University of Kentucky	95190
194	Bandyopadhyay, D	Central	Advarra	Pro00068420
204	Bemiss, B	Local	Northwestern University	STU00220558
211	Bernens, M	Central	Advarra	Pro00068420
228	Case, A	Local	WCG	1352256
301	Krishnan, A	Central	Advarra	Pro00068420
305	Badlam, J	Local	University of Vermont	STUDY00003061
338	Johri, S	Central	Advarra	Pro00068420
340	Barash, M	Local	Medical College of Wisconsin	PRO00048446
369	Mughal, M	Central	Advarra	Pro00068420
370	Mansour, A	Local	Brany	23-02-54701
371	Condos, R	Central	Advarra	Pro00068420
372	Stewart, J	Local	Dartmouth-Hitchcock	MOD00026240
400	Raval, A	Central	Advarra	Pro00068420
417	Paul, T	Central	Advarra	Pro00068420
469	Maddipati, V	Central	Advarra	Pro00068420
554	Lindner, D	Local	NCH Healthcare System	IRB0033
558	Beck, E	Local	University of Utah	IRB00169643
561	Hunsucker, M	Central	Advarra	Pro00068420
567	Kable, S	Central	Advarra	Pro00068420
599	Al-Astal, A	Central	Advarra	Pro00068420
644	Cruz Morel, K	Central	Advarra	Pro00068420
667	Liao, DW	Central	Advarra	Pro00068420
701	Brown, J	Central	Advarra	Pro00068420
702	Khan, A	Central	Advarra	Pro00068420
703	Madhani-Lovely, F	Central	Advarra	Pro00068420
704	Farah, H	Central	Advarra	Pro00068420
706	Corwin, D	Local	St. Lukes University	IRB-FY2024-289
708	Homoud, A	Central	Advarra	Pro00068420

SUPPLEMENTARY MATERIAL

Table S2. Characteristics of the preliminary population and pre-defined hemodynamic subgroups; data are reported as median (IQR) or N (%).

	Total	Pre-capillary PH	Ipc-PH	Cpc-PH	Elevated mPAP only	Elevated PAWP only	Elevated PVR only	Normal RHC
Number of patients	190	105	6	9	14	2	25	29
Demographics								
Age, years	73 (64-77)	74 (64-78)	76 (72-79)	77 (66-78)	73 (67-77)	68 (67-68)	73 (66-76)	69 (57-77)
Sex, male	103 (54%)	56 (53%)	4 (67%)	6 (67%)	8 (57%)	2 (100%)	10 (40%)	17 (59%)
Ethnicity, Hispanic/Latino	17 (9%)	11 (10%)	1 (17%)	0 (0%)	0 (0%)	1 (50%)	3 (12%)	1 (3%)
Race, White	154 (81%)	83 (79%)	6 (100%)	7 (78%)	13 (93%)	1 (50%)	20 (80%)	24 (83%)
Black	19 (10%)	10 (10%)	0	2 (22%)	1 (7%)	1 (50%)	2 (8%)	3 (10%)
BMI, kg/m ²	28 (25-33)	28 (25-32)	31 (29-35)	30 (27-33)	30 (28-34)	26 (25-26)	28 (23-31)	27 (24-32)
Medical History								
Time since ILD diagnosis, years	2.5 (1.1-5.4)	2.6 (1.1-5.8)	2.8 (2.0-5.9)	3.8 (1.4-6.3)	4.6 (2.7-5.2)	1.0 (0.3-1.7)	1.7 (0.4-3.4)	2.1 (1.3-6.2)
Antifibrotic use	64 (34%)	32 (30%)	2 (33%)	5 (56%)	5 (36%)	2 (100%)	14 (56%)	4 (14%)
Supplemental O ₂ use	100 (53%)	64 (62%)	3 (50%)	5 (56%)	9 (64%)	0 (0%)	10 (40%)	9 (31%)
O ₂ Flow rate, L/min	2 (0-4)	3 (0-4)	1.5 (0-4)	2 (0-6)	5 (0-5)	0 (0-0)	0 (0-2)	0 (0-2)
6MWD, meters	300 (210-396)	300 (196-389)	264 (225-372)	255 (183-280)	360 (179-460)	416 (375-456)	293 (137-366)	383 (297-454)
Labs & Physical Exam								
BNP, pg/mL	39 (18-92)	42 (20-107)	24 (13-255)	109 (97-156)	23 (16-52)	19 (9-28)	33 (16-71)	32 (17-78)
NT-proBNP, pg/mL	158 (82-348)	160 (89-497)	102 (50-447)	509 (317-718)	119 (100-280)	43 (41-45)	232 (42-353)	111 (66-269)
SCr, mg/dL	0.9 (0.7-1.1)	0.9 (0.7-1.0)	0.8 (0.6-0.9)	0.9 (0.8-1.1)	0.9 (0.7-1.2)	1.7 (1.1-2.3)	0.8 (0.6-1.0)	1.0 (0.8-1.1)
eGFR [†] , mL/min/1.73m ²	81 (67-97)	80 (67-98)	90 (88-102)	78 (58-90)	90 (67-95)	53 (31-75)	91 (72-99)	78 (70-95)
Peripheral edema	57 (30%)	30 (29%)	2 (33%)	7 (78%)	5 (36%)	0 (0%)	3 (12%)	10 (34%)
Loud P2/S2	43 (23%)	26 (25%)	0 (0%)	1 (11%)	1 (7%)	1 (50%)	8 (32%)	6 (21%)
JVD	14 (7%)	8 (8%)	0 (0%)	0 (0%)	2 (14%)	0 (0%)	2 (8%)	2 (7%)
Syncope	8 (4%)	6 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (3%)
Pulmonary Function								

