Plain Language Summary

Pulmonary arterial hypertension (PAH) is a disease in which the blood vessels in the lungs become narrow, forcing the heart to work harder to pump blood. Over time, this can damage the heart and lead to death. MK-5475 is a new medicine that may help widen the blood vessels in the lungs. MK-5475 is a powder that is breathed in through the mouth into the lungs using an inhaler.

In the INSIGNIA-PAH study, researchers looked at how MK-5475 or placebo may affect blood flow in the lungs and what side effects may occur. Three doses of MK-5475 (low, medium, and high) were compared against placebo, and 168 people with PAH already taking other medicines for PAH were assigned to each of the four treatment groups. After 12 weeks of treatment with MK-5475 or placebo, improvements in blood flow in the lungs were found in the medium and high-dose MK-5475 groups, compared with the placebo group. Changes in blood flow were not that different between the low dose MK-5475 and placebo groups. The study also looked at how MK-5475 or placebo may affect how far people can walk in 6 minutes and other measurements of heart function, but there were no differences between the MK-5475 groups and placebo in these areas.

Serious side effects happened about as often with MK-5475 (all three doses) as placebo, and none of the serious side effects were considered to be caused by the treatment. No one stopped taking treatment or quit the study because of side effects. Three people died during the study: two were in the placebo group and one was in the MK-5475 medium-dose group. The causes of death were not related to treatment. The researchers were interested in side effects of low blood pressure, coughing up blood, bleeding in the lungs, and liver injury. Only one person had low blood pressure and one person coughed up blood (both in the MK-5475 medium-dose group); no one had bleeding in the lungs or liver injury from treatment.

In summary, MK-5475 treatment at three doses was tolerated well by people with PAH who were already on other PAH medicines. MK-5475 given at the medium and high doses improved blood flow more than placebo did.

Power and sample size are based on the percent change from baseline in PVR at Week 12. Through 12 weeks post-randomization, drop-out is expected to be approximately 10% in each treatment group. Assuming the true percent change from baseline in PVR at Week 12 is 30% for each MK-5475 dose versus 0% for placebo, the assumed percent change from baseline in PVR at Week 12 using J2R to impute missing data would be 27% for each MK-5475 dose versus 0% for placebo. The assumed standard deviation of the difference of percent change from baseline in PVR at Week 12 between each MK-5475 and placebo is 0.4. Under these assumed percent change and standard deviation, a sample size of 41/group provides more than 85% power (approximately 86.4%) to demonstrate superiority for each of the MK-5475 treatment comparisons using a one-sided alpha=0.025.

The robust regression method is used to address the primary hypothesis. The robust regression model will include terms for treatment and WHO-FC (Class II and Class III/IV). Missing PVR observations at Week 12 from participants in all treatment groups will be imputed following a PMM. Missing data due to death will be imputed as the worst outcome among all observed data. Missing data due to treatment discontinuation will be imputed based on the observed PVR observations at Week 12 from the placebo group referred as J2R (detailed below). If there are missing Week 12 data for other reasons, J2R will also be used. The randomization seed for imputations will be 5475007.

The difference (MK-5475 minus placebo) in percent change from baseline and the associated 95% CI and p-value will be provided. A p-value for the comparison of MK-5475 versus placebo <0.025 (one-sided) will be considered statistically significant contingent upon the multiplicity strategy. For the Phase 2 Cohort Base Period, there are 3 treatment group comparisons that may be tested to address the primary hypothesis. Testing will be done in a sequential manner in descending order of MK-5475 randomised dose group, stopping at the point statistical

significance is not achieved. The multiplicity strategy strongly controls the Type I error at 2.5% (one-sided) to address the primary hypothesis.

The following steps will be taken to perform the primary analysis, including imputation for missing data. Percent change from baseline in PVR at Week 12 is the response variable:

Define imputation model for different missingness patterns:

Obtain the worst outcome among all observed data.

Within the placebo group, for subjects with both baseline and Week 12 data, fit an ANCOVA model including terms for treatment and WHO-FC (Class II and Class III/IV).

Impute missing data for different missingness patterns:

Death: for participants (in both treatment groups) who died before Week 12, the worst outcome among all observed data will be used to impute the missing Week 12 values.

