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Zokinvy® (lonafarnib): Giving More Years of Life to the Old Children

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Hutchingson-Gilford Progeria syndrome (HGPS), also known as progeria, is an autosomal dominant, rare, fatal, pediatric segmental premature aging disease that appears to affect males and females of all races equally.[1] As of September 2020, the Progeria Research Foundation reports the prevalence of progeria as 1 in 20 million births. It is estimated that 350- 400 patients with progeria exist worldwide.[2] Classic HGPS is caused by a single nucleotide substitution in the lamin A/C gene LMNA ((c.1824C>T [p.Gly608Gly]).[3,4] Nonclassical HGPS has similar characteristics to classic HGPS but also contains an autosomal dominant progerin-producing pathological variant on the exon 11 splice junction or intron 11 of LMNA and is thought to follow an autosomal recessive pattern of inheritance.[5-9]

Hutchingson-Gilford Progeria syndrome is a de novo heterozygous point mutation, changing a GGC sequence to GGT in exon 11 of the LMNA gene.[10] This mutation causes a 50 amino acid sequence deletion at the carboxyl terminus of prelamin A, producing a truncated progerin protein in the place of Lamin A.[11] Progerin lacks a cleavage site and remains permanently anchored to the nuclear membrane, binds to other proteins and causes nuclear blebbing (bulges forming around the nuclear membrane which then lead to cell death).[12] When progerin is present in place of Lamin A, the nuclear membrane takes on an abnormal morphology which includes blebbing and affects cellular functions such as signal transduction, mitosis and gene expression leading to devastating effects on multiple organ systems in the body.[8,11,13]

Children with HGPS appear normal at birth but within a year, their growth rate slows, and they physically appear much shorter and weigh much less than others their age. Despite adequate caloric intake, poor weight gain in children with HGPS leads to growth impairment, short stature and loss of subcutaneous fat. Failure to thrive, dermatologic, musculoskeletal abnormalities, neurologic abnormalities, life-limiting cardiovascular disease, audiologic, dental, and ophthalmologic complications are commonly present in patients with HGPS.[14] Diagnosing HGPS requires a thorough personal and family history, including symptoms, such as poor growth, and completing a physical examination. Failure to thrive and hair loss are the two most common symptoms. Genetic testing for classical HGPS and variants mutation in nonclassical HGPS help in the differential diagnosis. Patients with HGPS have an accelerated aging process with the majority presenting with complications of atherosclerotic disease but their lab values are usually unremarkable.[15] Those with HGPS may present with low serum leptin levels, insulin resistance, decreased bone density, and radiographic findings of acro-osteolysis (bone clavicular resorption) and coxa valga (deformity of hip between the angle of head and neck of the femur).

There is no cure for HGPS and no current standard of care treatment. Treatment strategies are focused at controlling the effects of premature aging. Patients typically present with low levels of antioxidants and are therefore treated with formulas of antioxidants, vitamins, lipoic acid, and coenzyme-Q. Treatment of HGPS is involved with preventing complications of cardiovascular disease with heart bypass or low dose aspirin. Patients presenting with shortened stature are placed on growth hormone therapy. Physical and occupational therapy around 2-3 times per week facilitate proper movement to perform activates of daily living.[16]

Zokinvy® (lonafarnib) is an oral faresytransferase inhibitor that received approval from the US Food and Drug Administration (FDA) on November 2020 for the treatment of processing-deficient progeroid laminopathies with a heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations to reduce the risk of mortality in HGPS in patients 12 months of age and older with a body surface area of 0.39 m^2 and above.[17] The FDA's priority review designation of lonafarnib early in development helped accelerate approval to the market.[18] Lonafarnib is the first drug used to treat children living with HGPS and has been shown to extend the life expectancy of children living with progeria by an average of 1.6 years on top of the average life expectancy of 14.6 years by preventing the buildup of defective progerin or progerin-like protein. Lonafarnib has been shown to improve cardiovascular outcomes, auditory function, increase weight gain and improve skeletal structure.[19] The purpose of this article to review the properties of lonafarnib and trials used to evaluate the safety and efficacy of lonafarnib as the first drug used to treat HGPS.

