FILSPARI™ (sparsentan)
Impact on Pregnancy, Lactation, and Fertility

Summary

Prescribing Information

- FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity[1]
- Based on animal data, FILSPARI can cause major birth defects if used during pregnancy. Due to risk of embryo-fetal toxicity, FILSPARI is contraindicated in pregnancy[1]
- Patients are advised not to breastfeed during treatment with FILSPARI[1]
- In a preclinical study, sparsentan did not negatively impact fertility in male or female rats[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]
- The potential for reproductive and developmental toxicity of sparsentan was evaluated in 4 Good Laboratory Practices studies: fertility and EED toxicity (rat), embryo-fetal toxicity (rat and rabbit), and peri- and post-natal developmental toxicity (rat)[5]
- The PROTECT study is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-control study of the efficacy and safety of sparsentan compared to irbesartan for the treatment of IgA nephropathy[6]
- The DUET study is a phase 2, randomized, multicenter, double-blind, active-control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients with FSGS[4]

Study Data

Preclinical Studies

- In rodent studies, sparsentan treatment resulted in serious fetal anomalies of the craniofacial region and skeleton, decreased fetal growth, and reduced postnatal survival and growth of offspring[5]

The PROTECT Study

- Patients who were pregnant or planned to become pregnant were excluded from the PROTECT study[7]

The DUET Study

- Five pregnancies occurred in the DUET trial. Of these, 1 resulted in a spontaneous abortion that was considered possibly related to sparsentan[5]

Prescribing Information

FILSPARI REMS

FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity.[1]

Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.[1]

Pregnancy

Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy.[1]

Available data from reports of pregnancy in clinical trials with FILSPARI are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of sparsentan to pregnant rats throughout organogenesis at 10-times the MRHD in mg/day caused teratogenic effects in rats, including craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights.[1]

To prevent pregnancy, patients who can become pregnant must use effective contraception prior to initiation of treatment, during treatment, and for one month after stopping FILSPARI.[1]

Lactation

There are no data on the presence of sparsentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for adverse reactions, such as hypotension in breastfed infants, advise patients not to breast feed during treatment with FILSPARI.

Fertility

In a fertility and early embryonic development study in rats, oral administration of sparsentan at doses of 20, 80, and 320 mg/kg/day for at least 36 (females) and 49 (males) days did not result in any adverse effects on estrous cycles, mating, fertility, sperm evaluation or pregnancy incidence at doses up to 320 mg/kg/day, which provided approximately 10 and 14 times the AUC at the MRHD for males and females, respectively. Male reproductive organ toxicity was not evident in chronic toxicity studies with sparsentan at exposures up to 10 times and 1.3 times the AUC of the MRHD in rats and monkeys, respectively.[1]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[8-10]

Preclinical Studies

The potential for embryo-fetal toxicity with sparsentan treatment was assessed in studies using pregnant rats and rabbits throughout the gestational period. Pregnant rats were given oral sparsentan at doses of 80, 160, and 240 mg/kg/day on GD 7 through 17.[5] The AUC at the lowest dose tested (80 mg/kg/day) was approximately 10 times the AUC at the MRHD of 400 mg/day.[1] Pregnant rabbits were administered oral sparsentan at doses of 2.5, 10, and 40 mg/kg/day on GD 7 through 19.[5] Doses of 10 and 40 mg/kg/day provided exposures approximately 0.1 times and 0.2 times the AUC at the MRHD, respectively.[1]

The PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan compared to 300 mg of irbesartan.[11] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[6,7] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (urinary protein excretion <0.3 g/day) and partial (urinary protein excretion <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[12] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[12,13]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[4]

Study Data

Preclinical Studies

- In pregnant rats and rabbits teratogenicity and/or developmental toxicity was attributed to the antagonism of ET_A and AT_1 receptors[1]
- In pregnant rats, oral administration of sparsentan at doses of 80, 160, and 240 mg/kg/day throughout embryonic development resulted in multiple dose-dependent teratogenic effects. These included craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights[1]
- In pregnant rabbits, sparsentan was administered at doses of 2.5, 10, and 40 mg/kg/day. Maternal death and abortions occurred at 10 and 40 mg/kg/day, which provided exposures approximately 0.1 times and 0.2 times the AUC at the MHRD[1]

The PROTECT Study

Pregnancy is contraindicated for all ERA treatments.[14] In the PROTECT study, patients who were pregnant or planned to become pregnant were excluded from enrollment.[7]