Reasons other than death: For subjects (in both treatment groups) missing the response variable, the fitted model in Step 1 will be used to impute the missing values.

Robust regression based on a Huber-type M estimator will be performed for the imputed dataset [Huber PJ. *Ann Statist*. 1973;1(5):799-821]. The model will include terms for treatment and WHO-FC (Class II and Class III/IV) unless the model fails to converge. If necessary to achieve model convergence, WHO-FC will be removed from the model.

Steps 2 and 3 will be repeated 50 times to create 50 complete datasets and 50 sets of parameter estimates.

The final parameter estimate for the mean percent change will be the average of the 50 parameter estimates for the mean percent change from Step 4.

Steps 1 through 5 will be repeated 200 times based on bootstrap resampling. The resulting standard error for the mean percent change will be the standard error of the resulting parameter

estimates obtained in the 200 bootstrap resampled datasets. The CI and p-value will be derived from a normal distribution based on the final parameter estimate and its standard error.

The approach for addressing the mean change from baseline in 6MWD and additional hyperdynamic parameters (secondary endpoints and post hoc analyses) at Week 12 will use the same robust regression method described above for the primary endpoint. Summary statistics will be provided for additional hemodynamic parameters (secondary endpoints and post hoc analyses).

Table S1. List of study investigators and participating centres for the INSIGNIA-PAH study

Country	Primary Investigator(s)	Affiliation
Argentina	Daniel Aimone	Hospital El Cruce Nestor Carlos Kirchner, Florencio Varela, Buenos Aires, Argentina
	Hernan Cohen Arazi	Cardiologia Palermo, Buenos Aires, CABA, Argentina
	Andres Nicolas Atamanuk	Hospital Universitario Austral, Pilar, Buenos Aires, Argentina
	Guillermo Roberto Bortman	Sanatorio de la Trinidad Mitre, Buenos Aires, CABA, Argentina
	Ana Rosa Diez	Instituto Cardiovascular de Rosario, Rosario, Santa Fe, Argentina
	Diego Federico Echazarreta	Centro Medico Capital, La Plata, Buenos Aires, Argentina
	Alberto Alfredo Fernandez	Instituto de Investigaciones Clinicas Quilmes, Quilmes, Buenos Aires, Argentina
	Oscar Alejandro Salomone	Hospital Privado Universitario de Córdoba, Cordoba, Cordoba, Argentina
Australia	Martin R Brown	Macquarie University, New South Wales, Australia
Canada	John T. Granton	University Health Network - Toronto General Hospital, Toronto, ON
	Naushad Hirani	Peter Lougheed Centre, Calgary, AB
	Steeve Provencher	IUCPQ, Quebec, QC
Colombia	Mauricio Orozco-Levi	Fundacion Cardiovascular de Colombia, Floridablanca, Santander, Colombia
	Clara Saldarriaga	Centro Cardiovascular Colombiano Clínica Santa María, Robledo Medellin, Antioquia, Colombia
	Claudio Villaquiran	Hospital Universitario San Ignacio, Bogota, Distrito Capital de Bogota, Colombia
France	Pascal De Groote	Institut Coeur Poumon - CHRU de Lille, Lille Cedex, Nord-Pas-de-Calais, France
	Gregoire Prevot	CHU de Toulouse - Hopital Larrey, Toulouse, Haute-Garonne, France
	Olivier Sitbon	CHU - Hopital Bicêtre (Assistance Publique Hôpitaux de Paris, Université Paris-Saclay), Le Kremlin-Bicêtre, Val-de-Marne, France
Germany	Henning Gall	UKGM Gießen/Marburg, Giessen, Germany
	Ekkehard Gruenig	Thoraxklinik Heidelberg gGmbH am Universitaetsklinikum Heidelberg, Heidelberg, Germany
	Marius Hoeper	Medizinische Hochschule Hannover Hannover, Germany
	Martin Kolditz	Uniklinikum Dresden, Dresden, Germany

