Efficacy and Safety of Lonafarnib For the Treatment of Progeria: A Systematic Review of Literature

PRO04

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BACKGROUND

- Progeria or Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare, genetic, premature aging disease in children.[1] The estimated incidence is 1 in 4 million births with over 350-400 children living with progeria worldwide currently[2,3]
- The median life expectancy of affected children is approximately 13 years;[4] the primary cause of premature death is cardiovascular complications such as myocardial infarction or stroke, due to severe progressive atherosclerosis[5]
- Currently, there are no approved treatments for progeria.[2] Lonafarnib, a farnesyltransferase inhibitor originally developed as a potential cancer treatment, is currently undergoing Phase II studies for the treatment of progeria.[6] However, lonafarnib has been granted Orphan Drug Designation for Progeria by the FDA[7] and has shown to be an effective treatment for the disease[8]
- To add to the existing evidence for progeria, this systematic review of the literature identified and summarized the studies that evaluated the efficacy and safety of lonafarnib for the treatment of progeria

METHODS

Search Strategy

- PubMed and Cochrane databases were searched on 18th October 2018 using keywords such as "progeria," "Hutchinson-Gilford Syndrome," "HGPS," and "premature aging syndrome." Detailed search strategy for these databases is presented in **Table 1**

Table 1: Search strategy for the PubMed database

S. No.	Query	Hits
	Pubmed Database	
1	Search progeria [MeSH Terms]	1384
2	Search Progeria	1916
3	Search "Hutchinson-Gilford Syndrome"	55
4	Search "Hutchinson Gilford Syndrome"	55
5	Search HGPS	428
6	Search "premature aging syndrome"	108
7	Search (#1 or #2 or #3 or #4 or #5 or #6)	2048
8	Search (Treatment OR "Farnesyltransferase Inhibitor" OR FTI OR Lonafarnib OR Pravastatin OR "Zoledronic Acid")	10247133
9	Search (#7) AND #8	407
10	Search (#7) AND #8 Filters: Humans	309
11	Search (#7) AND #8 Filters: Humans; English	285
	Cochrane Database	
1	MeSH descriptor: [Progeria] explode all trees	1
2	Progeria OR "Hutchinson-Gilford Syndrome" OR "Hutchinson Gilford Syndrome" OR HGPS OR " premature aging syndrome"	6
3	Treatment OR "Farnesyltransferase Inhibitor" OR FTI OR Lonafarnib OR Pravastatin OR "Zoledronic Acid"	564881
4	#1 or #2	6
5	#4 AND #3	4

Additionally, the titles of the abstracts submitted to the 8th International Scientific Workshop for the Progeria Research Foundation (2016) were searched for relevant studies. Searches were also performed at www.clinicaltrials.gov website and Google to identify any additional relevant studies using different combinations of keywords

Primary and Secondary Screening

- Two independent reviewers performed primary screening of the abstracts / titles and secondary screening of the full-texts, and a third independent reviewer resolved any discrepancy

Data Extraction and Quality Appraisal

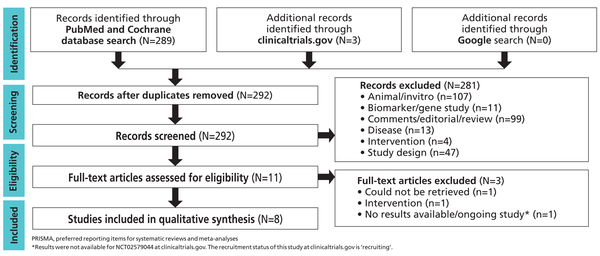
- Efficacy and safety data were extracted from the included studies after the secondary screening stage by a single reviewer
  - Efficacy outcomes included: the proportion of children who achieved a predefined rate of weight gain[9,10] or an improved echodensity,[9] changes in cardiovascular[9,10] and skeletal parameters,[9,10] neurologic signs and symptoms,[11] and mortality[2,12]
- The extracted data were checked against the original studies for data accuracy by another reviewer
- The quality of the included studies was assessed using *Downs and Black* checklist (27 questions assessing the quality of reporting, external and internal validity, selection bias, and power of the study)[13]

