NHS England Evidence Review:

Oral lonafarnib for the treatment of progeroid laminopathies

NHS England URN: 2402

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Oral lonafarnib for the treatment of progeroid laminopathies

Completed: August 2024

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of oral lonafarnib compared to no oral lonafarnib in the treatment of progeroid laminopathies.

Progeroid laminopathies are rare, fatal genetic conditions characterised by an appearance of accelerated aging in children. The majority of patients with progeroid laminopathies have the type, Hutchinson-Gilford Progeria Syndrome (HGPS), which can be referred to as classic or non-classic. This condition is also known as 'progeria'. HGPS is caused by a mutation in the gene called LMNA. This genetic mutation is sporadic and occurs without family history by a de novo mutation. The other types of progeroid laminopathies are even rarer than HGPS and are more heterogenous. They are caused by mutations in LMNA or proteins affecting the post-translational pathway of LMNA that result in progerin-like proteins. These farnesylated abnormal progerin-like proteins cause cellular damage.

Children with progeria begin to display many characteristics of accelerated aging within the first two years of life, including growth failure, loss of body fat and hair, aged-looking skin, stiffness of joints, hip dislocations, atherosclerosis, cardiovascular disease and stroke. Without treatment, children die of atherosclerosis (heart disease), living on average until teenage years.

The population covered by this review is people with a diagnosis, confirmed by phenotypic changes and on genetic testing, of HGPS or processing deficient progeroid laminopathy. There is no current commissioning policy or arrangement for these patients. Current standard of care involves clinical monitoring by local teams. Care is multi-disciplinary, with monitoring of growth and weight, bone density scans, dental reviews, cardiology reviews, hearing tests and psychological support due to visible differences. None of the current treatments involve reducing the accumulation of progerin and its expression.

Oral lonafarnib is a potent and specific inhibitor of farnesyltransferase, therefore blocking the farnesylation of progerin and reducing the accumulation of progerin and progerin-like proteins in the cells.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from oral lonafarnib more than others, and the ongoing schedules/doses used for oral lonafarnib and the concurrent therapies used in the included studies.

2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost effectiveness of oral lonafarnib compared to no oral lonafarnib in people with progeroid laminopathies. The searches for evidence published since 01 January 2012 were conducted on 24 May 2024 and identified 15 references. The titles and abstracts were screened, and 10 full text papers were obtained and assessed for relevance.

Six papers were identified for inclusion: two papers were non-comparative prospective, phase II single-arm clinical trials (Gordon et al 2012 and 2016), two papers were matched cohort studies (Gordon et al 2014 and 2018), one paper included three individual studies but has been treated as a cohort study in this evidence review (Gordon et al 2023), and one paper was a retrospective analysis of a phase II clinical trial (Ullrich et al 2013).

One prospective, phase II single-arm clinical trial (Gordon et al 2012) assessed the clinical effectiveness and safety of lonafarnib monotherapy for a minimum of two years in children with classic[1] Hutchinson-Gilford progeria syndrome (HGPS). One prospective, phase II single-arm clinical trial (Gordon et al 2016) assessed the clinical effectiveness and safety of triple therapy (i.e. lonafarnib in combination with a statin [i.e. pravastatin] and a bisphosphonate [i.e. zoledronic acid]) over 40 to 52 months in children with classic HGPS who had not previously received treatment with lonafarnib (i.e. treatment naïve; n=13) or who had received previous treatment with lonafarnib (i.e. non-treatment naïve; n=22).[2] Two matched cohort studies (Gordon et al 2014 and 2018) compared survival rates up to 2.2 years or at 5.3 years follow-up in patients with classic and non-classic[3] HGPS who had previously participated in one or more trials of lonafarnib monotherapy or triple therapy (i.e. treated patients) versus patients with HGPS who had not received previous lonafarnib treatment (i.e. untreated patients). One cohort study (Gordon et al 2023) assessed plasma progerin levels in patients with classic HGPS treated with lonafarnib monotherapy [trial 1], triple therapy [trial 2] or lonafarnib monotherapy [extension after triple therapy; trial 3] up to 10 years follow-up. One retrospective analysis of a phase II clinical trial (Ullrich et al 2013) assessed neurological outcomes in children with classic HGPS treated with lonafarnib monotherapy for a minimum of two years.

The included papers were published between 2012 and 2023. The papers included patients worldwide, but all patients were identified through the same source (i.e. The Progeria Research Foundation International Progeria Registry) and it was unclear how much overlap there may have been within and across the papers as patients may have participated in more than one contributing trial. No evidence relating to cost effectiveness was identified. No evidence was identified in relation to subgroups of interest.

In terms of clinical effectiveness:

Critical outcomes

- **Survival rate**
  - *Oral lonafarnib vs no oral lonafarnib:*
    Two matched cohort studies provided very low to low certainty evidence on survival rates, which showed a statistically significant increase in survival rates in patients

[1] HGPS can be referred to as classic and non-classic. Classic cases have the phenotype and are heterozygous c.1824C>T pathogenic variant in LMNA, and account for most cases of HGPS.
[2] Three children were taking statins at trial enrolment (it was unclear whether these children were lonafarnib treatment naïve or non-naïve), but none of the included children had previously received bisphosphonates.
[3] HGPS can be referred to as classic and non-classic. Non-classic cases have the phenotype and an autosomal dominant progerin-producing pathogenic variant in either the exon 11 splice junction or intron 11 of LMNA.

treated with lonafarnib monotherapy or triple therapy compared to untreated patients with HGPS up to 2.2 years follow-up (unadjusted HR 0.23 [95% CI 0.06 to 0.90]; p=0.04) and in patients treated with lonafarnib monotherapy (with or without previous triple therapy) compared to untreated patients with HGPS at 5.3 years follow-up (age- and sex-adjusted HR: 0.13 [95% CI 0.04 to 0.37]; p<0.001).

- *Oral lonafarnib vs no comparator:*

  No evidence was identified for this outcome.

- **Cardiovascular outcomes**
  - *Oral lonafarnib vs no oral lonafarnib:*

    No evidence was identified for this outcome.

  - *Oral lonafarnib vs no comparator:*

    Two prospective, phase II single-arm clinical trials provided very low certainty evidence on cardiovascular outcomes. One trial reported that carotid-femoral pulse wave velocity statistically significantly improved in children treated with lonafarnib monotherapy at 24 to 29 months follow-up (i.e. a median change of -4.5 m/second). By contrast, the second trial showed that treatment with triple therapy *"demonstrated no significant changes overall"* in carotid-femoral pulse wave velocity at 40 to 52 months follow-up.[4] The lonafarnib monotherapy trial showed statistically significant improvements in carotid artery wall echodensity at the intima media, adventitia luminal near wall and adventitia deep near wall. By contrast, the triple therapy trial reported *"no significant changes overall"* in echodensity of the deep common carotid artery adventitia.[3]

    The lonafarnib monotherapy trial reported that, overall, *"major ECG* [electrocardiogram] *abnormalities on 12-lead ECG did not change significantly"*, but no statistical measures were presented. The triple therapy trial reported that a statistically significant greater number of children had left ventricular hypertrophy after treatment (25% vs 3% at baseline) and carotid artery plaque after treatment (50% vs 5% at baseline). There was no statistically significant difference in the number of children who had superficial femoral artery plaque or in the number of children who had elevated systolic or diastolic blood pressure after triple therapy compared to before treatment.

- **Weight gain**
  - *Oral lonafarnib vs no oral lonafarnib:*

    No evidence was identified for this outcome.

  - *Oral lonafarnib vs no comparator:*

    Two prospective, phase II single-arm clinical trials provided very low certainty evidence on weight gain. One trial reported weight gain success (defined as a ≥50% increase in estimated annual rate of weight gain compared to pre-treatment, or change from pre-treatment weight loss to statistically significant on-treatment weight gain) in 36% children at 24 to 29 months follow-up on lonafarnib monotherapy. The second trial reported that at 40 to 52 months follow-up, 48.4% children receiving triple therapy achieved ≥10% increase in estimated annual rate of weight gain and 29% children achieved ≥50% increase in estimated annual rate of weight gain. Statistical measures were not reported in either trial.

Important outcomes

[4] The authors stated that there were no significant changes regardless of whether patients were treatment naïve or non-naïve at trial entry.

- **Neurological outcomes**
  - *Oral lonafarnib vs no oral lonafarnib:*

    No evidence was identified for this outcome.
  - *Oral lonafarnib vs no comparator:*

    One prospective, phase II single-arm clinical trial and one retrospective analysis of a phase II clinical trial provided very low certainty evidence on neurological outcomes. The retrospective analysis reported that clinical strokes were reduced from 15% of children before treatment to 7.69% of children at 24 to 29 months follow-up on lonafarnib monotherapy. The prospective, phase II single-arm clinical trial reported that 14% of children showed brain infarcts on magnetic resonance imaging before treatment with triple therapy compared to 8.1% of children who experienced new brain infarcts by 40 to 52 months follow-up on treatment. The retrospective analysis also reported that transient ischaemic attacks (TIAs) were reduced on lonafarnib monotherapy, with none of the children experiencing TIAs up to 24 to 29 months follow-up. The prospective, phase II single-arm clinical trial reported that by 40 to 52 months follow-up on triple therapy, 8.1% of children developed new TIAs (one of these patients also experienced a new infarct). No statistical measures were reported for any of these outcomes.

    The retrospective analysis reported a statistically significant reduction in the number of children experiencing headaches after treatment with lonafarnib monotherapy at 24 to 29 months follow-up compared to before treatment (28% vs 58%, respectively). The same trial also reported a 41% reduction in the frequency of headaches after treatment for those experiencing headaches, but no statistical measures were reported. The prospective, phase II single-arm clinical trial reported that the average frequency of headaches reduced from 1.2 per week in children at baseline to 0.81 per week at 40 to 52 months follow-up on triple therapy, but no statistical measures were reported. The retrospective analysis also reported a reduction in the number of children experiencing seizures from 15% before treatment with lonafarnib to *"no patient experienced recurrent or new onset of seizures during the study period",* but no statistical measures were reported.

- **Audiological outcomes**
  - *Oral lonafarnib vs no oral lonafarnib:*

    No evidence was identified for this outcome.
  - *Oral lonafarnib vs no comparator:*

    One prospective, phase II single-arm clinical trial provided very low certainty evidence on audiological outcomes. This trial reported that at 24 to 29 months follow-up on lonafarnib monotherapy, 44% of children showed a statistically significant ≥10 dB improvement in median low-frequency sensorineural hearing in the better-hearing and poorer-hearing ears. Median high-frequency sensorineural hearing remained unchanged in both ears for the five children who could be assessed. This trial also reported that *"no change was detected in low-frequency hearing in the poorer- or better-hearing ears"* in children who had conductive hearing loss at low frequency before treatment. For the seven children who had conductive hearing loss at high frequency before treatment, *"median hearing thresholds were significantly different for high-frequency conductive hearing in the poorer-hearing ear (p = 0.01) but not in the better-hearing ear"* at 24 to 29 months follow-up, but the direction of effect was not reported.

- **Bone structure**
  - *Oral lonafarnib vs no oral lonafarnib:*

No evidence was identified for this outcome.

- *Oral lonafarnib vs no comparator:*

  Two prospective, phase II single-arm clinical trials provided very low certainty evidence on bone structure. One trial reported that treatment with lonafarnib monotherapy resulted in statistically significant improvements in skeletal rigidity at 24 to 29 months follow-up. The second trial reported statistically significant improvements in bending, axial, and torsional rigidities at all radial sites (i.e. 4%, 20%, and 50%) at 40 to 52 months follow-up on treatment with triple therapy. The lonafarnib monotherapy trial also reported statistically significant improvements in the strength strain index (SSI) at the 20% and 66% radial sites, but no statistically significant difference at the 50% radial site.

  The lonafarnib monotherapy trial reported no statistically significant changes in areal bone mineral density (aBMD) for the whole body at 24 to 29 months follow-up. By contrast, the triple therapy trial showed statistically significant improvements in aBMD and height-adjusted Z-score for the whole body at 40 to 52 months. Similarly, the lonafarnib monotherapy trial reported no statistically significant change in aBMD for the lumbar spine, while the triple therapy trial showed statistically significant improvements in aBMD and height-adjusted Z-score for the spine. The lonafarnib monotherapy trial reported a statistically significant improvement in aBMD for the hip at 24 to 29 months follow-up, but radius volumetric bone mineral density (vBMD) remained normal at follow-up (no further details were provided). The triple therapy trial reported statistically significant improvements in vBMD at the 4%, 20%, and 50% radial sites.

  The lonafarnib monotherapy trial reported that fracture incidence reduced from 12% in children before treatment to 8% at 24 to 29 months follow-up, but statistical measures were not reported. The triple therapy trial reported that 15% of children with HGPS experienced appendicular fractures and 8% of children experienced skull fractures after treatment commenced, but the number of children with fractures before treatment was not reported and no statistical measures were presented. The same trial reported a statistically significant increase in extraskeletal calcifications (i.e. worsening) in children at 40 to 52 months follow-up compared to baseline (65.6% vs 34.4%, respectively. In addition, 8% of children experienced new hip dislocations and 8% of children experienced new shoulder dislocations after treatment commenced, but the number of dislocations before treatment was not reported and no statistical measures were presented.

- **Plasma progerin**
  - *Oral lonafarnib vs no oral lonafarnib:*

    No evidence was identified for this outcome.

  - *Oral lonafarnib vs no comparator:*

    One cohort study, including three individual trials, provided very low certainty evidence on plasma progerin. The cohort study reported a statistically significant decrease (i.e. improvement) in plasma progerin in patients during a four month dosing period using 115 mg/m^2 lonafarnib monotherapy (48% decrease) and at 2.2 years follow-up when the lonafarnib dose was 150 mg/m^2 (between 50% and 62% decrease) (trial 1). The cohort study also reported a statistically significant decrease in plasma progerin at six months follow-up on triple therapy (41% decrease), and at subsequent follow-up visits up to 3.5 years (between 35% and 47% decrease); and when triple therapy was discontinued and patients completed a lonafarnib monotherapy extension trial, there was no statistically significant difference in average plasma progerin between triple

therapy and lonafarnib monotherapy (trial 2). The cohort study also showed a statistically significant 36.7% decrease in plasma progerin at 2.4 years follow-up in patients treated with lonafarnib monotherapy (extension after triple therapy; trial 3).

In terms of safety:

- *Oral lonafarnib vs no oral lonafarnib:*
  No evidence was identified for this outcome.
- *Oral lonafarnib vs no comparator:*
  Two prospective, phase II single-arm clinical trials provided very low certainty evidence on the safety of lonafarnib monotherapy at 24 to 29 months follow-up or triple therapy at 40 to 52 months follow-up. Both trials indicated that treatments were generally well tolerated, but children did experience one or more toxicities possibly related to lonafarnib; these were mainly mild to moderate (i.e. grades 1 or 2), but a small proportion of children experienced grade 3 (i.e. severe) toxicities such as diarrhoea, vomiting, and hypokalaemia, and one child experienced a grade 4 (i.e. potentially life threatening) toxicity (i.e. fever). The triple therapy trial also reported that children experienced toxicities possibly related to zoledronic acid infusion, with most being grades 1 or 2, and only one child experiencing a grade 3 (i.e. severe) toxicity (i.e. hypocalcaemia). No pravastatin-related toxicities were identified. None of the children in either trial discontinued treatment due to toxicity.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified for subgroups.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The two matched cohort studies reported Kaplan-Meier survival estimates in treated versus untreated patients with HGPS. Due to the small number of patients included in the analyses, confidence intervals were wide, which increases the uncertainty in the findings. Both cohort studies combined data for treated patients from two different clinical trials each (lonafarnib monotherapy, triple therapy [i.e. lonafarnib in combination with a statin (pravastatin) and a bisphosphonate (zoledronic acid)], or lonafarnib monotherapy [extension after triple therapy]), none of these trials originally prespecified survival rates as an outcome due to the lack of an untreated comparator group. The authors of one matched cohort study stated that, although all treated patients were exposed to lonafarnib (and for the longest duration of time in most cases) the combination of different treatments from different trials (i.e. lonafarnib monotherapy or triple therapy) meant that it was not possible to distinguish the effect of each treatment on survival. Further research is therefore required to assess whether the addition of pravastatin and zoledronic acid provides additional benefit to lonafarnib alone.

One cohort study that provided evidence on plasma progerin levels in patients with HGPS, included data from three individual trials (trial 1: lonafarnib monotherapy; trial 2: triple therapy

then lonafarnib monotherapy extension; trial 3: lonafarnib monotherapy [extension after triple therapy]) but also combined results from all three trials in a subgroup of patients receiving long-term lonafarnib monotherapy. There may have been considerable overlap of patients within and across the three trials, and this should be taken into consideration when interpreting the findings. In addition, further validation of plasma progerin as a biomarker for HGPS is required, and further investigation into the effect of treatment on plasma progerin levels is also needed.

There was heterogeneity across the studies in terms of populations, with the papers including lonafarnib treatment naïve and/or non-treatment naïve patients. All of the included papers enrolled patients worldwide, but patients were identified through the same source (i.e. The Progeria Research Foundation International Progeria Registry) and there may have been considerable overlap in the patients reported in the various papers as they may have participated in one or more of the included trials. Sample sizes were small, ranging between 26 and 126 patients, which reflects the rarity of the condition.

The certainty in the clinical effectiveness evidence was very low to low for one critical outcome (survival rate), and very low for two critical outcomes (cardiovascular outcomes and weight gain). The certainty in the evidence was very low for all important outcomes (neurological outcomes, audiological outcomes, bone structure, and plasma progerin) and for safety. Factors reducing confidence in the outcomes reported in the papers include the very serious risk of bias due to, for example, recruitment methods and potential overlap of patients between the contributing trials, lack of statistical analysis or unclear statistical analysis (some papers stated that p-values did not reflect adjustment for multiple comparisons, and should be interpreted only descriptively) and incomplete outcome reporting (due to the inability of children to undergo certain outcome measures due to age or fragility). In addition, confidence in the findings was reduced because of serious indirectness, mainly due to the lack of a comparator in the two prospective, phase II single-arm clinical trials and retrospective analysis of a phase II clinical trial. The papers included in this evidence review reported various outcomes that were measured using objective methods, although the methods used to assess plasma progerin levels require further validation and additional research is needed to confirm the findings. Further limitations include the small number of patients included in the papers and the potential overlap within and across the papers as some patients may have participated in more than one of the contributing trials included in the various papers.

Conclusion

This review included two prospective, phase II single-arm clinical trials, two matched cohort studies, one cohort study (including three individual trials), and one retrospective analysis of a phase II clinical trial. The two matched cohort studies provided very low to low certainty evidence on one critical outcome (survival rates) in patients with HGPS treated with lonafarnib monotherapy (one study) or triple therapy (one study) compared to untreated patients with HGPS. The two prospective, phase II single-arm clinical trials, one cohort study, and one retrospective analysis provided very low certainty evidence on two critical outcomes (cardiovascular outcomes and weight gain), all the important outcomes (neurological outcomes, audiological outcomes, bone structure, and plasma progerin) and safety in patients with HGPS, following treatment with lonafarnib monotherapy and/or triple therapy.

The two matched cohort studies provided comparative evidence on survival rates in treated versus untreated patients with HGPS. Both studies showed statistically significant increases in survival rates in patients treated with lonafarnib monotherapy or triple therapy compared to untreated patients with HGPS at median 2.2 or 5.3 years follow-up, respectively.

The two prospective, phase II single-arm clinical trials (i.e. lonafarnib monotherapy trial and triple therapy trial) showed improvements in rate of weight gain and bone structure in a

proportion of children with HGPS. The lonafarnib monotherapy trial also reported improvements in audiological status in some children. Improvements in vascular stiffness were reported in the lonafarnib monotherapy trial, while the triple therapy trial reported a statistically significant increase (i.e. worsening) in left ventricular hypertrophy and carotid artery plaque, but no other significant changes in cardiovascular outcomes. The authors acknowledged that vascular plaques occur in untreated patients with HGPS and that the rates were increased with triple therapy, particularly in comparison to rates with monotherapy. It remains unclear whether the increase was due to the addition of zoledronic acid and further research is needed in this area. Two studies indicated that lonafarnib monotherapy or triple therapy reduced the prevalence of stroke or TIA and the prevalence and frequency of headaches, although statistical measures were only reported for prevalence of headaches, which showed a statistically significant reduction after treatment with lonafarnib monotherapy.

One cohort study (including three trials of lonafarnib monotherapy or triple therapy, reported individually and combined) provided evidence that plasma progerin levels decreased for lonafarnib monotherapy and triple therapy up to 10 years follow-up, but further research is needed and interpretation of findings should take into account the overlap between the trial populations.

The lonafarnib monotherapy and triple therapy trials reported that lonafarnib was generally well tolerated and none of the children discontinued lonafarnib due to adverse events. Most toxicities were mild to moderate (grades 1 or 2) and mainly related to gastrointestinal symptoms, although a small proportion of children experienced more severe toxicities (i.e. grade 3) such as diarrhoea, vomiting, and hypokalaemia, and one child experienced a potentially life threatening grade 4 toxicity (i.e. fever).

The evidence provided by the included studies should be considered as very low to low certainty due to the lack of a relevant treatment comparison group (with the exception of the studies reporting survival outcomes) and unclear statistical analyses or lack of statistical measures for some outcomes. Further limitations include the small number of patients included in the papers, the inclusion of treatment naïve and non-treatment naïve patients in different studies, and the potential overlap of some patients who may have participated in more than one of the contributing trials included in the various papers.

No evidence was available on cost effectiveness and no evidence was identified in relation to subgroups of interest.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with progeroid laminopathies, what is the clinical effectiveness of lonafarnib compared with no lonafarnib?
2. In people with progeroid laminopathies, what is the safety of lonafarnib compared with no lonafarnib?
3. In people with progeroid laminopathies, what is the cost effectiveness of lonafarnib compared with no lonafarnib?
4. From the evidence selected, are there any subgroups of patients that may benefit from lonafarnib more than the wider population of interest?
5. From the evidence selected what were the ongoing schedules/doses used for lonafarnib and what were the concurrent therapies?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 24 May 2024.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Six papers were identified for inclusion in this evidence review (Gordon et al 2012, 2014, 2016, 2018 and 2023, Ullrich et al 2013). Two papers were non-comparative prospective, phase II single-arm clinical trials (Gordon et al 2012 and 2016) that assessed the clinical effectiveness and safety of lonafarnib monotherapy (Gordon et al 2012) or triple therapy (i.e. lonafarnib in combination with a statin [i.e. pravastatin] and a bisphosphonate [i.e. zoledronic acid]) (Gordon et al 2016) in patients with classic[5] Hutchinson-Gilford progeria syndrome (HGPS). Two papers were matched cohort studies (Gordon et al 2014 and 2018) that compared survival rates up to 2.2 years or at 5.3 years follow-up in patients with HGPS who had previously participated in one or more trials of lonafarnib monotherapy or triple therapy (i.e. treated patients) versus patients with HGPS who had not previously received lonafarnib treatment (i.e. untreated patients). One paper was a cohort study (Gordon et al 2023) that assessed plasma progerin levels in patients with HGPS who had participated in one or more of three trials: lonafarnib monotherapy [trial 1], triple therapy [trial 2] or lonafarnib monotherapy [extension after triple therapy; trial 3]. One paper (Ullrich et al 2013) was a retrospective analysis of a phase II clinical trial assessing neurological outcomes in children with HGPS treated with lonafarnib monotherapy for a minimum of two years. It was unclear how much overlap there was between the patients enrolled in the included papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and the included patients may have participated in one or more of the trials.