	Elena Pfeuffer-Jovic	Klinikum Würzburg Mitte-Medizinische Klinik – Schwerpunkt Pneumologie & Beatmungsmedizin, Wuerzburg, Germany
	Hans-Juergen Seyfarth	Universitaetsklinikum Leipzig, Leipzig, Germany
Greece	Georgios Giannakoulas	AHEPA University General Hospital of Thessaloniki, Athens, Greece
Israel	Doron Aronson	Rambam Medical Center, Haifa, Israel
	Mordechai Reuben Kramer	Rabin Medical Center, Petah Tikva, Israel
	Yael Raviv	Soroka Medical Center, Beer Sheva, Israel
Italy	Stefano Ghio	Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
	Giuseppe Paciocco	Ospedale San Gerardo - ASST Monza, Monza, Italy
	Carmine Dario Vizza	Azienda Ospedaliera Policlinico, Roma, Italy
Mexico	Humberto Garcia Aguilar	Operadora de Hospitales Angeles. S.A. de C.V. - Sucursal Lomas Vialidad de la Barranca s/n, Huixquilucan, Mexico
	Gustavo Francisco Mendez Machado	Consultorio 1020 Hospital Angeles Xalapa, Xalapa, Veracruz, Mexico
	Tomas Rene Pulido Zamudio	Instituto Nacional de Cardiología -Ignacio Chavez, Tlalpan, Distrito Federal, Mexico
New Zealand	Lutz Beckert	Christchurch Hospital, Christchurch, Canterbury, New Zealand
	Sasiharan Sithamparanathan	Greenlane Clinical Centre, Auckland, Auckland, New Zealand
Poland	Grzegorz Kopec	Krakowski Szpital Specjalistyczny im. Jana Pawa II, Kraków, Poland
Russia	Olga Leonidovna Barbarash	Scientific Research Institute Complex Problems Cardiovascular Disease, Kemerovo, Russia
	Olga Mikhailovna Moiseeva	Almazov National Medical Research Centre of the Ministry of Health, Saint Petersburg, Russia
Sweden	Sven-Erik Bartfay	Sahlgrenska Universitetssjukhuset-Cardiology Research Unit, Gothenburg, Sweden
Turkey	Bahri Akdeniz	Dokuz Eylul University Faculty of Medicine, Izmir, Turkiye
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United Kingdom	Luke Howard	Imperial College Healthcare NHS Trust - Hammersmith Hospital, London, UK
	Martin Johnson	Golden Jubilee National Hospital, Glasgow, UK
	Jim Lordan	The Freeman Hospital Newcastle upon Tyne Hospital NHS Trust, Newcastle-upon-Tyne, UK
	Stephen John Wort	Royal Brompton and Harefield NHS Trust, London, UK
United States	David Brian Badesch	University of Colorado – Denver, Aurora, CO
	Christopher Barnett	UCSF Helen Diller Medical Center at Parnassus Heights, San Francisco, CA
	David Coriell Booth	University of Kentucky, Lexington, KY
	Marco Caccamo	West Virginia University-WVU Heart and Vascular Institute, Morgantown, WV
	Kelly M. Chin	University of Texas Southwestern Medical Center at Dallas, Dallas, TX
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	Michael Duncan Roberto Machado Roberto Bernardo	Indiana University Health Methodist Hospital, Indianapolis, IN
	Michael S Eggert	Sentara Norfolk General Hospital, Norfolk, VA
	Timothy Martin Fernande	University of California San Diego Health-Pulmonary Critical Care, La Jolla, CA
	Hubert James Ford III	Clinical Trials Unit at Eastowne, Chapel Hill, NC
	John W. McConnell	Norton Pulmonary Specialists, Louisville, KY
	Lana Melendres-Groves	University of New Mexico, Health Sciences Center, Albuquerque, NM
	Gautam Ramani	University of Maryland, Baltimore, MD
	Ricardo Restrepo-Jaramillo	Tampa General Hospital, Tampa, FL
	Sandeep Sahay	Houston Methodist Research Institute, Houston, TX
	Namita Sood	University of California, Davis Medical Center, Sherman Oaks, CA
	Leslie A Spikes	University of Kansas Medical Center, Kansas City, KS
	John Swisher	Statcare Pulmonary Consultants, Knoxville, TN
	James Tarver	AdventHealth Orlando, Orlando, FL
	Tammy Wichman	University of Nebraska Medical Center, Omaha, NE

Table S2. Exploratory endpoints

- Change in WHO functional class distribution from baseline at week 12
- Change in plasma levels of NT-proBNP from baseline at week 12
- Living with Pulmonary Hypertension (LPH) questionnaire, administered at baseline and week 12

Table S3. List of study inclusion and exclusion criteria.