SUPPLEMENTARY MATERIAL

FEV1, % predicted	70 (56-83)	68 (55-83)	63 (56-79)	60 (46-74)	78 (70-83)	95 (87-103)	73 (56-82)	73 (53-91)
FEV1, L	1.8 (1.3-2.3)	1.7 (1.3-2.3)	1.7 (1.5-2.1)	1.3 (1.2-1.7)	2.1 (1.8-2.5)	3.0 (2.4-3.5)	1.6 (1.3-2.3)	2.0 (1.5-2.6)
FVC, % predicted	65 (55-78)	63 (55-78)	60 (51-71)	57 (35-75)	71 (61-77)	83 (80-85)	63 (56-70)	72 (47-85)
FVC, L	2.1 (1.6-2.9)	2.0 (1.6-2.9)	2.3 (1.8-2.5)	1.5 (1.4-2.2)	2.4 (2.1-3.2)	3.4 (2.9-3.8)	1.9 (1.5-2.6)	2.4 (1.8-3.3)
DLCO, % predicted	41 (32-52)	38 (30-48)	44 (32-61)	45 (37-49)	41 (34-62)	38 (37-38)	43 (36-56)	45 (39-63)
DLCO, mL/min/mmHg	9 (7-13)	8 (6-12)	16 (14-18)	9 (8-11)	11 (8-14)	18 (10-26)	10 (8-14)	11 (9-16)
%FVC/%DLCO	1.6 (1.3-2.0)	1.6 (1.4-2.1)	1.6 (1.2-1.7)	1.4 (1.2-1.8)	1.7 (1.3-2.1)	2.2 (2.2-2.2)	1.3 (1.0-1.8)	1.3 (1.0-1.6)
Echocardiography								
TAPSE, mm	20 (17-23)	20 (17-23)	20 (16-22)	19 (14-20)	22 (18-25)	22 (19-25)	18 (17-23)	21 (18-24)
RVSP, mmHg	37 (28-46)	40 (31-49)	42 (28-58)	43 (39-64)	35 (23-78)	24 (24-24)*	33 (25-40)	30 (27-33)
TAPSE/RVSP	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.7 (0.3-0.8)	0.4 (0.2-0.4)	0.7 (0.7-0.8)	1.0 (1.0-1.0)*	0.6 (0.5-0.8)	0.7 (0.6-1.0)
RAP, mmHg	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-8.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)*	3.0 (3.0-3.0)	3.0 (3.0-3.0)
RAA, cm²	13 (11-17)	13 (11-18)	9 (8-10)	16 (12-19)	15 (12-17)	13 (12-13)	12 (11-16)	14 (11-18)
Pericardial effusion	6/166 (4%)	3/93 (3%)	0 (0%)	0 (0%)	1/11 (9%)	0 (0%)	0 (0%)	2/24 (8%)
RV/LV diameter	0.5 (0.4-0.7)	0.6 (0.4-0.7)	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.5 (0.5-0.5)	0.6 (0.4-0.9)	0.5 (0.5-0.6)	0.5 (0.4-0.6)
Strain, %	22 (18-26)	22 (17-25)	18 (17-20)	17 (14-19)	24 (23-28)	23 (19-26)	21 (17-25)	23 (21-28)
TRV, m/s	2.9 (2.4-3.3)	3.0 (2.5-3.4)	3.1 (2.5-3.7)	3.0 (3.0-3.7)	2.7 (2.2-3.0)	2.3 (2.3-2.3)*	2.5 (2.3-3.0)	2.6 (2.4-2.7)
Computed Tomography								
RV/LV ratio	0.9 (0.9-1.0)	1.0 (0.9-1.1)	1.0 (0.8-1.2)	0.9 (0.9-1.0)	0.9 (0.9-1.0)	1.0 (0.9-1.0)	0.9 (0.9-1.0)	0.8 (0.81.0)
RV/LV ratio >1	48/165 (29%)	34/89 (38%)	2/4 (50%)	2/8 (25%)	1/11 (9%)	0/2 (0%)	5/24 (21%)	4/27 (15%)
PA/aorta, ratio	0.9 (0.8-1.0)	1.0 (0.9-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	1.0 (0.9-1.0)	0.9 (0.9-1.0)	0.8 (0.8-1.0)	0.9 (0.8-1.0)
PA/aorta ratio >1	59/171 (35%)	39/93 (42%)	0 (0%)	3/9 (33%)	5/11 (45%)	0/2 (0%)	5/25 (20%)	7/27 (26%)
PA enlargement[†]	77/171 (45%)	53/93 (57%)	2/4 (50%)	4/9 (44%)	7/11 (64%)	0/2 (0%)	8/25 (32%)	3/27 (11%)
Peripheral PA enlargement[§]	83/171 (49%)	43/93 (46%)	1/4 (25%)	4/9 (44%)	8/11 (73%)	1/2 (50%)	14/25 (56%)	12/27 (44%)