RESULTS

Searches and Screening (Figure 1)

- Searches identified 292 records after removing the duplicates (289 from PubMed and Cochrane database searches and three from www.clinicaltrials.gov website)

Figure 1: PRISMA diagram[18]



PRISMA, preferred reporting items for systematic reviews and meta-analyses
*Results were not available for NCT02579044 at clinicaltrials.gov. The recruitment status of this study at clinicaltrials.gov is 'recruiting'.

Study Characteristics

- All publications reported data from Phase II, single-arm studies of lonafarnib[2,9-12,14-16]
  - Literature searches did not yield any randomized controlled studies although searches were not restricted to any specific study design
- Two of the included publications (Gordon et al., 2018; Gordon et al., 2014)[2,12] reported results from survival analyses of treated study cohorts and untreated children
  - The treated cohort in Gordon et al., 2018[2] included children from two lonafarnib monotherapy studies (Prolon 1 and Prolon 2) and Gordon et al., 2014[12] included children from lonafarnib monotherapy and triple therapy studies
- Lonafarnib was administered as monotherapy in Gordon et al., 2012, Ullrich et al., 2013 and Gerhard-Herman et al., 2012[10,11,14,16] and as triple therapy with zoledronic acid and pravastatin in Gordon et al., 2016[9] (in both the initial feasibility study as well as the subsequent Phase II study)

Safety Outcomes (Table 2)

- The reported treatment-related Grade ≥ 3 adverse events (AEs) with lonafarnib monotherapy were diarrhea, vomiting, elevated transaminase levels, and fever[10]
- In triple therapy study, lonafarnib-related AEs were similar to previously reported AEs for lonafarnib,[17] and no pravastatin-related AEs were identified[9]
  - Overall, 62% of the children experienced zoledronicacid related post-infusion AEs[9]
- 36% of the children reported one or more serious adverse events (SAEs) following lonafarnib monotherapy.[14] The SAEs were hypokalemia, vomiting, bacterial infection, extremity-lower (gait/walking), stroke, subdural hematoma, and sensory neuropathy[14]
- No children withdrew from the monotherapy or triple therapy studies due to treatment-related toxicity[9-11]

Table 2: Safety outcomes

Study and/or NCT no.	Treatment/Comparisons	Any AEs, n or n (%)	SAEs
Gordon et al., 2012[10]; Ullrich et al., 2013[11]	Lonafarnib (N=26)	Grade ≥ 3 drug-related adverse-events: • Diarrhea (Grade 3: 3) • Vomiting (Grade 3: 2) • ↑ AST (Grade 3: 1) • Fever (Grade 4: 1) • ↑ ALT (Grade 3: 1)	NR
NCT00425607[16]; Gerhard-Herman 2012[16]	Lonafarnib (N=28)	• n=0	n=10 (36%)
Gordon et al., 2016[9]	Lonafarnib, pravastatin, zoledronic acid (N=37)	Grade ≥ 3 toxicities possibly related to lonafarnib, excluding zoledronic acid post-infusion toxicities: • Diarrhea [Grade 3: 1 (2.7%)] • ↑ALT [Grade 3: 4 (10.8%)] Toxicities post-zoledronic acid infusion (first 48 hrs), possibly related to zoledronic acid: • Hypocalcemia [Grade 3: 1 (2.7%)]	NR
NCT00879034[14]	Lonafarnib, zoledronic acid, pravastatin (N=5)	• N=0	n=0

Note: No safety outcomes were reported in Gorden et al., 2018[2] and Gorden et al., 2014[12]. AE, adverse events; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; hrs, hours; NR, not reported; SAEs, serious adverse events; ↓, low; ↑, elevated

