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Phase 1 Study of MK-5475, an Inhaled Soluble Guanylate Cyclase Stimulator, in Participants with Pulmonary Hypertension Associated with Chronic Obstructive Pulmonary Disease

Ednan K Bajwa[1], Dawn Cislak[1], Amit Kumar[1], Dan Li[1], Eric J Messina[1], Tom Reynders[2], Jean-François Denef[2], Vasile Corcea[3], Ketan P Buch[4], Eseng Lai[1], S Aubrey Stoch[1]

[1]MRL, Merck & Co., Inc., Rahway, NJ, USA; [2]Translational Medicine, MSD Belgium, Brussels, Belgium; [3]PMSI Republican Clinical Hospital "T. Mosneaga", ARENSIA EM Unit, Chisinau, Republic of Moldova; [4]Department of Internal Medicine, Pulmonary and Critical Care Medicine, Lexington VA Healthcare, Lexington, KY, USA

Correspondence: Ednan K Bajwa, Translational Medicine, Merck Research Laboratories Massachusetts LLC, 33 Avenue Louis Pasteur, MAILSTOP BMB-3-420, Boston, MA, 02115-5727, USA, Tel +1 617 992-3470, Email ednan.bajwa@merck.com

Purpose: This phase 1 study (NCT04370873) evaluated safety and pharmacokinetics/pharmacodynamics (PK/PD) of MK-5475 in participants with pulmonary hypertension associated with COPD (PH-COPD).

Methods: Eligible participants were 40–80 years old with COPD (FEV_1/FVC <0.7; FEV_1 >30% predicted) and PH (mean pulmonary arterial pressure ≥25 mmHg). Participants were randomized 2:1 to MK-5475 or placebo via dry-powder inhaler once daily for 7 days in Part 1 (360 µg) or 28 days in Part 2 (380 µg). Safety was assessed by adverse events (AEs) and arterial blood oxygenation. Part-2 participants had pulmonary vascular resistance (PVR; primary PD endpoint) and pulmonary blood volume (PBV; secondary PD endpoint) measured at baseline and Day 28. A non-informative prior was used to calculate posterior probability (PP) that the between-group difference (MK-5475 – placebo) in mean percent reduction from baseline in PVR was less than −15%.

Results: Nine participants were randomized in Part 1, and 14 participants in Part 2. Median age of participants (86.4% male) was 68.5 years (41–77 years); 95.5% had moderate-to-severe COPD. Incidences of AEs were comparable between MK-5475 and placebo: overall (5/14 [36%] versus 5/8 [63%]), drug-related (1/14 [7%] versus 2/8 [25%]), and serious (1/14 [7%] versus 1/8 [13%]). MK-5475 caused no meaningful changes in arterial blood oxygenation or PBV. MK-5475 versus placebo led to numerical improvements from baseline in PVR (−21.2% [95% CI: −35.4, −7.0] versus −5.4% [95% CI: −83.7, 72.9]), with between-group difference in PVR less than −15% and calculated PP of 51%.

Conclusion: The favorable safety profile and numerical reductions in PVR observed support further clinical development of inhaled MK-5475 for PH-COPD treatment.

Keywords: pulmonary hypertension, chronic obstructive pulmonary disease, MK-5475, soluble guanylate cyclase stimulator, dry powder inhaler, pulmonary vascular resistance

Introduction

Chronic obstructive pulmonary disease (COPD) is an often-debilitating lung disease that can be further complicated by pulmonary hypertension (PH).[1,2] PH associated with COPD (PH-COPD) leads to greater morbidity, mortality, and utilization of healthcare resources than does COPD associated with normal pulmonary pressures.[3] The mechanisms by which PH arises in the context of COPD are unclear, but the associated pulmonary vascular remodeling is like that seen with other PH manifestations,[3–9] such as pulmonary arterial hypertension (PAH), including thickening of the pulmonary arterial walls, obliteration of the vascular lumen, and elevation of mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR).

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PH-COPD (World Health Organization [WHO] Group 3 PH) lacks any approved therapeutic treatment.[10,11] Despite the pathophysiological similarities with PAH (WHO Group 1 PH), the vasodilators used for the treatment of PAH[12] have not consistently shown efficacy against PH-COPD.[5,13–16] Vasodilators like phosphodiesterase type-5 inhibitors (PDE5i) and the soluble guanylate cyclase (sGC) stimulator, riociguat, act on the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway to increase the production of cGMP, which potentiates tissue relaxation in vascular smooth muscle cells.[17] Although nonclinical data suggest that targeting the NO-cGMP pathway with PDE5i and sGC stimulators may positively affect PH-COPD in animals,[18,19] studies of PDE5i and riociguat in patients with PH-COPD have shown mixed results.[20,21]

Another concern with coopting PAH treatment strategies for PH-COPD treatment is the potential for systemic side effects of vasodilation, particularly with combination therapy regimens. Systemic vasodilators may inhibit hypoxic pulmonary vasoconstriction in poorly ventilated regions of lung tissue in patients with PH-COPD, leading to a ventilation/perfusion (V/Q) mismatch and decreased arterial oxygenation.[3] New therapeutic approaches are required to reduce pulmonary pressures in patients with PH-COPD without inducing systemic side effects.

MK-5475 is an sGC stimulator under investigation for use in individuals with PH-COPD. Unlike riociguat, which is administered orally, MK-5475 is formulated for inhaled delivery by a dry powder inhaler (DPI) device. This method of inhaled drug administration is designed to deposit MK-5475 directly to the desired site of action—the deep lung tissue—thereby avoiding extrapulmonary side effects associated with systemic vasodilation. The preferential deposition of inhaled MK-5475 in non-diseased, aerated lung tissue allows for local action on the pulmonary vasculature of healthier tissue, potentially improving or maintaining blood oxygenation and reducing V/Q mismatching. The chemical properties of MK-5475 related to its oral bioavailability, residence time on sGC, and systemic half-life, combined with its inhaled delivery are what make MK-5475 a pulmonary selective vasodilator and promising therapeutic for PH-COPD.

We report the findings of a 2-part, randomized, placebo-controlled, Phase 1 clinical trial (NCT04370873) of multiple-dose inhaled MK-5475 administered via DPI once daily for either 7 days (Part 1) or 28 days (Part 2) in participants with PH-COPD (Figure 1). Part 1 assessed the safety, tolerability, and plasma PK profiles of inhaled MK-5475 360 µg. Part 2 assessed the safety, tolerability, and plasma PK profiles of inhaled MK-5475 380 µg, as well as its effects on PD endpoints including PVR and pulmonary blood volume (PBV) to test the hypothesis that once-daily inhaled MK-5475 reduces PVR and increases PBV.