Eligible participants must meet all the following criteria:
1. Has the following PAH groups, as defined by the Updated Clinical Classification of Pulmonary Hypertension [20]: a. Group 1.1 Idiopathic PAH b. Group 1.2 Heritable PAH c. Group 1.3 Drug- or toxin-induced PAH d. Group 1.4 PAH associated with: i. Connective tissue disease ii. HIV infection iii. Simple repaired congenital systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) with persistent PH at least one year after surgical repair and with no clinically significant residual shunt
2. Has a diagnosis of PAH performed as standard of care, per scientific guidelines, and documented by historical RHC at any time prior to Screening; if participant is postsurgical repair of systemic-to-pulmonary shunt, diagnostic RHC must have been performed at least one year after surgery
3. Has an eligibility RHC, meeting all the following criteria: a. mPAP ≥25 mmHg b. PVR of ≥3 Wood units c. PCWP or LVEDP ≤15 mmHg For the Phase 2 Cohort, the eligibility RHC should be performed during Screening and will be centrally reviewed. A participant with RHC performed within 30 days prior to Visit 1/Screening may have the RHC results submitted for central review and, if deemed adequate, the RHC may count as baseline. In each case, the RHC should be performed after at least 90 days of stable PAH-specific therapy.
4. Has WHO-FC symptoms Class II to IV
5. Has two 6MWD measurements between 150 and 500 meters, one at Screening and one at Randomization. The relative difference between the two measurements (ie, absolute difference/mean) must be ≤15%. If the relative difference between the two 6MWD measurements is >15%, the Randomization 6MWT may be repeated after at least 4 hours. If the relative difference between the two Randomization 6MWD measurements is ≤15%, the participant can be randomized and the last 6MWD will be considered the baseline value.
6. Has stable concomitant background PAH-specific therapy (no change in drug within 90 days and no change in dosage within 30 days prior to and over the duration of Screening) with any of the following agents: a. ERA and/or b. PDE5i and/or c. an oral prostacyclin analogue or oral prostacyclin receptor agonist (eg, oral beraprost, oral treprostinil, oral selexipag), an intravenous prostacyclin analogue (eg, IV treprostinil, IV epoprostenol, IV iloprost) or a subcutaneous prostacyclin analogue (eg, subcutaneous treprostinil)
7. If on vasodilators other than PAH-specific therapy (including calcium channel blockers or L-arginine supplementation), has stable concomitant use (no change in dose for at least 30 days prior to and over the duration of Screening).
8. If on calcium channel blockers, a participant from Groups 1.1, 1.2, and 1.3 must have a history of being a nonresponder to acute pulmonary vasoreactivity testing.

9. If on anticoagulants, has stable concomitant use (the same dosage of direct oral anticoagulants and in the same therapeutic range for vitamin K antagonists) for at least 30 days prior to and over the duration of Screening.
10. Is male or female, from 18 years to 75 years of age inclusive, at the time of signing the informed consent
11. Has a BMI between 18.5 kg/m^2 and 40 kg/m^2
12. Is willing to comply with scheduled visits, treatment plan, laboratory tests, and/or other study procedures and study restrictions
13. Agrees to allowing site contact via phone or e-mail for follow-up purposes

Male Participants

14. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 14 days after the last dose of study intervention:
    a. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR
    b. Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
        i. Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of child-bearing potential (WOCBP) who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
        ii. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

15. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    a. She is not a WOCBP OR
    b. She is a WOCBP and:
        i. Uses a contraceptive method that is highly effective (with a failure rate of <1% per year) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
        ii. Has a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
        iii. Abstains from breastfeeding during the study intervention period and for at least 14 days after study intervention.