Efficacy Outcomes (Table 3)

- Lonafarnib was efficacious in monotherapy studies[10,14]
  - 36% of the children achieved the primary outcome of successful rate of weight gain[10]
  - Cardiovascular parameters also improved in children treated with lonafarnib monotherapy compared with the pre-therapy values (significant decrease in PWVcf [P=0.0001] and echodensity of intima media [P=0.002], near adventitia [P=0.003] and deep adventitia [P=0.05])[10]
- Although no additional cardiovascular benefit was observed with triple therapy,[9] significant improvements over baseline in absolute and height-adjusted areal BMD (P<0.001), and radial volumetric BMD at all sites (for 4% site [P<0.001]; 20% site [P=0.006]; and 50% site [P<0.001]) were observed at the end of study[9]
  - 71% of children demonstrated improvements in weight gain or a decrease in echodensity with triple therapy, which was significantly higher than the prespecified goal of 4% children achieving improvements in weight gain or decrease in echodensity[9]
- Children treated with lonafarnib monotherapy had significantly lower mortality vs. matched untreated controls (hazard ratio [HR]: 0.12; 95% confidence interval [CI]: 0.01-0.93; P=0.04)[2]
- The combined cohort of children treated with lonafarnib (in monotherapy and triple therapy studies) was also associated with a significantly lower mortality rate vs. matched untreated cohort in Gordon et al., 2014[12] (HR: 0.15; 95% CI: 0.05 - 0.43)