Materials and Methods

Study Population

Eligible participants were adults 40–80 years of age with a body mass index ≤40 kg/m^2 and diagnosed with or suspected to have PH-COPD.[22] All participants had mild-to-severe COPD as defined by: a) postbronchodilator-measured forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) <0.7; b) FEV_1 value indicating "mild" (≥80% predicted), "moderate" (≥50 to <80% predicted), or "severe" (≥31 to <50% predicted) disease; and c) Modified Medical Research Council Dyspnea Score 1–3 at screening. Eligible participants were deemed medically stable by the study investigator if their hemoglobin measurements were >75% of the lower limit of normal range at screening. Participants were required to have a history of right heart catheterization (RHC) within the past 3 years with mPAP ≥25 mmHg and PVR ≥300 dyn•s•cm^{-5} measured at rest. Alternatively, participants were eligible if an echocardiogram conducted within the year prior to screening demonstrated pulmonary artery systolic pressure ≥38 mmHg (Part 1) or ≥50 mmHg (Part 2) in conjunction with tricuspid regurgitation velocity >3.0 m/s, significant right heart enlargement, or reduced right heart function. All participants underwent a baseline RHC procedure prior to initiation of dosing in Part 2.

Exclusion criteria included PH not associated with COPD, persistent or permanent atrial fibrillation with uncontrolled ventricular rate (>90 beats/min), active respiratory infection, history of combined pulmonary fibrosis and emphysema or severe bullous emphysema, and history of clinically significant uncontrolled disease. Further diagnostic exclusion criteria included estimated creatinine clearance ≤30 mL/min based on Cockcroft Gault equation at screening, QTc interval ≥480 ms for females or ≥470 ms for males, systolic blood pressure <100 mmHg, diastolic blood pressure <40 mmHg, heart

PART 1

Screening period	MK-5475 360 µg or placebo treatment period			Post-study period
Up to 35 Days	Day 1	Days 2-6	Day 7	~14 Days
Physical exam, hematology, urinalysis, blood chemistry	Physical exam, hematology, urinalysis, blood chemistry performed pre-dose		Physical exam, hematology, urinalysis, blood chemistry performed post-dose at 24 h	Physical exam, hematology, urinalysis, blood chemistry
	Blood samples taken pre-dose and post-dose at 5, 15, and 30 min, and 1, 2, 3, 4, and 8 h	Blood samples taken post-dose at 1 h	Blood samples taken pre-dose and post-dose at 5, 15, and 30 min, and 1, 2, 3, 4, and 8 h	

PART 2

Screening period	Baseline	MK-5475 380 µg or placebo treatment period					Post-study period
Up to 35 Days	Day −1	Day 1	Days 2-14	Day 15 (±1 day)	Days 16-27	Day 28 (+4/−1 day)	~14 Days
		Dosing / Safety / PK	At-home dosing	Dosing / Safety / PK	At-home dosing	Dosing / Safety / PK	
	FRI / RHC (Day −5 to −1)					FRI / RHC post-dose at 6-8 h	
	Physical exam, hematology, urinalysis, blood chemistry			Physical exam, hematology, urinalysis, blood chemistry performed pre-dose		Physical exam, hematology, urinalysis, blood chemistry performed pre-dose	Physical exam, hematology, urinalysis, blood chemistry
		Blood samples taken pre-dose and post-dose at 0.5, 1, 2, and 3 h		Blood samples taken post-dose at 1 h		Blood samples taken pre-dose and post-dose at 0.5, 1, 2, and 3 h	

Figure 1 Study design schematic.
Abbreviations: FRI, functional respiratory imaging; PK, pharmacokinetics; RHC, right heart catheterization.

rate >100 beats per minute at screening visit and pre-dose (Day 1 [Part 1] or Baseline Day −1 [Part 2]), and very severe COPD (FEV_1 <30% predicted) at screening.

In the Part 2 RHC period, the following pulmonary hemodynamic measures were required for eligibility and were collected 1–5 days prior to the first dose of study drug: mPAP ≥25 mmHg (obtained from two pre-dose measurements taken 5 minutes apart; the mean values from the last two measurements were used to calculate PVR baseline value), PVR ≥300 dyn•s•cm^{-5} (cardiac output [CO] calculated from data obtained by thermodilution method), and pulmonary artery wedge pressure (PAWP) ≤15 mmHg (obtained from the mean of two values used to calculate PVR). RHC measurements were collected during spontaneous respiration in a supine position. Using a manual level, the height of the transducer was positioned at the level of the mid-chest. All hemodynamic measurements were done at rest.

Per protocol, participants could not receive certain medications beginning approximately 2 weeks (or 5 half-lives) prior to the administration of the initial dose of study drug throughout the study until the post-study visit, including calcium channel blockers (as a specific treatment for PH), nitrates, immediate or extended-release diltiazem, PDE5i, sGC stimulators/activators, endothelin receptor antagonists (ERA), and inhaled prostacyclin. Certain calcium channel blockers not being used for the treatment of PAH were permitted, as were diuretics, angiotensin receptor blockers, and angiotensin converting enzyme inhibitors.

This study was conducted according to the principles outlined in the Declaration of Helsinki. The study protocol and all protocol amendments were approved by the relevant independent review board and/or independent ethics committee

at each study site (Supplementary Table S1) in compliance with local and/or national regulations. All participants provided informed consent before the initiation of study procedures.

Study Design and Treatment

As described in the clinical trial registry (Clinicaltrials.gov NCT04370873; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. Rahway, NJ, USA), this Phase 1, randomized, placebo-controlled, double-blind, multicenter, 2-part study (Figure 1) evaluated the effects of once-daily inhaled MK-5475 versus placebo (both delivered via matching DPI devices) in participants with PH-COPD. The study was conducted at six sites within the USA, two sites in Israel, and one site in The Republic of Moldova between June 5, 2020, and January 12, 2022.

MK-5475 dosages in this study were selected to bridge the 360-µg Phase 1 formulation (administered as 6 × 60-µg puffs by DPI; Part 1) with the 380-µg final formulation (administered as a single actuation by DPI; Part 2). Placebo was administered in the same manner as MK-5475 in each part. Upon completion of Part 1, participants could participate in Part 2 if deemed eligible. The study was initially designed to be conducted in 3 parts; however, the protocol was amended during the study to not initiate Part 3 because Part 2 enrolled an adequate number of participants to enable the prespecified analyses. The initiation of Part 2 was based on review of PK data from Part 1. After the end of treatment, each participant was monitored for 14 days.

Part 1 evaluated safety and tolerability, and PK of inhaled MK-5475 360 µg over 7 days of once-daily dosing (Figure 1 and Supplementary Methods). Participants were randomized in a 2:1 ratio to receive either inhaled, double-blind MK-5475 or matching placebo in the morning for 7 consecutive days. Participants were domiciled from pre-dose on Day 1 through Day 2, 1-hour post-dose and from pre-dose on Day 7 through 24-hour post-dose until study assessments were completed. Participants returned to the clinic daily on Days 3–6 for witnessing of drug dosing and scheduled study procedures. Standard meals were given at 4- and 10-hours post-dose and snacks at 7- and 13-hours post-dose on Days 1 and 7. Blood samples for plasma MK-5475 measurements were collected at timepoints as shown in Figure 1. Full physical examinations, hematology, urinalysis, and blood chemistry assessments occurred at timepoints as shown in Figure 1.