No cost effectiveness studies were identified for inclusion in this review. No evidence on subgroups of interest was identified.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Gordon et al 2012
 	
Prospective, phase II single-arm clinical trial
 	
16 countries (not specified)
	n=26 children[a, b] with genetically confirmed classic HGPS
	
	Lonafarnib: n=26
	
	Age (years), mean (SD; range)
	7.0 (3.0; 3.0 to 16)
	
	Sex, n (%)
	
	Male: 11 (44)
	
	Female: 14 (56)
	
	No relevant subgroups reported
		Intervention
		
		Lonafarnib capsule or liquid suspension every 12 (± 2) hours: initial dose 115 mg/m^2 increased to 150 mg/m^2 after an adjustment period of at least 4 months
		
		Comparison
		
		None (the included patients acted as their own control by comparing data on treatment with lonafarnib monotherapy to 12 months before treatment)
		
		5 children received recombinant growth hormone therapy; 2 children received antihypertensive treatment
		
		Treatment duration: 24 to 29 months
			Follow-up: 24 to 29 months
			
			Critical outcomes
			
			• Cardiovascular outcomes
			  • Carotid-femoral pulse wave velocity
			  • Carotid artery echodensity
			  • Frequency of ECG abnormalities [ECG changes consistent with LVH, isolated non-specific ST-T wave changes]
			• Weight gain
			  • Weight gain success (defined as ≥50% increase in estimated annual rate of weight gain or change in pre-treatment weight loss to a statistically significant weight gain at end of treatment)

[5] HGPS can be referred to as classic and non-classic. Classic cases have the phenotype and are heterozygous c.1824C>T pathogenic variant in LMNA, and account for most cases of HGPS. Non-classic cases have the phenotype and an autosomal dominant progerin-producing pathogenic variant in either the exon 11 splice junction or intron 11 of LMNA.

Study	Population	Intervention and comparison	Outcomes reported

			Important outcomes
			• Audiological outcomes
			  • Median sensorineural hearing
			  • Conductive hearing loss
			• Bone structure
			  • Skeletal rigidity
			  • % increase or decrease in SSI
			  • aBMD
			  • vBMD
			  • Fracture incidence
			• Safety
			  • Toxicity
			  • Toxicity leading to discontinuation

Gordon et al 2014
 	
Matched cohort study
 	
Africa, Asia, Europe, North and South America
	n=86 patients with clinically confirmed classic and non-classic HGPS by phenotype
	
	Lonafarnib monotherapy or triple therapy (lonafarnib + pravastatin + zoledronic acid): n=43
	
	Untreated: n=43
	
	<u>Age (years), range</u>
	
	Treated: 5.2 to 20.45
	
	Untreated: NR
	
	<u>Sex (male), n (%)</u>
	
	Treated: 17 (39.5)
	
	Untreated: 17 (39.5)
	
	<u>Known genotype, n (%)</u>
	
	Treated: 43 (100)
	
	Untreated: 24 (55.8)
	
	No relevant subgroups reported[6]
		Intervention
		
		Previous lonafarnib monotherapy or triple therapy (i.e. lonafarnib, pravastatin and zoledronic acid combined), no further details were reported
		
		Comparison
		
		No treatment (i.e. patients not previously treated with lonafarnib)
		
		5 patients were receiving recombinant growth hormones, but no other details on concomitant treatments were provided
		
		Treatment duration: Not reported
			Median (IQR) follow-up: 5.3 years (3.3 to 5.5)
			
			Critical outcomes
			• Survival rate
			  • Number of deaths
			  • Kaplan-Meier survival estimates

Gordon et al 2016
 	
Prospective, phase II single-arm clinical trial
 	
23 countries (not specified)
	n=37 patients with genetically confirmed classic HGPS
	
	Lonafarnib + pravastatin + zoledronic acid: n=37
	
	<u>Age (years), mean (SD)</u>
	
	8.0 (4.4)
	
	<u>Sex, n (%)</u>
	
	Male: 14 (40.0)
	
	No relevant subgroups reported
		Intervention
		
		Lonafarnib capsule or liquid suspension every 12 (± 2) hours: 150 mg/m^2 but if not tolerated, dose reductions to 115 mg/^{2} were permitted and then increased back to 150 mg/m^2
		
		Oral pravastatin once every 24 (± 2) hours: 5 mg for patients weighing <10 kg, 10 mg for patients weighing >10 kg
		
		IV zoledronic acid: initial infusion 0.0125 mg/kg body weight, then
			Follow-up: 40 to 52 months
			
			Critical outcomes
			• Cardiovascular outcomes
			  • Carotid-femoral pulse wave velocity
			  • Carotid artery adventitia echodensity
			  • Prevalence of carotid artery plaque
			  • Prevalence of superficial femoral artery plaque
			  • Prevalence of LVH
			  • Prevalence of elevated SBP and DBP

[6] Gordon et al (2014) did not present data separately for patients with classic versus non-classic forms of HGPS.

Study	Population	Intervention and comparison	Outcomes reported

		increased to 0.05 mg/kg body weight (infusions over 30 minutes at baseline, at 6, 12, 18 months and end of trial)
		Comparison
		None (the included patients acted as their own control by comparing data on treatment with triple therapy to before treatment)
		Oral calcium (500 mg) and vitamin D (1,000 IU) were supplemented daily, with calcium discontinued after 12 months
		Treatment duration: 40 to 52 months
			• Weight gain
			  • 10% and 50% increase in estimated annual rate of weight gain or change in pre-treatment weight loss to a statistically significant weight gain at end of treatment
			Important outcomes
			• Neurological outcomes
			  • Brain infarcts on MRI
			  • Frequency of TIA
			  • Frequency of headache
			• Bone structure
			  • Load bearing capacity
			  • aBMD
			  • vBMD
			  • Extraskeletal calcifications
			  • Calcific skin eruptions
			  • Number of fractures
			  • Number of new dislocations
			• Safety
			  • Lonafarnib toxicity
			  • Post-zoledronic acid infusion toxicity
			  • Triple therapy toxicity leading to discontinuation

Gordon et al 2018
Matched cohort study
Africa, Asia, Europe, North and South America
	n=126 patients with clinically confirmed classic and non-classic HGPS by phenotype
	Combined trials 1 and 2
	Lonafarnib: n=63
	Untreated: n=63
	Individual trials
	Trial 1 (treated [n=27] vs untreated [n=27] patients); trial 2 (treated [n=36] vs untreated [n=36] patients)
	Age (years), mean (SD)
	Treated: 6.9 (3.7)
	Untreated: 6.9 (3.7)
	Sex (male), n (%)
	Treated: 33 (52.4)
	Untreated: 33 (52.4)
	Known genotype, n (%)
	Treated: 62 (98.4)
	Untreated: 34 (54.0)
		Intervention
		Trial 1: lonafarnib every 12 (± 2) hours: initial dose 115 mg/m^2 increased to 150 mg/m^2 after an adjustment period of at least 4 months
		Trial 2: lonafarnib 150 mg/m^2 (after treatment of lonafarnib combined with pravastatin and zoledronic acid)
		Comparison
		Untreated (i.e. patients who had not previously received any clinical trial treatment)
		Details on concomitant treatments were not provided
		Treatment duration: Not reported
			Median (IQR) follow-up (years):
			Treated: 2.2 (1.6 to 2.3)
			Untreated: 1.7 (0.6 to 2.2)
			Critical outcomes
			• Survival rate
			  • Number of deaths
			  • Kaplan-Meier survival estimates

Study	Population	Intervention and comparison	Outcomes reported
	No relevant subgroups reported		
Gordon et al 2023 Cohort study Countries not stated	n=64 patients with genetically confirmed classic HGPS Trial 1 (lonafarnib monotherapy): n=25 Trial 2 (triple therapy): n=13, then n=10 switched to lonafarnib monotherapy Trial 3 (lonafarnib monotherapy after triple therapy): n=26 Baseline plasma progerin (pg/mL), mean (SD; median) Trial 1 (lonafarnib monotherapy) (n=26): 27,572 (7542; 27,669) Trial 2 (triple therapy) (n=13): 31,464 (16,958; 29,787) Trial 3 (lonafarnib monotherapy after triple therapy) (n=35): 38,154 (11,546; 37,225) No relevant subgroups reported, but plasma progerin changes on long-term lonafarnib treatment were reported for patients who had participated in trials 1, 2 and 3 (n=13)[d]	**Intervention** Trial 1: oral lonafarnib capsule or liquid suspension twice daily; initial dose 115 mg/m^2 increased to 150 mg/m^2 if well tolerated after at least 4 months Trial 2 (triple therapy): oral lonafarnib capsule or liquid suspension twice daily at dose 150mg/m^2, plus oral pravastatin (5 mg or 10 mg) and IV zoledronic acid (00125 mg/kg body weight initially, then 0.05 mg/kg every 6 months) Trial 3: oral lonafarnib capsule or liquid suspension twice daily at dose 150mg/m^2 **Comparison** None (the included patients acted as their own control by comparing data on treatment to before treatment)[c] Details on other concomitant treatments were not provided Treatment duration: 2.2 to 7.6 years (long-term subgroup analysis: 9.8 years (range 9.0 to 10.3)	Follow-up duration: 2.2 to 7.6 years (long-term subgroup analysis: 9.8 years (range 9.0 to 10.3) **Important outcomes** • Plasma progerin • Progerin changes from baseline [reported separately for trials 1, 2 and 3]

Ullrich et al 2012
 	
Retrospective analysis of a phase II clinical trial
 	
16 countries (not specified)
	n=26 children[a, b] with genetically confirmed classic HGPS
	
	Lonafarnib: n=26
	
	Sex, n (%)
	
	Male: 10 (38.5%)
	
	Female: 16 (61.5%)
	
	Age (years), mean (range)
	
	7.6 (3.0 to 16)
	
	No relevant subgroups reported
		Intervention
		
		Lonafarnib capsule or liquid suspension every 12 hours: initial dose 115 mg/m^2 increased to 150 mg/m^2 after an adjustment period of at least 4 months
		
		Comparison
		
		None (the included patients acted as their own control by comparing data on treatment with lonafarnib monotherapy to 12 months before treatment)
		
		17 (65%) children were receiving daily aspirin (average daily dose of 5.8 mg/kg); 3 (11.5%) were taking ≥1 antiplatelet or anticoagulant or acetazolamide; 6 (23.1%) children each were taking cholesterol-lowering
			Follow-up: 24 to 29 months
			
			Important Outcomes
			
			• Neurological outcomes
			  • Number of children experiencing strokes
			  • Average stroke frequency per year
			  • Number of children experiencing TIA
			  • Number of children experiencing headaches
			  • Average headache frequency per week
			  • Recurrent or new onset of seizures

Study	Population	Intervention and comparison	Outcomes reported
		treatments or recombinant human growth hormones Treatment duration: 24 to 29 months	

Abbreviations
aBMD: areal bone mineral density; ECG: electrocardiogram; HGPS: Hutchinson-Gilford progeria syndrome; LVH: left ventricular hypertrophy; m: metre; mg: milligram; n: number; SD: standard deviation; SSI: strength strain index; vBMD: volumetric bone mineral density.

Footnotes
a. Twenty-six children had baseline data, and 25 of the 26 completed at least two years of lonafarnib treatment; one child with a history of strokes died of a stroke after five months on the trial.
b. Although Ullrich et al (2012) mention the main publication (Gordon et al 2012) and the number of children included in both publications was the same (i.e. 26), there were differences in the baseline characteristics (i.e. age and sex) and it was therefore unclear how much overlap there was across the two populations.
c. The paper compared mean plasma progerin in HGPS patients versus non-HGPS patients, but these data are not reported in this evidence review.
d. Patients included in the longitudinal analyses, were required to have provided a baseline and end-of-trial on-treatment plasma sample.

5. Results

In people with progeroid laminopathies, what is the clinical effectiveness and safety of lonafarnib compared with no lonafarnib?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Survival rate **Certainty of evidence:** Very low to low	This outcome is important to patients because it reflects how long people live with treatment, although it does not take the cause of death into account or provide information about their health and wellbeing during that time. Two matched cohort studies provided evidence on survival rates in patients with genetically confirmed classic and non-classic HGPS. Both papers combined patients from two different trials and compared survival rates to matched cohorts of untreated patients with HGPS[7]. One paper combined patients from a trial assessing lonafarnib monotherapy with patients from a trial of triple therapy[8]. The second paper combined patients from a trial of lonafarnib monotherapy with patients from a lonafarnib monotherapy extension study (after triple therapy). It was unclear how much overlap there was between the treated patients in the contributing trials in the two cohort studies; all patients were identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and may have participated in more than one of the contributing trials reported in the cohort studies. Kaplan-Meier survival estimate *Oral lonafarnib vs no oral lonafarnib* **At median follow-up of 2.2 years (treated patients) and 1.7 years (untreated patients** • One matched cohort study (Gordon et al 2018; n=126) reported four deaths (6.3%)[9] in patients with HGPS treated in the lonafarnib monotherapy or triple therapy trials compared to 17 deaths (27%)[10] in untreated patients with HGPS at 2.2 years and 1.7 years follow-up, respectively. This represented a *statistically significant* greater survival rate in treated patients: unadjusted HR 0.23 (95% CI 0.06 to 0.90); p=0.04. **(VERY LOW)** **At median 5.3 years follow-up (when follow-up began at age of treatment initiation)** • One matched cohort study (Gordon et al 2014; n=86) reported five deaths (11.6%)[11] in patients with HGPS treated in the lonafarnib monotherapy or lonafarnib monotherapy extension trials compared to 21 deaths (48.8%)[12] in untreated patients with HGPS at 5.3 years follow-up. This represented a *statistically significant* greater survival rate in treated patients: age- and sex-

[7] Only 55.8% of untreated patients had known genotype (with most patients having classic HGPS).
[8] Lonafarnib in combination with pravastatin and zoledronic acid. Twenty four of 37 patients had previously participated in the lonafarnib monotherapy trial and had received continuous lonafarnib treatment for at least two years prior to enrolment in the triple therapy trial.
[9] Three (75%) patients died due to heart failure, one (25%) due to stroke.
[10] The authors did not state the cause of death.
[11] Three (60%) patients died from cardiovascular failure, one (20%) from head injury, and one (20%) from stroke.
[12] Cause of death in these patients was unclear as only deaths for the whole untreated population were reported (i.e. cardiovascular failure, head injury or trauma, stroke, respiratory infection superimposed on cardiovascular disease, and complications due to anaesthesia during surgery).

Outcome	Evidence statement
	adjusted HR: 0.13 (95% CI 0.04 to 0.37)[13] i.e. an increase in mean survival of 1.6 years (95% CI 0.8 to 2.4); p<0.001. **(LOW)** *Oral lonafarnib vs no comparator* No evidence was identified for this outcome. **Oral lonafarnib vs no oral lonafarnib:** **Two matched cohort studies provided very low to low certainty evidence that survival rates statistically significantly increased in patients treated with lonafarnib monotherapy or triple therapy compared to untreated patients with HGPS up to 2.2 years follow-up (unadjusted HR 0.23 [95% CI 0.06 to 0.90]; p=0.04) and in patients treated with lonafarnib monotherapy (with or without previous triple therapy) compared to untreated patients with HGPS at 5.3 years follow-up (age- and sex-adjusted HR: 0.13 [95% CI 0.04 to 0.37]; p<0.001).** **Oral lonafarnib vs no comparator:** **No evidence was identified for this outcome.**
Cardiovascular outcomes **Certainty of evidence:** Very low	This outcome is important to patients, as the majority of deaths in this condition are caused by cardiovascular complications (myocardial infarctions and heart failure), therefore, an improvement in cardiovascular changes could improve mortality and morbidity. Two prospective, phase II single-arm clinical trials provided non-comparative evidence on cardiovascular outcomes in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[14] (one trial). It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some children may have participated in both trials. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* Carotid femoral pulse wave velocity (m/second)[15] **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=18[16]) reported a median change from baseline in carotid-femoral pulse wave velocity of -4.5 m/second (range -7.4 to 1.9) (i.e. improvement) in children with HGPS treated with lonafarnib monotherapy at 24 to 29 months follow-up. The authors stated that carotid-femoral pulse wave velocity *"decreased by a median of 35% (range: 48% decrease to 26% increase)*". The change from baseline was *statistically significant* (p=0.0001). **(VERY LOW)** **At 40 to 52 months follow-up**

[13] The authors also reported outcomes for Kaplan-Meier estimates for age-, sex-, and continent-adjusted HRs; when follow-up began at birth with patients placed at risk at the age of treatment initiation; and time-dependent analyses in patients born after 1991. Findings remained statistically significant for all analyses, indicating increased survival in treated patients.
[14] Lonafarnib in combination with pravastatin and zoledronic acid. Twenty four of 37 patients had previously participated in the lonafarnib monotherapy trial and had received continuous lonafarnib treatment for at least two years prior to enrolment in the triple therapy trial.
[15] Carotid-femoral pulse wave velocity was measured using the propagation time of the pressure pulse from the carotid to femoral arteries.
[16] The authors stated that carotid-femoral pulse wave velocity was 3.5 times greater than published paediatric normal values, indicating high arterial stiffness and low distensibility.

Outcome	Evidence statement
	• One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23[17]) reported that treatment with triple therapy *"demonstrated no significant changes overall"* in carotid-femoral pulse wave velocity in children with HGPS at 40 to 52 months follow-up; p≤0.05. **(VERY LOW)** Carotid artery density by ultrasound (percentile 50) **At 24 to 29 months follow-up** Carotid artery intima media • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=22) reported improvements in carotid artery wall echodensity at the intima media in children with HGPS at 24 to 29 months on lonafarnib monotherapy compared to baseline (median: 72.0 [range 2.0 to 140.0] vs 87.0 [range 15.0 to 242.0], respectively). The difference compared to baseline was *statistically significant*; p=0.002. **(VERY LOW)** Carotid artery adventitia luminal near wall • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=22) reported improvements in carotid artery wall echodensity at the adventitia luminal near wall in children with HGPS at 24 to 29 months on lonafarnib monotherapy (median: 170.0 [range 70.0 to 252.0] vs 228.0 [range 61.0 to 254.0], respectively); the difference was *statistically significant* (p=0.003). **(VERY LOW)** Carotid artery adventitia deep near wall • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=22) reported improvements in carotid artery wall echodensity at the adventitia deep near wall in children with HGPS at 24 to 29 months on lonafarnib monotherapy (median: 121.0 [range: 12.0 to 215.0] vs 167.0 [range 30.0 to 254.0], respectively); the difference was *statistically significant* (p=0.05). **(VERY LOW)** Carotid artery adventitia echodensity success achieved[18] **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=35[19]) reported that 11 (31.4%) children with HGPS treated with triple therapy successfully achieved a reduction (i.e. improvement) in echodensity of the deep common carotid artery adventitia at 40 to 52 months follow-up. Statistical measures were not reported, but the authors stated that *"mean carotid artery wall echodensity of the intima-media, near or deep adventitia…demonstrated no significant changes overall"*. **(VERY LOW)** Frequency of ECG abnormalities **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported that eight (31%) children with HGPS experienced ECG abnormalities before treatment with lonafarnib monotherapy compared to four (16%) children at 24 to 29 months follow-up on treatment. Statistical measures were not reported, but the authors stated that *"major ECG abnormalities on 12-lead ECG did not change significantly during the course of the study"*. **(VERY LOW)**

[17] Nine patients had malfunction with ECG-to-ultrasound communication and were not included in the analysis.
[18] A patient was considered improved in echodensity of the deep common carotid artery adventitia 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.
[19] Echodensity analyses included two patients who did not have follow-up echodensity measurements and were counted as echodensity failures.

Outcome	Evidence statement
	ECG changes consistent with LVH (with or without LV strain patterns) **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported that three (12%) children with HGPS who were treated with lonafarnib monotherapy showed ECG changes consistent with LVH at 24 to 29 months follow-up. The authors also reported that *"borderline LVH was identified at entry or transiently during the study in four additional patients (15%). Atrial enlargement was noted in one patient with a history of supraventricular tachycardia"*. No statistical measures were reported. **(VERY LOW)** Prevalence of LVH **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32) reported that one (3%) child with HGPS had LVH before treatment with triple therapy compared to eight (25%) children[20] at 40 to 52 months on treatment; the difference was *statistically significant* (p=0.016). **(VERY LOW)** Isolated nonspecific ST-T wave changes **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported that ECG abnormalities reflecting isolated ST-T wave changes, which were identified transiently in four (15%) children with HGPS and consistently in one (3.8%) child[21] with HGPS at 24 to 29 months on lonafarnib monotherapy. Figures were not reported for patients prior to treatment. The authors also reported that *"Prolonged QT intervals (QTc > 0.44 s) were observed only transiently in 4 of 26 patients (15%), although none had QTc >0.45 s or demonstrated persistent QTc prolongation. Two patients had prior history of supraventricular tachycardia before entry, and none had uncontrolled rhythm disturbance identified during the course of study"*. Statistical measures were not reported. **(VERY LOW)** Prevalence of carotid artery plaque **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32 or unclear[22]) reported an increase in the prevalence of carotid artery plaque in children with HGPS treated with triple therapy from baseline (5%)[22] to 40 to 52 months follow-up (50%)[23]; the difference compared to baseline was *statistically significant*; p<0.001. **(VERY LOW)** Prevalence of superficial femoral artery plaque **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32 or unclear) reported that there was *no statistically significant* difference in the prevalence of superficial femoral artery plaque in children with HGPS before treatment with triple therapy compared to 40 to 52 months follow-up (0%[24] vs 13%) respectively; p=0.13. **(VERY LOW)**

[20] Including the one patient who had LVH before treatment.
[21] This patient had no other abnormalities.
[22] There was a discrepancy in the number of patients reported in the table, which indicated n=32, but this did not reflect the n=2 [5%] stated.
[23] There was a discrepancy in the numbers reported in the text (n=14) and table (n=16) and we have reported the number stated in the table.
[24] The authors stated that "5 patients were too young to tolerate baseline assessment. End-of-therapy assessment showed no plaque; therefore baseline was assumed negative".