Table 3: Key efficacy outcomes

Study Name [Study design]	Treatment/Comparisons	Efficacy Outcomes
Gordon et al., 2012 (NCT00916747)[10]; Ullrich et al., 2013[11] [single arm; open label]	Lonafarnib	• Wt gain*: 9/25 (36%) • Median (range) density of intima media, adventitia luminal near wall, and adventitia deep near wall decreased significantly at EOT vs study entry (P=0.002, P=0.0003, and P=0.05, respectively) • 4 children had history of stroke and 2 children experienced stroke during t/t • Avg. stroke freq./year decreased from 1.75 before t/t to 0.25 after t/t • TIA occurred in 3 children before t/t and none after t/t • Frequency of headache reduced from 15 to 7 children after t/t • Median (range) PWVcf decreased by 35% (-48% to +26%, P=0.0001)] • No changes in IR before and after t/t
	Age- and sex-matched cohort	• Median density of intima media and adventitia luminal near wall was significantly lower in age- and sex-matched cohort vs. HGPS children before t/t (P=0.002 and P=0.0004) but not after t/t (P=0.75 and P=0.46, respectively) • Median density of adventitia deep near wall was significantly higher in age- and sex-matched cohort vs. HGPS children after t/t (P=0.002)
NCT00425607[16]; Gerhard-Herman 2012[16] [single arm; open label]	Lonafarnib	• Wt gain*: 9/25 (36%) [95% CI: 18%-58%]
Gordon et al., 2016[9] (NCT00879034 and NCT00916747) [single arm; open label; comparison with monotherapy study group]	Lonafarnib, pravastatin, and zoledronic acid	• Wt gain or echodensity**: 22/31 (71%); P<0.001 vs. a pre-specified goal of 4% success rate • Wt gain success: 15/31 (48.4%) • Mean carotid artery echodensity of the intima-media, near or deep adventitia demonstrated no significant changes overall nor within treatment-naive and pretreated subgroups • Significant improvements in absolute and height-adjusted aBMD (P<0.001), and radial vBMD at all sites (P<0.001–0.006) at EOT vs. baseline in all children who received triple therapy • PWVcf: no significant changes overall nor within treatment-naive and treated subgroups • Rate of carotid artery plaque increased to 50% after t/t from 25% before t/t; P=0.001 • Rate of superficial femoral artery plaque increased to 13% after t/t from 0% before t/t; P=0.13 • Incidence of LVH increased to 25% after t/t from 3% before t/t; P=0.016 • Incidence of IR increased to 51.6% after t/t from 25.8% before t/t; P=0.02
Gordon et al., 2016[9] (NCT00879034 and NCT00916747) [single arm; open label; comparison with monotherapy study group]	Lonafarnib monotherapy study (NCT00425607) group	• Carotid artery echodensity significantly decreased with monotherapy (n=24; P<0.001) • Significant improvement from baseline was observed only for height-adjusted whole body aBMD (P=0.04) • PWVcf significantly improved with monotherapy (P=0.0025) • No change in rate of carotid and superficial femoral artery plaque and IR before and after t/t (P=1.00) • Incidence of LVH: 4% and 8% before and after t/t; P=0.38
NCT00879034[14]* ** [single arm; open label]	Lonafarnib, zoledronic acid, pravastatin	NR***
Gordon et al., 2018[2] (NCT00916747 was one of the included studies) [cohort study; NA; compared treated with contemporaneous untreated controls]	Full natural history cohort	• Mortality rate (eval. N=278): 124 (48.1%) [with follow-up starting at birth] • Mean and median survival ages: 14.5 and 14.6 years
	Treated children from Study 1	• Mortality rate (eval. N=27): 1 (3.7%) • Median follow-up time: 2.2 (IQR, 1.9-2.2) years • Conditional unadjusted HR for mortality rates of treated vs. untreated children: 0.12 (95% CI, 0.01-0.93; P=0.04)
	Matched untreated children for Study 1	• Mortality rate (eval. N=27): 9 (33.3%) • Median follow-up time: 2.1 (IQR, 1.0-2.2) years
	Treated children from Study 2	• Mortality rate (eval. N=36): 3 (8.3%) • Median follow-up time: 2.0 (IQR, 1.3-2.5) years • Treated vs. untreated, HR: 0.33; 95% CI, 0.07-1.59; P=0.17
	Matched untreated children for Study 2	• Mortality rate (eval. N=36): 8 (22.2%) • Median follow-up time: 1.9 (IQR, 1.0-2.4) years
	Treated from Study 1+2	• Mortality rate (eval. N=63): 4 (6.3%) • The random-effects meta-analytical conditional HR for treated vs. matched untreated children across the 2 studies: 0.23 (95% CI, 0.06-0.90; P=0.04). Median follow-up time was 2.2 (IQR, 1.4-2.3) years
	Matched untreated children for Study 1+2	• Mortality rate (eval. N=63): 17 (27.0%)
Gordon et al., 2014[12] NCT00425607, NCT00879034, NCT00916747) [cohort study; NA]	Full untreated cohort	• Mortality rate (eval. N=204): Mean and median survival was 14.6 and 14.5 years, respectively
	Matched untreated cohort	• Mortality rate (eval. N=43): 21 (48.8%) • HR: 0.15 (95% CI: 0.05-0.43); • Median follow-up from time of t/t initiation in both t/t groups untreated matched to treated): 5.3 years (quartiles of 3.3 – 5.5 years)
	Treated cohort	• Mortality rate (eval. N=43): 5 (11.6%) • K-M estimates demonstrated increased mortality for the matched untreated cohort over the treated cohort when follow-up begins at the age of t/t initiation for the treated pt in the matched pair (age-and sex-adjusted P<0.001)

*Primary outcome success was predefined as a 50% increase over pretherapy in the estimated rate of weight gain per annum or as a change from pretherapy weight loss to a statistically significant weight gain during the study. **Primary outcome success was defined as a composite of two components (weight gain or echodensity) relevant to disease in HGPS. The first was at least 10% increase over pre-therapy in the estimated annual rate of weight gain or a change from pre-therapy weight loss to statistically significant on-study weight gain. The second component of the primary outcome was a decrease in echobrightness of the internal carotid artery (ICA) adventitia, with quantification of echodensity as a measure of vascular tissue distensibility. A patient was considered improved if either the echodensity of the adventitia was reduced to ≤ 90% of the value at study entry or the patient-specific 10th percentile of the density of the adventitia was reduced to ≤ 90% of the value at study entry). ***This was an initial feasibility study of lonafarnib treatment for the first 4 weeks in five children and reported only adverse events and toxicity outcomes.