Part 2 evaluated the safety and tolerability, PK, and PD (via RHC and functional respiratory imaging [FRI]) of inhaled MK-5475 380 µg over 28 days of once-daily dosing (Figure 1 and Supplementary Methods). In Part 2, participants were randomized in a 2:1 ratio to receive either inhaled, double-blind MK-5475 or matching placebo in the morning for 28 consecutive days. Staff witnessed study drug dosing on Days 1, 15 (±1 day) and 28 (+4 days/–1 day). Self-dosing occurred outside the clinic on other days. Participants were domiciled only in the evening prior to Day 28 (+4 days/–1 day). Blood samples for plasma MK-5475 measurements were collected on Day 1, on Day 15, and the day or days when end-of-study RHC and FRI were performed (approximately Day 28; if RHC and FRI were performed on different days, repeat PK samples were drawn on both) (Figure 1). Hematology, urinalysis, and blood chemistry assessments occurred at timepoints as shown in Figure 1. Computed tomography (CT) scans for FRI and RHC were both performed at baseline on Day −1 (Days −5 to −1) and 6–8 hours post-dose on Day 28 (Days 27–32).

Vital signs (heart rate, systolic blood pressure, and diastolic blood pressure) were evaluated on participants in a supine or semi-recumbent position at rest (≥10 minutes). Arterial blood gas analyses of partial pressure of oxygen in arterial blood (PaO_2), arterial oxygen saturation (SaO_2), partial pressure of carbon dioxide (PCO_2), and blood pH were performed by puncture of radial or femoral artery in Parts 1 and 2 of the study. All blood gas analyses were performed on room air if tolerated. Vital signs and arterial blood gas measurements were measured pre-dose on Day 1 (baseline) and 24 hours post-dose on Day 7 (on-treatment) in Part 1 and pre-dose on Day −1 (baseline) and pre-dose on Day 28 (on-treatment) in Part 2.

Assignment and Blinding

All eligible participants were allocated to treatment groups randomly by a computer-generated allocation schedule in both parts of the study. A central reader blinded to RHC timing assessed RHC parameters.

Study Procedures

Right Heart Catheterization

In Part 2 of the study, RHC was performed with the individual in the supine position. Individuals who could not lay flat were excluded. PVR (an indirect RHC measurement calculated as 80 × [mPAP – PAWP]/CO), CO, cardiac index (CO indexed to body surface area), mPAP, right atrial pressure (RAP), and systemic vascular resistance (SVR, an indirect RHC measurement calculated as 80 × [mean systemic arterial pressure – RAP]/CO) were measured at rest. Systemic arterial pressure was calculated from blood pressure measurements obtained by blood pressure cuff. PVR was calculated using the thermodilution method.[23] Up to four RHC measurements could be performed at baseline if needed. All on-treatment RHC measurements were performed twice and ≥5 minutes apart. Waveform analysis was performed by a blinded central reader.

Functional Respiratory Imaging

CT scans of the thoracic cavity were performed in Part 2 to assess PBV at baseline and after 28 days of once-daily dosing. For each scanning session, participants were prepped and placed in a supine position on the scanner bed, and an iodinated contrast was administered via a bolus intravenous injection. Time in the scanner for each acquisition was <15 minutes.

Study Outcomes

Safety and Tolerability

Safety and tolerability were primary endpoints in both parts of the study. Safety monitoring included an evaluation of adverse events (AEs), electrocardiograms, respiratory and vital signs, clinical laboratory parameters, urinalysis, and physical examinations.

Primary PD Outcome

The primary PD outcome measurement was change from baseline in PVR for MK-5475 versus placebo groups on Day 28 in Part 2. PVR was calculated from RHC variables. A secondary endpoint was percent change from baseline in PBV, assessed by FRI, for MK-5475 versus placebo on Day 28.

Pharmacokinetics

See Supplementary Methods for details of PK measurement and assessment, and Supplementary Results for PK results (Supplementary Figures S1 and S2).

Statistical Analyses

Mean percent change from baseline in PVR on Day 28 (Part 2) was analyzed using an ANCOVA model with a categorical effect for treatment group and a continuous covariate for baseline mPAP. The ANCOVA-derived least-squares (LS) mean percent change from baseline in PVR with the associated 95% confidence intervals (CI) were provided for both treatment groups. Summary statistics including arithmetic mean PVR ± standard deviation (SD) and within-group arithmetic mean percent change from baseline with the associated CIs also were provided for both treatment groups. To test the primary hypothesis, a non-informative prior was used to estimate the posterior probability of the event that the between-treatment group difference (MK-5475 – placebo) in arithmetic mean percent change from baseline in PVR was below the prespecified threshold of −15% (the minimum difference considered to be clinically meaningful). The primary research hypothesis was deemed supported if this posterior probability exceeded 60%. For all other endpoints, summary statistics such as arithmetic means ± SD and within-group change from baseline with the associated 95% CIs were provided for both treatment groups.

Safety and tolerability were analyzed by summary statistics. Depending on the safety parameter, the difference from baseline was computed either on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Power Calculation

The operating characteristics calculation for percent change from baseline in PVR assumed a true between-subject standard deviation of 19.2%. With 24 participants predicted to complete the study (16 on MK-5475 and 8 on placebo) and a posterior probability threshold of 60%, the likelihood of supporting the primary hypothesis, if the true difference in the arithmetic mean PVR reduction between MK-5475 and placebo groups was −25%, was estimated at 83%. A true mean difference (MK-5475 – placebo) of 15% in the arithmetic mean percent change values for PVR was prespecified as a clinically meaningful effect.

Results

Participant Disposition

The planned total enrollment across both parts of the study was 24–48 participants. Of 34 participants screened for eligibility across all sites, 23 total participants were enrolled (Figure 2). The primary reason for screen failure was participants declined enrollment (n=4 in Part 1 and n=2 in Part 2).

In Part 1, 9 participants were randomized to placebo (n=3) and inhaled MK-5475 360 µg (n=6). In Part 2, 14 participants, including 1 participant who completed Part 1, were randomized to placebo (n=5) and inhaled MK-5475 380 µg (n=9). No participants discontinued Part 1 of the study for any reason. One participant in the MK-5475 group in Part 2 withdrew from the study due to serious COVID-19 pneumonia that prevented Day 28 assessments from being completed. The 13 remaining participants randomized in Part 2 completed dosing per protocol and had post-study assessments, except one participant in the placebo group who experienced worsening heart failure and was hospitalized prior to RHC on Day 28. All participants in Part 1 (n=9) and Part 2 (n=14) were evaluable for safety and tolerability, and 12 participants in Part 2 were evaluable for PD effects.

