Zokinvy™ (lonafarnib) – New orphan drug approval

- On November 20, 2020, Eiger BioPharmaceuticals announced the FDA approval of Zokinvy (lonafarnib), in patients 12 months of age and older with a body surface area (BSA) of 0.39 m^2 and above:

    - To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)
    - For the treatment of processing-deficient Progeroid Laminopathies with either: heterozygous *LMNA* mutation with progerin-like protein accumulation or homozygous or compound heterozygous *ZMPSTE24* mutations.

- Zokinvy is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based upon its mechanism of action, Zokinvy would not be expected to be effective in these populations.

- Progeria, or HGPS, and Progeroid Laminopathies are separate and distinct ultra-rare, genetic premature aging diseases that accelerate mortality in young patients. Children with these conditions typically die of heart disease at an average age of 14.5 years. Disease manifestations include severe failure to thrive, scleroderma-like skin, global lipodystrophy, alopecia, joint contractures, skeletal dysplasia, global accelerated atherosclerosis with cardiovascular decline, and debilitating strokes.

    - It is estimated that there are 400 children worldwide with Progeria and 200 children with Progeroid Laminopathies. Of these patients, approximately 180 children and young adults have been identified, including 20 in the U.S.

- Zokinvy blocks the accumulation of defective, farnesylated proteins which form tight associations with the nuclear envelope, leading to cellular instability and the process of premature aging in children and young adults with Progeria and processing-deficient Progeroid Laminopathies.

- The efficacy of Zokinvy was based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two Phase 2 studies in patients with HGPS to those from a natural history cohort. Study 1 was a Phase 2 open-label, single-arm trial that evaluated the efficacy of Zokinvy in 28 patients. Following completion of study 1, 26 patients enrolled in a second Phase 2 open label, single-arm trial which consisted of two study phases. In the first phase, patients received Zokinvy with additional therapies for about 5 years. In the second phase of Study 2, patients received Zokinvy for a period of up to 3 years. There were 35 treatment naïve patients with HGPS enrolled into the second phase of study 2.

    - The retrospective survival analysis was based on the mortality data from 62 treated patients (27 patients in study 1 and 35 treatment-naïve patients in study 2) and data from matched, untreated patients in a separate natural history cohort.
    - The mean lifespan of HGPS patients treated with Zokinvy increased by an average of 3 months through the first 3 years of follow-up (hazard ratio [HR] 0.30, 95% CI: 0.10, 0.89) and 2.5 years through the last follow-up time (11 years) compared to untreated patients (HR 0.40, 95% CI: 0.21, 0.77).

- Zokinvy is contraindicated in patients taking:

    - Strong or moderate CYP3A inhibitors or inducers
    - Midazolam
    - Lovastatin, simvastatin, or atorvastatin

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- Warnings and precautions for Zokinvy include risk of reduced efficacy or adverse reactions due to drug interactions; laboratory abnormalities; nephrotoxicity; retinal toxicity; impaired fertility; and embryo-fetal toxicity.

- The most common adverse reactions (≥ 25%) with Zokinvy use were vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, musculoskeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase.

- The recommended starting dosage of Zokinvy for patients with a BSA of 0.39 m^2 and above is 115 mg/m^2 orally twice daily with morning and evening meals to reduce the risk of gastrointestinal adverse reactions. After 4 months of treatment, the dosage should be increased to 150 mg/m^2 twice daily.

    — The capsules should be swallowed whole. If unable to swallow capsules, the contents should be mixed with Ora Blend SF®, Ora-Plus®, orange juice, or applesauce.
    — Refer to the Zokinvy drug label for additional instructions on dosing, preparation and administration.

- Eiger BioPharmaceuticals' launch plans for Zokinvy are pending. Zokinvy will be available as 50 mg and 75 mg capsules.