Note: All included studies were Phase II studies, except Gordon et al., 2018 and Gordon et al., 2014, which presented survival analyses results of these treated study cohorts and matched untreated cohorts. The assessed cardiovascular parameters included carotid-femoral pulse wave velocity, distal common carotid artery far wall intima-media thickness and plaque evaluations[10] and skeletal parameters included skeletal rigidity and areal bone mineral density.[9,10]

aBMD, areal bone mineral density; CI, confidence interval; eval., evaluable; EOT, end of therapy; HR, hazard ratio; IQR, interquartile range; IR, insulin resistance; K-M, Kaplan-Meier; LVH, left ventricular hypertrophy; NR, not reported; PWVcf, carotid-femoral pulse wave velocity; TIA, transient ischemic attack; t/t, treatment; vBMD, volumetric bone mineral density; Wt, weight

Critical Appraisal

- The quality of reporting of the studies as indicated by the responses for Questions 1 to 10 was good for all the studies (sum score ≥ 9 out of 11)
- The external validity (indicated by the responses for Questions 11 to 13) of the two publications,[2,12] which reported survival analyses results, was good (responses were 'yes' for all three questions)
- The internal validity of the studies was poor to moderate (indicated by the responses for Questions 14-26) as all studies had open-label and single-arm design
- For Question 27, which refers to the power of study, instead of rating based on range of study powers, we rated it as 1 or 0 based on whether or not power calculations were performed. Only two studies performed power calculations[9,10]

Figure 2: Critical appraisal of included studies

S. No.	Question	1	2	3	4	5	6
1	Is the hypothesis/aim/objective of the study clearly described?	🟡	🟡	🟡	🟡	🟡	🟡
2	Are the main outcomes to be measured clearly described in the introduction or methods section?	🟡	🟡	🟡	🟡	🟡	🟡
3	Are the characteristics of the participants included in the study clearly described?	🟡	🟡	🟡	🟡	🟡	🟡
4	Are the interventions of interest clearly described?	🟡	🟡	🟡	🟡	🟡	🟡
5	Are the distributions of principal confounders in each group of patients to be compared clearly described?	🟢	🟢	🟢	🟢	🟢	🟢
6	Are the main findings of the study clearly described?	🟡	🟡	🟡	🟡	🟡	🟡
7	Does the study provide estimates of the random variability in the data for the main outcomes?	🟡	🟡	🟡	🟡	🟡	🔴
8	Have all important adverse events that may be a consequence of the intervention been reported?	🟡	🟡	🔴	🟡	🟡	🟡
9	Have the characteristics of participants lost to follow-up been described?	🟡	🟡	🟡	🟡	🟡	🟡
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	🟡	🟡	🟡	🟡	🔴	🔴
11	Were the participants asked to participate in the study representative of the entire population from which they were recruited?	🔴	🔴	🟡	🟡	🔴	🔴
12	Were those participants who were prepared to participate representative of the entire population from which they were recruited?	🔴	🔴	🟡	🟡	🔴	🔴
13	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of participants receive?	🟡	🟡	🟡	🟡	🟡	🟡
14	Was an attempt made to blind study participants to the intervention they have received?	🔴	🔴	🔴	🔴	🔴	🔴
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	🔴	🔴	🔴	🔴	🔴	🔴
16	If any of the results of the study were based on "data dredging", was this made clear?	🔴	🟡	🟡	🟡	🟡	🟡
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of participants, or in case-control studies, is the time periodbetween the intervention and outcome the same for cases and controls?	🔴	🔴	🟡	🟡	🟡	🟡
18	Were the statistical tests used to assess the main outcomes appropriate?	🟡	🟡	🟡	🟡	🔴	🔴
19	Was compliance with the intervention(s) reliable?	🔴	🔴	🔴	🔴	🔴	🔴
20	Were the main outcome measures used accurate (valid and reliable)?	🟡	🟡	🟡	🟡	🔴	🔴
21	Were the participants in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	🟡	🟡	🟡	🟡	🟡	🟡
22	Were study participants in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	🔴	🔴	🟡	🟡	🟡	🟡
23	Were study participants randomised to intervention groups?	🔴	🔴	🔴	🔴	🔴	🔴
24	Was the randomised intervention assignment concealed from both participants and health care staff until recruitment was complete and irrevocable?	🔴	🔴	🔴	🔴	🔴	🔴
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	🟡	🟡	🟡	🟡	🔴	🔴
26	Were losses of participants to follow-up taken into account?	🟡	🟡	🟡	🟡	🟡	🟡
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	🟡	🟡	🔴	🔴	🔴	🔴