Outcome	Evidence statement
	Prevalence of elevated SBP for chronologic age[25] **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32) reported that there was *no statistically significant* difference in the number of children with HGPS who had elevated SBP before treatment with triple therapy compared to 40 to 52 months follow-up on treatment (19% vs 3%) respectively; p=0.125. **(VERY LOW)** Prevalence of elevated DBP for chronologic age[25] **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32) reported that there was *no statistically significant* difference in the number of children with HGPS who had elevated DBP before treatment with triple therapy compared to 40 to 52 months follow-up (28% vs 6%) respectively; p=0.065. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **Two prospective, phase II single-arm clinical trials provided very low certainty evidence on cardiovascular outcomes. One trial reported that carotid-femoral pulse wave velocity was *statistically significantly* improved (change of -4.5 m/second) in children with HGPS treated with lonafarnib monotherapy at 24 to 29 months follow-up. By contrast, the second trial showed that treatment with triple therapy *"demonstrated no significant changes overall"* on carotid-femoral pulse wave velocity at 40 to 52 months follow-up. The lonafarnib monotherapy trial reported *statistically significant* improvements in carotid artery wall echodensity at the intima media, adventitia luminal near wall and adventitia deep near wall at 24 to 29 months follow-up. By contrast, the triple therapy trial reported *"no significant changes overall"* in echodensity of the deep common carotid artery adventitia at 40 to 52 months follow-up.** **The lonafarnib monotherapy trial reported that, overall, *"major ECG abnormalities on 12-lead ECG did not change significantly"* at 24 to 29 months follow-up, but no statistical measures were reported. The triple therapy trial reported a *statistically significant* greater number of children with HGPS who had LVH at 40 to 52 months follow-up compared to baseline (25% vs 3%, respectively) and a *statistically significant* greater prevalence of carotid artery plaque at 40 to 52 months follow-up compared to before treatment (50% vs 5%, respectively), but there was *no statistically significantly* difference in the prevalence of superficial femoral artery plaque or in the number of children who had elevated SBP or DBP at 40 to 52 months follow-up compared to before treatment.**
Weight gain **Certainty of evidence:** Very low	This is important to patients because it reflects an improvement in their nutritional status, growth and can result in changes in their appearance that they might find valuable. It also provides physical evidence of treatment response. Two prospective, phase II single-arm clinical trials provided non-comparative evidence on weight gain in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[26] (one trial). It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation

[25] Elevated blood pressure was defined as at or above the 95th percentile.
[26] Lonafarnib in combination with pravastatin and zoledronic acid.

Outcome	Evidence statement
	International Progeria Registry) and some children may have participated in both trials. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* <u>Weight gain success (defined as >50% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss to a statistically significant weight gain)</u>[27] **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=25) reported that weight gain success was achieved in 9 (36%) children with HGPS but not achieved in 16 (64%)[28] children with HGPS at 24 to 29 months follow-up on lonafarnib monotherapy. The median rate of weight gain in children who achieved weight gain success increased from 0.04 kg/year [range −0.55 to 0.18] at baseline to 0.52 kg/year [range 0.14 to 1.33] at 24 to 29 months follow-up on lonafarnib monotherapy.[29] For children who did not achieve weight gain success, the median rate of weight gain decreased from 0.57 kg/year [range 0.14 to 1.69] at baseline to 0.31 kg/year [range -0.53 to 0.70] at 24 to 29 months follow-up.[30] No statistical measures were reported for any outcome. **(VERY LOW)** <u>≥10% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss to a statistically significant weight gain</u>[31] **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=31[32]) reported that at 40 to 52 months follow-up, a ≥10% increase in estimated annual rate of weight gain was achieved in 15 (48.4%) children receiving triple therapy. **(VERY LOW)** <u>≥50% increase in estimated annual rate of weight gain compared to pre-treatment</u> **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=31[32]) reported that at 40 to 52 months follow-up, a ≥50% increase in estimated annual rate of weight gain was achieved in 9 (29%) children receiving triple therapy. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **Two prospective, phase II single-arm clinical trials provided very low certainty evidence on weight gain. One trial reported weight gain success**

[27] Weight gain before study enrolment was estimated using least squares regression for the prior year's data.
[28] Ten patients had stable weight (±50%) and six had weight decreases of >50%.
[29] The fold change for pre-treatment versus follow-up weight gain was reported in the paper for children who achieved weight gain success (median: 5.98 [range 0.75 to 25.5]), but it was unclear how this was calculated and the results could therefore not be interpreted with confidence.
[30] The fold change for pre-treatment versus follow-up weight gain was reported in the paper for children who did not achieve weight gain success (median: 0.57 [range -1.07 to 1.42]), but it was unclear how this was calculated and the results could therefore not be interpreted with confidence.
[31] A patient was considered improved in rate of weight gain if they experienced either a 10% annualised increase in rate of weight gain compared to pre-study entry, or if annualised change in weight converted from decreasing pre-study entry to increasing on-treatment. Rates of weight change were estimated by the slope of patient-specific least squares regressions versus age using data collected within the year prior to study entry and data collected during treatment.
[32] Four patients were excluded from this analysis a priori due to being under the age of three years, which the authors stated is too young to establish weight gain thresholds.

Outcome	Evidence statement
	(defined as ≥50% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss to a statistically significant weight gain) in 36% of children with HGPS at 24 to 29 months follow-up on lonafarnib monotherapy. The second trial reported that at 40 to 52 months follow-up, 48.4% of children receiving triple therapy achieved ≥10% increase in estimated annual rate of weight gain and 29% of children achieved ≥50% increase in estimated annual rate of weight gain. Statistical measures were not reported in either trial.
Important outcomes	
Neurological outcomes **Certainty of evidence:** Very low	This is important to patients because they frequently report neurological symptoms that can reduce their quality of life and can result in disability. One prospective, phase II single-arm clinical trial and one retrospective analysis of a phase II clinical trial provided non-comparative evidence on neurological outcomes in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[33] (one trial). It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some patients may have participated in both trials. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* Clinical strokes **At 24 to 29 months follow-up** • One retrospective analysis of a phase II clinical trial (Ullrich et al 2013; n=26) reported that clinical strokes were reduced in children with HGPS from four (15%) children before treatment to two (7.69%) children[34] at 24 to 29 months follow-up on lonafarnib monotherapy. The authors stated that *"one child with a history of strokes died of a stroke after 5 months on the study. None of the 3 other patients who had reported clinical strokes at trial entry experienced recurrent TIA or stroke during treatment…one patient with no known history of clinically evident stroke and no prior neuroimaging studies experienced acute hemiparesis accompanied by headache and increased fatigue"*. The same trial reported that before treatment with lonafarnib monotherapy, the average stroke frequency in the four children with HGPS with a history of stroke was 1.75 strokes per year (range 1 to 3). At 24 to 29 months follow-up, the two children who experienced strokes on treatment with lonafarnib monotherapy had a frequency of 0.25 strokes per year (range not reported). No statistical measures were reported. **(VERY LOW)** Brain infarcts on MRI **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that the number of children with HGPS with brain infarcts on MRI reduced from five (14%) children before treatment with triple therapy to three (8.1%) children [two patients developed new infarcts and one had infarcts pre-treatment and while on treatment; four patients with brain infarcts at baseline did not develop additional infarcts during treatment] at 40 to 52 months follow-up on treatment. No statistical measures were reported. **(VERY LOW)** TIA in children with a history of strokes **At 24 to 29 months follow-up**

[33] Lonafarnib in combination with pravastatin and zoledronic acid.
[34] One stroke occurred in the patients with a history of clinical strokes and one occurred in a patient without previous history of clinical strokes.

Outcome	Evidence statement
	• One retrospective analysis of a phase II clinical trial (Ullrich et al 2013; n=4) reported that of the four children with a history of strokes, three (75%) also experienced TIAs before receiving lonafarnib monotherapy. At 24 to 29 months follow-up on treatment, none (0%) of the children reported TIAs. No statistical measures were reported. **(VERY LOW)** Number of TIAs **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that three (8.1%) children with HGPS developed new TIAs at 40 to 52 months follow-up on triple therapy (one of these patients also experienced a new infarct). The authors did not report the number of children who had TIAs before treatment and no statistical measures were presented. **(VERY LOW)** Number of children with headaches **At 24 to 29 months follow-up** • One retrospective analysis of a phase II clinical trial (Ullrich et al 2013; n=25) reported a *statistically significant* reduction in the number of children with HGPS experiencing headaches after treatment with lonafarnib monotherapy at 24 to 29 months follow-up compared to before treatment (7/25, 28% vs 15/26 58%, respectively; p=0.005). The authors reported that there were no new patients experiencing headaches during the study. The same trial reported that, for the children with HGPS who experienced headaches, the average frequency of headaches reduced from 0.9 per week (n=15) before lonafarnib monotherapy compared to 0.37 per week (n=7) at 24 to 29 months follow-up on treatment. This reflected a 41% reduction in headache frequency for children who experienced headaches, but no statistical measures were reported. **(VERY LOW)** **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=NR) reported that the average frequency of headaches reduced from 1.2 per week in children with HGPS before triple therapy to 0.81 per week at 40 to 52 months follow-up on treatment. No statistical measures were reported. **(VERY LOW)** Recurrent or new onset of seizures **At 24 to 29 months follow-up** • One retrospective analysis of a phase II clinical trial (Ullrich et al 2013; n=25) suggested a reduction in the number of children with HGPS experiencing seizures at 24 to 29 months on treatment with lonafarnib monotherapy *"no patient experienced recurrent or new onset of seizures during the study period"* compared to 15% before treatment. No statistical measures were reported. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **One prospective, phase II single-arm clinical trial and one retrospective analysis of a phase II clinical trial provided very low certainty evidence on neurological outcomes. The retrospective analysis reported that clinical strokes were reduced from 15% in children with HGPS before treatment to 7.69% at 24 to 29 months follow-up on lonafarnib monotherapy. The prospective, phase II single-arm clinical trial reported that 14% of children with HGPS had brain infarcts on MRI before treatment with triple therapy compared to 8.1% of children who experienced new brain infarcts by 40 to 52 months follow-up on treatment. The retrospective analysis also reported that at 24 to 29 months follow-up on lonafarnib monotherapy, none of the children**

Outcome	Evidence statement
	reported TIAs compared to three children before treatment. The prospective clinical trial reported that by 40 to 52 months follow-up on triple therapy, 8.1% of children developed new TIAs (one of these patients also experienced a new infarct). No statistical measures were reported for any of these outcomes. **The retrospective analysis reported a *statistically significant* reduction in the number of children with HGPS experiencing headaches with lonafarnib monotherapy at 24 to 29 months compared to before treatment (28% vs 58%, respectively). The same trial also reported a 41% reduction in the frequency of headaches for those experiencing headaches, but no statistical measures were reported. The prospective clinical trial reported that the average frequency of headaches in children with HGPS reduced to 0.81 per week at 40 to 52 months follow-up on triple therapy from 1.2 per week before triple therapy, but no statistical measures were reported. The retrospective analysis also reported a reduction in the number of children with HGPS experiencing seizures at 24 to 29 months on lonafarnib monotherapy *"no patient experienced recurrent or new onset of seizures during the study period"* compared to 15% before treatment, but no statistical measures were reported.**
Audiological outcomes **Certainty of evidence:** Very low	This is important to patients because hearing loss is associated with this condition, and improved low frequency hearing may improve their ability to function in their activities of daily living and social lives. One prospective, phase II single-arm clinical trial provided non-comparative evidence on audiological outcomes in children with classic HGPS treated with lonafarnib monotherapy for 24 to 29 months. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* Sensorineural hearing, ≥10 dB improvement in median low-frequency sensorineural hearing **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=18) stated that before treatment with lonafarnib monotherapy *"Sensorineural hearing was in the normal or low-normal range in both ears for all assessable patients".* At 24 to 29 months follow-up, *statistically significant* improvements in low-frequency sensorineural hearing were reported in the better-hearing ear (n=18; p=0.008) and poorer-hearing ear (n=16; p=0.002) in children with HGPS. The authors reported that, clinically, eight (44%) children experienced ≥10 dB improvement in average low-frequency sensorineural hearing. **(VERY LOW)** Sensorineural hearing, ≥10 dB improvement in median high-frequency sensorineural hearing **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=5) stated that median high-frequency sensorineural hearing remained unchanged in both ears after 24 to 29 months treatment with lonafarnib monotherapy in the five assessable children with HGPS. **(VERY LOW)** Conductive hearing loss at low frequency **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=NR) reported that 21 children with HGPS had conductive hearing loss at low frequency before treatment with lonafarnib monotherapy. At 24 to 29 months

Outcome	Evidence statement
	follow-up, the authors stated that *"no change was detected in low-frequency hearing in the poorer- or better-hearing ears"*. The authors also reported that *"From a clinical perspective, no ear changed by ≥10 dB"*. No statistical measures were reported. **(VERY LOW)** Conductive hearing loss at high frequency **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=NR reported that seven children with HGPS had conductive hearing loss at high frequency before treatment with lonafarnib monotherapy. At 24 to 29 months follow-up, the authors stated that *"median hearing thresholds were significantly different for high-frequency conductive hearing in the poorer-hearing ear (p = 0.01) but not in the better-hearing ear"*, but the direction of effect was not reported. The authors also reported that *"From a clinical perspective, no ear changed by ≥10 dB"*. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **One prospective, phase II single-arm clinical trial provided very low certainty evidence on audiological outcomes. This trial reported that at 24 to 29 months follow-up, 44% of children with HGPS showed a *statistically significant* ≥10 dB improvement in median low-frequency sensorineural hearing in the better-hearing and poorer-hearing ears. Median high-frequency sensorineural hearing remained unchanged in both ears for the five children who could be assessed. This trial also reported that *"no change was detected in low-frequency hearing in the poorer- or better-hearing ears"* in children with HGPS who had conductive hearing loss at low frequency before treatment with lonafarnib monotherapy. For the seven children with HGPS who had conductive hearing loss at high frequency before treatment with lonafarnib monotherapy *"median hearing thresholds were significantly different for high-frequency conductive hearing in the poorer-hearing ear (p = 0.01) but not in the better-hearing ear"* at 24 to 29 months follow-up, but the direction of effect was not reported.**
Bone structure **Certainty of evidence:** Very low	This is important to patients because osteoporosis and osteopenia can be a consequence of this condition, and improved bone strength can reduce risks of painful fractures and subsequent reduced mobility. Two prospective, phase II single-arm clinical trials provided non-comparative evidence on bone structure in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[35] (one trial). It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some children may have participated in both trials. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* Skeletal rigidity **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=11) reported that treatment with lonafarnib monotherapy *"led to median percent increases at the four radial sites tested* [i.e. 4%, 20%, 50% and 66% distance

[35] Lonafarnib in combination with pravastatin and zoledronic acid.

Outcome	Evidence statement
	from the distal radial epiphysis]*, of 40-50% in axial rigidity, 170-228% in flexural rigidity, and 167-229% in torsional rigidity in the subset of 11 patients who could be tested"* at 24 to 29 months follow-up. Findings at the 20% (n=11), 50% (n=10), and 66% (n=9) radial sites were similar, with the improvements reported to be *statistically significant* (p=0.007 to p=0.03). **(VERY LOW)** Percent increase or decrease in SSI at the 20% radial site **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=22) reported a median increase from baseline in SSI at the 20% radial site of 9% (range 17% decrease to 193% increase) at 24 to 29 months follow-up in children with HGPS treated with lonafarnib monotherapy*;* the difference compared to baseline was *statistically significant* (p=0.002). **(VERY LOW)** Percent increase or decrease in SSI at the 50% radial site **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=13) reported a median increase from baseline in SSI at the 50% radial site of 9% [range 13% decrease to 30% increase] at 24 to 29 months follow-up in children with HGPS treated with lonafarnib monotherapy, the difference compared to baseline was *not statistically significant* (p=0.06). **(VERY LOW)** Percent increase or decrease in SSI at the 66% radial site **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=10) reported a median increase from baseline in SSI at the 66% radial site of 35% (range 3% decrease to 138% increase) at 24 to 29 months follow-up in children with HGPS treated with lonafarnib monotherapy*;* the difference compared to baseline was *statistically significant* (p=0.01). **(VERY LOW)** Load bearing capacity – bending rigidity [EI] ($N \bullet M^2$) at 4% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in bending rigidity at the 4% radial site from baseline (median: 695 $N \bullet M^2$ [IQR 353 to 994]) to 40 to 52 months follow-up on treatment with triple therapy (median: 855 $N \bullet M^2$ [IQR 696 to 1,076]); p<0.001. **(VERY LOW)** Load bearing capacity – bending rigidity [EI] ($N \bullet M^2$) at 20% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in bending rigidity at the 20% radial site from baseline (median: 891 $N \bullet M^2$ [IQR 567 to 1,187]) to 40 to 52 months follow-up on treatment with triple therapy (median: 1,131 $N \bullet M^2$ [IQR 722 to 1,289]); p<0.001. **(VERY LOW)** Load bearing capacity – bending rigidity [EI] ($N \bullet M^2$) at 50% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in bending rigidity at the 50% radial site from baseline (median: 785 $N \bullet M^2$ [IQR 529 to 1,100]) to 40 to 52 months follow-up on treatment with triple therapy (median: 952 $N \bullet M^2$ [IQR 827 to 1,192]); p<0.001. **(VERY LOW)**

Outcome	Evidence statement
	Load bearing capacity - axial rigidity [EA] (MN) at 4% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in axial rigidity at the 4% radial site from baseline (median: 2.32 MN [IQR 1.44 to 2.83]) to 40 to 52 months follow-up on treatment with triple therapy (median: 2.66 MN [IQR 2.34 to 3.14]); p<0.001. **(VERY LOW)** Load bearing capacity - axial rigidity [EA] (MN) at 20% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in axial rigidity at the 20% radial site from baseline (median: 2.18 MN [IQR 1.60 to 2.76]) to 40 to 52 months follow-up on treatment with triple therapy (median: 2.70 MN [IQR 2.24 to 3.17]); p<0.001. **(VERY LOW)** Load bearing capacity - axial rigidity [EA] (MN) at 50% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in axial rigidity at the 50% radial site from baseline (median: 2.14 MN [IQR 1.51 to 2.98]) to 40 to 52 months follow-up on treatment with triple therapy (median: 2.78 MN [IQR 2.23 to 3.26]); p<0.001. **(VERY LOW)** Load bearing capacity - torsional rigidity [GJ] (N●M^4) at 4% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in torsional rigidity at the 4% radial site from baseline (median: 754 N●M^4 [IQR 416 to 1,095]) to 40 to 52 months follow-up on treatment with triple therapy (median: 868 N●M^4 [IQR 711 to 1,087]); p=0.0003. **(VERY LOW)** Load bearing capacity - torsional rigidity [GJ] (N●M4) at 20% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in torsional rigidity at the 20% radial site from baseline (median: 925 N●M^4 [IQR 593 to 1,233]) to 40 to 52 months follow-up on treatment with triple therapy (median: 1,148 N●M^4 [IQR 739 to 1,312]); p<0.001. **(VERY LOW)** Load bearing capacity - torsional rigidity [GJ] (N●M4) at 50% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=23 to 24) reported a *statistically significant* improvement in torsional rigidity at the 50% radial site from baseline (median: 798 N●M^4 [IQR 536 to 1,121]) to 40 to 52 months follow-up on treatment with triple therapy (median: 961 N●M^4 [IQR 850 to 1,203]); p<0.001. **(VERY LOW)** aBMD[36] (total body) **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=25) reported that 11 children with HGPS demonstrated a *clinically significant* ≥3%

[36] Clinically significant improvement in aBMD was predefined as a ≥3% increase.

Outcome	Evidence statement
	increase in aBMD for the whole body[37] at 24 to 29 months follow-up on lonafarnib monotherapy, while four children showed a >3% decrease. The percent change from pre-treatment to follow-up was *not statistically significant* (p=0.15). **(VERY LOW)** aBMD (whole body) **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=31) reported an increase (i.e. improvement) in aBMD for the whole body from baseline to 40 to 52 months follow-up on triple therapy (0.49 g/cm^2 vs 0.54 g/cm^2, respectively); the difference compared to baseline was *statistically significant* (p<0.001). It was unclear whether the statistic used was mean or median. **(VERY LOW)** aBMD height-adjusted Z-score (whole body) **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=19) reported a *statistically significant* increase (i.e. improvement) in aBMD height adjusted Z-score for the whole body from baseline (-2.75 [-3.20 to -2.10]) to 40 to 52 months follow-up on triple therapy (-2.11 [-2.80 to -1.20]); p<0.001. It was unclear whether the statistic used was mean or median. **(VERY LOW)** aBMD[36] (lumbar spine) **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=25) reported that 11 children with HGPS demonstrated a *clinically significant* ≥3% increase in aBMD for the lumbar spine at 24 to 29 months follow-up on lonafarnib monotherapy, while seven children showed a >3% decrease. The percent change from pre-treatment to follow-up was *not statistically significant* (p=0.33). **(VERY LOW)** aBMD (spine) **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32) reported a *statistically significant* increase (i.e. improvement) in aBMD for the spine from baseline to 40 to 52 months follow-up on triple therapy (0.44 g/cm^2 vs 0.52 g/cm^2, respectively); p<0.001. It was unclear whether the statistic used was mean or median. **(VERY LOW)** aBMD height-adjusted Z-score (spine) **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=19) reported a *statistically significant* increase (i.e. improvement) in aBMD height adjusted Z-score for the spine from baseline (-1.68 [IQR -2.50 to -0.80]) to 40 to 52 months follow-up on triple therapy (-0.74 [IQR -1.30 to -0.10]); p=0.001. It was unclear whether the statistic used was mean or median. **(VERY LOW)** aBMD[36] (hip) **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=25) reported that 11 children with HGPS demonstrated a *clinically significant* ≥3%

[37] Clinically significant >3% increase at one or more sites: 19/25 (76%). Decreases at one or more sites: 10/25 (40%). The authors reported that "*Seven children experienced both clinically significant losses and gains at different sites. Two children had improvements in all three measured sites: total body, hip, and spine. Ten children had improvements in two of three sites, and seven had improvements in one site only*".