Baseline Demographics and Disease Characteristics

The baseline characteristics are shown in Table 1. Because Part 1 and Part 2 of the study occurred sequentially, participants for each part were screened and enrolled separately. Participants randomized in each part of the study were generally balanced between the MK-5475 and placebo groups, although the number of participants randomized to

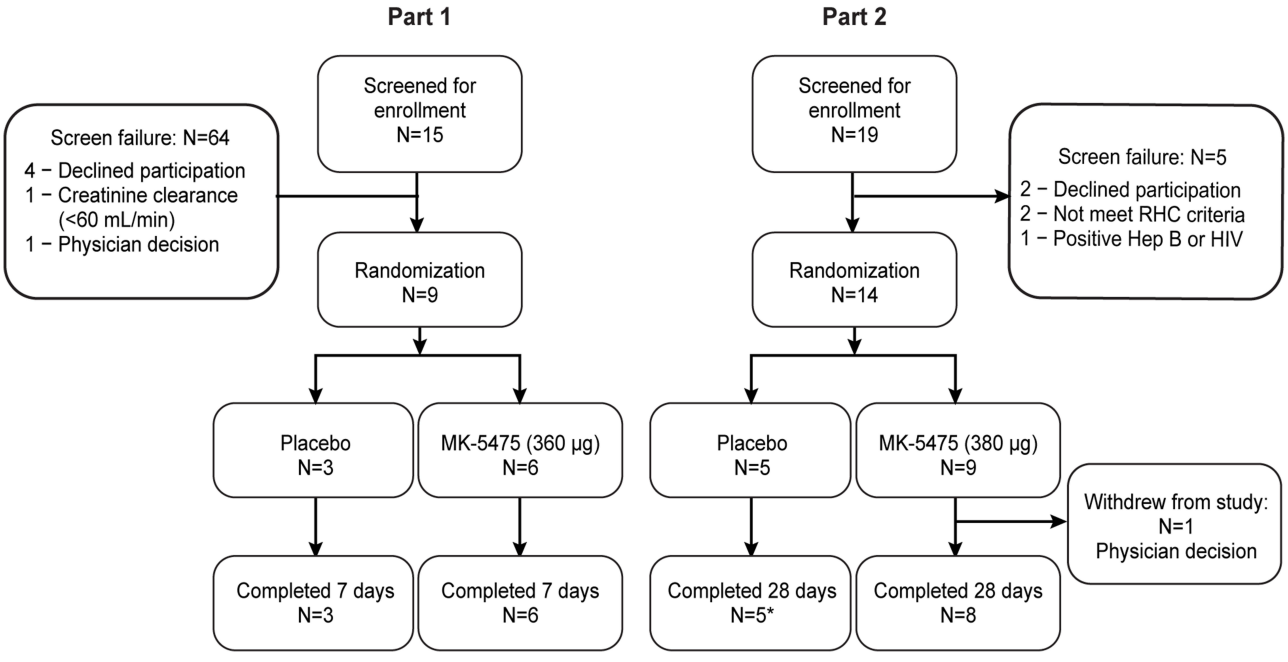

Figure 2 Flow chart illustrating the disposition of participants spanning the screening, randomization, study treatment and follow-up phases of the study. *One participant randomized to the placebo group in Part 2 completed dosing per protocol but did not complete RHC procedure on Day 28.
Abbreviations: Hep, hepatitis; HIV, human immunodeficiency virus; RHC, right heart catheterization.

Table 1 Demographics and Baseline Characteristics for the Randomized Study Population Within Parts 1 and 2 and Combined Overall

	Part 1		Part 2		Overall
	Placebo N=3	**MK-5475 360 µg N=6**	**Placebo N=5**	**MK-5475 380 µg N=9**	**Pooled Across Treatment Groups N=22**
Male (n [%])	1 (33.3)	5 (83.3)	5 (100.0)	8 (88.9)	19 (86.4)
Age, years					
Mean ± SD	62.3 ± 8.7	62.2 ± 12.7	66.6 ± 5.6	70.2 ± 5.2	65.8 ± 8.4
Median (range)	60.0 (55.0 to 72.0)	64.0 (41.0 to 77.0)	67.0 (60.0 to 73.0)	70.0 (62.0 to 77.0)	68.5 (41.0 to 77.0)
BMI, kg/m^2 (mean ± SD)	33.2 ± 1.8	26.4 ± 4.6	23.7 ± 5.8	30.3 ± 4.7	28.4 ± 5.6
Race (n [%])					
White	3 (100.0)	6 (100.0)	5 (100.0)	9 (100.0)	22 (100.0)
Ethnicity (n [%])					
Not Hispanic or Latino	3 (100.0)	6 (100.0)	5 (100.0)	9 (100.0)	22 (100.0)
Time since PH diagnosis, years (mean ± SD)	8.0 ± 12.2	4.8 ± 2.1	2.2 ± 1.9	5.0 ± 2.4	4.7 ± 4.6
Hemoglobin, g/dL (mean ± SD)	13.1 ± 2.3	13.8 ± 1.4	14.4 ± 1.1	15.1 ±1.5	14.5 ± 1.6
COPD therapy (n [%])					
No prior COPD therapy	1 (33.3)	3 (50)	2 (40)	1 (11.1)	7 (31.8)
Adrenergics in combination with anticholinergics	0 (0)	0 (0)	1 (20)	2 (22.2)	3 (13.6)
Anticholinergics	0 (0)	0 (0)	0 (0)	1 (11.1)	1 (4.6)
Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	0 (0)	0 (0)	2 (40)	4 (44.4)	6 (27.3)
Selective beta-2-adrenoreceptor agonists	2 (66.7)	0 (0)	2 (40)	5 (55.6)	9 (40.9)
Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	1 (33.3)	3 (50)	2 (40)	5 (55.6)	10 (45.5)
Supplemental O_2	0 (0)	0 (0)	0 (0)	1 (11.1)	1 (4.6)
COPD parameters					
FEV_1, % predicted (mean ± SD)	53.5 ± 8.4	46.5 ± 14.6	51.8 ± 19.9	47.5 ± 11.6	48.9 ± 13.5
Mild (FEV_1 >80%) (n [%])	0 (0)	0 (0)	1 (20)	0 (0)	1 (4.6)
Moderate (FEV_1 50–80%) (n [%])	2 (66.7)	2 (33.3)	1 (20)	3 (33.3)	8 (36.4)
Severe (FEV_1 <50%) (n [%])	1 (33.3)	4 (66.7)	3 (60)	6 (66.7)	13 (59.1)
FVC, L (mean ± SD)	3.0 ± 0.6	3.2 ± 1.3	2.7 ± 0.9	2.7 ± 0.9	2.9 ± 1.0
FEV_1/FVC, % (mean ± SD)	48.8 ± 6.1	47.8 ± 10.4	53.6 ± 12.7	47.4 ± 11.4	49.1 ± 10.5

(*Continued*)

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Table 1 (Continued).

	Part 1		Part 2		Overall
	Placebo N=3	**MK-5475 360 µg N=6**	**Placebo N=5**	**MK-5475 380 µg N=9**	**Pooled Across Treatment Groups N=22**
D_{LCO}, % predicted (mean ± SD)	70 ± 31.6	57.0 ± 32.9	34.9 ± 17.5	39.6 ± 15.6	47.1 ± 25.2
D_{LCO}, mL/min/mmHg (mean ± SD)	5.6 ± 2.8	5.4 ± 3.5	3.0 ± 1.8	3.5 ± 1.4	4.1 ± 2.5
Clinical parameters					
6MWD, m (mean ± SD)	332.7 ± 56.1	349.5 ± 124.9	304.2 ± 62.4	300.4 ± 59.7	318.9 ± 79.6
BDS[a] (mean ± SD)	1.5 ± 1.3	2.3 ± 1.0	2.8 ± 0.8	3.4 ± 1.1	2.7 ± 1.2
Level ≤4 BDS dyspnea (n [%])	3 (100.0)	6 (100.0)	5 (100.0)	7 (77.8)	20 (90.9)

Notes: [a]Self-rating tool used to measure dyspnea during submaximal exercise on a scale that ranges from 0 to 10. Level 0: Nothing at all; Level 0.5: Very, very slight (just noticeable); Level 1: Very slight; Level 2: Slight; Level 3: Moderate; Level 4: Somewhat severe; Level 5–6: Severe; Level 7–8: Very severe; Level 9: Very, very severe (almost maximal); Level 10: Maximal.

