

Category

Best Pharmaceutical Product

General Information**Company Name ***

Merck & Co. Inc.

Product/Solution Name *

WINREVAIR™(sotatercept-csrk) for injection, 45mg, 60mg

Compound/Tech Name*

Sotatercept

Trade Name *

WINREVAIR™

Corporate Name *

WINREVAIR™

Date of Approval *

2024-03-26

Indications *

WINREVAIR™ is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events

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Therapeutic Areas *

Treatment for Pulmonary Arterial Hypertension (PAH)

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Background information and need for drug / device

(please be as specific as possible in your description; limit 500 words)

Pulmonary Arterial Hypertension (PAH) is a rare, chronic, progressive, and life-threatening disorder in which blood vessels in the lungs thicken and narrow, causing significant strain on the heart.

This condition affects approximately 33 to 113 individuals per million population globally [BluePrint Orphan 2022]. PAH affects a broad spectrum of patients in the prime of life with the majority being female. The mean age at diagnosis ranges from 30 to 70 with a median of 53.4 years [BluePrint Orphan 2022]. The typical symptoms of PAH include breathlessness, fainting, and chest pain (particularly during physical activity), fatigue, and dizziness [EPHA, 2012]. The median time from symptom onset to diagnosis is approximately 3 years [BluePrint Orphan 2022]. Delays in diagnosis may be due to the relatively non-specific nature of early PAH symptoms and the need for referral to a specialty center for the detailed evaluation necessary to establish diagnosis.

Despite the availability of several medications and treatment of many patients with 2 or 3 classes of PAH therapies [Humbert, M., et al 2022], PAH remains a chronic, progressive, physically debilitating disease with a poor long-term prognosis. The estimated rate of 5- to 7-year survival is approximately 66% after diagnosis [BluePrint Orphan 2022] [Yung, L. M., et al 2020] [Benza, R. L., et al 2012] [McLaughlin, V. V., et al 2002]. PAH symptoms can severely impact a patient's ability to carry out normal daily activities. As the disease progresses, some patients may experience continuous breathlessness and fatigue so that even simple tasks, such as getting dressed and walking short distances, become difficult. Productivity may also be limited by the side effects of PAH treatment regimens, including flushing, headaches, nasal congestion, nausea, diarrhea, and chronic pain [Helgeson, Menon et al. 2020]. PAH also continues to have considerable negative impacts on patients' well-being and emotional and social functioning [Delcroix and Howard 2015]. Patients with PAH have more frequent symptoms related to depression, anxiety, and stress and significantly lower overall health-related quality of life (HRQOL) than the sex- and age-matched general population [Vanhoof, Delcroix et al. 2014].

WINREVAIR™ is an activin receptor type IIA fusion protein that traps excess Activin A to inhibit activin signaling and rebalance the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation. WINREVAIR has demonstrated significant improvement in exercise capacity, WHO Functional Class (FC) and the risk of clinical worsening events as a treatment for PAH on top of existing therapies and will offer healthcare providers a novel therapeutic option that targets a new pathway in PAH treatment.

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History of the development of the solution/product *

(please be as specific as possible in your description; 500 words)

WINREVAIR was initially studied as a potential treatment for refractory anemia in non-Pulmonary Hypertension (PH) indications through a collaboration between Acceleron Pharma Inc and Celgene. When development for this original indication was discontinued, researchers at Acceleron continued development of WINREVAIR in PH. Merck & Co Inc. acquired exclusive rights to WINREVAIR in the PH field through its acquisition of Acceleron.

WINREVAIR is proposed to directly target the underlying cellular mechanisms that contribute to the narrowing of the lungs blood vessels in patients with PAH. In preclinical models, WINREVAIR induced

cellular changes that were associated with thinner vessel walls, partial reversal of right ventricular remodeling, and improved hemodynamics leading to reverse remodeling and restoration of vessel structure and function.