Outcome	Evidence statement
	increase in aBMD for the hip at 24 to 29 months follow-up on lonafarnib monotherapy, while four children showed a >3% decrease. The percent change from pre-treatment to follow-up was *statistically significant* (p=0.03). **(VERY LOW)** vBMD **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=NR) reported that radius vBMD was normal before treatment and at 24 to 29 months follow-up on lonafarnib monotherapy, but no further details were reported. **(VERY LOW)** vBMD at 4% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=24) reported a *statistically significant* increase (i.e. improvement) in vBMD at the 4% radial site from baseline (median: 0.73 [IQR 0.67 to 0.83]) to 40 to 52 months follow-up on triple therapy (median: 0.89 [IQR 0.86 to 1.55]); p<0.001. **(VERY LOW)** vBMD at 20% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=24) reported a *statistically significant* increase (i.e. improvement) in vBMD at the 20% radial site from baseline (median: 1.20 [IQR 1.08 to 1.32]) to 40 to 52 months follow-up on triple therapy (median: 1.30 [IQR 1.24 to 1.76]); p=0.006. **(VERY LOW)** vBMD at 50% radial site **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=24) reported a *statistically significant* increase (i.e. improvement) in vBMD at the 50% radial site from baseline (median: 1.20 [IQR 1.08 to 1.36]) to 40 to 52 months follow-up on triple therapy (median: 1.34 [IQR 1.25 to 1.76]); p=0.001. **(VERY LOW)** Fracture incidence **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=25) reported that fracture incidence reduced from three (12%) children with HGPS before treatment to two (8%) children at 24 to 29 months follow-up on lonafarnib monotherapy, but statistical measures were not reported. **(VERY LOW)** **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that at 40 to 52 months follow-up on triple therapy, six (15%) children with HGPS experienced appendicular fractures and three (8%) children experienced skull fractures. The number of children with fractures before treatment was not reported and no statistical measures were presented. **(VERY LOW)** Extraskeletal calcifications (positive by X-ray) **At 40 to 52 months follow-up**

Outcome	Evidence statement
	• One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=32) reported a *statistically significant* increase in extraskeletal calcifications in children with HGPS from baseline (11 [34.4%]) to 40 to 52 months follow-up on triple therapy (21 [65.6%]); p=0.006. The authors reported that *"calcifications were also observed as calcific skin eruptions in 3 participants [who] demonstrated these at baseline, and 7 participants exhibited new eruptions while on triple therapy"*. **(VERY LOW)** Number of new dislocations **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that at 40 to 52 months follow-up on triple therapy, three (8%) children with HGPS experienced new hip dislocations and three (8%) children experienced new shoulder dislocations. The number of dislocations before treatment was not reported and no statistical measures were presented. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **Two prospective, phase II single-arm clinical trials provided very low certainty evidence on bone structure. One trial reported that treatment with lonafarnib monotherapy resulted in *statistically significant* improvements in skeletal rigidity. The second trial reported *statistically significant* improvements in bending, axial, and torsional rigidities at all radial sites (i.e. 4%, 20%, and 50%) at 40 to 52 months follow-up on treatment with triple therapy. The lonafarnib monotherapy trial also reported *statistically significant* improvements in SSI at the 20% and 66% radial sites, but *no statistically significant* difference at the 50% radial site.** **The lonafarnib monotherapy trial reported *no statistically significant* change in aBMD for the whole body from baseline to 24 to 29 months follow-up. By contrast, the triple therapy trial showed *statistically significant* improvements in aBMD and height-adjusted Z-score for the whole body at 40 to 52 months follow-up. Similarly, the lonafarnib monotherapy trial reported *no statistically significant* change in aBMD for the lumbar spine, while the triple therapy trial showed *statistically significant* improvements in aBMD and height-adjusted Z-score for the spine at 40 to 52 months follow-up. The lonafarnib monotherapy trial reported a *statistically significant* improvement in aBMD for the hip at 24 to 29 months follow-up, but the radius vBMD remained normal (no further details were reported). The triple therapy trial reported *statistically significant* improvements in vBMD at the 4%, 20%, and 50% radial sites at 40 to 52 months follow-up.** **The lonafarnib monotherapy trial reported that fracture incidence reduced from 12% of children before treatment to 8% of children after treatment, but statistical measures were not reported. The triple therapy trial reported that 15% of children experienced appendicular fractures and 8% of children experienced skull fractures after treatment commenced, but the number of children with fractures before treatment was not reported and no statistical measures were presented. The triple therapy trial also reported a *statistically significant* increase in extraskeletal calcifications (i.e. worsening) in children at 40 to 52 months follow-up compared to baseline (65.6% vs 34.4%, respectively, and that 8% of children experienced new hip dislocations and 8% of children experienced new shoulder dislocations after treatment commenced, but the number of dislocations before treatment was not reported and no statistical measures were presented for this outcome.**
Plasma progerin	Progerin is the pathogenic protein that causes organ damage in these patients. A reduction in plasma progerin is important to patients as it potentially indicates that

Outcome	Evidence statement
Certainty of evidence: Very low	treatment is reducing disease progression, comorbidities, and potentially increasing life-expectancy. One cohort study provided evidence on plasma progerin in children with classic HGPS treated with lonafarnib monotherapy (trial 1), triple therapy[38] (trial 2), or lonafarnib monotherapy extension (after triple therapy; trial 3). It was unclear how much overlap there was between the children included in these trials as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some patients may have participated in more than one contributing trial. *Oral lonafarnib vs no oral lonafarnib* No evidence was identified for this outcome. *Oral lonafarnib vs no comparator* <u>Progerin changes</u> *Trial 1* **At 4 months follow-up** • One cohort study (Gordon et al 2023; n=25) reported a 48% decrease (i.e. improvement) in plasma progerin in patients with HGPS during the four months dosing period of 115 mg/m^2 lonafarnib monotherapy. The change compared to baseline was *statistically significant;* p<0.0001. **(VERY LOW)** **At 2.2 years follow-up** • One cohort study (Gordon et al 2023; n=22 to 25) reported that *"For each of the 5 remaining patient visits where lonafarnib dose was 150 mg/m^2, average decreases from baseline ranged between 50%* and *62% (n=22–25 patients, all P<0.0001)".*[39] **(VERY LOW)** *Trial 2* **At 6 months follow-up** • One cohort study (Gordon et al 2023; n=13) reported a 41% decrease (i.e. improvement) in plasma progerin in patients with HGPS at six months follow-up on triple therapy. The change compared to baseline was *statistically significant*; p=0.0018. **(VERY LOW)** **At 3.5 years follow-up** • One cohort study (Gordon et al 2023; n=12 to 13) reported that at subsequent follow-up visits *"average progerin remained significantly decreased from baseline by 35% to 47% (n=12–13 patients, visits 3–5, P=0.0015–0.0058)".* **(VERY LOW)** **Up to 7.6 years follow-up** • One cohort study (Gordon et al 2023; n=10) reported that after triple therapy was discontinued, 10 patients completed a lonafarnib monotherapy extension trial. Average progerin plasma levels during treatment with triple therapy compared to lonafarnib monotherapy extension were *not statistically significant* (p=0.99). **(VERY LOW)** *Trial 3* **At 2.4 years follow-up** • One cohort study (Gordon et al 2023; n=26) reported a 36.7% decrease (i.e. improvement) in plasma progerin in patients with HGPS at 2.4 years follow-up

[38] Lonafarnib in combination with pravastatin and zoledronic acid.
[39] At 8 months (4 months after transitioning from 115 to 150 mg/m^2 dosing) (n=25): p=0.06; the authors stated that *"at each of the 4 subsequent trial visits, progerin was significantly decreased while taking 150 mg/m^2 of lonafarnib over the 115 mg/m^2 dose (n=22–25 patients, all P<0.05). There were no significant differences between average progerin at the 8-month 150 mg/m^2 visit and subsequent visits at the same drug dose (n=22–25 patients, all P≥0.05)".*

Outcome	Evidence statement
	on lonafarnib monotherapy. The change compared to baseline was *statistically significant*; p<0.0001. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **One cohort study involving three individual trials provided very low certainty evidence on plasma progerin. The cohort study reported a *statistically significant* 48% decrease in plasma progerin in patients with HGPS during the four months dosing period using 115 mg/m^2 lonafarnib monotherapy and between 50% to 62% decrease at 2.2 years follow-up where lonafarnib dose was 150 mg/m^2 (trial 1). The cohort study also reported a *statistically significant* 41% decrease in plasma progerin in patients with HGPS at six months follow-up on triple therapy and between 35% to 47% decrease at subsequent follow-up visits up to 3.5 years, and when triple therapy was discontinued and patients completed lonafarnib monotherapy extension, there was *no statistically significant* difference in average plasma progerin between triple therapy and lonafarnib monotherapy (trial 2). The cohort study also showed a *statistically significant* 36.7% decrease in plasma progerin at 2.4 years follow-up in patients treated with lonafarnib monotherapy (trial 3).**
Safety	
Toxicity **Certainty of evidence:** Very low	Safety of lonafarnib is important to patients as it allows patients to make an informed response when considering commencing treatment. Two prospective, phase II single-arm clinical trials provided non-comparative evidence on safety in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[40] (one trial). Both trials reported on toxicity (grades 1 to 4) possibly related to lonafarnib treatment. In addition, the triple therapy trial reported on toxicity (grades 1 to 3) possibly related to zoledronic acid or pravastatin. It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some children may have participated in both trials. Lonafarnib toxicity – mild (grade 1) or moderate (grade 2)[41] **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported the following mild (grade 1) or moderate (grade 2) toxicities, possibly related to lonafarnib,[42] in children with HGPS at 24 to 29 months follow-up: gastrointestinal (n=49), constitutional (n=53), organ function (n=24), low absolute leukocyte count (n=43), metabolic (n=50), and other toxicities (n=3). **(VERY LOW)** **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) of triple therapy reported the following mild (grade 1) or moderate (grade 2) toxicities, possibly related to lonafarnib treatment,[43] in children with HGPS at

[40] Lonafarnib in combination with pravastatin and zoledronic acid.
[41] Per patient count is once for that patient's highest toxicity grade, but patients could experience more than one type of toxicity (e.g. for gastrointestinal toxicities, patients could experience diarrhoea, vomiting, dehydration, constipation and dyspepsia).
[42] Gastrointestinal (diarrhoea, vomiting, constipation, and dyspepsia); constitutional (fatigue, nausea, anorexia, and fever); organ function (elevated AST, ALT and alkaline phosphatase); low absolute leukocyte count (low white blood cell count, low absolute neutrophil count, and low haemoglobin); metabolic (hypermagnesemia, hyperkalaemia, hypokalaemia, hyponatremia, hypocalcaemia, hypercalcaemia, depressed serum bicarbonate, hypoglycaemia, and hyperglycaemia); other (granuloma, perineal oedema, Raynaud's phenomenon). Patients could experience more than one type of toxicity.
[43] Gastrointestinal (diarrhoea, dyspepsia, and vomiting); constitutional (anorexia, fatigue, headache, nausea, and weight loss); organ function (elevated AST, ALT, alkaline phosphatase and CPK, and low ANC, ALC, haemoglobin, platelets and WBC);

Outcome	Evidence statement
	40 to 52 months follow-up: gastrointestinal (n=41), constitutional (n=41), organ function (n=34), metabolic (n=10), and other toxicities (n=2). **(VERY LOW)** Lonafarnib toxicity – severe (grade 3) or potentially life threatening (grade 4)[41] **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported the following severe (grade 3) or potentially life threatening (grade 4) toxicities, possibly related to lonafarnib,[44] in children with HGPS at 24 to 29 months follow-up: gastrointestinal (n=6; grade 3), constitutional (n=1; grade 4), organ function (n=2; grade 3), and metabolic (n=5; grade 3). **(VERY LOW)** **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) of triple therapy reported the following severe (grade 3) toxicities, possibly related to lonafarnib treatment,[45] in children with HGPS at 40 to 52 months follow-up: gastrointestinal (n=1), and organ function (n=4). **(VERY LOW)** Post-zoledronic acid infusion toxicity (first 48 hours) – mild (grade 1) or moderate (grade 2)[41] **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) of triple therapy reported the following mild (grade 1) or moderate (grade 2) toxicities, possibly related to zoledronic acid, in children with HGPS: abdominal (n=3; 8.1%), chills (n=1; 2.7%), dehydration (n=1; 2.7%), diarrhoea: (n=1; 2.7%), fatigue (n=3; 8.1%), fever (n=12; 32.4%), flu-like syndrome (n=1; 2.7%), headache (n=3; 8.1%), hypocalcaemia (n=4; 10.8%), muscle/joint/body pain (n=11; 29.7%), nausea (n=1; 2.7%), neuropathy (n=1; 2.7%), vomiting (n=5; 13.5%). **(VERY LOW)** Post-zoledronic acid infusion toxicity (first 48 hours) – severe (grade 3) **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) of triple therapy reported that one (2.7%) child with HGPS experienced severe (grade 3) hypocalcaemia after zoledronic acid infusion. **(VERY LOW)** Pravastatin toxicity **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that *"There were no pravastatin-related side effects identified"*. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **Two prospective, phase II single-arm clinical trials provided very low certainty evidence on safety in children with HGPS receiving lonafarnib monotherapy or triple therapy. Both trials reported that children with HGPS experienced one or more toxicities possibly related to lonafarnib at 24 to 29 and 40 to 52 months follow-up, with most being mild (grade 1) or moderate (grade 2) toxicities, although a small proportion of children experienced more**

metabolic (elevated magnesium and potassium, and low CO2 and sodium); other (colitis and dry mouth). Patients could experience more than one type of toxicity. Patients could experience more than one type of toxicity.

[44] Gastrointestinal (diarrhoea, vomiting, and dehydration); constitutional (fever); organ function (elevated AST and ALT); metabolic (hypokalaemia, and hypoglycaemia). Patients could experience more than one type of toxicity.

[45] Gastrointestinal (diarrhoea); organ function (elevated ALT). Patients could experience more than one type of toxicity.

Outcome	Evidence statement
	severe (i.e. grade 3) toxicities such as diarrhoea, vomiting, and hypokalaemia, and one child experienced a potentially life threatening grade 4 toxicity (i.e. fever). The triple therapy trial also reported that children experienced toxicities, possibly related to zoledronic acid infusion, but no pravastatin-related toxicities were identified.
Adverse events leading to discontinuation **Certainty of evidence:** Very low	Safety of lonafarnib is important to patients as it allows patients to make an informed response when considering commencing treatment. Two prospective, phase II single-arm clinical trials provided non-comparative evidence on adverse events leading to discontinuation in children with classic HGPS treated with lonafarnib monotherapy (one trial) or triple therapy[46] (one trial). It was unclear how much overlap there was between the children included in these two papers as they were all identified from the same source (i.e. The Progeria Research Foundation International Progeria Registry) and some children may have participated in both trials. <u>Lonafarnib toxicity leading to discontinuation</u> **At 24 to 29 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported that *"therapy was well tolerated, and no child came off study because of toxicity"*. **(VERY LOW)** **At 40 to 52 months follow-up** • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that *"therapy was well tolerated, and no participant came off study due to treatment-related toxicity"*. **(VERY LOW)** **Oral lonafarnib vs no oral lonafarnib:** **No evidence was identified for this outcome.** **Oral lonafarnib vs no comparator:** **Two prospective, phase II single-arm clinical trials provided very low certainty evidence on adverse events leading to discontinuation. Both trials reported that none of the children with HGPS treated with lonafarnib monotherapy or triple therapy discontinued treatment due to toxicity.**
Abbreviations aBMD: areal bone mineral density; cm: centimetre; CI: confidence interval; dB: decibel; DBP: diastolic blood pressure; ECG: electrocardiogram; g: gram; HGPS: Hutchinson-Gilford progeria syndrome; HR: hazard ratio; IQR: interquartile range; kg: kilogram; LV: left ventricular; LVH: left ventricular hypertrophy; m: metre; mg: milligram; MRI: magnetic resonance imaging; n: number; NR: not reported; QTc: corrected QT interval; SBP: systolic blood pressure; SSI: strength strain index; TIA: transient ischaemic attack; vBMD: volumetric bone mineral density.	

In people with progeroid laminopathies, what is the cost effectiveness of lonafarnib compared with no lonafarnib?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness.

[46] Lonafarnib in combination with pravastatin and zoledronic acid.

From the evidence selected, are there any subgroups of patients that may benefit from lonafarnib more than the wider population of interest?

Subgroup	Evidence statement
Subgroup	No evidence was identified for any subgroups.

From the evidence selected, what were the ongoing schedules/doses used for lonafarnib and what were the concurrent therapies?

Outcome	Evidence statement
Lonafarnib ongoing schedules/doses	Two prospective, phase II single-arm clinical trials (Gordon et al 2012 and 2016), one retrospective analysis of a phase II clinical trial (Ullrich et al 2013), and one matched cohort study (Gordon et al 2018) reported ongoing schedules/doses of lonafarnib as monotherapy or as part of triple therapy[47] in patients with HGPS. One cohort study (Gordon et al 2014) did not provide details for ongoing schedules/doses. • One prospective, phase II single-arm clinical trial (Gordon et al 2012; n=26) reported that children with HGPS initially received a dose of 115 mg/m^2 lonafarnib (capsule or liquid suspension) every 12 (± 2) hours. The dose was then increased to 150 mg/m^2 after an adjustment period of at least four months. Twenty four of 26 (92.3%) children tolerated a dose of 150 mg/m^2. One child experienced brawny oedema in the perineal region (of unknown aetiology) and the dose was de-escalated from 150 mg/m^2 to 115 mg/m^2, as a result of which the symptoms resolved. A second child experienced increased bowel gas, vomiting, and gastric pain at both doses of lonafarnib (i.e. 115 mg/m^2 and 150 mg/m^2) and treatment was stopped for two weeks. Lonafarnib was re-started at 115 mg/m^2 in this child and was well tolerated and then escalated to 150 mg/m^2 for the remainder of the trial duration. • One retrospective analysis of a phase II clinical trial (Ullrich et al 2013; n=26) reported that all patients received an initial dose of 115 mg/m^2 lonafarnib (capsule or liquid suspension) twice daily. The dose was then increased to 150 mg/m^2 if well tolerated after at least four months. No further details were reported. • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that all patients (lonafarnib treatment naïve and non-treatment naïve) received lonafarnib (capsule or liquid suspension) 150 mg/m^2 twice daily in combination with pravastatin and zoledronic acid. Patients experiencing grade 3 or 4 adverse events that were not responsive to supportive care, reduced the lonafarnib dose to 115 mg/m^2, with the dose then increased back to 150 mg/m^2 if tolerated. • One matched cohort study (Gordon et al 2018; n=126) included patients who had previously participated in two clinical trials; trial 1 administered oral lonafarnib every 12 (± 2) hours at 115 mg/m^2 for four months and then increased to 150 mg/m^2 for the remainder of the trial duration. Trial 2 was a lonafarnib monotherapy extension study (after completion of triple therapy) with lonafarnib administered at a dose of 150 mg/m^2 throughout the trial duration. • One cohort study including three trials (Gordon et al 2023; n=64) reported patients in one trial (lonafarnib monotherapy) initiated treatment at 115 mg/m^2 for four months before increasing to 150 mg/m^2. Two trials (triple therapy and lonafarnib monotherapy extension) initiated treatment at 150 mg/m^2 in all patients. **Two prospective, phase II single-arm clinical trials, one retrospective analysis of a phase II clinical trial, and one matched cohort study reported ongoing**

[47] Lonafarnib in combination with pravastatin and zoledronic acid.

Outcome	Evidence statement
	schedules/doses of lonafarnib in patients with HGPS. There was overlap in patient populations within and across the different trials, with patients initially receiving lonafarnib monotherapy at a dose of 115 mg/m^2 (increased to 150 mg/m^2 if well tolerated) or at a dose of 150 mg/m^2 (in lonafarnib treatment naïve and non-treatment naïve patients) as part of triple therapy or ongoing lonafarnib monotherapy after triple therapy (with the option to reduce to 115 mg/m^2 if not tolerated). One cohort study did not provide details on lonafarnib ongoing schedules/doses.
Concurrent therapies	Two prospective, phase II single-arm clinical trials (Gordon et al 2012 and 2016), one retrospective analysis of a phase II clinical trial (Ullrich et al 2013), and two cohort studies (Gordon et al 2014 and 2023) reported the use of concurrent treatments in patients with HGPS. One matched cohort study (Gordon et al 2018) did not provide details of concurrent treatments. • One prospective, phase II single-arm clinical trial of lonafarnib monotherapy (Gordon et al 2012; n=26) reported that five (19.2%) children with HGPS received recombinant growth hormone therapy and two (7.7%) patients received antihypertensive treatment (angiotensin-converting enzyme inhibitor or calcium-channel blocker), no further details were reported. • One retrospective analysis of a phase II clinical trial of lonafarnib monotherapy (Ullrich et al 2013; n=26) reported that 17 (65%) children with HGPS were receiving daily aspirin (average daily dose of 5.8 mg/kg); 3 (11.5%) were taking ≥1 antiplatelet or anticoagulant or acetazolamide; and 6 (23.1%) children each were taking cholesterol-lowering treatments or recombinant human growth hormones. During treatment with lonafarnib, two children discontinued clopidogrel and one patient discontinued warfarin because of improved clinical symptoms and lack of new strokes or TIAs, although all three children continued with daily aspirin. Two children without prior stroke symptoms discontinued aspirin because of minor bleeding. • One matched cohort study (Gordon et al 2014; n=86) included two individual trials. One trial treated patients with HGPS with lonafarnib monotherapy and the second treated patients with HGPS with lonafarnib in combination with pravastatin and zoledronic acid. Five patients received growth hormone treatment, but no further details were provided. • One prospective, phase II single-arm clinical trial (Gordon et al 2016; n=37) reported that children with HGPS received lonafarnib in combination with pravastatin and zoledronic acid. Oral pravastatin was administered at a dose of 5 mg for patients weighing under 10 kg, and 10 mg for patients weighing over 10 kg, once every 24 (± 2) hours. Zoledronic acid was administered intravenously over 30 minutes, at baseline, at six, 12, and 18 months, and at end the end of the study. The initial infusion was 0.0125 mg/kg body weight; all other infusions were 0.05 mg/kg body weight. The authors stated that three patients were taking statins at study enrolment, but none had previously received bisphosphonates. Oral calcium (500 mg) and vitamin D (1000 IU) were supplemented daily to avoid hypocalcaemia and vitamin D deficiency. Calcium supplementation was discontinued after 12 months. • One cohort study (Gordon et al 2023; n=64) included three trials. Two trials treated patients with HGPS with lonafarnib monotherapy (one trial being an extension study after triple therapy), and the third trial treated patients with HGPS with lonafarnib in combination with pravastatin and zoledronic acid. No further details were provided on concurrent treatments. **Two prospective, phase II single-arm clinical trials, one retrospective analysis of a phase II clinical trial, and two cohort studies reported the use of concurrent treatments in patients with HGPS, including, for example, pravastatin and zoledronic acid, recombinant growth hormone therapy, antihypertensives, aspirin, and vitamin supplementation. One matched cohort study did not provide details on concurrent treatments.**

Outcome	Evidence statement
Abbreviations HGPS: Hutchinson-Gilford Progeria Syndrome; IU: international units; kg: kilogram; m: metre; mg: milligram; n: number; TIA: transient ischaemic attack.	

6. Discussion

This review examined the clinical effectiveness, safety and cost effectiveness of oral lonafarnib compared to no oral lonafarnib in patients with progeroid laminopathies. The critical outcomes of interest were survival rate, cardiovascular outcomes, and weight gain. The important outcomes of interest were neurological outcomes, audiological outcomes, bone structure, plasma progerin levels, and safety.

Evidence for the clinical effectiveness and safety of lonafarnib was available from six papers (Gordon et al 2012, 2014, 2016, 2018, 2023, Ullrich et al 2013). Two papers were prospective, phase II single-arm clinical trials (Gordon et al 2012 and 2016) that provided non-comparative evidence on the effectiveness and safety of lonafarnib monotherapy over a minimum treatment duration of two years (Gordon et al 2012) or lonafarnib in combination with a statin [i.e. pravastatin] and a bisphosphonate [i.e. zoledronic acid] (i.e. triple therapy) over 40 to 52 months (Gordon et al 2016) in children with classic Hutchinson-Gilford progeria syndrome (HGPS). Two papers were matched cohort studies (Gordon et al 2014 and 2018) that combined patients with HGPS who had previously been treated in two different trials (lonafarnib monotherapy, triple therapy, or lonafarnib monotherapy extension [after triple therapy]) and compared survival rates up to a median follow-up duration of 2.2 years or 5.3 years in matched patients with HGPS who had not received previous lonafarnib treatment. One matched cohort study (Gordon et al 2018) also reported survival rates separately for treated patients who participated in the two individual trials (i.e. lonafarnib monotherapy trial and lonafarnib monotherapy [extension after triple therapy]). One paper was a cohort study (Gordon et al 2023) that developed an immunoassay to evaluate plasma progerin levels in patients with HGPS. This cohort study included patients who had participated in one or more of three clinical trials, i.e. lonafarnib monotherapy [trial 1], triple therapy [trial 2], and lonafarnib monotherapy extension after triple therapy [trial 3], follow-up was up to 7.6 years follow-up, with a long-term analysis up to 10 years in a subset of patients combined from the three trials. One paper was a retrospective analysis of a phase II clinical trial (Ullrich et al 2013), which provided non-comparative evidence on one important outcome (neurological outcomes) in children with classic HGPS treated with lonafarnib for at least two years. Although Ullrich et al (2013) indicated that their study provided additional outcomes to a *"parent study"* (i.e. Gordon et al 2012), it was unclear how much overlap there may have been between the included populations as there were differences in baseline characteristics in terms of age and sex.

