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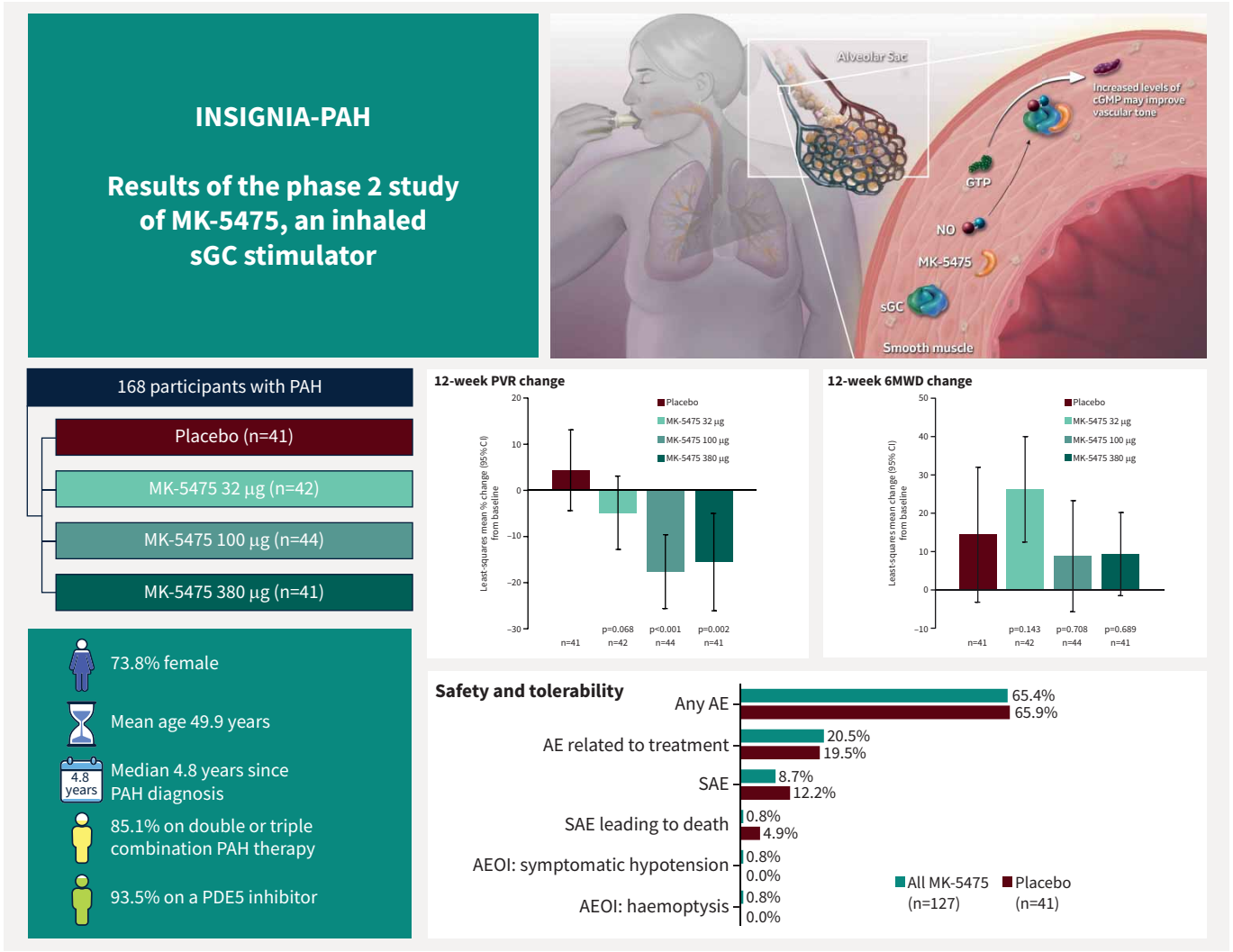

GRAPHICAL ABSTRACT Inhaled MK-5475 is proposed to directly stimulate soluble guanylate cyclase (sGC), independently of and synergistically with nitric oxide (NO), to increase levels of intracellular cyclic guanosine monophosphate (cGMP). Treatment with inhaled MK-5475 at 100 µg and 380 µg significantly reduced pulmonary vascular resistance (PVR) in participants with pulmonary arterial hypertension (PAH). Change in 6-min walk distance (6MWD) was not significant. Treatment with MK-5475 at all three doses was well tolerated. Error bars in graphs represent 95% confidence intervals. AE: adverse event; AEOI: adverse event of interest; GTP: guanosine triphosphate; PDE5: phosphodiesterase 5; SAE: serious adverse event.

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Shareable abstract (@ERSpublications)
The inhaled soluble guanylate cyclase stimulator MK-5475 reduced PVR and was well tolerated in patients with PAH, without evidence of systemic side-effects such as hypotension, suggesting a pulmonary selective pharmacodynamic effect https://bit.ly/4dJ2nAs

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Abstract

Background MK-5475 is an investigational inhaled soluble guanylate cyclase stimulator hypothesised to avoid most side-effects of systemic vasodilation.

Methods The phase 2 INSIGNIA-PAH (NCT04732221) trial randomised adults with pulmonary arterial hypertension (PAH) on stable background therapy 1:1:1:1 to once-daily dosing with placebo, MK-5475 32 µg, 100 µg or 380 µg *via* dry powder inhalation for 12 weeks.

Objectives The objectives were to evaluate pulmonary vascular resistance (PVR; primary), 6-min walk distance (6MWD; secondary), additional selected haemodynamic parameters, and safety and tolerability in participants with PAH.

Results 168 participants were randomised to placebo (n=41), MK-5475 32 µg (n=42), 100 µg (n=44), and 380 µg (n=41). Median age was 51 years. Most participants were female (73.8%), diagnosed with idiopathic PAH (63.7%), receiving concomitant phosphodiesterase type 5 inhibitors (PDE5i; 93.5%), and treated with double or triple combination therapy (85.1%). At week 12, the placebo-corrected changes in PVR by least-squares means were −9.2% (95% CI −21.3%, 2.9%; p=0.068) with 32 µg, −22.0% (95% CI −33.7%, −10.3%; p<0.001) with 100 µg, and −19.9% (95% CI −33.4%, −6.4%; p=0.002) with 380 µg MK-5475. No treatment differences *versus* placebo were observed in 6MWD. Treatment-related adverse events and serious adverse events were similar across treatment groups. Three participants died: two on placebo and one on MK-5475 100 µg. One participant had symptomatic hypotension and one had haemoptysis (both on MK-5475 100 µg).

Conclusions In participants with PAH on stable background therapy, including PDE5i, inhaled MK-5475 reduced PVR and was well tolerated, without evidence of systemic side-effects such as hypotension, suggesting a pulmonary selective pharmacodynamic effect.