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Mechanism of Action

Lonafarnib's mechanism of action is suggested to inhibit farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane which is thought to be associated with the premature aging process in children.[17]

Pharmacokinetics

The true oral bioavailability of lonafarnib has not been established in trials.[17] The maximum peak plasma concentrations (Cmax) of lonafarnib after oral administration in fasted conditions of healthy subjects was reported to be 834 ng/mL and 964 ng/mL, corresponding to lonafarnib 75 mg and lonafarnib 100 mg twice daily doses respectively. After twice daily oral administration of lonafarnib with food and at steady state, lonafarnib's time to reach maximum concentration (Tmax) in patients with HGPS has been reported to be two and four hours based on clinical trials. High fat meals decreased Cmax by 55% and AUC by 29% when compared to fasted conditions after administration of a single dose of lonafarnib 75 mg based on clinical trials. Lonafarnib has extensive plasma protein binding (99%) with volume of distribution (Vd) between 87.8 and 97.4 L post administration of 100 mg and 75 mg of lonafarnib twice daily, respectively. In vitro studies have identified lonafarnib primarily being metabolized by CYP3A and to a lesser extent by CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1. The mean half-life (T1/2) is approximately 4-6 hours after oral administration of lonafarnib 100 mg twice daily in healthy subjects. Lonafarnib is primarily excreted through fecal elimination with up to 62 % of the total radiolabeled dosed recovered in the feces and ≤1% excreted in the urine.[17]

Table 1 | Select Lonafarnib Pharmacokinetics[17]

Absorption	
T_{max}[a]	2 hours
Distribution	
Vd[b]	97.4 L
Protein Binding	≥ 99%
Metabolism	
Liver	CYP3A (Major), CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1 (Minor)
Elimination	
$T_{1/2}$[c]	4-6 hours
Fecal	62%
Urine	≤ 1%

[A]Time to maximum concentration; [b]Volume of distribution; [c]Half-life

Clinical Trials

Approval of lonafarnib was based on results from a retrospective observational cohort survival study. This study used the data from two prospective phase II single arm studies in patients with HGPS compared to those from a natural history cohort. The prospective studies looked at other clinical markers for therapeutic efficacy and then data was combined to assess survival.

Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome (ProLon1)

Conducted by the manufacturer Eiger BioPharmaceuticals, Inc., this trial was a Phase II prospective single arm clinical trial of lonafarnib treatment in patients with classic HGPS that enrolled 26 patients from 16 different countries from May through October 2007.[19] The purpose of this clinical trial was to assess the efficacy of lonafarnib in increasing or maintaining weight gain in patients with HGPS. Measures of toxicity and disease progression were also assessed during this clinical trial. Inclusion criteria included subjects ≥3 years of age with genetically confirmed c.1824 C > T, p. Gly608Gly classic HGPS mutation, adequate organ and marrow function, and the ability to travel for regular study visits. Exclusion criteria included nonclassical mutation of HGPS. The primary outcome was a 50% increase from baseline in estimated annual rate of weight gain or as a change from baseline weight loss. Since this was a single arm trial, all participants received lonafarnib to test for efficacy. All other usual care was completed throughout the clinical trial. Changed in nutrition was assessed with daily caloric intake using 7-day food records at study entry and end of therapy from baseline. Changes in cardiovascular outcomes of fasting pulse wave velocity (PWVcf) (a measure of arterial stiffness), diagnostic carotid artery ultrasonography, mean distal internal carotid artery velocity, distal common carotid artery far-wall intima media thickness, and echodensity procedures were measured with a change from baseline being reported as results. Dual-energy x-ray absorptiometry (DXA) of the lumbar spine total hip and whole body were measured as well as areal bone mineral density (aBMD) with a clinically significant improvement predefined as a ≥3 increase from baseline. Various measures of rigidity that were reflective of structural properties of the cancellous and cortical bones were also assessed at 4%, 20%, 50% and 66% distances. Auditory measurements were assessed by bone and air conduction by improvements in low frequency hearing loss (hearing thresholds > 15 decibels (dB) averaged over 250, 500 and 1000 Hertz (Hz)) and high frequency hearing loss, which was defined over 2,000, 4,000 and 8,000 Hz as described previously by Kenna et al.[20] Significance was determined to be a difference of ≥ 10 db across the three frequencies in each respective category.