Where reported, the trials included in this evidence review were conducted in patients with a mean age of 6.9 to 8.0 years (with ages ranging from 3.0 to 20.45 years). Details on other demographic characteristics were limited, but indicated a higher proportion of females. Sample sizes were small, ranging between 26 and 126 patients, which reflects the rarity of the condition. The included papers enrolled patients worldwide, but all patients were identified through the same source (i.e. The Progeria Research Foundation International Progeria Registry) and there may have been considerable overlap in the patients reported within and across the various papers as patients may have participated in one or more of the trials reported in the papers. Where reported, the majority of treated patients with known genotypes had classic HGPS (i.e. heterozygous for LMNA c.1824C>T, p.Gly608Gly). For the two papers that included a matched cohort of untreated patients with HGPS, approximately 55% had a known genotype which was mainly classic HGPS. Although one paper reported plasma progerin levels by genotype subgroups (classic versus non-classic forms of HGPS), the results have not been reported in this evidence review as it was unclear whether all patients had been treated. A second paper included patients with classic and non-classic forms of HGPS but did not present data separately for the two genotypes. Relevant subgroup analysis in patients with HGPS or processing-deficient progeroid laminopathies was not reported in any of the included papers.

Lonafarnib monotherapy was administered twice daily at a starting dose of 115 mg/m^2 in one trial, with the dose increased to 150 mg/m^2 if well tolerated (but with the option to reduce back to 115 mg/m^2, if necessary). The remaining trials (i.e. triple therapy or lonafarnib monotherapy extension [after triple therapy]) administered lonafarnib at a dose of 150 mg/m^2. Five included papers provided details on concurrent treatments (i.e. supportive medical care), which included the use of concomitant pravastatin and zoledronic acid, antihypertensives, antiplatelets (with or without anticoagulants), aspirin, cholesterol-lowering treatment, recombinant growth hormone therapy, or supplementation with oral calcium and vitamin D. It should be noted that the PICO document specified pravastatin and zoledronic acid as part of supportive medical care (for both the intervention and comparator groups), but the inclusion of pravastatin and zoledronic acid in three trials included in this review (Gordon et al 2014, 2016, and 2023) was as part of triple therapy (i.e. lonafarnib in combination with pravastatin and zoledronic acid) and was therefore considered to be part of the specific progerin-targeted care to additionally inhibit progerin prenylation.

The two matched cohort studies (Gordon et al 2014 and 2018) reported Kaplan-Meier survival estimates in treated patients with HGPS (who had participated in one or more trials of lonafarnib monotherapy or triple therapy) versus untreated patients with HGPS. Both cohort studies showed a statistically significant increase in survival rates in treated versus untreated patients up to 2.2 years and at median follow-up of 5.3 years. Due to the small number of patients included in the analyses, confidence intervals were wide, which increases the uncertainty in the results. The cause of death in treated patients was mainly due to heart failure (60% and 75% of patients). The cause of death in untreated patients was not reported separately for the matched untreated patients, but across a wider cohort of untreated patients with HGPS, the cause of death was also mainly due to heart failure (approximately 80%). Both matched cohort studies combined data from two separate clinical trials, neither of which originally prespecified survival rates as an outcome due to the lack of an untreated comparator group. Untreated patients were identified from the same source as treated patients (i.e. the Progeria Research Foundation International Registry), but had not participated in any treatment trials. Untreated patients were matched to treated patients with regard to confounding factors such as age, gender, and birth dates, which reduces potential for bias. The authors of one matched cohort study (Gordon et al 2014) highlighted that, although all patients were exposed to lonafarnib, and for the longest duration of time in most cases, the combination of two different treatment trials (i.e. one of lonafarnib monotherapy and one of triple therapy) meant that it was not possible to distinguish the effect of each drug on survival. Further research is required to assess whether the addition of pravastatin and zoledronic acid provides additional benefit to lonafarnib alone.

The two prospective, phase II single-arm clinical trials reported cardiovascular outcomes in children with HGPS treated with either lonafarnib monotherapy or triple therapy. Treatment with lonafarnib monotherapy (Gordon et al 2012) resulted in statistically significant improvements in arterial pulse wave velocity, and some carotid artery ultrasound findings (i.e. intima media and adventitia luminal near wall) at 24 to 29 months follow-up. By contrast, several measures did not change significantly with lonafarnib monotherapy, including major ECG abnormalities, and some carotid ultrasound findings. Gordon et al (2016) showed that less than 50% of patients achieved the primary measure of success for improvement in carotid artery echodensity when children with HGPS were treated with triple therapy. Findings for other cardiovascular outcomes were mixed. Gordon et al (2016) reported that there was a statistically significant increase in the prevalence of left ventricular hypertrophy and carotid artery plaque at 40 to 52 months follow-up, but no statistically significant changes in carotid-femoral pulse wave velocity or the number of children with elevated blood pressure before and after treatment. Gordon et al (2016) acknowledged that vascular plaques occur in untreated patients with HGPS, but that the rates were increased with triple therapy, particularly when compared with findings from the previous lonafarnib monotherapy trial. The authors suggested that this indicated that triple therapy did not provide additional benefit over lonafarnib monotherapy, but further research is needed to

explore this and to investigate whether zoledronic acid may exacerbate the increased rate of vascular plaques.

The two prospective, phase II single-arm clinical trials also reported on weight gain and bone structure in children with HGPS treated with either lonafarnib monotherapy or triple therapy. The two trials showed that rate of weight gain increased by 50% or more in 29% or 36% of children on triple therapy or lonafarnib monotherapy, respectively. Both trials also reported statistically significant increases (improvements) in skeletal rigidity (axial, flexural and torsional), but the extent of improvements in the lonafarnib monotherapy trial varied depending on the radial site (i.e. 20%, 50% and 66%) and only a subset of children were available for assessment (i.e. nine to 11 children). Findings on areal bone mineral density (aBMD) differed across the two trials. Although treatment with lonafarnib monotherapy (Gordon et al 2012) showed clinically significant changes (i.e. >3% increase) in aBMD in some children, and a statistically significant increase in aBMD at the hips, there were no statistically significant changes in aBMD for the whole body or lumber spine, or for volumetric bone mineral density (vBMD) at 24 to 29 months follow-up. By contrast, treatment with triple therapy (Gordon et al 2016) showed statistically significant increases in both aBMD (whole body and spine, and Z-scores) and vBMD (at 4%, 20% and 50% radial sites) at 40 to 52 months follow-up. Gordon et al (2016) suggested that the increase in both aBMD and vBMD on triple therapy reflects the inhibition of osteoclastic bone resorption by zoledronic acid, but this requires further investigation. By contrast, the prevalence of extraskeletal calcifications statistically significantly increased on triple therapy. Only a small proportion of children in both trials experienced fractures or dislocations before and after treatment.

One of the prospective, phase II single-arm clinical trials (Gordon et al 2012) also reported on audiological outcomes at 24 to 29 months follow-up on lonafarnib monotherapy. Treatment with lonafarnib monotherapy resulted in statistically significant improvements in sensorineural hearing, while conductive hearing generally remained unchanged.

Two papers (one retrospective analysis of a phase II clinical trial and one prospective, phase II single-arm clinical trial) reported on neurological outcomes in children with HGPS. The retrospective analysis (Ullrich et al 2013) reported that lonafarnib monotherapy may improve neurological outcomes in children with HGPS. This was reflected by a reduction in the prevalence and frequency of strokes or transient ischaemic attacks (TIAs), seizures and headaches, but only the reduction in the number of headaches was reported as being statistically significant, statistical measures were not reported for the remaining outcomes.[48] The prospective, phase II single-arm clinical trial (Gordon et al 2016) reported a reduction in the frequency of headaches in patients with HGPS over a median of 5.3 years on triple therapy. For the remaining neurological outcomes assessed in this clinical trial, two patients developed new brain infarcts on MRI, while one of the five patients who had infarcts on their baseline brain MRIs, had an infarct while on triple therapy (the other four patients with baseline data did not develop additional infarcts during the trial duration). In addition, three (8.1%) patients experienced new TIAs (one of whom also experienced a new infarct).

One cohort study (Gordon et al 2023) provided evidence on plasma progerin in patients with HGPS, including findings from three individual trials (trial 1: lonafarnib monotherapy; trial 2: triple therapy then lonafarnib monotherapy extension; trial 3: lonafarnib monotherapy [extension after triple therapy]) but also combined results from all three trials in a subgroup of patients receiving long-term lonafarnib monotherapy. Follow-up durations ranged from four months (lonafarnib dose 115 mg/m^2) to up to 10 years (lonafarnib dose 150 mg/m^2). Plasma levels were statistically significantly decreased in treated patients up to 3.5 years follow-up in the analyses

[48] The authors acknowledged that neurologic outcomes were not reported as primary or secondary outcomes in the main publication (Gordon et al 2012) because the prevalence rates of clinical stroke, TIA, and seizure were unknown and presumed to be too low to conduct statistical analysis to measure treatment efficacy.

of individual trials and up to 10 years in the combined long-term analysis. Comparison between lonafarnib monotherapy extension and triple therapy in trial 2 showed no statistically significant differences in average progerin at 7.6 years follow-up. This suggests that the addition of pravastatin and zoledronic acid may not provide additional benefit to lonafarnib alone in terms of plasma progerin levels, but further research and validation into plasma progerin as a biomarker for HGPS is required, and further investigation into the effect of treatment on plasma progerin is also needed. It should also be noted that there may have been considerable overlap in the trials in terms of patients participating in more than one contributing trial.

Two prospective, phase II single-arm clinical trials reported treatment toxicity during 24 to 29 months of lonafarnib monotherapy or 40 to 52 months of triple therapy. Lonafarnib was generally well tolerated and none of the children discontinued lonafarnib due to adverse events. Lonafarnib-related toxicities were mainly mild (grade 1) to moderate (grade 2), although a small proportion of children experienced more severe (i.e. grade 3) toxicities such as diarrhoea, vomiting, and hypokalaemia, and one child experienced a potentially life threatening grade 4 toxicity (i.e. fever). Zoledronic acid was also reported to be generally well tolerated, with toxicities including, for example, flu-like symptoms and hypocalcaemia. No pravastatin-related side effects were reported and none of the children discontinued treatment due to toxicity. Extraskeletal calcifications and calcific skin eruptions may also be considered to be adverse events, but were reported under skeletal outcomes as this is how they were reported in the paper. Although, it should be noted that these outcomes may not be adverse events directly related to lonafarnib, and may instead be related to treatment with zoledronic acid.

The certainty in the clinical effectiveness evidence was very low to low for one critical outcome (survival rate), and very low for two critical outcomes (cardiovascular outcomes and weight gain). The certainty in the evidence was very low for all important outcomes (neurological outcomes, audiological outcomes, bone structure, and plasma progerin) and for safety. Factors reducing confidence in the outcomes reported in all the papers include the very serious risk of bias due to, for example, recruitment methods, unclear statistical analysis (some papers stated that p-values did not reflect adjustment for multiple comparisons, and should be interpreted only descriptively) or lack of statistical analysis and incomplete outcome reporting (due to the inability of children to undergo certain outcome measures due to age or fragility). In addition, confidence in the findings was reduced because of serious indirectness due to the lack of a comparator in the two prospective, phase II single-arm clinical trials, one cohort study, and the retrospective analysis of a phase II clinical trial. The papers included in this evidence review reported various outcomes that were measured using objective methods, although the methods used to assess plasma progerin require further validation and the findings need further clarification and confirmation. Further limitations include the small number of patients included in the papers, the inclusion of treatment naïve and non-treatment naïve patients in different studies, and the potential overlap of some patients who may have participated in more than one of the contributing trials included in the various papers.

No evidence was available on cost effectiveness and no evidence was identified in relation to subgroups of interest.

7. Conclusion

This review included two prospective, phase II single-arm clinical trials, two matched cohort studies, one cohort study (including three individual trials), and one retrospective analysis of a phase II clinical trial. The two matched cohort studies provided very low to low certainty evidence on one critical outcome (survival rates) in patients with HGPS treated with lonafarnib monotherapy (one study) or triple therapy (one study) compared to untreated patients with HGPS. The two prospective, phase II single-arm clinical trials, one cohort study, and one retrospective analysis provided very low certainty evidence on two critical outcomes (cardiovascular outcomes and weight gain), all the important outcomes (neurological outcomes, audiological outcomes, bone structure, and plasma progerin) and safety in patients with HGPS, following treatment with lonafarnib monotherapy and/or triple therapy.

The two matched cohort studies provided comparative evidence on survival rates in treated versus untreated patients with HGPS. Both studies showed statistically significant increases in survival rates in patients treated with lonafarnib monotherapy or triple therapy at median 2.2 or 5.3 years follow-up, respectively.

The two prospective, phase II single-arm clinical trials (i.e. lonafarnib monotherapy trial and triple therapy trial) showed improvements in rate of weight gain and bone structure in a proportion of children with HGPS. The lonafarnib monotherapy trial also reported improvements in audiological status in some children. Improvements in vascular stiffness were reported in the lonafarnib monotherapy trial, while the triple therapy trial reported a statistically significant increase (i.e. worsening) in left ventricular hypertrophy and carotid artery plaque, but no other significant changes in cardiovascular outcomes. The authors acknowledged that vascular plaques occur in untreated patients with HGPS and that the rates were increased with triple therapy, particularly in comparison to rates with monotherapy. It remains unclear whether the increase was due to the addition of zoledronic acid and further research is needed in this area. Two studies indicated that lonafarnib monotherapy or triple therapy reduced the prevalence of stroke or TIA and the prevalence and frequency of headaches, although statistical measures were only reported for prevalence of headaches, which showed a statistically significant reduction after treatment with lonafarnib monotherapy.

One cohort study (including three trials of lonafarnib monotherapy or triple therapy, reported individually and combined) provided evidence that plasma progerin levels decreased for lonafarnib monotherapy and triple therapy up to 10 years follow-up, but further research is needed and interpretation of findings should take into account the overlap between the trial populations.

The lonafarnib monotherapy and triple therapy trials reported that lonafarnib was generally well tolerated and none of the children discontinued treatment due to adverse events. Most adverse events were mild to moderate (grades 1 or 2) and mainly related to gastrointestinal symptoms, although a small proportion of children experienced more severe toxicities (i.e. grade 3) such as diarrhoea, vomiting, and hypokalaemia, and one child experienced a potentially life threatening grade 4 toxicity (i.e. fever).

The evidence provided by the included studies should be considered as very low to low certainty due to the lack of a relevant treatment comparison group (with the exception of the studies reporting survival) and unclear statistical analyses or lack of statistical measures for some outcomes. Further limitations include the small number of patients included in the papers, the inclusion of treatment naïve and non-treatment naïve patients in different studies, and the potential overlap of some patients who may have participated in more than one of the contributing trials included in the various papers.

No evidence was available on cost effectiveness and no evidence was identified in relation to subgroups of interest.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with progeroid laminopathies, what is the clinical effectiveness of lonafarnib compared with no lonafarnib?
2. In people with progeroid laminopathies, what is the safety of lonafarnib compared with no lonafarnib?
3. In people with progeroid laminopathies, what is the cost effectiveness of lonafarnib compared with no lonafarnib?
4 From the evidence selected, are there any subgroups of patients that may benefit from lonafarnib more than the wider population of interest?
5. From the evidence selected what were the ongoing schedules/doses used for lonafarnib and what were the concurrent therapies?

P –Population and Indication	People with a diagnosis confirmed by phenotypic changes and on genetic testing of: • Hutchinson-Gilford Progeria Laminopathy, which is also referred to as 'progeria'. • Processing deficient Progeroid Laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation [Hutchinson-Gilford Progeria Laminopathy can be referred to as classic and non-classic. Classic cases have the phenotype and are heterozygous c.1824C>T pathogenic variant in LMNA, and account for the majority of cases. Non-classic cases have the phenotype and an autosomal dominant progerin-producing pathogenic variant in either the exon 11 splice junction or intron 11 of LMNA. Both forms are included in this population. Both classic and non-classic genotypes have similar clinical features and spectrum of severity] [The processing-deficient progeroid laminopathies full mutation list is as follows: • ZMPSTE24 mutations • LMNA c.1868C>G (p.Thr623Ser) generating prelamin AΔ35 • LMNA c.1940T>G (p.Leu647Arg) • LMNA mutations generating prelamin AΔ90 • LMNA c.1968G>A and c.1968+5G>A leading to production of progerin • LMNA c.1968+1G>A, c.1968+5GC>A and c.1868C>G] [Non-laminopathy progeroid syndromes are not eligible for inclusion] Subgroups of interest: - Hutchinson-Gilford Progeria Laminopathy - Processing-deficient progeroid laminopathies
I – Intervention	Oral lonafarnib (SCH 66336; Zokinvy) [lonafarnib treatment is in the form of oral capsules, administered twice daily]

	[Patients could be receiving some supportive care (such as physiotherapy, dietetic support, occupational therapy and psychological support) and medical care (medications that treat the cardiovascular complications (e.g. aspirin, statins) neurological or musculoskeletal complications (e.g. bisphosphonates) of the disease)] [The recommended starting dose is 115 mg/m^2 twice daily, before increasing to 150 mg/m^2 twice daily after 4 months of treatment. Dosing is based on body surface area]
C – Comparator(s)	No oral lonafarnib [Patients could be receiving some supportive care (such as physiotherapy, dietetic support, occupational therapy and psychological support) and medical care (medications that treat the cardiovascular complications (e.g. aspirin, statins) neurological or musculoskeletal complications (e.g. bisphosphonates) of the disease)]
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. As this is a progressive and life-long condition, there are no timepoints of particular interest thus changes against the progression trajectory must be noted. *<u>Critical to decision-making:</u>* • **Survival rate** *This outcome is important to patients because it reflects how long people live with treatment, although it does not take the cause of death into account or provide information about their health and wellbeing during that time.* [This can be reported as survival, life-expectancy, or mortality rate] • **Cardiovascular outcomes** *This outcome is important to patients, as the majority of deaths in this condition are caused by cardiovascular complications (myocardial infarctions and heart failure), therefore, an improvement in cardiovascular changes could improve mortality and morbidity.* [Rates of heart failure, or episodes of myocardial infarction are of particular importance. Other outcomes are carotid-femoral pulse wave velocity, carotid artery echo-density, prevalence of blood vessel plaque, left ventricular hypertrophy, aortic stiffness, systolic and diastolic blood pressure adjusted for age] • **Weight gain** *This is important to patients because it reflects an improvement in their nutritional status, growth and can result in changes in their appearance that they might find valuable. It also provides physical evidence of treatment response.* [This can be measured by rate or percentage of weight gain, body mass index or growth Z score] *<u>Important to decision-making:</u>* • **Neurological outcomes**

	This is important to patients because they frequently report neurological symptoms that can reduce their quality of life and can result in disability. [This can be reported as number of intracerebral infarcts, number of transient ischemic attacks, headache frequency, and seizure frequency] • **Audiological outcomes** *This is important to patients because hearing loss is associated with this condition, and improved low frequency hearing may improve their ability to function in their activities of daily living and social lives.* [This can be measured by sensorineural or conductive hearing loss] • **Bone structure** *This is important to patients because osteoporosis and osteopenia can be a consequence of this condition, and improved bone strength can reduce risks of painful fractures and subsequent reduced mobility.* [This can be measured by strength strain index (SSI), areal bone mineral density (bone mineral density per unit area g/cm^2), volumetric bone mineral density, rate of bone fractures, structural rigidity parameters, rate of dislocations] • **Plasma progerin** *Progerin is the pathogenic protein that causes organ damage in these patients. A reduction in plasma progerin is important to patients as it potentially indicates that treatment is reducing disease progression, comorbidities, and potentially increasing life-expectancy.* [This is measured by plasma or serum progerin] • **<u>Safety</u>** *Safety of lonafarnib is important to patients as it allows patients to make an informed response when considered commencing treatment.* [Examples include, but not limited to: • Toxicity • Frequency of adverse events • Mortality attributed to the drug • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2024

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 12 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, guidelines and case reports were excluded.