iv. Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
16. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. A supplemental documented informed consent/assent is required for participation in the Phase 2 Cohort Extension Period. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Participants were excluded if they met any of the following criteria:
1. Has Group 2 PH, Group 3 PH (including PH associated with idiopathic interstitial pneumonia), Group 4 PH, or Group 5 PH according to the Updated Clinical Classification of Pulmonary Hypertension
2. Has Group 1.5 PAH, long-term responders to calcium channel blockers, defined by sustained clinical improvement to WHO-FC I or II and sustained hemodynamic improvement after at least one year on calcium channel blockers only
3. Has Group 1.6 PAH, with overt features of venous/capillary (PVOD/PCH) involvement
4. For participants with Group 1.4 HIV-associated PAH, has any of the following within 90 days prior to and for the duration of Screening: a. Concomitant active opportunistic infections b. Plasma HIV-1 RNA ≥50 copies/mL or CD4+ T-cell count <200/mm3 c. Changes in antiretroviral regimen
5. Has evidence of more-than-mild obstructive lung disease on pulmonary function testing at Screening with FEV_1/FVC <70% and FEV_1 <60% of predicted value after bronchodilator administration
6. Has evidence of more-than-mild parenchymal lung disease based on medical history and chest imaging (eg, high-resolution CT), and/or restrictive lung disease with total lung capacity <60% of predicted on pulmonary function testing at Screening
7. Has evidence of more-than-mild obstructive sleep apnea that is untreated. Participants with well controlled, treated obstructive sleep apnea are eligible
8. Has evidence or history of left heart disease, including any of the following: a. Left ventricular ejection fraction (LVEF) ≤45% b. Moderate or severe left-sided valvular disease (aortic or mitral valve stenosis or regurgitation) c. Grade 3 and 4 left ventricular diastolic function on echocardiographic evaluation A historical transthoracic Doppler echocardiogram performed within 6 months prior to Screening is acceptable to demonstrate echocardiographic eligibility criteria. If a historical echocardiogram is not available, a transthoracic Doppler echocardiogram will be performed during Screening.
9. Has three or more of the following risk factors for heart failure with preserved ejection fraction: a. BMI >30 kg/m^2 b. History of essential systemic hypertension c. Diabetes mellitus of any type d. History of coronary artery disease established by any of the following: history of stable angina, history of myocardial infarction, previous or planned percutaneous coronary intervention or coronary artery bypass

graft, angiographic evidence of significant coronary artery disease (>70% stenosis in more than one vessel), positive stress test
10. Has oxygen saturation measured by pulse oximetry (SpO_2) <90%, despite supplemental oxygen therapy. In case the accuracy of oxygen saturation measurement by pulse oximetry is unreliable, arterial blood gas sampling (SaO_2) should be performed
11. Had clinically unstable or acutely decompensated right heart failure within 30 days prior to and over the duration of Screening including, but not limited to, hospitalization or emergency room visit for acute decompensated heart failure
12. Has seated systolic BP >160 mmHg or <90 mmHg or seated diastolic BP >100 mmHg
13. Has significant chronic renal insufficiency, as defined by eGFR <30 mL/min/1.73 m^2 (calculated using the MDRD equation) or by ongoing dialytic support
14. Has evidence of chronic liver disease (ie, Child-Pugh B or C), portal hypertension, cirrhosis, or hepatic laboratory abnormalities (ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN)
15. Is included in a cardiopulmonary rehabilitation program initiated within 90 days prior to Screening or is planning to initiate cardiopulmonary rehabilitation during the study
16. Has acute or chronic impairment(s) (other than dyspnoea), limiting the ability to perform 6MWT
17. Is a current smoker or currently uses electronic cigarettes (vapes)
18. Is unable to correctly use the dry powder inhaler prior to randomization due to, but not limited to, cognitive impairment or physical limitations
19. Has other severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or that would confound study analysis or impair study participation or cooperation
20. Has a history of cancer (malignancy). Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated, with appropriate follow-up, and therefore unlikely to recur for the duration of the study, in the opinion of the investigator (eg, malignancies which have been successfully treated ≥5 years prior to Screening)
21. Has a known hypersensitivity to any of the ingredients or excipients of the investigational medical product
22. At the time of signing the informed consent, is a user of illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence
23. Has a known psychiatric or any other cognitive disorder that would, in the opinion of the investigator, interfere with the participant's ability to cooperate with the requirements of the study
24. Is a woman of childbearing potential who has a positive urine pregnancy test within 24 hours before the first dose of study intervention. If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive
Prior/Concomitant Therapy
25. Has used intravenous inotropes including, but not limited to levosimendan, dopamine, dobutamine, epinephrine, norepinephrine, noradrenaline or milrinone within 30 days prior to and over the duration of Screening
26. Has concomitant use of inhaled prostacyclin analogues (eg, inhaled iloprost, inhaled epoprostenol or inhaled treprostinil), inhaled NO, or oral sGC modulators (eg, riociguat, vericiguat), or has used these medications within 90 days prior to and over the duration of Screening