A total of 26 patients were included in the trial however one patient passed away within 5-months of starting the study leaving only 25 patients included in the analysis. Subjects were initiated on lonafarnib 115 mg/m² then after four months were increased to 150 mg/m². The dose was reduced back to 115 mg/m² for patients who experienced severe drug related toxicities which did not respond to supportive care. Lonafarnib was administered via oral capsules or liquid suspensions dispersed in Ora-Blend SF or Ora-Plus every 12 hours for a period of 24-29 months. Hepatic, renal, and hematological toxicity was monitored monthly for the first three months and then every 4 months for the duration of the study.

Nine of twenty-five patients [36%; 95% confidence interval (CI): 18–58%] achieved statistically significant success with weight gain from muscle and bone. Ten subjects had stable rates (+/-50%) and six had decreases in weights of > 50%. At baseline 18 subjects had PWVcf 3.5 times greater than the established pediatric normal values, indicating high arterial stiffness and low distensibility (median: 12.9 m/s; range: 7.2–18.8 m/s). At the end of treatment, PWVcf decreased by a median of 35% (range: -48% to 26%, P = 0.0001). Skeletal function improved from baseline in areas of rigidity and aBMD with a median percent increase at four radial sites of the bones. The radial sites tested 40-50% in axial rigidity, 170 – 228% in flexural rigidity and 167 – 229% in torsional rigidity in 11 patients who were tested. Levels of the subjects were close to their age and sex matched controls post treatment. A clinically and statistically significant increase at one or more sites was observed in 76% of children (19/25; exact 95% CI: 55–91%) compared with 40% of the participants (10/25; exact 95% CI: 21–61%) who exhibited decreases at one or more sites. Audiological function demonstrated an improvement in median low frequency sensorineural hearing in both ears, represented by 8/18 children and 13/34 ears had an average of ≥10 db improvements. Of the 25 subjects analyzed for the primary outcome, 44% were male. Within this patient population, some patients could not perform various tests due to age restrictions or fragility, but despite this limitation results were obtained for the primary and secondary outcomes and considerations for future experiments could be inclusive about fragile patients. Lonafarnib treatment was well tolerated for most patients with the most common side effects reported as mild diarrhea, fatigue, nausea, vomiting, anorexia, and depressed serum hemoglobin which improved over time with most patients.

Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children with Hutchinson-Gilford Progeria Syndrome (ProLon2)

Gordon et al performed a second trial in children with HGPS with lonafarnib plus pravastatin, and zoledronic acid.[21] This phase II single arm study enrolled participants ≥2-years-old with clinically diagnosed classical HGPS to evaluate the effectiveness of triple therapy in halting progression of HGPS disease. The rationale for adding on zoledronic acid and pravastatin was hypothesized to be greater progerion prenylation upstream of the farnesylation step and decreased efficacy of lonafarnib at maximum tolerated doses.

Thirty-seven patients with adequate organ and marrow function were enrolled in the study. Twenty-four of the thirty-seven had been on lonafarnib monotherapy treatment for at least two years from the previous clinical trial. Inclusion criteria was similar to previous clinical trial discussed. Trial medications were administered for a period of 40-52 months with lonafarnib with treatment naive subjects starting at 150 mg/m^2 twice daily doses and non-treatment naive patients, most of which participated in ProLon1, taking their established dose. Oral 5 mg pravastatin was administered for participants weighing <10 kg and oral 10 mg pravastatin for participants weighing >10 kg once every 24±2 hours. Zoledronic acid was administered intravenously over 30 minutes at baseline, 6, 12, and 18 months and at the end of therapy. Oral lonafarnib was given either in capsule form or liquid suspension dispersed in Ora-Blend SF or Ora-Plus every 12 hours. The primary outcome was a composite of an estimated annual rate of weight gain from baseline and decrease in echobrightness of the internal carotid artery adventitia with quantification of echodensity as a measure of vascular tissue distensibility. If either of these outcomes was achieved then the intervention would have counted as a success according to the authors. Key secondary outcomes included PWVcf, distal common carotid artery far wall intima-media thickness, and plaque evaluations established with ultrasonography, changes in neuro imaging and skeletal function.

