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# Successful therapy for previously incurable advanced pulmonary hypertension

**The new drug sotatercept stops the remodelling of the pulmonary vessels and even helps patients with advanced pulmonary arterial hypertension (PAH) who have not yet been treated.**

Pulmonary arterial hypertension (PAH) is a rare form of pulmonary hypertension. It occurs because progressive vascular changes cause the small pulmonary arteries to narrow. As a result, the right side of the heart has to pump harder to transport blood to the lungs and the blood pressure in the pulmonary circulation rises. The active ingredient sotatercept, which is administered by injection under the skin, has been approved for treatment since September 2024. Its effectiveness was previously investigated in stable patients in the international STELLAR clinical trial. The follow-up study ZENITH has now also demonstrated the benefits of the drug in patients with advanced PAH with a high risk of dying within a year. Prof. Dr Marius Hoeper, Acting Director of the Clinic for Pneumology and Infectiology at Hannover Medical School (MHH) and scientist at the German Centre for Lung Research (DZL) at the BREATH Hannover site, is significantly involved in both studies. 'Sotatercept gives us the opportunity to control the disease in a completely new way - even in patients who were previously considered untreatable despite maximum therapy,' emphasises Professor Hoeper. The results of the ZENITH study have been published in the 'New England Journal of Medicine', a leading international medical journal.

Sotatercept stops pathological signalling

PAH is a rare disease, but it is very serious. It mainly affects women between the ages of 30 and 60. Diagnosis is difficult because symptoms such as shortness of breath, fatigue, swollen feet, chest pain or circulatory problems are confused with those of other heart and lung diseases. Because the chronically elevated blood pressure in the pulmonary circulation also puts a strain on the right side of the heart, PAH not only leads to limited physical activity, but also to right-sided heart failure, heart failure and reduced life expectancy. The cause is a malfunction in the small pulmonary arteries.
The small blood vessels in our body that lead from the heart to the lungs are constantly being remodelled: Cells in the inner layer of the blood vessels die off and new endothelial cells grow back. In PAH, these remodelling processes within these arterioles are out of balance. More endothelial cells are formed than die. Instead of a single layer of endothelial cells, new layers are therefore constantly deposited on top of each other on the inside of the vessel and the vessels become narrower. The biological switch for the formation of new endothelial cells is a protein called activin. Sotatercept acts as a 'ligand trap', blocks the activin function and interrupts the pathological signal transmission. 'With Sotatercept, we are intervening in the fundamental mechanisms of vascular regulation for the first time ever in medicine,' says Professor Hoeper.

Clinical breakthrough in PAH therapy

In the ZENITH study, all participants were already receiving the maximum tolerated standard therapy for PAH. The patients were additionally treated with either sotatercept or a placebo. The result: in the sotatercept group, the risk of deterioration resulting in a longer hospital stay, a lung transplant or even death was reduced by more than 75 per cent

compared to the placebo group. Sotatercept also showed clear advantages over the placebo in terms of quality of life, exercise tolerance and pulmonary vascular resistance. Due to this superiority, the study was terminated prematurely - a continuation of the placebo group would have been unacceptable for ethical reasons, according to an independent monitoring committee. 'Such a decision is very rare and shows that we have achieved a clinical breakthrough in PAH therapy with sotatercept and now have a highly effective treatment option for a broad spectrum of PAH patients,' says Professor Hoeper.

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The original paper of the ZENITH study 'Sotatercept in Patients with Pulmonary Arterial Hypertension at High Risk for Death' can be found here: https://www.nejm.org/doi/full/10.1056/NEJMoa2415160

The original paper of the predecessor study STELLAR 'Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension' can be found here: https://pubmed.ncbi.nlm.nih.gov/36877098/

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New study shows efficacy of Sotatercept also in advanced pulmonary hypertension.
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