Abbreviations: 6MWD, 6-minute walk distance; BDS, Borg dyspnea scale; COPD, chronic obstructive pulmonary disease; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; n, number of participants in the category.

placebo in Part 1 was small. In both Part 1 and Part 2, the enrolled participants were mostly older males. Most participants in each part of the study had severe COPD at baseline, with low (<75% predicted) mean diffusing capacity of the lung for carbon monoxide [D_{LCO}] value and low (<350 m) mean 6-minute walk distance (6MWD) across treatment groups in both parts. At inclusion, 68% were taking at least one COPD therapy, primarily adrenergic-based combination therapy or monotherapy with selective beta-2-adrenoreceptor agonists. At inclusion, all participants were treatment-naive to PAH-targeted therapy.

Because Part 1 and Part 2 enrolled separately, there were some notable differences between study groups suggesting more advanced disease in the Part 2 cohort (Table 1), including more pronounced gas exchange impairment (lower D_{LCO}, PaO_2, and SaO_2 values), more severe clinical symptoms (lower 6MWD and higher Borg dyspnea score), and higher blood pressure.

Safety and Tolerability

Safety and tolerability of the Part 1, Part 2, and pooled populations are summarized in Table 2. Of the 9 participants of Part 1 included in the safety analysis, 3 (33.3%) had at least one AE, although none were serious AEs. Two participants, one in each treatment group, had an AE of headache that was deemed related to treatment. Listing AEs by system organ class (SOC) and preferred terms, headache was the only type of AE reported in Part 1 (Table 3). Of the 14 participants of Part 2 included in the safety analysis, 7 (50.0%) had at least one AE, including 2 participants, one in each treatment group, who had serious AEs not related to treatment (Table 2). As stated earlier, one participant in the placebo group had a serious AE of worsening heart failure and one participant in the MK-5475 group had a serious AE of COVID-19 pneumonia, which was associated with additional resulting AEs of acute respiratory distress and encephalopathy. One participant in the placebo group of Part 2 had a mild AE of increased lacrimation that was deemed treatment-related. By SOC and preferred terms, agitation was the only AE occurring in both treatment groups. All other AEs reported occurred in either the placebo or the MK-5475 treatment group only (Table 3). Importantly, no participant in either part of the study experienced an AE that led to death or treatment discontinuation. All AEs occurring in both study parts fully resolved by study end. There were no meaningful differences in the incidences or types of specific AEs when examined either overall or by SOC across the study parts or treatment groups.

Table 2 Summary of AEs[a] (n/N; %) Across Part 1 and Part 2 of the Study in the Safety Set Population[b]

	Part 1		Part 2		Pooled Population[c]	
	Placebo N=3	MK-5475 N=6	Placebo N=5	MK-5475 N=9	Placebo N=8	MK-5475 N=14
Any AE	1 (33.3%)	2 (33.3%)	4 (80.0)	3 (33.3)	5 (62.5)	5 (35.7)
Leading to discontinuation of treatment	0	0	0	0	0 (0)	0 (0)
Drug-related[d] AEs	1[f] (33.3%)	1[f] (16.7)	1[g] (20.0)	0	2 (25.0)	1 (7.1)
Leading to discontinuation of treatment	0	0	0	0	0 (0)	0 (0)
Serious[e] AEs	0	0	1[h] (20.0)	1[i] (11.1)	1 (12.5)	1 (7.1)
Leading to discontinuation of treatment	0	0	0	0	0 (0)	0 (0)
Serious[e] drug-related[d] AEs	0	0	0	0	0 (0)	0 (0)
AEs leading to death	0	0	0	0	0 (0)	0 (0)

Notes: [a]Data are presented as n/N (%). All AEs, serious AEs, and other safety events were reported by the investigator from the time of randomization through 14 days after cessation of study drug. [b]Safety set population includes all randomized participants who received ≥1 dose of study medication. [c]Results combined across Part 1 and Part 2. One participant was enrolled and treated in both Part 1 and Part 2; this participant was counted separately in Part 1 and in Part 2 but counted only once in the pooled population. [d]Any AE deemed by the investigator to be related to study treatment. [e]Any untoward medical event that results in death, is life-threatening, requires hospitalization, causes prolongation of existing hospitalization, results in persistent or significant disability, may have caused a congenital abnormality/birth defect, or requires intervention to prevent permanent impairment or damage. [f]Includes 1 non-serious, mild AE of headache and 1 non-serious, moderate AE of headache deemed drug-related by the study investigator during Part 1. [g]n=1 non-serious mild, drug-related AE of increased lacrimation during Part 2. [h]n=1 serious non-drug related AE of worsening heart failure during Part 2. [i]n=1 serious non-drug related AE of COVID-19 infection during Part 2.

Abbreviations: AE, adverse event; COVID-19, Coronavirus Disease 2019; n, number of participants with specified adverse event; N, total number of participants in the safety set population contributing to the safety analyses.

Table 3 Summary of AEs[a] (n/N; %) Occurring in One or Both Treatment Groups Presented by SOC[b] in the Safety Set Population[c] Within Part 1 and Part 2 of the Study

	Part 1		Part 2	
	Placebo N=3	MK-5475 360 µg N=6	Placebo N=5	MK-5475 380 µg N=9
Any AE	1 (33.3)	2 (33.3)	4 (80.0)	3 (33.3)
Cardiac disorders	0 (0)	0 (0)	1 (20.0)	0 (0)
Cardiac failure	0 (0)	0 (0)	1 (20.0)[d]	0 (0)
Eye disorders SOC	0 (0)	0 (0)	1 (20.0)	0 (0)
Lacrimation increased	0 (0)	0 (0)	1 (20.0)	0 (0)
General disorders and administration site conditions	0 (0)	0 (0)	0 (0)	1 (11.1)
Infusion and extravasation	0 (0)	0 (0)	0 (0)	1 (11.1)
Infections and infestations	0 (0)	0 (0)	1 (20.0)	1 (11.1)
COVID-19	0 (0)	0 (0)	0 (0)	1 (11.1)[d]
COVID-19 pneumonia	0 (0)	0 (0)	0 (0)	1 (11.1)
Urinary tract infection	0 (0)	0 (0)	1 (20.0)	0 (0)
Injury, poisoning and procedural complications	0 (0)	0 (0)	1 (20.0)	0 (0)
Accidental overdose	0 (0)	0 (0)	1 (20.0)	0 (0)
Investigations	0 (0)	0 (0)	1 (20.0)	0 (0)
Blood creatinine increased	0 (0)	0 (0)	1 (20.0)	0 (0)
Nervous system disorders (SOC)	1 (33.3)	2 (33.3)	1 (20.0)	1 (11.1)
Dizziness	0 (0)	0 (0)	1 (20.0)	0 (0)
Encephalopathy	0 (0)	0 (0)	0 (0)	1 (11.1)
Headache	1 (33.3)	2 (33.3)	0 (0)	0 (0)
Psychiatric disorders	0 (0)	0 (0)	1 (20.0)	1 (11.1)
Agitation	0 (0)	0 (0)	1 (20.0)	1 (11.1)
Respiratory, thoracic, and mediastinal disorders	0 (0)	0 (0)	0 (0)	1 (11.1)
Acute respiratory distress syndrome	0 (0)	0 (0)	0 (0)	1 (11.1)