Overall, 22/31 participants (9 were treatment naïve and 13 non naïve) obtained statistically significant results for either weight gain or echodensity. Statistical significance associated with weight gain was obtained in 15/31 participants (4 treatment naïve and 11 non-naïve), echodensity was achieved in 11/ 35 participants (8 treatment naïve and 3 non-naïve) and statistical significance among both primary outcome components was achieved in 6/35 participants. Results were reported as number of people in each group that achieved weight change of 10% (if the participated in ProLon1) or 50% from baseline for all the other groups. The authors reported how many patients obtained significant results but changes in baseline values apart from were obtained as one criteria of the primary outcomes or were not clearly specified in the results section.

There was no significant difference on daily average fat or carbohydrate energy intake, but protein intake was increased for the groups that achieved success defined as a 50% rate of weight grain. The weight gain was associated with an increase in lean body mass and bone assessed by DXA. Mean carotid artery wall echodensity of the intima-media, near or deep adventitia, and PWVcf demonstrated no significant changes, suggesting no change in vascular stiffness among triple therapy compared to monotherapy. A greater prevalence of carotid artery plaque increase was reported to be increased with statistically significant increase from 5% at baseline to 50% int eh triple therapy group (P<0.001) at eh end of the study. Statistically significant height adjusted aBMD were observed.

Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome

Gordon et al performed a cohort study to analyzed survival outcomes for treated vs untreated HGPS patients.[22] The cohort analysis included 161 untreated subjects of which 102 were deceased and 59 were living or lost to follow up that were identified through publications, the Progeria Research Foundation Interna-

Table 2 | Weight Gain Outcomes of Lonafarnib Trials[26]

Trial	Outcomes	Intervention	Result (95% CI[a])	P-Value
ProLon1	Proportion of patients achieving >50% increase in slope for weight gain or a change from negative to positive slope	Lonafarnib 115-150 mg/m^2 Placebo	36% (0.18-0.58)	N/R[b]
ProLon2	100% or complete clearance of lesions ≥75% or partial clearance of lesions Reduction of echodensity of deep common carotid artery adventitia ≤90% of the value at entry	Pravastatin, zoledronic acid and lonafarnib vs baseline values	48.4% (N/R) 31.4% (N/R)	<0.001

[A]95% Confidence Interval; [b]Not Reported tional Registry. Forty-three previously treated patients with lonafarnib were included in this analysis. The untreated and treated patients consisted of 100% clinical trial patients. Untreated subjects had not received clinical trial medications within any clinical treatment trial for HGPS of which only lonafarnib monotherapy, or in combination with pravastatin and zoledronic acid have been studied. Treated subjects received trial medications for any length of time; treatment initiation and duration varied.

Inclusion criteria included, HGPS phenotype confirmation by study investigators participation in progeria clinical trials (NCT00425607 (lonafarnib monotherapy) and NCT00879034 and NCT00916747 (lonafarnib, zoledronate, and pravastatin combination therapy). Patients were classified as either being born before 1991 and after 1991 using treatment initiation as a time dependent covariate.

In this analysis, 52% were males and were distributed among the continents of Africa, Asia, Australia, Europe, North America, and South America. Other demographic information were equal between groups. Causes of death were identified for 50 of the 102 deceased untreated subjects and were attributed to CV failure (n=40; 80%), head injury or trauma (n=5; 10%), stroke (n=2; 4%), respiratory infection superimposed on CV disease (n=2; 4%), and complications from anesthesia during surgery (n=1; 2%). Similarly, cause of death in the five deceased trial participants included CV failure (n=3; 60%), head injury (n=1; 20%), and stroke (n=1; 20%). Kaplan Meier plots analysis showed significant improvements in life expectancy from approximately one to four years with 20 years being the cutoff of life expectancy for the treated groups. An 85% reduction in death was observed in the treated vs untreated groups in which treatment was defined as the follow up time when treatment with lonafarnib started in either ProLon1 or ProLon2. The untreated group was derived from historical registry data from the Progeria Research Foundation, Rhode Island Hospital and Brown University. The earliest patient observation for both the treated cohort and untreated contemporaneous controls used in the treatment mortality analysis was in 1991. Each treated group matched to an untreated historical patient was matched by age, sex and continent of residency to control for confounding. Hazard ratios adjusted by age, sex, and continent-adjusted for mortality of treated subjects in the matched analysis was 0.15 indicating positive association with survival. An 89% reduction in mortality was observed in the treatment vs untreated groups in which treatment was defined as follow up starting at birth for individuals born on or after 1991 but the hazard ratio (HR) analysis was defined as starting at the time of treatment initiation for treated patients. The authors showed improvements in survival with their matched groups but were unclear in their description of what follow up at birth meant. During the first six years after treatment initiation for the treated patients in the matched pair found a life extension of 1.6 years [95% CI of 0.8 to 2.4 years ($P<0.001$)] compared to non-treated patients. This study demonstrated that the progerin-associated morbidity is the overriding factor in survival. This study is the first to demonstrate a positive effect of any treatment on estimated survival in HGPS. Results were consistent across eight different possible confounding variables (sex, continent of origin, mutation status, birth year, medical advances, growth hormone treatment, failing health, trial site clinical treatment).