Search dates: 01 January 2012 to 24 May 2024

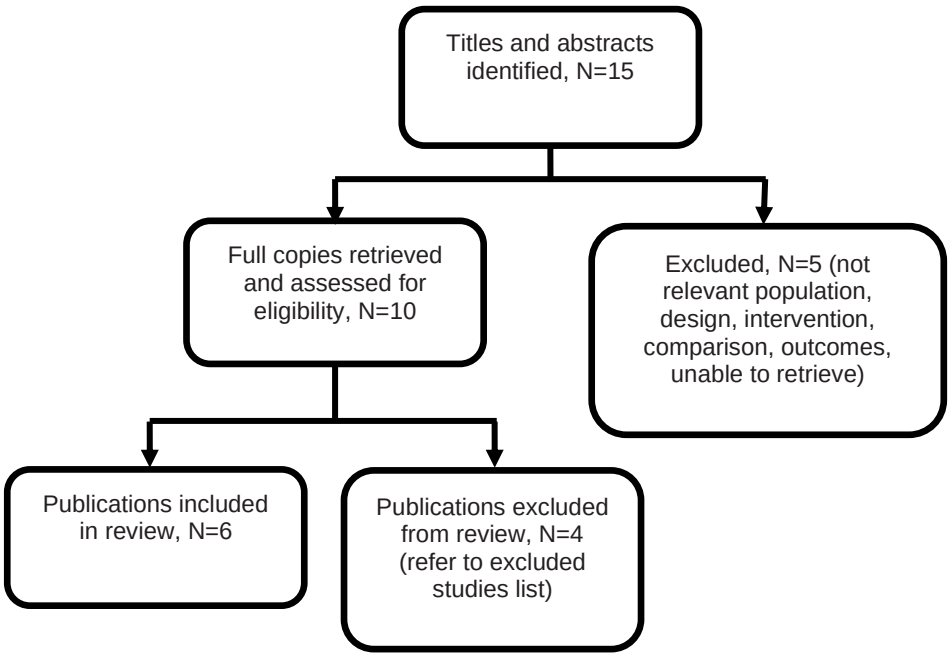
Medline search strategy

1	("23012407" or "29710166" or "36919608").ui.
2	Progeria/
3	(progeria? or progeroid or hgps or hutchinson gilford).mp.
4	2 or 3
5	Farnesyltranstransferase/ai [Antagonists & Inhibitors]
6	(lonafarnib or zokinvy or sch 66336 or sch66336).mp.
7	(farnesyl* adj3 (inhibitor? or block*)).ti,ab,kf.
8	5 or 6 or 7
9	4 and 8
10	limit 9 to (english language and yr="2012 -Current")

Appendix C Evidence selection

The literature searches identified 15 references. These were screened using their titles and abstracts and 10 references were obtained in full text and assessed for relevance. Of these, six references are included in the evidence summary. The remaining four references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Gordon LB, Kleinman ME, Miller DT, Neuberg DS, Giobbie-Hurder A, Gerhard-Herman M, Smoot LB, Gordon CM, Cleveland R, Snyder BD, Fligor B, Bishop WR, Statkevich P, Regen A, Sonis A, Riley S, Ploski C, Correia A, Quinn N, Ullrich NJ, Nazarian A, Liang MG, Huh SY, Schwartzman A, Kieran MW. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2012 Oct 9;109(41):16666-71. doi: 10.1073/pnas.1202529109. Epub 2012 Sep 24. PMID: 23012407; PMCID: PMC3478615	Include
Gordon LB, Shappell H, Massaro J, D'Agostino RB Sr, Brazier J, Campbell SE, Kleinman ME, Kieran MW. Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. JAMA. 2018 Apr 24;319(16):1687-1695. doi: 10.1001/jama.2018.3264. PMID: 29710166; PMCID: PMC5933395	Include
Gordon LB, Norris W, Hamren S, Goodson R, LeClair J, Massaro J, Lyass A, D'Agostino RB Sr, Tuminelli K, Kieran MW, Kleinman ME. Plasma Progerin in Patients With Hutchinson-Gilford Progeria Syndrome:	Include

Immunoassay Development and Clinical Evaluation. Circulation. 2023 Jun 6;147(23):1734-1744. doi: 10.1161/CIRCULATIONAHA.122.060002. Epub 2023 Mar 15. PMID: 36919608; PMCID: PMC10237348	

Appendix D Excluded studies table

Study reference	Reason for exclusion
Arnold R, Vehns E, Randl H, Djabali K. Baricitinib, a JAK-STAT Inhibitor, Reduces the Cellular Toxicity of the Farnesyltransferase Inhibitor Lonafarnib in Progeria Cells. Int. 2021;22(14):12.	Study out of scope - in vitro study assessing the effect of combined treatment of lonafarnib plus JAK1/2 STAT1/3 inhibitor (Baricitinib) on cellular function and cell pathways.
Atalaia A, Ben Yaou R, Wahbi K, De Sandre-Giovannoli A, Vigouroux C, Bonne G. Laminopathies' Treatments Systematic Review: A Contribution towards a 'Treatabolome'. Journal of Neuromuscular Diseases. 2021;8(3):419-39.	Systematic review including both in scope and out of scope populations. The three trials including in scope patients (i.e. children with HGPS) were identified in this literature search and were assessed separately; the systematic review does not provide any additional data.
Gordon CM, Cleveland RH, Baltrusaitis K, Massaro J, D'Agostino RB, Sr., Liang MG, et al. Extraskeletal Calcifications in Hutchinson-Gilford Progeria Syndrome. Bone. 2019;125:103-11.	Outcomes out of scope; not assessing CVD/arteries. Calcification outcome not clearly related to bone structure and more relevant studies identified reporting more directly on bone structure outcome stated in the PICO document.
Lai WF, Wong WT. Progress and trends in the development of therapies for Hutchinson-Gilford progeria syndrome. Aging Cell. 2020;19(7):e13175.	Systematic review providing an overview of HGPS treatment over the past 10 years, including preclinical and clinical studies. Clinical studies assessing lonafarnib have been identified in this literature search and assessed separately; the systematic review does not provide any additional data.
Suzuki M, Jeng LJB, Chefo S, Wang Y, Price D, Li X, et al. FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies. Genet Med. 2023;25(2):100335.	Background only - FDA approval summary; reference list checked and no additional evidence identified to those studies identified in this evidence review.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Gordon LB, Kleinman ME, Miller DT, Neuberg DS, Giobbie-Hurder A, Gerhard-Herman M, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2012;109(41):16666-71. **Study location** 16 countries (not specified) **Study type** Prospective, phase II single-arm clinical trial **Study aim** To assess the effectiveness and safety of lonafarnib in children with HGPS who were treated for at least two years **Study dates** May to October 2007	Children with genetically confirmed classic HGPS **Inclusion criteria** Patients aged ≥3 years with clinically and genetically confirmed c.1824 C > T, p. Gly608Gly classic HGPS and adequate organ and marrow function **Exclusion criteria** Patients with non-classic mutations **Total sample size** N=26 **No. of participants in each treatment group** Lonafarnib: N=26 **Baseline characteristics (n=25)**	**Interventions** Oral lonafarnib capsule or liquid suspension every 12 (± 2) hours: initial dose 115 mg/m^2 increased to 150 mg/m^2 after an adjustment period of at least 4 months 24 of 26 children tolerated a dose of 150 mg/m^2; 1 of 26 children escalated from 115 mg/m^2 to 150 mg/m^2 but then de-escalated to 115 mg/m^2 because of brawny oedema in the perineal region (of unknown aetiology), which resolved at the lower dose 1 of 26 children experienced increased bowel gas, vomiting, and gastric pain at 115 mg/m^2 and 150 mg/m^2; after 2 weeks off treatment, lonafarnib was re-started at 115 mg/m^2 and was well tolerated and then escalated to 150 mg/m^2 for the remainder of the study duration	Follow-up: 24 to 29 months **Critical outcomes** **Cardiovascular outcomes** Defined as carotid-femoral pulse wave velocity (m/second)[50], median (range) Pre-treatment (n=18):[51] 12.9 (7.2 to 18.8) Follow-up (n=18): the authors stated that carotid-femoral pulse wave velocity *"decreased by a median of 35% (range: 48% decrease to 26% increase, P = 0.0001)"* *Median change from pre-treatment to follow-up: −4.5 (range −7.4 to 1.9)* The authors reported that when only children aged ≥7 years old were included (published normal values encompass ages ≥7 years), there was no difference in results, but data were not presented in the paper Defined as carotid artery echodensity,[52] median density in pixels (range)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Yes for 25 children, no for 1 child 7. Yes for 25 children, no for 1 child 8. Yes 9. No 10. Unclear **Other comments:** This phase II single-arm clinical trial included 75% of identified HGPS cases at the time of study enrolment and an estimated 13% of the population worldwide. 26 patients were enrolled in the study, but one child with a history of prior strokes died of a stroke after 5 months on

[50] Fasting carotid-femoral pulse wave velocity was measured using the propagation time of the pressure pulse from the carotid to femoral arteries.
[51] The authors reported that carotid-femoral pulse wave velocity in 18 patients was 3.5 times greater than the established paediatric normal values, indicating high arterial stiffness and low distensibility.
[52] Carotid artery echodensity is the measure of arterial wall density (thickness), with greater wall density associated with vascular abnormalities (therefore a decrease in wall thickness indicates benefit).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Age at study enrolment (years), mean (SD; range) 7.0 (3.0; 3.0 to 16) Sex (male), n (%) Male: 11 (44) Weight (kg), mean (SD; range) 10.4 (2.7; 6.6 to 17.6) Z-scores[49] for weight, mean (SD; range) -10.18 (5.9; -33.69 to -5.3) Height (cm), mean (SD; range) 94.9 (11.9; 76.7 to 122.0) Z-scores[49] for height, mean (SD; range) -5.41 (1.33; -7.34 to -3.47)	**Comparators** None (the included patients acted as their own control by comparing outcomes pre-treatment to the same outcomes while receiving treatment) 5 (19.2%) patients received recombinant growth hormone therapy (1 achieved successful weight gain and 4 did not); 2 (7.7%) patients received antihypertensive treatment (angiotensin-converting enzyme inhibitor or calcium-channel blocker). No further details were reported Treatment duration: 24 to 29 months	*Carotid artery intima media (50th percentile)* Pre-treatment (n=22): 87.0 (15.0 to 242.0) Follow-up (n=22): 72.0 (2.0 to 140.0); *difference between pre-treatment vs follow-up: p=0.002* *Carotid artery adventitia luminal near wall (50th percentile)* Pre-treatment (n=22): 228.0 (61.0 to 254.0) Follow-up (n=22): 170.0 (70.0 to 252.0); *difference between pre-treatment vs follow-up: p=0.003* *Carotid artery adventitia deep near wall (50th percentile)* Pre-treatment (n=22): 167.0 (30.0 to 254.0) Follow-up (n=22): 121.0 (12.0 to 215.0); *difference between pre-treatment vs follow-up: p=0.05* Defined as frequency of ECG abnormalities, n (%) Pre-treatment (n=26): 8 (31) Follow-up (n=25): 4 (16); 14 (54) patients had no abnormalities at any time over the study duration The authors stated that *"major ECG abnormalities on 12-lead ECG did not change significantly during the course of the study"*	the study; baseline characteristics were not reported for this child and data for all 26 children are only available for the outcomes of interest ECG abnormalities and safety. Data for other outcomes were not reported in all children due to their inability to perform various tests because of age or fragility. The authors did not provide demographic details of the included sites/clinics and it was unclear whether statistical analyses for secondary outcomes were appropriate as the authors stated that the p-values did not reflect adjustments for multiple comparisons and should therefore only be interpreted descriptively. The authors stated that the study had 90% power to detect a 25% rate of weight gain improvement (the primary outcome). Carotid artery density by ultrasound outcomes were compared between children with HGPS and age- and sex- matched controls without HGPS. Data for this comparator group are not presented in this evidence review because they do not match the comparator group defined in the PICO document (as these patients did not have HGPS). The authors reported pulse wave velocity for the 2 patients receiving antihypertensive treatments, but the

[49] Z-scores were derived from age- and sex-adjusted reference values using 2000 Centres for Disease Control Growth Charts. Negative z-scores indicate that values are below the mean value of the reference population (i.e. values are worse compared to the reference population).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			<u>Defined as ECG changes consistent with LVH (with or without LV strain pattern), n (%)</u> Pre-treatment: NR Follow-up (n=26): 3 (12)[53] The authors stated that *"borderline LVH was identified at entry or transiently during the study in four additional patients (15%). Atrial enlargement was noted in one patient with a history of supraventricular tachycardia"* <u>Defined as isolated nonspecific ST-T wave changes at follow-up, n (%)</u> Pre-treatment: NR *Follow-up* Transiently (n=26): 4 (15) Consistently (n=26): 1 (3.8) patient without other abnormalities The authors reported that *"Prolonged QT intervals (QTc > 0.44 s) were observed only transiently in 4 of 26 patients (15%), although none had QTc >0.45 s or demonstrated persistent QTc prolongation. Two patients had prior history of supraventricular tachycardia before entry, and none had uncontrolled rhythm disturbance identified during the course of study"* **Weight gain**	results did not differ to patients not receiving these treatments. The authors also reported comparisons in carotid artery density by ultrasound between children with HGPS versus age- and sex-matched controls, but the results are not reported in this evidence review. The authors also reported data on carotid artery density for the 10th percentile, but these data are not presented in this evidence review. Reporting on evidence for skeletal rigidity was limited due to data being presented as graphical representations. The authors stated that there were no associations between age at time of treatment and the outcomes that showed improvements at the end of the study duration (i.e. rate of weight gain, pulse wave velocity, echodensity, aBMD, pQCT-derived structural rigidities, and audiology). The authors also reported that significant LVH was identified more in older patients (11.9 years) compared to patients with normal ECGs or with isolated ST-T wave changes (6.7 years). **Source of funding:** The Progeria Research Foundation, the Dana-Farber Cancer Institute Stop & Shop Paediatric Brain

[53] The authors stated that left ventricular hypertrophy tended to be in older patients (i.e. 11.9 years) compared to patients with normal ECGs or those with isolated ST-T wave changes (i.e. 6.7 years). Two of three patients with left ventricular hypertrophy had been prescribed antihypertensive medication before entering the trial.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Weight gain success (defined as >50% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss to a statistically significant weight gain at follow-up)[54], n/N (%) Weight gain success achieved: 9/25 (36) Weight gain success not achieved: 16/25 (64)[55] Defined as rate of weight gain (kg/year) in patients who achieved vs did not achieve weight gain success, median (range) Achieved (n=9): Pre-treatment 0.04 (−0.55 to 0.18); Follow-up 0.52 (0.14 to 1.33); fold change: 5.98 (0.75 to 25.5)[56] Not achieved (n=16): Pre-treatment 0.57 (0.14 to 1.69); Follow-up 0.31 (−0.53 to 0.70); fold change: 0.57 (−1.07 to 1.42) **Important outcomes** **Audiological outcomes** Defined as median sensorineural hearing, n/N (%) Pre-treatment (n=NR): the authors stated that *"Sensorineural hearing*	Tumour Programme, C J Buckley Fund, the Kyle Johnson Fund, and the National Centre for Research Resources, National Institutes of Health Grants.

[54] Weight gain before study enrolment was estimated using least squares regression for the prior year's data.
[55] 10 patients had stable weight (±50%) and six had weight decreases of >50%.
[56] No explanation was provided on how fold change was calculated; therefore this figure could not be interpreted with any confidence.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			was in the normal or low-normal range in both ears for all assessable patients" Follow-up: ≥10 dB improvement in median low-frequency sensorineural hearing: 8/18 (44%); representing improvements in the better-hearing ear (n=18; p=0.008) and poorer-hearing ear (n=16; p=0.002[57]) Median high-frequency sensorineural hearing remained unchanged in both ears (n=5) <u>Defined as conductive hearing loss, n</u> Pre-treatment hearing loss at low frequencies (n=23): 21 Follow-up (n=NR): the authors reported that *"no change was detected in low-frequency hearing in the poorer- or better-hearing ears"* Pre-treatment hearing loss at high frequencies (n=23): 7 Follow-up (n=NR): the authors reported that *"median hearing thresholds were significantly different for high-frequency conductive hearing in the poorer-hearing ear (P = 0.01) but not in the better-hearing ear"*, but the direction of effect was not reported.	

[57] There was a discrepancy in the p value reported in the main publication text (p=0.002) and supplementary data graphical representation (p=0.0002) and we have presented the value reported in the main text.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			The authors also reported that *"From a clinical perspective, no ear changed by ≥10 dB"* **Bone structure**[58] Defined as skeletal rigidity, median % The authors reported that treatment with lonafarnib *"led to median percent increases at the four radial sites tested* [i.e. 4%, 20%, 50%, and 66%] *of 40-50% in axial rigidity, 170-228% in flexural rigidity, and 167-229% in torsional rigidity"* (n=11) Findings at the 20% (n=11), 50% (n=10), and 66% (n=9) radial sites were similar, with the improvements pre-treatment vs follow-up reported to be statistically significant (p=0.007 to p=0.03) Defined as % increase or decrease in SSI at the end of treatment, median At 20% radial site (n=22): 9% increase (17% decrease to 193% increase); *change compared to pre-treatment p=0.002* At 50% radial site (n=13): 9% increase (13% decrease to 30% increase); *change compared to pre-treatment p=0.06* At 66% radial site (n=10): 35% increase (3% decrease to 138%	

[58] aBMD, SSI, and load-bearing capacity (axial [EA], bending [EI], and torsional [GJ] rigidities) were calculated using pQCT images obtained at serial cross-sections through the radius. These rigidity values reflect the structural properties of the cancellous and cortical bones at 4%, 20%, 50%, and 66% distances from the proximal end.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			increase); *change compared to pre-treatment p=0.01* <u>Defined as aBMD, n (% where reported)</u> Clinically significant >3% increase at one or more sites (n=25): 19 (76) Decreases at one or more sites (n=25): 10 (40) The authors reported that *"Seven children experienced both clinically significant losses and gains at different sites. Two children had improvements in all three measured sites: total body, hip, and spine. Ten children had improvements in two of three sites, and seven had improvements in one site only"* *Total body (n=25):* >3% increase: 11[59] >3% decrease: 4 No significant change: 10 *Percent change from pre-treatment to follow-up: p=0.15* *Lumbar spine (n=25):* >3% increase: 11[59] >3% decrease: 7 No significant change: 7 *Percent change from pre-treatment to follow-up: p=0.33*	

[59] A >3% increase from pre-treatment to follow-up was defined as clinically significant.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Hip (n=25): >3% increase: 11[59] >3% decrease: 4 No significant change: 10 *Percent change from pre-treatment to follow-up: p=0.03* Defined as vBMD The authors stated that radius vBMD was normal pre-treatment and at follow-up, but no further details were reported Defined as fracture incidence, n Pre-treatment (n=25): 3 Follow-up (n=25): 2; p-values were not reported **Safety[60]** Defined as toxicity during entire trial period – mild (grade 1) or moderate (grade 2), n Gastrointestinal[61] (n=26): 49 Constitutional[62] (n=26): 53 Organ function[63] (n=26): 24	

[60] Per patient count is once for that patient's highest toxicity grade, but patients could experience more than one type of toxicity (e.g. for gastrointestinal toxicities, patients could experience diarrhoea, vomiting, dehydration, constipation and dyspepsia).
[61] Including diarrhoea, vomiting, constipation, and dyspepsia.
[62] Including fatigue, nausea, anorexia, and fever.
[63] Including elevated AST, ALT and alkaline phosphatase.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Low absolute leukocyte count[64] (n=26): 43 Metabolic[65] (n=26): 50 Other[66] (n=26): 3 <u>Defined as toxicity during entire trial period – severe (grade 3) or potentially life threatening (grade 4)</u> Gastrointestinal[67] (n=26): 6 [grade 3] Constitutional[68] (n=26): 1 [grade 4] Organ function[69] (n=26): 2 [grade 3] Metabolic[70] (n=26): 5 [grade 3] <u>Defined as toxicity leading to discontinuation</u> The authors reported that *"therapy was well tolerated, and no child came off study because of toxicity"*	
Gordon LB, Massaro J, D'Agostino RB, Sr., Campbell SE, Brazier J, Brown WT, et al. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome.	Patients with classic and non-classic HGPS confirmed by clinical phenotype **Inclusion criteria** Patients with clinically confirmed HGPS by phenotype; information	**Interventions** Previous lonafarnib monotherapy or triple therapy (i.e. lonafarnib, pravastatin and zoledronic acid combined), no further details were reported	Median (IQR) follow-up: 5.3 years (3.3 to 5.5) **Critical outcomes** **Survival rate** <u>Defined as number of deaths, n (%)</u> Treated (n=43): 5 (11.6)[71]	This study was appraised using the JBI checklist for cohort studies. 1. No 2. NA 3. Yes

[64] Including low white blood cell count, low absolute neutrophil count, and low haemoglobin.
[65] Including hypermagnesemia, hyperkalaemia, hypokalaemia, hyponatremia, hypocalcaemia, hypercalcaemia, depressed serum bicarbonate, hypoglycaemia, and hyperglycaemia.
[66] Including granuloma, perineal oedema, Raynaud's phenomenon.
[67] Including diarrhoea, vomiting, and dehydration.
[68] Including fever.
[69] Including elevated AST and ALT.
[70] Including hypokalaemia, and hypoglycaemia.
[71] Three (60%) patients died from cardiovascular failure, one (20%) from head injury, and one (20%) from stroke.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Circulation. 2014;130(1):27-34. **Study location** Africa, Asia, Europe, North and South America **Study type** Matched cohort study **Study aim** To assess survival in treated versus untreated children with HGPS **Study dates** May 2007, no further details reported	on living age or age at death; and inclusion in previous progeria clinical trials **Exclusion criteria** Non-progerin producing progeroid laminopathies **Total sample size** N=86 **No. of participants in each treatment group** Lonafarnib monotherapy or triple therapy (lonafarnib + pravastatin + zoledronic acid: n=43 Untreated **(**i.e. patients not previously treated with lonafarnib): n=43 **Baseline characteristics** Age (years), range Treated: 5.2 to 20.45 Untreated: NR Sex (male), n (%) Treated: 17 (39.5) Untreated: 17 (39.5) Known genotype, n (%)	**Comparators** Untreated (i.e. patients not previously treated with lonafarnib) 5 patients were receiving recombinant growth hormones, but no other details on concomitant treatments were provided Treatment duration: Not reported	Untreated (n=43): 21 (48.8)[72] Defined as Kaplan-Meier survival estimates when follow-up begins at age of treatment initiation for treated vs matched untreated patients (adjusted for different confounding variables) Age- and sex-adjusted HR: 0.13 (95% CI 0.04 to 0.37); p<0.001 (the authors stated that treatment increased mean survival by 1.6 years (95% CI 0.8 to 2.4); p<0.001) Age-, sex- and continent-adjusted HR: 0.15 (95% CI 0.04 to 0.43); p<0.001 **Important outcomes** **Safety** See other comments	4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes **Other comments:** This cohort study compared n=43 treated patients versus n=43 matched untreated patients (matched for age, gender, birth dates, and other potential confounding factors). Treated patients had known genotypes and were identified from previous clinical trials that administered different treatments. Only 55.8% of the historical control group (i.e. untreated patients) had a known genotype. Kaplan-Meier survival estimates were calculated. Untreated patients living as of the start of data analysis, and patients appearing in a published report living at the time of the report, but then lost to follow-up, were censored at the time of last known living age. The authors performed additional analysis to

[72] Cause of death in these patients was unclear as only deaths for the whole untreated population were reported (i.e. cardiovascular failure, head injury or trauma, stroke, respiratory infection superimposed on cardiovascular disease, and complications due to anaesthesia during surgery).