Notes: [a]Data are presented as n/N (%). All AEs, serious AEs, and other safety events were reported by the investigator from the time of randomization through 14 days after cessation of study drug. [b]The highest level of the MedDRA (https://www.meddra.org/) hierarchy, etiology, or purpose. CTCAE terms are grouped by MedDRA Primary SOC. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade). [c]Safety set population includes all randomized participants who received ≥1 dose of study medication. [d]Serious non-drug-related AE. This participant recovered but was discontinued from the study per investigator and sponsor decision.

Abbreviations: AE, adverse event; COVID-19, Coronavirus Disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.

Changes from baseline in vital signs, arterial blood gases, and blood pH were evaluated as safety parameters in both parts of the study (Figure 3; Supplementary Table S2). At baseline, the treatment groups were generally well balanced with respect to these safety parameters within Part 1 and Part 2. Treatment with MK-5475 or placebo did not produce clinically meaningful effects on resting systolic blood pressure, diastolic blood pressure, heart rate, SaO_2, PaO_2, or blood pH following 7 days (Part 1) or 28 days (Part 2) of consecutive once-daily dosing (Figure 3; Supplementary Table S2). For each parameter, the 95% CIs for the within-group changes from baseline encompassed zero for both MK-5475 and placebo groups in both Part 1 and Part 2, except blood pH. The magnitude of the decrease in blood pH seen in the placebo group of Part 2 (−0.53%) was small and not clinically meaningful.

Pharmacodynamic Endpoints

Pharmacodynamic endpoints were assessed in only Part 2 of the study. Baseline values for RHC-derived hemodynamic parameters were generally well balanced across treatment groups in Part 2 (Figure 4; Table 4). Following once-daily inhalation of MK-5475 380 µg for 28 days, the within-group mean percent changes from baseline in PVR (primary PD endpoint) were −5.39% (95% CI: −83.69, 72.91) for placebo and −21.23% (95% CI: −35.4, −7.0) for MK-5475, resulting in a between-group difference of −15.84% favoring MK-5475. The calculated posterior probability was 51.2%, which was below the prespecified threshold of 60%. An ANCOVA model used to characterize the percent change in PVR from

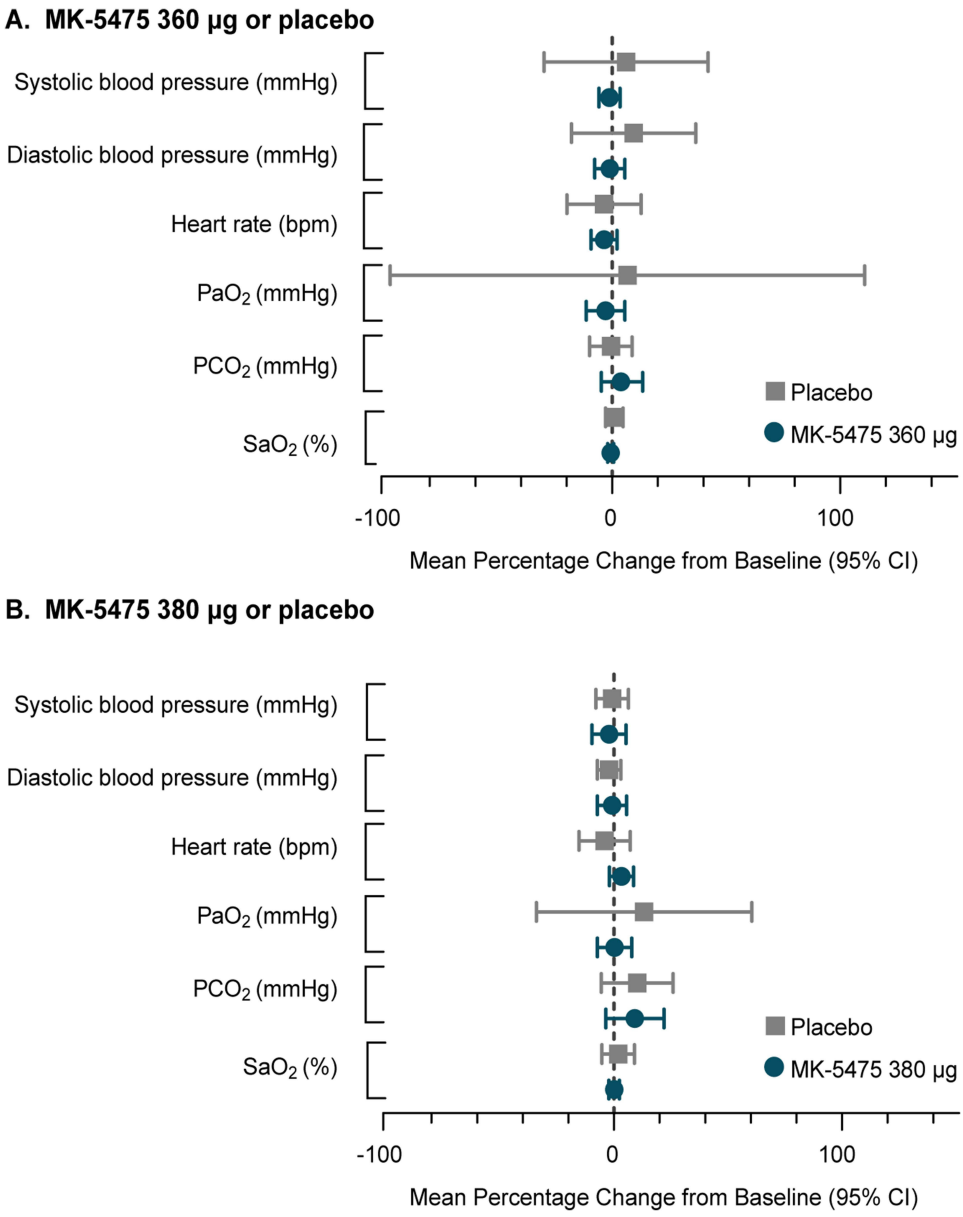

Figure 3 Within-group mean percent change (95% CI) from baseline in vital signs and arterial blood gases following once-daily inhalation of placebo or MK-5475 360 µg in Part 1 (**A**) and placebo or MK-5475 380 µg in Part 2 (**B**). (**A**) MK-5475 360 µg or placebo. (**B**) MK-5475 380 µg or placebo.
Abbreviations: CI, confidence interval; PaO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; SaO_2, arterial oxygen saturation.

baseline as a dependent variable with treatment arms and baseline mPAP as covariates (Figure 4; Table 4) showed similar mean percent reduction in PVR from baseline.

