Supplementary Material

Supplementary Table 1: Ongoing or Recently Completed Phase 2 and Phase 3 Clinical Trials in Pulmonary Arterial Hypertension

	Mechanism of Action	Trial Name and Registration	Phase	Sample Size	Primary Outcome	Status
Ambrisentan	Endothelin receptor antagonist	TAPE (NCT04972656)	3	420	Incidence of PAH (mPAP ⩾25 mmHg) at 1 year* Change in PVR at 1 year	Recruiting
Dapagliflozin	Sodium glucose co-transporter-2 inhibitor	DAPAH (NCT05179356)	2	52	Change in V'O2max at 3 months	Recruiting
DHEA	Activation of NO synthase, suppresses ET-1, cardiac remodeling	EDIPHY (NCT03648385)	2	24	RV longitudinal strain on CMR	Active, not recruiting
Empagliflozin	Sodium glucose co-transporter-2 inhibitor	Emphower PoC (NCT05493371)	2a	8	Tolerability, feasibility, safety at 12 weeks	Completed
eNOS-enhanced endothelial progenitor cells	Angiogenic stem cells	SAPPHIRE (NCT03001414)	2 cross over	12	Change in 6MWD at 6 months	Terminated
Famotidine	Antihistamine	REHAB-PH (NCT03554291)	2	80	Change in 6MWD at week 24	Completed
FK506	Activation of BMPRII signaling	TransformPAH (NCT01647945)	2a	23	Safety	Completed
KER-012	Activin signaling inhibitor	TROPOS (NCT05975905)	2	90	Change in PVR at week 24	Active, not recruiting
Ifetroban	Selective thromboxan	NCT02682511	2	34	Adverse events and serious adverse events up to week 56	Recruiting

	e receptor antagonist					
Imatinib	Oral tyrosine kinase inhibitor	PIPAH (NCT04416750)	2	43	Highest tolerated dose; PVR at week 24	Active, not recruiting
Imatinib DPI (AV-101)	Inhaled tyrosine kinase inhibitor	IMPAHCT (NCT05036135)	2b/3	462	Phase 2b: PVR at week 24; Phase 3: change in 6MWD at week 24	Terminated
LAM-001	Inhaled mTOR inhibitor	NCT05798923	2a	15	Change in V'O2 at 24 weeks	Recruiting
LTP001	SMURF1 inhibitor	NCT05135000	2	47	PVR at week 25	Terminated
Macitentan (75 mg)	Endothelin receptor antagonist	UNISUS (NCT04273945)	3	900	Morbidity or mortality events (up to 4 years)	Active, not recruiting
Metformin	Decreases gluconeogenesis, increases fatty acid oxidation, and reduces oxidative stress	NCT03617458	2	82	Change in 6MWD at week 2; Change in WHO-FC at week 12	Active, not recruiting
MK-5475	Inhaled soluble guanylate cyclase stimulator	INSIGNIA-PAH (NCT04732221)	2/3	450	Phase 2: PVR at week 12; Phase 3: change in 6MWD at week 12	Completed
Olaparib	Poly(ADP-ribose) polymerase inhibitor	OPTION (NCT03782818)	2	20	Treatment-emergent adverse events at week 24	Terminated
Ralinepag	Prostacyclin receptor agonist	ADVANCE (NCT03626688)	3	1,000	TTCW	Recruiting
Satralizumab	IL-6 receptor antagonist	SATISFY-JP (NCT05679570)	2	24	Change in PVR at week 24	Active, not recruiting
Seralutinib (GB002)	Inhaled PDGF-R,	PROSERA	3	350	Change in 6MWD at week 24	Recruiting

	CSF1R and c-KIT inhibitor	(NCT05934526)				
Sodium valproate (CS1)	Histone deacetylase inhibition	NCT05224531	2	30	Patient-reported adverse events	Completed
Sotatercept	Activin-signaling inhibitor	HYPERION (NCT04811092)	3	444	TTCW	Active, not recruiting
		ZENITH (NCT04896008)	3	166	Time to first morbidity or mortality event	Active, not recruiting
		MOONBEAM – pediatric PAH (NCT05587712)	2	42	Adverse events, pharmacokinetics/ pharmacodynamics	Recruiting
		MK-7962-020 (NCT05818137)	3	46	Change in PVR at week 24	Active, not recruiting
Spironolactone	Mineralocorticoid receptor antagonist	NCT01712620	2	70	Change in 6MWD at 6 months	Recruiting
Tamoxifen	Selective estrogen receptor modulator	T3PAH (NCT03528902)	2	18	TAPSE on echo at week 24	Completed
Treprostinil liposomal suspension (L606)	Inhaled prostacyclin analogue	NCT04691154	3	60	Adverse events after switching from inhaled treprostinil (Tyvaso)	Active, not recruiting
Treprostinil palmitil DPI	Inhaled prostacyclin analogue	NCT05147805	2b	99	PVR at week 24	Active, not recruiting
Vardenafil DPI (RT234)	Inhaled phosphodiesterase type-5 inhibitor	VIPAH-PRN (NCT04266197)	2b	60	Adverse events, change in vital signs, change in peak V'O2	Active, not recruiting

Summary of selected ongoing or recently completed phase 2 and 3 clinical trials evaluating novel therapies for pulmonary arterial hypertension (PAH), including targeted mechanisms, trial design, and outcomes.

Studies are ordered alphabetically, by intervention. DHEA: dehydroepiandrosterone; eNOS: endothelial nitric oxide synthase; DPI: dry powder inhaler; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; V'O2: oxygen consumption; NO: nitric oxide; ET: endothelin; RV: right ventricle; CMR: cardiac magnetic resonance imaging; PoC: proof of concept; 6MWD: 6-min walk distance; BMPR: bone morphogenetic protein receptor; mTOR: mammalian target of rapamycin; SMURF1: Smad-specific E3 ubiquitin-protein ligase 1; WHO: World Health Organization; FC: functional class; IL: interleukin; PDGFR: platelet-derived growth factor receptor; CSF1R: colony-stimulating factor 1 receptor; TTCW: time to clinical worsening; TAPSE: tricuspid annular plane systolic excursion. #: status as of 10 May 2024; *: only patients with resting mean arterial pressure 21–24 mmHg are eligible.

Source: Weatherald et al. 2024. Reproduced with permission from the European Respiratory Society.

Weatherald J, Fleming TR, Wilkins MR, et al. Clinical trial design, end-points, and emerging therapies in pulmonary arterial hypertension. Eur Respir J 2024;64:2401205. https://doi.org/10.1183/13993003.01205-2024; PMID: 39209468.