Pre-capillary PH = mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU; isolated post-capillary PH (Ipc-PH) = mPAP >20 mmHg, PAWP >15 mmHg, and PVR ≤2 WU; combined pre- and post-capillary PH (Cpc-PH) = mPAP >20 mmHg, PAWP >15 mmHg, and PVR >2 WU; isolated mPAP elevation = mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR ≤2; isolated PAWP elevation = mPAP ≤20 mmHg, PAWP >15 mmHg, and PVR ≤2 WU; isolated PVR elevation = mPAP ≤20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU; normal RHC = mPAP ≤20 mmHg, PAWP ≤15 mmHg, and PVR ≤2 WU. [†]CKD-EPI 2021; *Only 1 of 2 patients in this group had data available;

SUPPLEMENTARY MATERIAL

[‡]Composite evaluation of central pulmonary arteries integrating trunk diameter >30-32 mm, PA/Aorta ratio >1, and subjective enlargement of the main and interlobular arteries; [§]Based on non-tapering vessels, vessels extending to pleural surface, and acute peripheral arterial dilation after visually excluding any areas with fibrosis. BMI: body mass index; BNP: B-type natriuretic peptide; CI: confidence interval; DLCO: diffusing capacity of lungs for carbon monoxide; eGFR: estimated glomerular filtration rate; FEV1: forced expiratory volume; FVC: forced vital capacity; JVD: jugular venous distention; LV: left ventricle; NT-proBNP: N-terminal pro-BNP; O₂: oxygen; PA: pulmonary artery; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAA/RAP, right atrial area/pressure; RV: right ventricle; RVSP: right ventricular systolic pressure; SCr: serum creatinine; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; 6MWD: 6-minute walk distance.

Table S3. Regression analysis for correlation to the presence of pulmonary hypertension in the preliminary population; results are reported as odds ratio (OR), confidence interval (CI), and p-value. Bolded parameters were statistically significant (p<0.05) for at least one of the two regression analyses.