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	Treated: 43 (100) Untreated: 24 (55.8) <u>Mutation group for patients with known genotype, n (%)</u> *c.1824 C>T; p.G608G* Treated: 39 (90.7) Untreated: 18 (75) *c.1822 G>A, p.G608S* Treated: 2 (4.7) Untreated: 1 (4.2) *Intron 11, c.1968+1 G>C* Treated: 0 (0) Untreated: 1 (4.2) *Intron 11, c.1968+1 G>A* Treated: 1 (2.3) Untreated: 2 (8.3) *Intron 11, c.1968+2 T>A* Treated: 0 (0) Untreated: 1 (4.2) *Intron 11, c.1968+2 T>C* Treated: 0 (0) Untreated: 1 (4.2) *Intron 11, c 1968+5 G>C* Treated: 1 (2.3)			include follow-up from birth rather than age of treatment initiation (unadjusted HR: p<0.001). Subgroup comparisons were conducted: male versus female, known versus unknown genotype, <1986 versus ≥1986, and whole cohort versus censored cohort (removing patients who enrolled in treatment trials). The authors did not present data separately for patients with classic or non-classic forms of HGPS. Sensitivity analysis was also conducted to account for potential confounding by excluding or censoring patients who did not enrol in the untreated group due to health issues, patients taking recombinant growth hormones in the treated group, and patients receiving clinical care in hospital. Time-dependent analyses were also conducted on patients born after 1991. Findings from these analyses showed no significant differences between comparison groups, but data are not presented in this evidence review (these were not listed as subgroups of interest in the PICO document). The authors reported brief details on lonafarnib monotherapy related side effects (cross-referencing to Gordon et al 2012) and stated that the triple therapy trial was ongoing, but notable side effects at the time of publication included zoledronic acid related post-infusion flu-like symptoms and pravastatin induced transient muscle discomfort and

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	Untreated: 0 (0)			mildly elevated creatine phosphokinase. Side effects from these trials are reported in the corresponding studies, which are included in this review. **Source of funding:** The Progeria Research Foundation, National Heart, Lung, and Blood Institute, National Institutes of Health.
Gordon LB, Kleinman ME, Massaro J, D'Agostino RB, Sr., Shappell H, Gerhard-Herman M, et al. Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. Circulation. 2016;134(2):114-25. **Study location** 23 countries (not specified) **Study type** Prospective, phase II single-arm clinical trial **Study aim**	Patients with genetically confirmed classic HGPS **Inclusion criteria** Patients aged ≥2 years with clinically and genetically confirmed c.1824 C > T, p. Gly608Gly classic HGPS and adequate organ and marrow function **Exclusion criteria** Not stated **Total sample size** N=37 **No. of participants in each treatment group**	**Interventions** Lonafarnib capsule or liquid suspension every 12 (± 2) hours: 150 mg/m^2 but if not tolerated, dose reductions to 115 mg/^{2} were permitted and then increased back to 150 mg/m^2 Oral pravastatin once every 24 (± 2) hours: 5 mg for patients weighing <10 kg, 10 mg for patients weighing >10 kg IV zoledronic acid: initial infusion 0.0125 mg/kg body weight, then increased to 0.05 mg/kg body weight (infusions over 30 minutes at baseline, at 6, 12, 18 months and end of trial)	Follow-up: 40 to 52 months **Critical outcomes** **Cardiovascular outcomes** Defined as carotid-femoral pulse wave velocity[74] (n=23[75]) The authors stated that triple therapy *"demonstrated no significant changes overall"* (p≥0.05) and that this was the same regardless of whether patients were lonafarnib treatment naïve or non-naïve at trial entry Defined as carotid artery adventitia echodensity, n/N (%) Echodensity success achieved:[76] 11/35 (31.4%)[77] The authors stated that *"all four participants too young to be included*	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. No 10. Unclear **Other comments:**

[74] Carotid-femoral pulse wave velocity was measured using the propagation time of the pressure pulse from the carotid to femoral arteries.
[75] Nine patients had malfunction with ECG-to-ultrasound communication and were not included in the analysis.
[76] A patient was considered improved in echodensity of the deep common carotid artery adventitia 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.
[77] Echodensity analyses included two patients who did not have follow-up echodensity measurements and were counted as echodensity failures.

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To assess the effectiveness and safety of combination treatment (lonafarnib, pravastatin and zoledronic acid) in patients with HGPS **Study dates** Not stated	Lonafarnib + pravastatin + zoledronic acid: N=37 **Baseline characteristics (n=35)[73]** Age (years), mean (SD) 8.0 (4.4) Sex, n (%) Male: 14 (40.0) Weight (kg), mean (SD) 11.0 (2.7) Weight Z-score, mean (SD) -3.96 (0.7) BMI, mean (SD) 11.9 (1.4) Standing height Z-score, mean (SD) -4.8 (1.7)	[3 patients were taking statins at the start of the trial, but no patients had previously received bisphosphonates] **Comparators** None (the included patients acted as their own control by comparing outcomes pre-treatment to the same outcomes while receiving treatment) Oral calcium (500 mg) and vitamin D (1,000 IU) were supplemented daily, with calcium discontinued after 12 months Treatment duration: 40 to 52 months	*in the weight gain analysis experienced echodensity failure"* The authors also stated that *"mean carotid artery wall echodensity of the intima-media, near or deep adventitia…demonstrated no significant changes overall"*; p-values were not reported *Subgroup analyses (echodensity success achieved), n (%)* Lonafarnib treatment naïve (n=13): 8 (61.5) Lonafarnib treatment non-naïve (n=22): 3 (13.6); p-values were not reported Defined as prevalence of carotid artery plaque, n (%) Pre-treatment (n=unclear[78]): 2 (5) Follow-up (n=32): 16[79] (50); *difference compared to pre-treatment p<0.001* *Subgroup analyses, n (%)* Lonafarnib treatment naïve (n=12) Baseline: 0 (0) Follow-up: 4 (33); *difference compared to baseline (p=0.13)* Lonafarnib treatment non-naïve (n=20) Baseline: 2 (10)	This phase II single-arm clinical trial included 37 patients, 24 of whom had received prior lonafarnib monotherapy for at least two years; 13 patients had no prior exposure to lonafarnib (i.e. treatment naïve). There were some discrepancies in the number of patients reported to have data for some outcomes, and also for the number of patients who had previously received lonafarnib monotherapy which was sometimes reported as n=24 or n=25. The authors did not provide demographic details of the included sites/clinics. The authors stated that the study had 82% power to reject the null hypothesis, and that p-values do not reflect adjustment for multiple comparisons, and should be interpreted only descriptively. The authors reported success in primary outcomes (weight gain and echodensity) in treatment naïve and non-naïve patients, but these data are not presented in this evidence review. In addition, the authors reported comparisons in outcomes between triple therapy versus previous lonafarnib monotherapy, but these findings are not reported in this evidence review because the effectiveness of pravastatin and zoledronic acid is not included in the questions for this review (the PICO

[73] Two patients who withdrew voluntarily due to non-medical issues within 6 months of the trial were omitted from the baseline data.
[78] There was a discrepancy in the numbers reported in the table, which indicated n=32, but this did not reflect the 5% stated.
[79] There was a discrepancy in the numbers reported in the text (n=14) and table (n=16) and we have reported the number stated in the table.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Follow-up: 9 (45); *difference compared to baseline (p=0.016)* <u>Defined as prevalence of superficial femoral artery plaque, n (%)</u> Pre-treatment (n=32[80]): 0 (0) Follow-up (n=32): 4 (13); *difference compared to pre-treatment p=0.13* *Subgroup analyses, n (%)* Lonafarnib treatment naïve (n=12) Baseline: 0 (0) Follow-up: 1 (8); *difference compared to baseline (p=1.00)* Lonafarnib treatment non-naïve (n=20) Baseline: 0 (0)[81] Follow-up: 3 (15); *difference compared to baseline (p=0.25)* <u>Defined as prevalence of left ventricular hypertrophy, n (%)</u> Pre-treatment (n=32): 1 (3) Follow-up (n=32): 8 (25) [including the 1 patient who had this pre-treatment]; *difference compared to pre-treatment p=0.016* *Subgroup analyses, n (%)* Lonafarnib treatment naïve (n=12) Baseline: 0 (0)	states that statins and bisphosphonates may be included for patients in the intervention group and the comparator group). The authors reported that there were no pravastatin side effects. Zoledronic acid-related side effects were reported in the paper but are not presented in this evidence review. 5 patients withdrew from the study (2 withdrew voluntarily due to non-medical issues within 6 months of the trial, 3 died during the trial). **Source of funding:** The Progeria Research Foundation, NIH National Heart, Lung, and Blood Institute, The Harvard Clinical and Translational Science Centre.

[80] The authors stated that *"5 patients were too young to tolerate baseline assessment. End-of-therapy assessment showed no plaque; therefore baseline was assumed negative".*
[81] The authors reported that five patients were too young to tolerate baseline assessments, and assessments at follow-up on treatment showed no plaque, baseline values were assumed to be negative.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Follow-up: 2 (17); *difference compared to baseline (p=0.5)* Lonafarnib treatment non-naïve (n=20) Baseline: 1 (5) Follow-up: 6 (30); *difference compared to baseline (p=0.063)* Defined as prevalence of elevated SBP[82] for chronologic age, n (%) Pre-treatment (n=32): 6 (19) Follow-up (n=32): 1 (3); *difference compared to pre-treatment p=0.125* *Subgroup analyses, n (%)* Lonafarnib treatment naïve (n=12) Baseline: 4 (33) Follow-up: 1 (8); *difference compared to baseline (p=0.375)* Lonafarnib treatment non-naïve (n=20) Baseline: 2 (10) Follow-up: 0 (0); *difference compared to baseline (p=0.5)* Defined as prevalence of elevated DBP[82] for chronologic age, n (%) Pre-treatment (n=32): 9 (28) Follow-up (n=32): 2 (6); *difference compared to pre-treatment p=0.065* *Subgroup analyses, n (%)* Lonafarnib treatment naïve (n=12)	

[82] Elevated blood pressure was defined as at or above the 95th percentile.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Baseline: 6 (50) Follow-up: 0 (0); *difference compared to baseline (p=0.031)* Lonafarnib treatment non-naïve (n=20) Baseline: 3 (15) Follow-up: 2 (10); *difference compared to baseline (p=1.0)* **Weight gain** Defined as ≥10% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss to a statistically significant weight gain at follow-up[83], n/N (%) Weight gain success achieved: 15/31[84] (48.4) *Subgroup analyses (≥10% weight gain success achieved at follow-up), n (%)* Lonafarnib treatment naïve (n=9): 4 (44.4) Lonafarnib treatment non-naïve (n=22): 11 (50.0); p-values were not reported Defined as ≥50% increase in estimated annual rate of weight gain compared to pre-treatment, n/N (%)	

[83] A patient was considered improved in rate of weight gain if they experienced either a 10% annualised increase in rate of weight gain compared to pre-study entry, or if annualised change in weight converted from decreasing pre-study entry to increasing on-treatment. Rates of weight change were estimated by the slope of patient-specific least squares regressions versus age using data collected within the year prior to study entry and data collected during treatment.
[84] Four patients were excluded from this analysis *a priori* due to being under the age of three years, which the authors stated is too young to establish weight gain thresholds.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Weight gain success achieved: 9/31[84] (29.0) *Subgroup analyses (≥50% weight gain success achieved at follow-up), n (%)* Lonafarnib treatment naïve (n=9): 3 (33.3) Lonafarnib treatment non-naïve (n=22): 6 (27.2); p-values were not reported **Important outcomes** **Neurological outcomes** Defined as brain infarcts on MRI, n (%) Pre-treatment (n=37): 5 (14) Follow-up (n=37): 3 (8.1) (2 patients developed new infarcts and 1 had infarcts pre-treatment and while on treatment; 4 patients with brain infarcts at baseline did not develop additional infarcts during treatment); p-values were not reported Defined as TIA, n (%) Pre-treatment: NR Follow-up (n=37): 3 (8.1) developed new TIAs (1 of these patients also experienced a new infarct); p-values were not reported Defined as average frequency of headache Pre-treatment (n=NR): 1.2/week Follow-up (n=NR): 0.81/week; p-values were not reported	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Bone structure[85] Defined as load bearing capacity, median (IQR) Bending [EI] ($N \bullet M^2$) *4% radial site* Pre-treatment (n=23 to 24): 695 (353 to 994) Follow-up (n=23 to 24): 855 (696 to 1,076); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 249 (129 to 291) Follow-up: 765 (721 to 866); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 823 (621 to 1,071) Follow-up: 891 (671 to 1,159); *difference compared to baseline (p<0.001)* *20% radial site* Pre-treatment (n=23 to 24): 891 (567 to 1,187)	

[85] vBMD, and load-bearing capacity (axial [EA], bending [EI], and torsional [GJ] rigidities) were calculated using pQCT images obtained at serial cross-sections through the radius. These rigidity values reflect the structural properties of the cancellous and cortical bones at 4%, 20%, 50%, and 66% distances from the distal radial epiphysis. An increase in values indicates benefit.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Follow-up (n=23 to 24): 1,131 (722 to 1,289); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 276 (237 to 495) Follow-up: 1,070 (862 to 1,122); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 1,088 (646 to 1,205) Follow-up: 1,175 (698 to 1,301); *difference compared to baseline (p<0.001)* *50% radial site* Pre-treatment (n=23 to 24): 785 (529 to 1,100) Follow-up (n=23 to 24): 952 (827 to 1,192); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 287 (124 to 361) Follow-up: 942 (755 to 1,054); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 879 (744 to 1,105)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Follow-up: 952 (838 to 1,196); *difference compared to baseline (p<0.001)* <u>Axial [EA] (MN)</u> *4% radial site* Pre-treatment (n=23 to 24): 2.32 (1.44 to 2.83) Follow-up (n=23 to 24): 2.66 (2.34 to 3.14); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 0.98 (0.72 to 1.34) Follow-up: 2.5 (2.41 to 2.62); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 2.56 (2.05 to 3.18) Follow-up: 2.84 (2.27 to 3.53); *difference compared to baseline (p<0.001)* *20% radial site* Pre-treatment (n=23 to 24): 2.18 (1.60 to 2.76) Follow-up (n=23 to 24): 2.70 (2.24 to 3.17); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Baseline: 0.96 (0.71 to 1.70) Follow-up: 2.46 (2.14 to 2.69); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 2.47 (2.11 to 2.81) Follow-up: 2.84 (2.43 to 3.23); *difference compared to baseline (p<0.001)* *50% radial site* Pre-treatment (n=23 to 24): 2.14 (1.51 to 2.98) Follow-up (n=23 to 24): 2.78 (2.23 to 3.26); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 0.81 (0.40 to 1.05) Follow-up: 2.77 (2.39 to 2.83); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 2.64 (2.05 to 3.03) Follow-up: 2.88 (2.23 to 3.31); *difference compared to baseline (p<0.001)* Torsional rigidities [GJ] ($N \bullet M^4$) *4% radial site*	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Pre-treatment (n=23 to 24): 754 (416 to 1,095) Follow-up (n=23 to 24): 868 (711 to 1,087); *difference compared to pre-treatment p=0.0003* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 264 (148 to 331) Follow-up: 781 (738 to 879); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 886 (714 to 1,149) Follow-up: 904 (686 to 1,176); *difference compared to baseline (p=0.03)* *20% radial site* Pre-treatment (n=23 to 24): 925 (593 to 1,233) Follow-up (n=23 to 24): 1,148 (739 to 1,312); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 285 (245 to 514) Follow-up: 1,085 (875 to 1,134); *difference compared to baseline (p=0.03)*	

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			Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 1,122 (718 to 1,241) Follow-up: 1,190 (717 to 1,312); *difference compared to baseline (p<0.001)* *50% radial site* Pre-treatment (n=23 to 24): 798 (536 to 1,121) Follow-up (n=23 to 24): 961 (850 to 1,203); *difference compared to pre-treatment p<0.001* *Subgroup analyses, median (IQR)* Lonafarnib treatment naïve (n=6) Baseline: 292 (129 to 368) Follow-up: 952 (771 to 1,062); *difference compared to baseline (p=0.03)* Lonafarnib treatment non-naïve (n=17 to 18) Baseline: 904 (786 to 1,138) Follow-up: 961 (855 to 1,215); *difference compared to baseline (p<0.001)* Defined as aBMD (it was unclear whether the statistics used for each outcome were the mean or median) Whole body, g/cm^2 (n=31): Pre-treatment 0.49; Follow-up 0.54; *difference compared to pre-treatment p<0.001*	

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			Height-adjusted Z-score whole body (n=19):[86] Pre-treatment -2.75 (-3.20 to -2.10); Follow-up -2.11 (-2.80 to -1.20); *difference compared to pre-treatment p<0.001* Spine, g/cm^2 (n=32): Pre-treatment 0.44; Follow-up 0.52; *difference compared to pre-treatment p<0.001* Height-adjusted Z-score spine (n=19):[87] Pre-treatment -1.68 (-2.50 to -0.80); Follow-up -0.74 (-1.30 to -0.10); *difference compared to pre-treatment p=0.001* Defined as vBMD, median (IQR) 4% radial site (n=24): Pre-treatment 0.73 (0.67 to 0.83); Follow-up 0.89 (0.86 to 1.55); *difference compared to pre-treatment p<0.001* 20% radial site (n=24): Pre-treatment 1.20 (1.08 to 1.32); Follow-up 1.30 (1.24 to 1.76); *difference compared to pre-treatment p=0.006* 50% radial site (n=23): Pre-treatment 1.20 (1.08 to 1.36); Follow-up 1.34 (1.25 to 1.76); *difference compared to pre-treatment p<0.001* Defined as number of children with new fractures during treatment, n (%) Appendicular (n=37): 6 (16)	

[86] Normative values for DXA BMD Z-scores are generally available for ages over three years, with more information available for the spine and whole body compared to the hip. Therefore, no Z-scores were generated for patients with height-age under age three years.
[87] Normative values for DXA BMD Z-scores are generally available for ages over three years, with more information available for the spine and whole body compared to the hip. Therefore, no Z-scores were generated for patients with height-age under age three years.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Skull (n=37): 3 (8) Defined as extraskeletal calcifications (positive by X-ray), n (%) Pre-treatment (n=32): 11 (34.4) Follow-up (n=32): 21 (65.6); *difference compared to pre-treatment p=0.006* The authors reported that *"calcifications were also observed as calcific skin eruptions in 3 participants demonstrated these at baseline, and 7 participants exhibited new eruptions while on triple therapy"* Defined as number of new dislocations during treatment, n (%) Hip (n=37): 3 (8) Shoulder (n=37): 3 (8) **Safety**[88] Defined as lonafarnib toxicity during entire trial period – mild (grade 1) or moderate (grade 2 – excluding zoledronic acid post-infusion toxicity), n – n=37 Gastrointestinal:[89] 41 Constitutional:[90] 41 Organ function:[91] 34	

[88] Per patient count is once for that patient's highest toxicity grade, but patients could experience more than one type of toxicity (e.g. for gastrointestinal toxicities, patients could experience diarrhoea, vomiting, dehydration, constipation and dyspepsia).
[89] Including diarrhoea, dyspepsia, and vomiting.
[90] Including anorexia, fatigue, headache, nausea, and weight loss.
[91] Including elevated AST, ALT, alkaline phosphatase and CPK, and low ANC, ALC, haemoglobin, platelets and WBC.

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			Metabolic:[92] 10 Other:[93] 2 Defined as lonafarnib toxicity during entire trial period – severe (grade 3), n – n=37 Gastrointestinal:[94] 1 Organ function:[95] 4 Defined as post-zoledronic acid infusion toxicity (first 48 hours), n (%) - n=37 Overall, 23 (62) patients experienced post-zoledronic infusion toxicity. *Grades 1 (mild) or 2 (moderate)*[96] Abdominal: 3 (8.1) Chills: 1 (2.7) Dehydration: 1 (2.7) Diarrhoea: 1 (2.7) Fatigue: 3 (8.1) Fever: 12 (32.4) Flu-like syndrome: 1 (2.7) [97] Headache: 3 (8.1)	

[92] Including elevated magnesium and potassium, and low CO_2 and sodium.
[93] Including colitis and dry mouth.
[94] Including diarrhoea.
[95] Including elevated ALT.
[96] Per patient count is once for that patient's highest toxicity grade.
[97] Within 48 hours of zoledronic acid infusions (measured at baseline, months six, 12, 18 and at the end of study treatment), patients developed one or more flu-like symptoms at rates of 11.1%, 25.7%, 14.3%, 2.9% and 6.7%, respectively.

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			Hypocalcaemia: 4 (10.8)[98] Muscle/joint/body pain: 11 (29.7) Nausea: 1 (2.7) Neuropathy: 1 (2.7) Vomiting: 5 (13.5) *Grade 3 (severe)*[96] Hypocalcaemia: 1 (2.7) Defined as pravastatin toxicity - n=37 The authors stated that *"There were no pravastatin-related side effects identified"* Defined as triple therapy toxicity leading to discontinuation The authors reported that *"therapy was well tolerated, and no participant came off study due to treatment-related toxicity"*	
Gordon LB, Shappell H, Massaro J, D'Agostino RB, Sr., Brazier J, Campbell SE, et al. Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. Jama. 2018;319(16):1687-95. **Study location**	Patients with classic and non-classic HGPS confirmed by clinical phenotype **Inclusion criteria** Patients with clinically confirmed HGPS by phenotype; information on living age or age at death **Exclusion criteria**	**Interventions** Trial 1: lonafarnib every 12 (± 2) hours: initial dose 115 mg/m^2 increased to 150 mg/m^2 after an adjustment period of at least 4 months Trial 2: lonafarnib 150 mg/m^2 **Comparators** Untreated (i.e. patients who had not previously received any clinical trial treatment)	Median (IQR) follow-up (years): Treated: 2.2 (1.4 to 2.3) Untreated: 1.7 (0.6 to 2.2) **Critical outcomes** **Survival rate** *Trial 1 and 2 combined treated patients vs matched untreated patients* Defined as deaths, n (%)	This study was appraised using the JBI checklist for cohort studies. 1. No 2. NA 3. Yes 4. Yes 5. Yes 6. Yes

[98] Patients developed hypocalcaemia (measured at baseline, months six, 12, 18 and at the end of study treatment), at rates of 5.6%, 5.7%, 8.6%, 0%, and 3.3%, respectively.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Africa, Asia, Europe, North and South America **Study type** Matched cohort study **Study aim** To assess mortality rates in patients with HGPS treated with lonafarnib monotherapy versus untreated patients **Study dates** 2007 to 2010 (trial 1) and 2013 (trial 2)	Non-progerin producing progeroid laminopathies **Total sample size** N=126 **No. of participants in each treatment group** Lonafarnib monotherapy: n=63 Untreated (i.e. patients who had not previously received any clinical trial treatment): n=63 **Baseline characteristics** Age (years), mean (SD) Treated: 6.9 (3.7) Untreated: 6.9 (3.7) Sex (male), n (%) Treated: 33 (52.4) Untreated: 33 (52.4) Known genotype, n (%) Treated: 62 (98.4) Untreated: 34 (54.0) Mutation group, n (%) *c.1824 C>T; p.G608G*	Details on concomitant treatments were not provided Treatment duration: Not reported	Treated (n=63): 4 (6.3)[99] Untreated (n=63): 17 (27);[100] p=0.03 Defined as Kaplan-Meier survival estimates in treated vs matched untreated cohorts Unadjusted HR: 0.23 (95% CI 0.06 to 0.90); p=0.04 *Individual analyses* *Trial 1 treated patients vs untreated patients* Median (IQR) follow-up (years): Treated: 2.2 (1.9 to 2.2) Untreated: 2.1 (1.0 to 2.2) Defined as deaths, n (%) Treated (n=27): 1 (3.7) Untreated (n=27): 9 (33.3) Defined as Kaplan-Meier survival estimates in treated vs matched untreated cohorts Unadjusted HR: 0.12 (95% CI 0.01 to 0.93); p=0.04 *Trial 2 treated patients vs matched untreated patients (post hoc analysis)* Median (IQR) follow-up (years): Treated: 2.0 (1.3 to 2.5) Untreated: 1.9 (1.0 to 2.4) Defined as deaths, n (%)	7. Yes 8. Unclear 9. Yes 10. Yes 11. Yes **Other comments:** This cohort study included 63 patients on lonafarnib monotherapy, of which n=27 patients were treated with lonafarnib monotherapy (trial 1), and n=36 patients were treated with lonafarnib monotherapy after treatment with triple therapy (i.e. lonafarnib plus pravastatin and zoledronic acid). The cohort study also included untreated patients from a natural history study (n=103), but only findings for comparisons between treated (n=63) and age-, sex- and continent of residency matched untreated patients (n=63) are presented in this evidence review. 98.4% of treated patients had known genotypes and were identified from two previous clinical trials. Only 54.0% of the historical control group (i.e. untreated patients) had a known genotype. Kaplan-Meier survival estimates were calculated. Untreated patients living as of the start of data analysis, and patients appearing in a