Improvements from baseline were observed for the exploratory RHC hemodynamic endpoints of mPAP and RAP following 28 days of once-daily MK-5475 dosing (Figure 4; Table 4). Formal between-group comparisons were not performed on exploratory RHC-derived hemodynamic parameters. No meaningful changes were observed in PAWP, SVR, CO, cardiac index (exploratory PD endpoints assessed by RHC, Table 4), or PBV (secondary PD endpoint assessed by FRI, Figure 4; Supplementary Table S3) for either treatment group at Day 28 in Part 2.

Discussion

Systemic vasodilators approved for the treatment of PAH have been ineffective and potentially unsafe for use in patients with PH-COPD due to the inhibition of hypoxia-induced vasoconstriction and induction of V/Q mismatching and

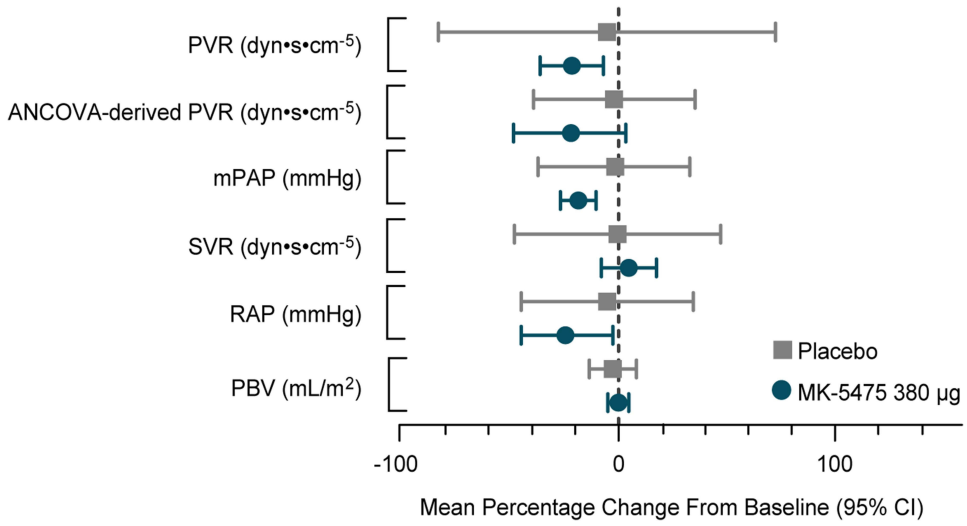

Figure 4 Within-group mean percent change (95% CI) from baseline in hemodynamic endpoints after 28 days of once-daily inhalation of MK-5475 380 µg or placebo in Part 2 of the study.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; mPAP, mean pulmonary artery pressure; PBV, pulmonary blood volume; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance.

hypoxemia. A pulmonary selective vasodilator that is administered directly to lung tissue may offset these challenges and be beneficial for the treatment of PH-COPD. MK-5475 is an inhaled sGC stimulator designed for direct deposition via a dry powder inhaler into the deep lung tissue, with chemical properties that minimize its systemic exposure. Moreover, the once-daily dosing frequency of MK-5475 may represent an advantage over other inhaled vasodilators that must be dosed multiple times per day. This Phase 1 study evaluated the safety, PK, and PD effects of dosing with MK-5475 in participants with PH-COPD. Reductions from baseline were noted in PVR following once-daily inhalation of MK-5475 380 µg over 28 days. Per the primary hypothesis, the between-group difference in arithmetic mean percent change from baseline in PVR (−15.8%) favored MK-5475, but the calculated posterior probability of 51.2% fell below the pre-specified 60% threshold. As such, caution should be applied when interpreting these findings.

The arithmetic and ANCOVA-modeled mean percent reductions from baseline in PVR seen following multiple dosing with MK-5475 380 µg in this study were similar in magnitude with those reported (−14% and −29% reductions, respectively) following single dosing with MK-5475 in participants with PAH (NCT03744637).[24] Importantly, the change in PVR seen on Day 28 in the current study expands upon the results of the single-dose PAH study and suggests a durable corrective effect on PVR with multi-day dosing. Furthermore, the short systemic half-life of MK-5475 of 2–3 hours in the current study (Supplementary Table S4), along with previous findings of rapid and sustained PD effects on PBV out to 24 hours post-dose after single doses of MK-5475 in PAH,[24] suggests selective pulmonary vasodilation with limited adverse effects on systemic hemodynamics may be possible with chronic dosing of MK-5475 in PH-COPD. Since PBV was measured at baseline and Day 28 of Part 2, further studies would be needed to determine whether changes in PBV are detectable post-dosing.

The mPAP and RAP treatment effects found in the current study are consistent with vasodilation of the pulmonary vasculature (as measured by PVR) and right ventricle unloading. Whether MK-5475 has other effects on pulmonary physiology remains to be investigated. No meaningful changes from baseline or between-group differences in other exploratory hemodynamic parameters were observed, including left atrial pressure surrogate (PAWP), CO, and cardiac index, suggesting that the reductions in PVR seen with MK-5475 treatment in this study were driven mainly by effects on mPAP. In patients with PH-COPD, elevations in mPAP frequently result from PVR elevations causing increases in the transpulmonary arterio-venous pressure gradient and, in severe cases, diminished CO.[25] The Part 2 study cohort had mean resting baseline CO values across the placebo and MK-5475 groups that indicated impaired CO. Whether MK-5475 delivers measurable beneficial effects on CO and cardiac index with longer-term dosing should be explored in future studies.

Table 4 Mean Percent Change from Baseline in RHC-Measured Hemodynamic Endpoints After 28 Days of Once-Daily Inhalation of MK-5475 380 µg or Placebo in Part 2 of the Study

	Placebo N=4[†]			MK-5475 (380 µg) N=8[†]		
	Baseline Mean ± SD	**Day 28 Mean ± SD**	**Within-group mean % change from baseline[§] (95% CIs)**	**Baseline Mean ± SD**	**Day 28 Mean ± SD**	**Within-group mean % change from baseline[§] (95% CIs)**
Arithmetic PVR (dyn•s•cm^{-5})	394.32 ± 141.18	342.89 ± 159.97	−5.39 (−83.69, 72.91)[¥]	409.52 ± 166.47	325.88 ± 153.22	−21.23 (−35.4, −7.0)[¥]
ANCOVA-modeled PVR (dyn•s•cm^{-5})	-	-	−2.16 (−39.70, 35.40)[‡]	-	-	−22.84 (−48.7, 3.0)[‡]
mPAP (mmHg)	25.63 ± 2.29	25.25 ± 6.41	−1.67 (−36.40, 33.06)	29.75 ± 5.99	24.38 ± 5.69	−18.23 (−26.18, −10.28)
PAWP	11.38 ± 1.49	12.13 ± 3.88	6.11 (−39.69, 51.90)	10.44 ± 2.46	9.50 ± 3.05	−8.58 (−26.41, 9.25)
SVR (dyn•s•cm^{-5})	2463.53 ± 697.19	2304.70 ± 180.65	−0.58 (−48.17, 47.02)	1894.47 ± 435.42	1948.68 ± 386.52	4.43 (−7.93, 16.78)
RAP (mmHg)	9.13 ± 3.47	8.75 ± 4.09	−5.26 (−45.22, 34.71)	8.25 ± 2.39	6.63 ± 3.72	−23.95 (−45.22, −2.69)
CO (L/min)	2.94 ± 0.74	3.07 ± 0.13	6.81 (−45.79, 59.41)	3.74 ± 0.90	3.71 ± 0.74	−2.49 (−14.24, 9.25)
Cardiac index (L/min/m^2)	1.66 ± 0.35	1.76 ± 0.42	6.81 (−45.79, 59.41)	1.86 ± 0.39	1.83 ± 0.29	−2.49 (−14.23, 9.25)