	Pre-capillary PH vs Normal RHC			Pre-capillary PH vs All other patients		
	OR	CI	P-value	OR	CI	P-value
Demographics						
Age, years	1.02	0.99-1.06	0.1839	1.01	0.98-1.03	0.6565
Sex, male	0.81	0.35-1.86	0.6131	0.92	0.52-1.64	0.7875
Ethnicity, Hispanic/Latino	3.46	0.43-27.96	0.2446	1.57	0.55-4.43	0.3986
Race, White	0.69	0.08-6.21	0.7420	0.47	0.09-2.49	0.3727
Black	0.67	0.05-8.16	0.7510	0.45	0.07-2.89	0.3959
BMI, kg/m ²	1.01	0.94-1.08	0.8029	0.99	0.95-1.04	0.7644
Medical History						
Time since ILD diagnosis, years	1.04	0.92-1.16	0.5590	1.02	0.95-1.10	0.6251
Antifibrotic use	3.42	0.75-15.70	0.1132	0.81	0.39-1.67	0.5633
Supplemental O₂ use	3.65	1.51-8.81	0.0040	2.19	1.22-3.94	0.0090
O ₂ Flow rate, L/min	1.2	1.00-1.40	0.0533	1.09	1.00-1.20	0.0613
6MWD, meters	0.995	0.992-0.999	0.0141	1.00	1.00-1.00	0.3644
Labs & Physical Exam						
BNP, pg/mL	1.36	0.90-2.05	0.1465	1.25	0.95-1.66	0.1092
NT-proBNP, pg/mL	1.50	0.93-2.40	0.0941	1.22	0.91-1.63	0.1797
SCr, mg/dL	0.30	0.09-0.99	0.0494	0.64	0.26-1.55	0.3227
eGFR*, mL/min/1.73m ²	1.01	0.99-1.03	0.4996	1.00	0.99-1.02	0.8946
Peripheral edema	0.76	0.32-1.82	0.5387	0.86	0.46-1.60	0.6331
Loud P2/S2	1.26	0.46-3.44	0.6494	1.32	0.66-2.63	0.4361
JVD	1.11	0.22-5.55	0.8958	1.09	0.36-3.26	0.8837
Syncope	1.70	0.20-14.69	0.6310	2.52	0.49-12.79	0.2664
Pulmonary Function						
FEV1, % predicted	1.00	0.98-1.01	0.6184	1.00	0.98-1.01	0.6788
FEV1, L	0.69	0.39-1.24	0.2146	0.83	0.54-1.26	0.3712
FVC, % predicted	1.00	0.98-1.02	0.6548	1.00	0.99-1.02	0.7343
FVC, L	0.73	0.48-1.10	0.1353	0.86	0.63-1.17	0.3371
DLCO, % predicted	0.96	0.93-0.98	0.0006	0.97	0.95-0.99	0.0018
DLCO, mL/min/mmHg	0.89	0.82-0.97	0.0045	0.90	0.84-0.96	0.0016
%FVC/%DLCO	1.13	1.03-1.24	0.0080	1.08	1.02-1.14	0.0047
Echocardiography						
TAPSE, mm	0.94	0.85-1.04	0.2182	0.99	0.93-1.07	0.8489
RVSP, mmHg	1.09	1.03-1.15	0.0023	1.03	1.004-1.06	0.0247

SUPPLEMENTARY MATERIAL

TAPSE/RVSP	0.82	0.70-0.97	0.0198	0.88	0.78-0.998	0.0466
TRV, m/s	4.42	1.53-12.83	0.0062	2.12	1.13-4.00	0.0200
RAP, mmHg	1.32	0.91-1.92	0.1410	1.17	1.002-1.36	0.0470
RAA, cm ²	0.99	0.90-1.09	0.8518	1.01	0.95-1.07	0.7626
Pericardial effusion	0.37	0.06-2.33	0.2875	0.78	0.15-3.97	0.7626
RV/LV diameter	1.27	0.93-1.73	0.1329	1.13	0.93-1.37	0.2304
Strain, %	1.08	0.98-1.18	0.1235	1.04	0.98-1.11	0.2395
Computed Tomography						
RV/LV diameter	1.53	1.07-2.20	0.0207	1.30	1.03-1.62	0.0246
RV/LV ratio >1	3.55	1.13-11.16	0.0299	2.74	1.33-5.63	0.0062
PA/aorta, ratio	1.66	1.18-2.34	0.0038	1.42	1.14-1.78	0.0020
PA/aorta ratio >1	2.06	0.80-5.36	0.1368	2.09	1.09-4.03	0.0268
PA enlargement[†]	10.6	2.98-37.69	0.0003	2.98	1.58-5.61	0.0007
Peripheral PA enlargement [‡]	1.05	0.44-2.50	0.9212	0.76	0.41-1.41	0.3852

Pre-capillary PH = mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU; normal RHC = mPAP ≤20 mmHg, PAWP ≤15 mmHg, and PVR ≤2 WU. *CKD-EPI 2021; [†]Composite evaluation of central pulmonary arteries integrating trunk diameter >30-32 mm, PA/Aorta ratio >1, and subjective enlargement of the main and interlobular arteries; [‡]Based on non-tapering vessels, vessels extending to pleural surface, and acute peripheral arterial dilation after visually excluding any areas with fibrosis. BMI: body mass index; BNP: B-type natriuretic peptide; CI: confidence interval; DLCO: diffusing capacity of lungs for carbon monoxide; eGFR: estimated glomerular filtration rate; FEV1: forced expiratory volume; FVC: forced vital capacity; JVD: jugular venous distention; LV: left ventricle; NT-proBNP: N-terminal pro-BNP; O2: oxygen; PA: pulmonary artery; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAA/RAP, right atrial area/pressure; RV: right ventricle; RVSP: right ventricular systolic pressure; SCr: serum creatinine; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; 6MWD: 6-minute walk distance.

SUPPLEMENTARY MATERIAL

Figure S1. Investigator Suspicion of Pulmonary Hypertension Questionnaire.

INVESTIGATOR SUSPICION OF PULMONARY HYPERTENSION

Instructions to the Investigator: please complete this questionnaire after all other study assessments are performed, but prior to the RHC.

Using your clinical judgment, your suspicion of PH in the patient is:

- ☐ Low
- ☐ Medium
- ☐ High