Note: 🔴 indicates a response score of 0 (lowest score) which means a 'no/unable to determine' response for a question (any question between 1-26); 🟡 indicates a response score of 1 (highest possible score for Question no. 1-4 and 6-26) which mean a 'yes' response for Question no. 1-4 and 6-26 and a 'partially yes' response for Question no. 5; 🟢 indicates a response score of 2 (highest possible score for Question no. 5) which indicates a 'yes' response for Question no. 5. 1. Gordon et al., 2012; Ullrich et al., 2013, 2. Gordon et al., 2016, 3. Gordon et al., 2018, 4. Gordon et al., 2014, 5. NCT00425607; Gerhard-Herman 2012, 6. NCT00879034

CONCLUSIONS

- Both lonafarnib monotherapy and triple-therapy were efficacious: a significantly greater proportion of children achieved the predefined rate of on-study weight gain with both lonafarnib monotherapy and triple therapy compared with the prespecified goals of success
- Lonafarnib monotherapy improved echodensity and survival rates
- Except for the increased BMD, none of the improvements (cardiovascular parameters: PWVcf and echodensity improvements, and insulin resistance) following triple therapy exceeded those observed with monotherapy
- Lonafarnib was generally well-tolerated in all the studies
- **Limitation:** All studies had single-arm design and small sample sizes (N<50)

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REFERENCES

1. Blagosklonny MV. Aging 2011;3(7):685-91.
2. Gordon LB, et al. JAMA 2018;319(16):1687-95.
3. Progeria Research Foundation. Available from: https://www.progeriaresearch.org/prf-by-the-numbers/
4. Piekarowicz K, et al. Cells 2019;8(2).
5. Gonzalo S, et al. Ageing Res Rev 2017;33:18-29.
6. Wang J, et al. Med Chem Comm 2017;8(5):841-54.
7. Biopharmaceuticals E. Available from: http://www.eigerbio.com/eiger-announces-breakthrough-therapy-designation-granted-by-fda-for-lonafarnib-for-treatment-of-hepatitis-delta-virus-hdv-infection/.
8. Progeria Research Foundation. Available from: https://www.progeriaresearch.org/first-ever-progeria-treatment/
9. Gordon LB, et al. Circulation 2016;134(2):114-25.
10. Gordon LB, et al. Proc Natl Acad Sci U S A 2012;109(41):16666-71.
11. Ullrich NJ, et al. Neurology 2013;81(5):427-30.
12. Gordon LB, et al. Circulation 2014;130(1):27-34.
13. Downs SH & Black N. J Epidemiol Community Health 1998;52(6):377-84.
14. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT00425607.
15. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT00879034.
16. Gerhard-Herman M, et al. Hypertension 2012;59(1):92-7.
17. Kieran MW, et al. J Clin Oncol 2007;25(21):3137-43.
18. Moher D, et al. PLoS Med 2009;6(7):e1000097.

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