Drug Interactions

The FDA approved labeling recommends avoiding consumption of grapefruit juice or Seville oranges while taking lonafarnib. Per FDA labeling, avoid if possible coadministration with weak CYP3A inhibitors, CYP2C9 inhibitors, sensitive CYP3A substrates and CYP2C19 substrates.[17] If any of the drug classes above are unavoidable, it is recommended to monitor closely for adverse drug events. Coadministration with CYP3A inhibitors could result in increased exposure of lonafarnib resulting in toxicity. Due to unknown effects on QT intervals related to increased lonafarnib exposure, arrythmias, palpitations and signs of syncope should be monitored. Lonafarnib is contraindicated with co-administration of strong or moderate CYP3A inhibitors and inducers, as well as midazolam, simvastatin, lovastatin, or atorvastatin. FDA labeling recommends temporary discontinuing lonafarnib for 10-14 days before and two days after administration of midazolam.[17]

Table 3 | Common Adverse Effects[17]

Adverse Effect	Incidence
Vomiting	90%
Diarrhea	81%
Infection	78%
Nausea	56%
Decreased Appetite	53%
Fatigue	51%

Adverse Effects

The most common reported side effects of lonafarnib were nausea (56%) vomiting (90%), diarrhea (81%), decreased appetite (53%) and fatigue (51%) and infection (78%). Additional adverse drug events reported include changes in serum potassium and sodium levels, decreased white blood cell counts and increased liver blood tests which were observed during clinical trials. Routine blood work including a basic metabolic panel and complete blood cell count is recommended. Hypertension deriving from normotensive patients and elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported in clinical trials and should be monitored while on lonafarnib. Nephrotoxicity, ocular toxicity and electrolyte abnormalities were observed in animal studies, thus it is recommended to monitor renal function, have regular eye exams and monitor electrolytes respectively in patients being treated with lonafarnib.[17]

Dosage and Administration

The FDA recommended starting dose of lonafarnib is 115 mg/m^2 twice daily with morning and evening meals.[17] After four months, the dose can be increased to 150 mg/m^2 twice daily if tolerated by the patient. Lonafarnib is available as 50 mg and 75 mg capsules with each bottle containing 30 capsules per bottle. Capsules are recommended to be stored at temperatures between 20°C-25°C . If patients are unable to swallow capsules whole, contents can be mixed with Ora-Blend SF, Ora-Plus, orange juice or applesauce. Each mixture must be prepared at the time of administration for each dose and taken within ten minutes of mixing. Avoid consumption of grapefruit or Seville oranges when taking lonafarnib.[17]

Cost and availability

Lonafarnib is available as an investigational drug in ongoing trials with an estimated cost of $21,500 and $32,000 for 50 mg and 75 mg capsules for a 30-day supply per a November 23, 2020 press release. Eiger OneCare from Eiger Biopharmaceuticals will be the program involved in providing accessible and uninterrupted therapy through expansion of patient assistance programs, significantly reduced co-pays with patients and co-pay assistance programs.[23]

Clinical Implications

The primary strength of lonafarnib's approval was that its target population of HGPS patients had no approved treatment. This likely facilitated its approval from an observational survival cohort analysis of two phase II trials (ProLon1 and ProLon2), rather than a traditional phase III trial. ProLon1 and ProLon2 were single arm phase two trials both including a primary outcome associated with weight gain. The selection of weight gain is appropriate considering that HGPS patients have individualized weight gain thresholds that remain stable over time despite age or reaching puberty. Use of a single arm trial was supported with pretrial clinical data indicating that although interpatient variability is diverse, intra-patient variability in weight gain remains consistent after 2 years of age in patients HGPS.[24] This supported the use of using the same patient as their own control. ProLon2 used a composite of weight gain and reduction in echodensity to assess not only weight gain, but also improvements in cardiovascular comorbidities which are the most common cause of death among patients with HGPS and furthers strengthens findings.