Notes: [†]In Part 2, 5 participants were randomized to placebo and 9 participants were randomized to MK-5475, but only 4 and 8 participants, respectively, were evaluable for Day 28 RHC-derived hemodynamic values. [‡]Expressed as least squares (LS) mean (95% CI). The LS means were calculated using an ANCOVA model with categorical effect for treatment group and a continuous covariate for baseline mPAP value. Arithmetic and ANCOVA-modeled baseline and Day 28 PVR values are identical. Posterior probability analysis was performed on the arithmetic mean percent change in PVR. [§]Unless otherwise stated, arithmetic mean percent change from baseline and 95% CI are presented in this column. [¥]The between-group difference in arithmetic mean percent reduction from baseline in PVR between MK-5475 and placebo groups (−15.84%) was less than −15%. This between-group difference for change in PVR did not achieve statistical significance because the calculated PP (51.2%) did not exceed the prespecified threshold (60%; see Methods).

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CO, cardiac output; LS, least-squares; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SVR, systemic vascular resistance.

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MK-5475 demonstrated an overall favorable safety profile in participants with PH-COPD, with comparable incidence rates of AEs in the MK-5475 and placebo groups. There were no differences in the incidence rates of AEs, types of AEs, or laboratory safety tests seen with multiple-inhaled doses of MK-5475 across Part 1 (360 µg) and Part 2 (380 µg), thus bridging the safety and tolerability profiles of the two formulations. Furthermore, there was no evidence that inhaled MK-5475 provoked V/Q mismatch or caused appreciable systemic vasodilation, two key safety concerns associated with PAH-approved systemic vasodilators when used for PH-COPD.[3] In addition, there were no clinically meaningful changes in PaO_2 or SaO_2 following treatment with MK-5475, supporting the expectation that inhaled delivery of the drug circumvents excessive pulmonary vasodilation in damaged lung tissue and consequent hypoxia in participants with PH-COPD. Similarly, there was no evidence indicating undesirable systemic vasodilatory effects, further suggesting that the effects of MK-5475 were restricted to the targeted pulmonary sites of drug deposition. These safety findings provide encouraging evidence that once-daily treatment with inhaled MK-5475 produces improvements on PVR, mPAP, and RAP without the unwanted side effects typically associated with other orally administered sGC stimulators.

This Phase 1 study has several caveats that limit the strength of the conclusions, particularly the small sample sizes in both study parts and the racial and ethnic homogeneity of the study cohorts. The total number of participants evaluable across both parts of the study (N=22) was substantially smaller than the original enrollment target of 24–48 participants. The small sample size, attributable in part to the study's initiation during the early period of the COVID-19 pandemic, decreased the statistical power to detect a significant difference between the treatment groups thereby lowering the posterior probability below the 60% threshold. Nevertheless, these findings suggest a possible modest corrective effect on PVR in the PH-COPD participants treated with MK-5475 380 µg in this study.

There were baseline imbalances between the study groups suggesting that the Part 2 cohort had more severe disease than the Part 1 cohort. The imbalances between the two cohorts may be accounted for by the different objectives of Part 1 and Part 2, which necessitated different eligibility criteria for Part 1 and Part 2, and possibly to country-specific issues with access to healthcare and/or medications. Imbalances notwithstanding, the observed changes from baseline in PVR, mPAP, and RAP, as well as their respective 95% CIs, provide encouraging evidence of a beneficial and pulmonary-selective hemodynamic effect with once-daily inhaled dosing of MK-5475 in participants with PH-COPD. This Phase 1 study did not assess change from baseline in exercise capacity, as measured by 6MWD. However, an ongoing, Phase 2, randomized, placebo-controlled, double-blind study in participants with PH-COPD (NCT05612035) will evaluate the efficacy and safety of multiple dosing with inhaled MK-5475 (380 µg once daily) for 24 weeks. The primary endpoint will be the change from baseline at week 24 in 6MWD. Furthermore, ongoing and future studies of MK-5475 are or will be conducted in accordance with updated guidelines for the treatment of pulmonary hypertension.[26]

Conclusion

The overall favorable safety and tolerability profile, absence of drug-induced arterial hypoxemia, lack of systemic hemodynamic effects, and numerical improvements in PVR, mPAP, and RAP seen in this small Phase 1 study suggest that MK-5475 may hold promise as a selective pulmonary vasodilator administered by dry-powder inhaler for the treatment of PH-COPD and supports further investigation.

Abbreviations

6MWD, 6-minute walk distance; AE, adverse event; ANCOVA, analysis of covariance; AUC, area under the curve; $AUC_{0\text{-inf}}$, area under the curve from 0 hours to infinity; $AUC_{0–3h}$, area under the curve from 0 to 3 hours; $AUC_{0–24h}$, area under the curve from 0 to 24 hours; BDS, Borg dyspnea scale; C_{1h}, plasma concentration at 1 hour post-dose; CI, confidence interval; C_{max} maximum plasma concentration; C_{24h}, plasma concentration at 24 hours; CO, cardiac output; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; D_{LCO}, diffusing capacity of the lung for carbon monoxide; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FRI, functional respiratory imaging; FVC, forced vital capacity; HR, heart rate; LLQ, lower limit of quantification; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PaO_2, partial pressure of oxygen in arterial blood; PCO_2, partial pressure of carbon dioxide; PD, pharmacodynamics; PDE5i, phosphodiesterase type-5 inhibitors;

PH, pulmonary hypertension; PH-COPD, pulmonary hypertension associated with chronic obstructive pulmonary disease; PK, pharmacokinetics; PBV, pulmonary blood volume; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SaO_2, Arterial oxygen saturation; sGC, soluble guanylate cyclase; SD, standard deviation; SOC, system organ class; SVR, systemic vascular resistance; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration; V/Q, ventilation/perfusion.

Data Sharing Statement

The dataset (supporting the conclusions of this article), including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the study data can be submitted through the Engage Zone site or via Email to dataaccess@merck.com.

Ethics Approval

This study was conducted according to the principles outlined in the Declaration of Helsinki. The study protocol and all protocol amendments were approved by the relevant independent review board and/or independent ethics committee at each study site (see Supplementary Table S1) in compliance with local and/or national regulations. All participants provided informed consent before the initiation of study procedures.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

EKB, DC, AK, DL, EJM, TR, J-FD, EL, and SAS are current or former employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. VC and KPB received material support and investigational medical products from MSD during the clinical trial. The authors report no other conflicts of interest in this work.

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