Prior/Concurrent Clinical Study Experience
27. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to Screening. This window will be derived from the date of the last dose of study medication taken in the previous study. Participants enrolled in observational studies may be included and will be reviewed on a case-by-case basis for approval by the Sponsor
28. For Phase 2 Cohort Extension Period: has not completed Visit 6/Week 12 study assessments
29. For Phase 2 Cohort Extension Period: has discontinued study intervention or completed the Phase 2 Cohort Base Period before this amendment was approved and the Extension Period became available
Other Exclusions
30. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study

Table S4. Summary of participant disposition

	Placebo	MK-5475 32 µg	MK-5475 100 µg	MK-5475 380 µg	Total
Randomised, n	41	42	44	41	168
Completed the Base Period, n (%)	39 (95.1)	41 (97.6)	43 (97.7)	41 (100)	164 (97.6)
Discontinued the Base Period, n (%)	2 (4.9)	1 (2.4)	1 (2.3)	0	4 (2.4)
Death	2 (4.9)	0	0	0	2 (1.2)
Withdrawal by participant	0	1 (2.4)	1 (2.3)	0	2 (1.2)
Discontinued study treatment, n (%)	2 (4.9)	2 (4.8)	1 (2.3)	0	5 (3.0)
Adverse event	0	1 (2.4)	0	0	1 (0.6)
Death	2 (4.9)	0	0	0	2 (1.2)
Withdrawal by participant	0	1 (2.4)	1 (2.3)	0	2 (1.2)
Continued into the Extension Period, n (%)	30 (73.2)	34 (81.0)	37 (84.1)	34 (82.9)	135 (80.4)
Extension Period not available	6 (14.6)	3 (7.1)	5 (11.4)	5 (12.2)	19 (11.3)
Not continuing into Extension Period	3 (7.3)	4 (9.5)	1 (2.3)	2 (4.9)	10 (6.0)

Table S5. Summary of WHO functional class and NT-proBNP results for the Base Period (week 12), by treatment group.

		Placebo (n=41)	MK-5475 32 µg (n=42)	MK-5475 100 µg (n=44)	MK-5475 380 µg (n=41)
WHO functional class	No. of evaluable participants[a]	39	40	43	41
	Not worse relative to baseline, n (%)	37 (94.9)	39 (97.5)	42 (97.7)	38 (92.7)
	Improved, n (%)	5 (12.8)	4 (10.0)	6 (14.0)	9 (22.5)
	Unchanged, n (%)	32 (82.1)	35 (87.5)	36 (83.7)	29 (72.5)
NT-proBNP, pg/mL	No. of evaluable participants[a]	37	39	40	36
	Mean (SD) at baseline	632.7 (944.6)	623.6 (1438.3)	914.6 (1852.5)	495.2 (664.0)
	Mean change (SD) from baseline	61.0 (527.8)	−182.1 (778.7)	−51.4 (408.7)	−46.5 (238.3)

[a]Number of participants with baseline and treatment values, which are required for participants to be counted at a timepoint.

[b]By least-squares means obtained from fitting a robust regression estimate based on a Huber-type M estimator including terms for treatment and WHO functional class at baseline. Missing data at week 12 due to death were imputed using the worst observed value and other missingness were imputed using jump-to-reference method.

6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SE, standard error, WHO, World Health Organization.