While Gordon et al did find positive outcomes in patients with HGPS, there were limitations. In the two trials and the observational cohort survival analysis, the samples sizes were limited due to the study population estimated to total around 300 - 450 individuals worldwide. Of this population, 26 and 37 patients were included in ProLon1 and ProLon2 respectively, which might have also limited the feasibility of performing a Phase III trial at this time. The single arm study design provided no blinding, and the active comparator were the same patients before and after treatment. This does have a rationale as there is limited interpatient variability after two years of age for HGPS patients. However, lonafarnib is approved for children aged 12 years or younger and the primary studies had no inclusion of patients from this age group, leading to internal validity within this age group. In the observational survival cohort analysis conducted by Gordon et al based ProLon1 and ProLon2, matching was performed by age, sex, and continent of residency. No severity of disease was described which could have affected the validity of treated vs untreated groups despite being documented within the Progeria Research Foundation's Registries profile.[25] Having a contemporaneous historical control group instead of an active comparator during the clinical trial has been seen as an acceptable way for drug evaluation in other rare pediatric diseases but limitations of small sample sizes continue to be a concern for validity.

Due to the prevalence of HGPS being one in 20 million, Eiger BioPharmaceuticals, Inc obtained Orphan Drug Designation to ameliorate the costs associated with drug development, marketing and locating patients that may qualify for treatment with lonafarnib. At the time of this manuscript, Eiger Biopharmaceutical has identified 155 HGPS and 26 progeroid laminopathies worldwide. The manufacturer has set up patient assistance programs to provide personalized support to patients and care givers with co-pay assistance, specialized care mangers, reimbursement experts and other patient support services designed to assist patients seeking access to lonafarnib. Patients awaiting verification and authorizations can get up to a 60-day supply of lonafarnib free of charge and begin therapy immediately. This is especially important considering the average dose regimen of 175 mg twice daily for each patient averages around $650,000 per patient.

Lonafarnib is the first treatment approved for processing-deficient progeroid laminopathies with a heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations and reduce the risk of mortality in patients with HGPS. It should therefore assume frontline placement in the treatment of these issues. The side effect profile was well tolerated with no discontinuations due to toxicities, and generally any issues decreased over time with use. Trial data presented above indicates this medication can extend the life of patients for as much as 1.6 years. Oddly, the authors report an improvement on average of 2.5 years, which might have been from post clinical trial evaluation but this was not clear. Either way, adding extra years of life to a condition in whose patients have a life expectancy of 25 years is a step forward.

Another point of interest is other applications for lonafarnib include aging in general. Progerin is normally produced in the elderly population, therefore farnesyl inhibitors such as lonafarnib have the potential for improving cardiovascular outcomes, survival, aBMD and auditory function in this population. These other areas of use require further investigation.

References

Zokinvy® (lonafarnib) is the first FDA approved medication used to treat HGPS. Through clinical trials, improvements in survival, weight gain, cardiovascular, skeletal function and auditory outcomes in children with HGPS were seen in addition to an increase of up to 1.6 years of extra years of life and a reduction in 60% risk of mortality in patients with HGPS or progeroid laminopathies. Multiple gene therapies and cell modulating treatments are currently in development but are expected to take some time until they reach the market.25 With the development of new animal models and locating more patients with progeria, a greater understanding of progeria or HGPS with progeroid laminopathies can be made to further enhance research moving forward.

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Drug Updates: New Indications and Dosage Forms May 2021

Ferriprox® (deferiprone) Tablets and Oral Solution
New Indication: Treatment of transfusional iron overload due to Sickle Cell Disease

Keytruda® (pembrolizumab) Injection
New Indication: First-line treatment in locally advanced unresectable or metastatic HER2-Positive gastric or gastroesophageal junction adenocarcinoma in combination with trastuzumab

Opdivo® (nivolumab) Injection
New Indication: Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer in patients who have received neoadjuvant chemoradiotherapy

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