Two Phase 2 studies in PAH were initiated in 2018 (PULSAR and SPECTRA). Results of the PULSAR study were published in The New England Journal of Medicine in 2021. WINREVAIR demonstrated significantly greater reductions in pulmonary vascular resistance (PVR) versus placebo and was shown to reduce PVR in patients receiving all background therapy regimens, including those who were receiving maximum triple-therapy [Humbert, M., et al 2021]. Based on these results, multiple Phase 3 studies were initiated. The FDA granted Orphan drug status to WINREVAIR for PAH in 2019 and Breakthrough Therapy Designation for PAH in 2020. The EMA granted PRIME designation for PAH and Orphan drug designation for PAH in 2020.

STELLAR, the pivotal Phase 3 study was initiated in 2020. Results were also published in The New England Journal of Medicine in 2023. STELLAR enrolled 323 patients with PAH (WHO Group 1 FC II or III) randomized 1:1 to WINREVAIR (n=163) or placebo (n=160) plus stable background therapy administered subcutaneously once every 3 weeks. Most participants were receiving either three (61%) or two (35%) background therapies for PAH, and 40% were receiving prostacyclin infusions.

The primary efficacy endpoint in the STELLAR trial was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD), a well-established registrational endpoint in PAH that assesses exercise capacity. In the WINREVAIR treatment group, the placebo-adjusted median increase in 6MWD was 40.8 meters (95% CI: 28, 54; $p < 0.001$). The result was both statistically and clinically very meaningful. The safety profile was manageable. WINREVAIR demonstrated statistically significant and clinically meaningful improvements in eight of nine secondary outcome measures. These endpoints were chosen to assess the impact of WINREVAIR on disease hemodynamics, on disease severity and outcomes and on biomarkers that correlate with the prognosis of the disease and on patient-reported outcomes. A key secondary outcome measure was time to death or clinical worsening. WINREVAIR reduced the risk of clinical worsening or death by 84% compared to placebo with a median follow-up of 32.7 weeks (HR=0.16 [95% CI, 0.08-0.35]; $p < 0.001$) [Hoeper, MM, et al 2023]. This effect size has not been observed with any other PAH study.

WINREVAIR was approved by US-FDA on 26-Mar-2024 USPI . The EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending approval on 27-June-2024.

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

PAH is a devastating disease for patients and their loved ones. The introduction of WINREVAIR represents a groundbreaking advancement in the treatment of PAH, introducing a new mechanism that targets the cellular signaling related to vascular hyperproliferation and pathological remodeling.

This breakthrough therapy promises to have a transformative impact on the treatment landscape for PAH.

For patients and families, PAH severely diminishes survival, quality of life and daily functioning, and decreases independence. The common presenting symptoms of PAH include dyspnea, fatigue, and dizziness / fainting, which become increasingly debilitating as the disease progresses. Research has also revealed that the act of providing care for a PAH patient was frequently associated with exhaustion and a reduction of household income [Guillevin L, 2013].

Current treatments for PAH do not address the vascular remodeling, which is the underlying cause of PAH. There is a need for a treatment option that improves functional ability and patient quality of life while ultimately reducing the risk of clinical worsening or death [Humbert M, 2023].

WINREVAIR is the first and only activin signaling inhibitor for the treatment of PAH and is proposed to modulate the vascular proliferation underlying PAH. WINREVAIR demonstrated robust clinical results in the Phase 3 STELLAR trial, with clinically meaningful improvements in 6MWD of 40.8m, reduced the risk of death or clinical worsening by 84% and delivered broad benefit across functional, hemodynamic, and HRQOL measures. WINREVAIR has a manageable and well-characterized adverse event profile. WINREVAIR represents a true innovation in PAH.

Additional studies are underway in adult patients to further explore WINREVAIR(TM) treatment in patients with PAH (WHO Group 1) at intermediate or high risk of disease progression or mortality (ZENITH), as well as with pulmonary hypertension due to left heart disease (WHO Group 2) (CADENCE). Additionally, WINREVAIR(TM) is being investigated in pediatric patients with WHO Group 1 PAH (MOONBEAM).

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Please provide appropriate references (PubMed, Abstract, Website) *

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Attached Files:

- [2024 WINREVAIR Abstract Page.docx](#)