Table S6. Serious adverse events[a] occurring in any participant[b] in any treatment arm

Preferred term	Placebo (n=41)	MK-5475 32 µg (n=42)	MK-5475 100 µg (n=44)	MK-5475 380 µg (n=41)	Total (N=168)
Acute respiratory failure[c]	1 (2.4)	0	0	0	1 (0.6)
Aneurysm thrombosis	0	0	0	1 (2.4)	1 (0.6)
Atrial flutter	1 (2.4)	0	0	0	1 (0.6)
Chest pain	0	1 (2.4)	0	0	1 (0.6)
Complications associated with device	0	1 (2.4)	0	0	1 (0.6)
Dehydration	0	0	0	1 (2.4)	1 (0.6)
Dyspnoea	0	1 (2.4)	0	0	1 (0.6)
Erysipelas	0	0	1 (2.3)	0	1 (0.6)
Gastrointestinal haemorrhage	0	1 (2.4)	0	0	1 (0.6)
Hypervolemia	0	0	0	1 (2.4)	1 (0.6)
Lung neoplasm malignant[c]	0	0	1 (2.3)	0	1 (0.6)
Pneumonia	1 (2.4)	0	0	0	1 (0.6)
Pulmonary arterial hypertension	2 (4.8)	0	0	0	2 (1.2)
Pulmonary embolism	0	0	1 (2.3)	0	1 (0.6)
Sudden death[c]	1 (2.4)	0	0	0	1 (0.6)
Systemic lupus erythematosus	0	0	0	1 (2.4)	1 (0.6)
Uterine haemorrhage	0	0	1 (2.3)	0	1 (0.6)
Vascular device occlusion	0	0	0	1 (2.4)	1 (0.6)

[a]Adverse event terms are from the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1.

[b]Participants are counted a single time for each applicable row and column.

[c]Serious adverse event leading to death. Death due to lung neoplasm malignant occurred after study completion and therefore not reflected in Table S4.

Table S7. Change in the Living With Pulmonary Hypertension (LPH) questionnaire over time during the Base Period (week 12), by treatment group.

		Placebo	MK-5475 32 µg	MK-5475 100 µg	MK-5475 380 µg
No. of participants	Randomised	41	42	44	41
	With values at baseline[a]	40	40	43	41
	With values at baseline and week 12	36	37	40	40
LPH Physical Dimension Score[b]	Mean (SD) at baseline[c]	12.2 (9.9)	14.8 (11.2)	15.4 (8.1)	15.6 (9.4)
	Mean change (SD) from baseline	0.6 (6.9)	−2.7 (6.8)[e]	−1.8 (6.2)[e]	−2.3 (8.3)[e]
LPH Total Score[d]	Mean (SD) at baseline[c]	27.7 (22.1)	35.4 (26.4)	32.7 (17.3)	35.7 (20.2)
	Mean change (SD) from baseline	−0.9 (13.7)	−7.1 (17.1)[e]	−4.3 (13.1)	−5.5 (18.6)[e]

SD, standard deviation.

[a]Baseline is defined as the last value before the first dose of study treatment in the Base Period. A baseline and treatment value are required for a participant to be counted at a timepoint.

[b]The LPH Physical Dimension questionnaire comprises 8 questions, with a score ranging from 0-40. A higher score means that an individual is more affected by the condition.

