

Supplementary Material

Safety, Tolerability, and Pharmacokinetics of Treprostinil Palmitil Inhalation Powder for Pulmonary Arterial Hypertension: A Phase 1, Randomized, Double-Blind, Single- and Multiple-Dose Study

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Participant Inclusion Criteria

Each participant was required to meet all of the following criteria:

- Men or women aged 18 to 45 years at the time of consent
- In good general health as determined by medical history, physical examination findings, vital sign measurements, 12-lead electrocardiogram (ECG) results, and clinical laboratory test results within normal limits or considered not clinically significant by the investigator at screening
- Agreement to comply with all protocol requirements
- Ability to provide written informed consent

Participant Exclusion Criteria

Participants who met any one of the following criteria were excluded:

- Allergy, documented hypersensitivity, or contraindication to the ingredients or to any of the excipients of treprostinil palmitil inhalation powder or treprostinil
- Use of any prescription (excluding hormonal birth control) or over-the-counter medications, including herbal or nutritional supplements, within 14 days before the first dose of study drug or throughout the study
- Surgical procedure that required general anesthesia (or equivalent) within 90 days before screening
- Body mass index <19.0 or >32.0 kg/m² at screening
- History of
 - Anaphylaxis or previously documented hypersensitivity reaction to any drug
 - Syncope not due to dehydration or vasovagal syncope (eg, congenital cardiac arrhythmias such as Wolff-Parkinson-White syndrome, nodal tachycardia, ventricular tachycardia)
 - HIV infection
 - Abnormal bleeding or bruising
 - Malignancy in the past 5 years, with exception of nonmelanoma skin cancer
- Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 m² by Chronic Kidney Disease Epidemiology Collaboration equation) at screening
- ECG abnormalities: QRS >120 ms, QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 ms

- Active liver disease or hepatic dysfunction at screening or check-in visits manifested as:
 - Elevated liver function test results (alanine aminotransferase or aspartate aminotransferase $>2 \times$ upper limit of normal [ULN])
 - Bilirubin $>1.5 \times$ ULN (isolated bilirubin $>1.5 \times$ ULN; ULN acceptable if bilirubin is fractionated and direct bilirubin $<35\%$)
 - Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones
- Participant in any other interventional clinical studies within 30 days of randomization
- Current history (within the past 12 months) of substance and/or alcohol abuse
- Current user of cigarettes (average of ≥ 1 cigarette/day) or e-cigarettes within 30 days before screening
- Positive test result for drugs of abuse, alcohol, or cotinine (indicating active current smoking) at screening or before the first dose of study drug or throughout the study
- Clinically significant abnormal laboratory value, test result, or physical examination finding at screening; diseases or disorders that, in the opinion of the investigator, may have put the participant at risk by participating in the study, interfered with the participant's treatment and assessment, influenced the results of the study; or had compliance issues with the study
- Pregnant or breastfeeding
- Women of childbearing potential (premenopausal, not surgically sterile for at least 3 months before screening) who were not using highly effective contraception method(s) and/or were unwilling to be tested for pregnancy from day 1 to at least 35 days after the last dose of study drug
 - Highly effective contraception methods included true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner
- Males with female partners of childbearing potential who were not using highly effective contraception from day 1 to at least 90 days after the last dose of study drug
- In the opinion of the investigator, the participant was not suitable for entry into the study