The DUET Study

Women who were pregnant, breastfeeding, or of child-bearing age and unwilling to use 2 reliable methods of contraception were excluded from the study.[2]

As of August 1, 2021, 5 pregnancies have occurred during the DUET trial.[5]

- One spontaneous abortion occurred at 13 weeks, 4 days gestation and was considered to be possibly related to the investigational product sparsentan
- One resulted in the premature birth of a male at 32 weeks of gestation, with no health issues noted
- In 1 case a healthy infant was born at 37 weeks gestation but the patient was then lost to follow up
- Two patients underwent elective abortions

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AUC, area under the curve; EED, early embryonic development; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; FSGS, focal segmental glomerulosclerosis; GD, gestation day; IgA, immunoglobulin A; KF, kidney failure; KRT, kidney replacement therapy; MRHD, maximum recommended human dose; OLE, open-label extension; REMS, risk evaluation and mitigation strategies; UACR, urine albumin-creatinine ration; UPCR, urine protein-creatinine ratio.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
2. Komers R, Gipson DS, Nelson P, et al. Efficacy and safety of sparsentan compared with irbesartan in patients with primary focal segmental glomerulosclerosis: Randomized, controlled trial design (DUET). *Kidney Int Rep*. 2017;2(4):654-664. doi:10.1016/j.ekir.2017.02.019
3. Raczynska A, Pawlowicz-Szlarska E, Nowicki M. Sparsentan–a dual antagonist–literature review on endothelin and endothelin antagonists. *Nephrol Dial Pol*. 2021;25:77-82.
4. Trachtman H, Nelson P, Adler S, et al. DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754. doi:10.1681/ASN.2018010091
5. Sparsentan (RE-021) investigator's brochure. 2021.
6. Wong M, Barratt J, Komers R, Mercer A, Rosenberg N. Baseline characteristics of adults enrolled in the ongoing phase 3 randomized, double-blind, active-control trial of sparsentan for the treatment of immunoglobulin A nephropathy (PROTECT). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
7. Barratt J, Rovin B, Diva U, Mercer A, Komers R, PROTECT Study Design Group. Supplementary material: Implementing the kidney health initiative surrogate efficacy endpoint in patients with IgA nephropathy (the PROTECT trial). *Kidney Int Rep*. 2019;4(11):1633-1637. doi:10.1016/j.ekir.2019.08.007
8. Nagasawa H, Suzuki H, Jenkinson C, et al. Sparsentan, the dual endothelin angiotensin receptor antagonist (DEARA), attenuates albuminuria and protects from the development of renal injury to a greater extent than losartan in the gddY mouse model of IgA nephropathy: A 16-week study. Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
9. Nagasawa H, Suzuki H, Jenkinson C, et al. The dual endothelin type A receptor (ET_AR) and angiotensin II type 1 receptor (AT_1R) antagonist, sparsentan, protects against the development of albuminuria and glomerulosclerosis in the gddY mouse model of IgA nephropathy. Poster presented at: ERA-EDTA Virtual Congress; June 6-9, 2020; Virtual Meeting.
10. Bedard P, Jenkinson C, Komers R. Sparsentan protects the glomerular basement membrane and glycocalyx, and attenuates proteinuria in a rat model of focal segmental glomerulosclerosis (FSGS). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
11. Barratt J, Rovin B, Wong MG, et al. IgA nephropathy patient baseline characteristics in the sparsentan PROTECT study. *Kidney Int Rep*. 2023:1-36. doi:10.1016/j.ekir.2023.02.1086
12. Heerspink HJ, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: A prespecified interim analysis from a randomised double-blind active-controlled clinical trial. *Lancet*. Published online April 1, 2023;doi:https://doi.org/10.1016/S0140-6736(23)00569-X
13. Thompson A, Carroll K, Inker LA, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14(3):469-481. doi:10.2215/CJN.08600718
14. US Department of Veterans Affairs Pharmacy Benefits Management Services. Endothelin receptor antagonists (ERAs) in pulmonary arterial hypertension (PAH), bosentan (TRACLEER),

ambrisentan (LETAIRIS), macitentan (OPSUMIT): Criteria for use. Updated February 2017. Accessed February 2, 2023. https://www.va.gov/formularyadvisor/DOC_PDF/Endothelin_Receptor_Antagonists_ERA_Feb_2017.pdf