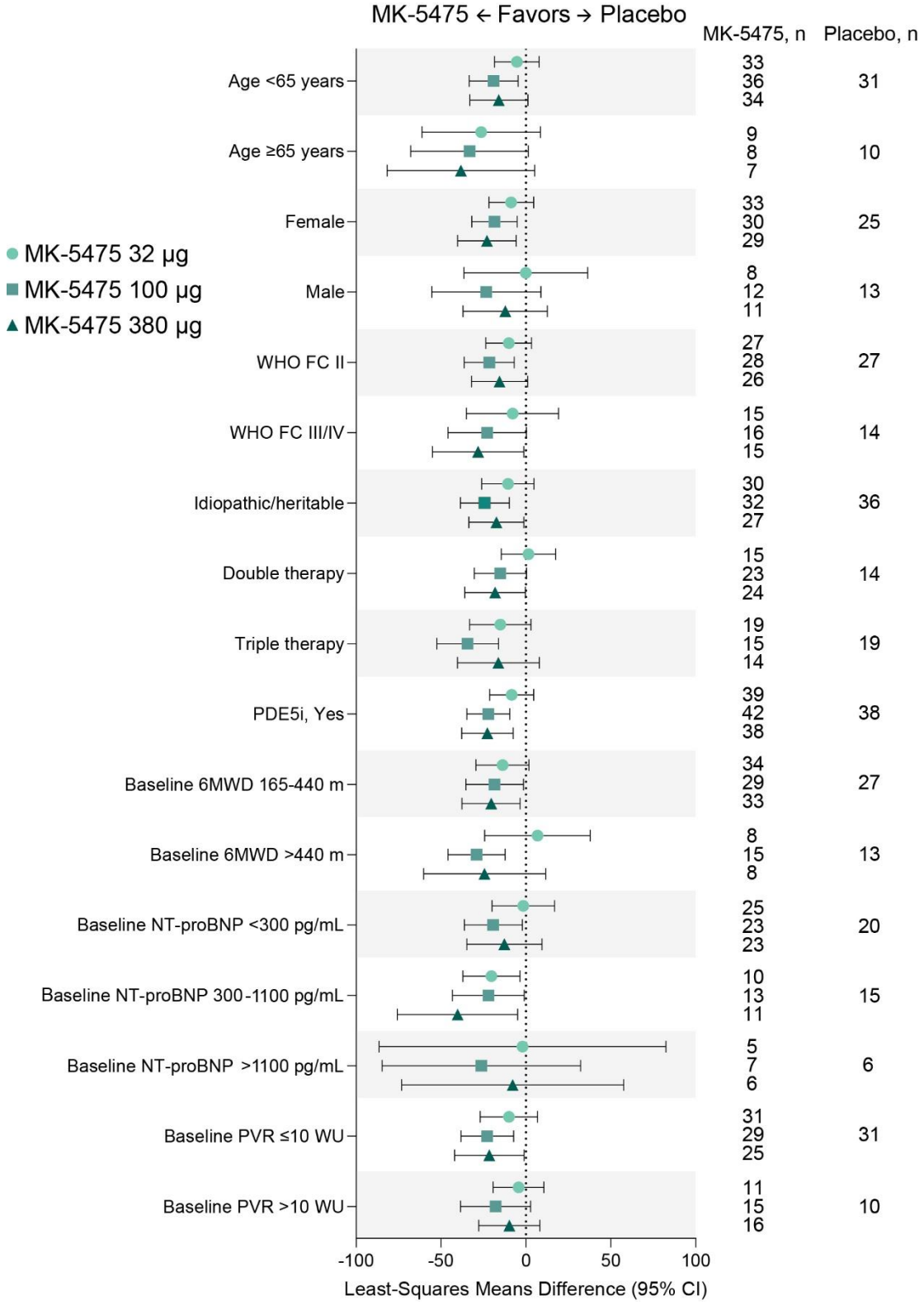
[c]Baseline values are reported for the participants who had values at both baseline and week 12.

[d]The LPH questionnaire comprises 21 questions, with a score ranging from 0-105. A higher score means that an individual is more affected by the condition.

[e]Anchor-based responder definitions have been calculated to be an absolute value score change of 1.48-3.69 in the LPH Physical Dimension score and 4.41-11.02 in the LPH total score [12]. Accordingly, mean change in Physical Dimension scores for all MK-

5475 treatment groups are considered clinically meaningful improvement based upon the responder definition. Mean change in the 32-µg and 380-µg total scores are also considered clinically meaningful improvement based upon the responder definition.

Figure S1. Between-group differences (MK-5475 *vs* placebo) in least-squares means of percent change from baseline at week 12 in pulmonary vascular resistance (PVR, WU), by subgroup.[a]



[a]Least-squares means, least-squares means differences, and 95% CIs were computed only for subgroups with at least 5 participants in each treatment group. Not computable for subgroups: PAH subtype CTD-APAH, Others; Background Therapy, Monotherapy; Background Therapy, PDE5i, No; Baseline 6MWD <165 m.

Figure S2. Least-squares mean change (95% CI) in NT-proBNP levels (pg/mL) from baseline at week 12.