[99] Three (75%) died due to heart failure, one (25%) due to stroke.
[100] Cause of death in the 63 matched untreated patients was not clear. Cause of death for all untreated patients (69 of 124) was due to heart failure (80%), head injury (9%), complications of surgery (4%), stroke (3%), trauma from motor vehicle accidents (3%), and complications of gastroenteritis and pneumonia (1%).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Treated: 59 (95.2) Untreated: 28 (82.4) *c.1822 G>A, p.G608S* Treated: 1 (1.6) Untreated: 1 (2.9) *Intron 11, c.1968+1 G>A* Treated: 1 (1.6) Untreated: 3 (8.8) *Intron 11, c.1968+2 T>A* Treated: 1 (1.6) Untreated: 1 (2.9) *Intron 11, c.1968+2 T>C* Treated: 0 (0) Untreated: 1 (2.9)		Treated (n=36): 3 (8.3) Untreated (n=36): 8 (22.2) Defined as Kaplan-Meier survival estimates in treated vs matched untreated cohorts Unadjusted HR: 0.33 (95% CI 0.07 to 1.59); p=0.17	published report living at the time of the report, but then lost to follow-up, were censored at the time of last known living age. The authors stated that longer term effects on mortality rate would be valuable to determine the potential for lifelong treatment with lonafarnib. Follow-up in trial 2 was incomplete at the time of publication of the included paper and the authors therefore stated that the results were preliminary. Confounding variables were identified and the authors reported subgroup comparisons, including male versus female, known versus unknown genotype, <1991 versus ≥1991, and whole cohort versus censored cohort (removing patients who enrolled in treatment trials). Findings from these analyses showed no significant differences between comparison groups, but data are not presented in this evidence review. Sensitivity analysis was also conducted to account for potential confounding by excluding patients who did not enrol in the untreated group due to health issues, and censoring patients receiving clinical care in hospital. **Source of funding:** The Progeria Research Foundation.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Gordon LB, Norris W, Hamren S, Goodson R, LeClair J, Massaro J, et al. Plasma Progerin in Patients With Hutchinson-Gilford Progeria Syndrome: Immunoassay Development and Clinical Evaluation. Circulation. 2023;147(23):1734-44. **Study location** Not stated **Study type** Cohort study **Study aim** To develop a plasma progerin assay to assess the response to progerin-targeted treatment in patients with HGPS **Study dates** Not stated	Patients with genetically confirmed classic HGPS **Inclusion criteria** Patients with genetically confirmed c.1824 C > T, HGPS **Exclusion criteria** Not stated **Total sample size** N=64 **No. of participants in each treatment group** Trial 1 (lonafarnib monotherapy): n=25 Trial 2 (triple therapy): n=13, then n=10 switched to lonafarnib monotherapy Trial 3 (lonafarnib monotherapy after triple therapy): n=26 **Baseline characteristics** Plasma progerin (pg/mL), mean (SD; median) Trial 1 (lonafarnib monotherapy) (n=26): 27,572 (7542; 27,669)	**Interventions** Trial 1: oral lonafarnib capsule or liquid suspension twice daily; initial dose 115 mg/m^2 increased to 150 mg/m^2 if well tolerated after at least 4 months Trial 2 (triple therapy): oral lonafarnib capsule or liquid suspension twice daily at dose 150mg/m^2, plus oral pravastatin (5 mg or 10 mg)[101] and IV zoledronic acid (0.0125 mg/kg body weight initially, then 0.05 mg/kg every 6 months) Trial 3: oral lonafarnib capsule or liquid suspension twice daily at dose 150mg/m^2 **Comparators** None (the included patients acted as their own control by comparing data to 12 months before treatment with lonafarnib) Details on other concomitant treatments were not provided Treatment duration: 2.2 to 7.6 years (long-term subgroup analysis: 9.8 years (range 9.0 to 10.3)	Follow-up duration: 2.2 to 7.6 years (long-term subgroup analysis: 9.8 years (range 9.0 to 10.3) **Important outcomes** **Plasma progerin** Defined as progerin changes from baseline (i.e. before trial drug initiation) *Trial 1 (lonafarnib monotherapy)* At 4 months (n=25): 48% decrease during the dosing period using 115 mg/m^2 lonafarnib; *difference compared to baseline (p<0.0001)* The authors stated that *"For each of the 5 remaining patient visits where lonafarnib dose was 150 mg/m^2, average decreases from baseline ranged between 50% and 62% (n=22–25 patients, all P<0.0001)"* At 8 months (4 months after transitioning from 115 to 150 mg/m^2 dosing) (n=25): p=0.06; the authors stated that *"at each of the 4 subsequent trial visits, progerin was significantly decreased while taking 150 mg/m^2 of lonafarnib over the 115 mg/m^2 dose (n=22–25 patients, all P<0.05). There were no significant differences between average progerin at the 8-month 150 mg/m^2 visit and subsequent visits at the same drug dose (n=22–25 patients, all P≥0.05)"* *Trial 2 (triple therapy)*	This study was appraised using the JBI checklist for cohort studies. 1. No 2. NA 3. Yes 4. Unclear 5. Unclear 6. No 7. Unclear 8. Yes 9. No 10. Unclear 11. Unclear **Other comments:** This cohort study included treated patients from three clinical trials: Trial 1 (n=25) - patients received oral lonafarnib monotherapy, Trial 2 (n=13) - patients received triple therapy [i.e. lonafarnib + pravastatin + zoledronic acid] but then 10 patients completed lonafarnib monotherapy extension for an additional 4.1 (0.5) years, Trial 3 (n=13) – patients received lonafarnib monotherapy after triple therapy [i.e. lonafarnib + pravastatin + zoledronic acid]. The authors did not present details on patient characteristics.

[101] Children weighing <10 kg were administered 5 mg pravastatin; children weighing >10 kg were administered 10 mg pravastatin.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Trial 2 (triple therapy) (n=13): 31,464 (16,958; 29,787) Trial 3 (lonafarnib monotherapy after triple therapy) (n=35): 38,154 (11,546; 37,225)		At 6 months (n=13): 41% decrease; *difference compared to baseline (p=0.0018)* At subsequent follow-up visits, the authors stated that *"average progerin remained significantly decreased from baseline by 35% to 47% (n=12–13 patients, visits 3–5, P=0.0015–0.0058)"* In patients who discontinued triple therapy and completed lonafarnib monotherapy extension study (n=10) there were no statistically significant differences in average progerin between triple therapy and lonafarnib monotherapy (p=0.99) *Trial 3 (lonafarnib monotherapy after triple therapy)* At 2.4 years (n=26): 36.7% decrease*; difference compared to baseline (p<0.0001)* *Longitudinal analyses*[102] <u>Defined as progerin changes with long-term lonafarnib treatment compared to baseline (i.e. before trial drug initiation)</u> At month 4 (n=13): 48% decrease during the dosing period using 115 mg/m^2; *difference compared to baseline (p<0.0001)* The authors stated that *"For all subsequent time points, average decreases from baseline during 150 mg/m^2 dosing ranged from 56% to*	Statistical analyses were limited and no adjustments were made for multiple comparisons. It was unclear whether confounding variables were identified and taken into account. The authors reported that baseline progerin levels were statistically significantly higher in Trial 3 compared to Trial 1 (p<0.0001), but there were no significant differences in progerin in Trial 1 or Trial 3 compared to Trial 2 (p=0.44 and p=0.12, respectively). Data were not reported for all patients, but the authors did not provide reasons for loss to follow-up. Investigators assessing blood samples were blind to whether they were for patients with or without HGPS (non-HGPS data are not presented in this evidence review). The authors reported data on the association between progerin and patient survival (including blood samples from HGPS and non-HGPS patients); data are not presented in this evidence review. Data on the association between progerin and patient survival were also reported for patients with HGPS, but these data were only presented graphically. Plasma progerin levels were also reported in classic versus non-classic forms of HGPS, but these results have not been reported in this evidence review as it was unclear whether all patients had or

[102] Patients included in the longitudinal analyses, were required to have provided a baseline and end-of-trial on-treatment plasma sample.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			74% (P<0.0001). Compared with the first time point on 150 mg/m^2 (time point 3 at 0.66 year), time points 5, 8, and 9 were significantly lower (P<0.05), and all other time points (4, 6, 7, 10–13) were similar to time point 3 (P≥0.05)"[103]	had not been treated with lonafarnib – the authors stated that baseline to end of study decreases in progerin on treatment in patients with non-classic HGPS (i.e. 40.3% to 57.5%) were not statistically different to patients with classic HGPS (p=0.85). **Source of funding:** The Progeria Research Foundation, DSF Charitable Foundation, US FDA, Singulex SMC technology innovation award.
Ullrich NJ, Kieran MW, Miller DT, Gordon LB, Cho YJ, Silvera VM, et al. Neurologic features of Hutchinson-Gilford progeria syndrome after lonafarnib treatment. Neurology. 2013;81(5):427-30. **Study location** 16 countries (not specified) **Study type** Retrospective analysis of a phase II clinical trial **Study aim** To assess the neurologic status of children with HGPS before and after treatment with lonafarnib	Children with genetically confirmed classic HGPS[104] **Inclusion criteria** Patients aged ≥3 years with clinically and genetically confirmed c.1824 C > T, p. Gly608Gly classic HGPS **Exclusion criteria** Not stated **Total sample size** N=26 **No. of participants in each treatment group**	**Interventions** Oral lonafarnib capsule or liquid suspension twice daily: initial dose 115 mg/m^2 increased to 150 mg/m^2 if well tolerated after at least 4 months; no further details provided **Comparators** None (the included patients acted as their own control by comparing data to 12 months before treatment with lonafarnib) 17 patients were receiving antiplatelet/anticoagulants at study entry (aspirin alone: n=14; aspirin + clopidogrel: n=1; aspirin + clopidogrel +	Follow-up: 24 to 29 months **Important outcomes** **Neurological outcomes** Defined as clinically evident stroke, n (%) Pre-treatment (n=26): 4 (15) Follow-up (n=26): 2 (7.69) The authors stated that *"one child with a history of strokes died of a stroke after 5 months on the study. None of the 3 other patients who had reported clinical strokes at trial entry experienced recurrent TIA or stroke during treatment…one patient with no known history of clinically evident stroke and no prior neuroimaging studies experienced acute*	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. No 10. No **Other comments:**

[103] Timepoints in years: 2 (0.3 years); 3 (0.6 years); 4 (1.0 year); 5 (1.3 years); 6 (1.6 years); 7 (2.2 years); 8 (2.7 years); 9 (3.2 years); 10 (3.7 years); 11 (5.7 years); 12 (7.3 years); 13 (9.8 years).

[104] Although the authors mention the main publication (Gordon et al 2012) and the number of children included in both publications was the same (i.e. 26), there were differences in the baseline characteristics (i.e. age and sex) and it was therefore unclear how much overlap there was across the two populations.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study dates Not stated	Lonafarnib: N=26 **Baseline characteristics (n=26, unless otherwise stated)** Age (years), mean (range) 7.6 (3.0 to 16) Sex, n Male: 10 Female: 16 Neurological features, n (%) Evidence of infarction by MRI (n=13): 8 (62)	acetazolamide: n=1; aspirin + ticlopidine + warfarin + cilostazol: n=1) During treatment with lonafarnib, two children discontinued clopidogrel and one patient discontinued warfarin because of improved clinical symptoms and lack of new strokes or TIAs, although all three children continued with daily aspirin. Two children without prior stroke symptoms discontinued aspirin because of minor bleeding Treatment duration: 24 to 29 months	*hemiparesis accompanied by headache and increased fatigue"*.[105] Defined as average stroke frequency in patients with known strokes Pre-treatment (n=4): 1.75/year (range: 1 to 3 per year) Follow-up (n=2): 0.25/year Defined as TIA, n (%) Pre-treatment (n=4 children with history of strokes): 3 (75) Follow-up (n=4 children with history of strokes): 0 (0) Defined as number of children with headaches[106], n (%) Pre-treatment (n=26): 15 (58) Follow-up (n=25): 7 (28); the authors reported that there were no new patients experiencing headaches during the study *Difference in headache incidence from pre-treatment to follow-up: p=0.005* Defined as average headache frequency Pre-treatment (n=15): 0.9/week Follow-up (n=7): 0.37/week	This retrospective analysis of a phase II clinical trial included 75% of identified HGPS cases at the time of study enrolment and an estimated 10% to 13% of the population worldwide. The authors did not provide demographic details of the included sites/clinics and statistical analyses were limited; the authors acknowledged that neurologic outcomes were not reported as primary or secondary outcomes in the main publication (Gordon et al 2012) because the prevalence rates of clinical stroke, TIA, and seizure were unknown and presumed to be too low to conduct statistical analysis to measure treatment efficacy. The authors only reported statistical measures (i.e. p-values) for one outcome (i.e. the number of children with headaches). Prior MRI was reported for 13 of 26 children at baseline, which showed that 8 of 13 (62%) children had evidence of prior infarction. **Source of funding:** The Progeria Research Foundation, the Dana-Farber Cancer Institute Stop & Shop Paediatric Brain Tumour Programme, C J Buckley Fund, the Kyle Johnson Fund, and the National Centre for Research

[105] The authors reported that CT angiogram showed dense calcification and stenosis of both cervical internal carotid arteries, and follow-up MRI showed a subacute infarction in the left frontal region in the patient with no known history of clinically evident stroke and no prior neuroimaging studies who experienced acute hemiparesis. The authors presumed that baseline cerebrovascular disease in the setting of relative dehydration contributed to the stroke.
[106] The authors reported that headaches had a migraine quality. Photosensitivity was noted in the majority of patients, with or without headache.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Difference in headache frequency from pre-treatment to follow-up: 41% reduction Defined as recurrent or new onset of seizures, n (%) Pre-treatment (n=26): 4 (15) Follow-up (n=25): 0 (0); the authors stated that *"no patient experienced recurrent or new onset of seizures during the study period"*	Resources, National Institutes of Health Grants.

Abbreviations

aBMD: areal bone mineral density; cm: centimetre; CI: confidence interval; dB: decibel; DBP: diastolic blood pressure; ECG: electrocardiogram; FDA: Food and Drug Administration; g: gram; HGPS: Hutchinson-Gilford progeria syndrome; HR: hazard ratio; IQR: interquartile range; IU: international units; IV: intravenous; kg: kilogram; LV: left ventricular; LVH: left ventricular hypertrophy; m: metre; mg: milligram; MRI: magnetic resonance imaging; n: number; NA: not applicable; NR: not reported; pg/mL: picogram/millilitre; pQCT: peripheral quantitative computed tomography; QTc: corrected QT interval; s: second; SBP: systolic blood pressure; SD: standard deviation; SMC: single molecule counting; SSI: strength strain index; TIA: transient ischaemic attack; US: United States; vBMD: volumetric bone mineral density.

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

For abbreviations and footnotes see end of tables

Table 1: Oral lonafarnib vs no oral lonafarnib

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Oral lonafarnib	No oral lonafarnib	Result		
Survival rate (2 matched cohort studies)									
Kaplan-Meier survival estimate, HR (95% CI) at median follow-up of 2.2 years (IQR 1.4 to 2.3) in treated patients and 1.7 years (IQR 0.6 to 2.2) in untreated patients									
1 matched cohort study Gordon et al 2018	Very serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	63	63	Treated (lonafarnib monotherapy): 4 (6.3) deaths[a] Untreated: 17 (27) deaths[b] Unadjusted HR: 0.23 (95% CI 0.06 to 0.90); p=0.04	Critical	VERY LOW
Kaplan-Meier survival estimate when follow-up begins at age of treatment initiation, HR (95% CI) at median follow-up of 5.3 years									
1 matched cohort study Gordon et al 2014	Very serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	43	43	Treated (lonafarnib monotherapy or triple therapy): 5 (11.6) deaths[c] Untreated: 21 (48.8) deaths[d] Age- and sex-adjusted HR: 0.13 (95% CI 0.04 to 0.37); p<0.001 *The authors stated that treatment increased mean survival by 1.6 years (95% CI 0.8 to 2.4); p<0.001*[e]	Critical	LOW
Abbreviations CI: confidence interval; HR: hazard ratio; IQR: interquartile range; n: number.									

1 Risk of bias: very serious limitations due to recruitment of treated and untreated patients from different populations and potential overlap of treated patients within and across the different trials.
2 Imprecision: serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold of 0.8.

a Three (75%) patients died due to heart failure, one (25%) due to stroke.

b Cause of death in these patients was unclear as only deaths for the whole untreated population (not limited to the matched untreated control group) were reported (i.e. heart failure, head injury, complications of surgery, stroke, trauma from motor vehicle accidents, and complications of gastroenteritis and pneumonia).
c Three (60%) patients died from cardiovascular failure, one (20%) from head injury, and one (20%) from stroke.
d Cause of death in these patients was unclear as only deaths for the whole untreated population (not limited to the matched untreated control group) were reported (i.e. cardiovascular failure, head injury or trauma, stroke, respiratory infection superimposed on cardiovascular disease, and complications due to anaesthesia during surgery).
e The authors also reported outcomes for Kaplan-Meier estimates for age-, sex-, and continent-adjusted HRs; when follow-up began at birth with patients placed at risk at the age of treatment initiation; and time-dependent analyses on patients born after 1991. The findings remained statistically significant, indicating increased survival in treated patients.

Table 2: Oral lonafarnib vs no comparator

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Oral lonafarnib	No comparator	Result		
Cardiovascular outcomes (2 prospective, phase II single-arm clinical trials)									
Carotid-femoral pulse wave velocity (m/second),[a] median change (range) at 24 to 29 months follow-up (benefit is indicated by decreased values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	18[b]	0	Pre-treatment: 12.9 (7.2 to 18.8) Median change from pre-treatment to follow-up: −4.5 (−7.4 to 1.9) The authors stated that carotid-femoral pulse wave velocity *"decreased by a median of 35% (range: 48% decrease to 26% increase, p = 0.0001)"*	Critical	VERY LOW
Carotid-femoral pulse wave velocity[a] at 40 to 52 months follow-up (benefit is indicated by decreased values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23[c]	0	The authors stated that triple therapy *"demonstrated no significant changes overall"*; p≥0.05	Critical	VERY LOW
Carotid artery density by ultrasound – intima media (percentile 50), median density in pixels (range) at 24 to 29 months follow-up (benefit is indicated by lower result)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	22	0	Pre-treatment: 87.0 (15.0 to 242.0) Follow-up: 72.0 (2.0 to 140.0) *Difference between pre-treatment vs follow-up: p=0.002*	Critical	VERY LOW

Carotid artery density by ultrasound – adventitia luminal near wall (percentile 50), median density in pixels (range) at 24 to 29 months follow-up (benefit is indicated by lower result)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	22	0	Pre-treatment: 228.0 (61.0 to 254.0) Follow-up: 170.0 (70.0 to 252.0) *Difference between pre-treatment vs follow-up: p=0.003*	Critical	VERY LOW
Carotid artery density by ultrasound – adventitia deep near wall (percentile 50), median density in pixels (range) at 24 to 29 months follow-up (benefit is indicated by lower result)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	22	0	Pre-treatment: 167.0 (30.0 to 254.0) Follow-up: 121.0 (12.0 to 215.0) *Difference between pre-treatment vs follow-up: p=0.05*	Critical	VERY LOW
Carotid artery adventitia echodensity success achieved,[d] n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	35[e]	0	Pre-treatment: NR Follow-up: 11 (31.4) The authors stated that *"all four participants too young to be included in the weight gain analysis experienced echodensity failure"* The authors also stated that *"mean carotid artery wall echodensity of the intima-media, near or deep adventitia…demonstrated no significant changes overall"*	Critical	VERY LOW
Frequency of ECG abnormalities, n (%) at 24 to 29 months follow-up									
1 prospective, phase II single-arm	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Pre-treatment (n=26): 8 (31) Follow-up (n=25): 4 (16)	Critical	VERY LOW

clinical trial (lonafarnib monotherapy) Gordon et al 2012							The authors stated that *"major ECG abnormalities on 12-lead ECG did not change significantly during the course of the study"*		
ECG changes consistent with LVH (with or without LV strain patterns), n (%) at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Pre-treatment: NR Follow-up: 3 (12) The authors stated that *"borderline LVH was identified at entry or transiently during the study in four additional patients (15%). Atrial enlargement was noted in one patient with a history of supraventricular tachycardia"*	Critical	VERY LOW
Prevalence of LVH, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment: 1 (3) Follow-up: 8 (25) [including the 1 patient who had this pre-treatment] *Difference compared to pre-treatment p=0.016*	Critical	VERY LOW
Isolated nonspecific ST-T wave changes, n (%) at 24 to 29 months follow-up									

1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Pre-treatment: NR *Follow-up:* Transiently: 4 (15) Consistently: 1 (3.8) patient without other abnormalities The authors reported that *"Prolonged QT intervals (QTc > 0.44 s) were observed only transiently in 4 of 26 patients (15%), although none had QTc >0.45 s or demonstrated persistent QTc prolongation. Two patients had prior history of supraventricular tachycardia before entry, and none had uncontrolled rhythm disturbance identified during the course of study"*	Critical	VERY LOW
Prevalence of carotid artery plaque, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment (n=unclear[f]): 2 (5) Follow-up: 16 (50)[g] *Difference compared to pre-treatment p<0.001*	Critical	VERY LOW
Prevalence of superficial femoral artery plaque, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment (n=unclear): 0 (0)[h] Follow-up: 4 (13) *Difference compared to pre-treatment p=0.13*	Critical	VERY LOW
Prevalence of elevated SBP for chronologic age,[i] n (%) at 40 to 52 months follow-up									

1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment: 6 (19) Follow-up: 1 (3) *Difference compared to pre-treatment p=0.125*	Critical	VERY LOW
Prevalence of elevated DBP for chronologic age,[i] n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment: 9 (28) Follow-up: 2 (6); *difference compared to pre-treatment p=0.065*	Critical	VERY LOW
Weight gain (2 prospective, phase II single-arm clinical trials)									
Weight gain success (defined as ≥50% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss[j] to a statistically significant weight gain) at 24 to 29 months follow-up, n (%)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	25	0	Weight gain success achieved: 9 (36) (median rate of weight gain pre-treatment: 0.04 [range −0.55 to 0.18] vs follow-up: 0.52 [range 0.14 to 1.33]; fold change: 5.98 [range 0.75 to 25.5])[k] Weight gain success not achieved: 16 (64) (median rage of weight gain pre-treatment: 0.57 [range 0.14 to 1.69] vs follow-up: 0.31 [range −0.53 to 0.70]; fold change: 0.57 [range -1.07 to 1.42])[k,l]	Critical	VERY LOW
≥10% increase in estimated annual rate of weight gain compared to pre-treatment or change in pre-treatment weight loss[j] to a statistically significant weight gain at 40 to 52 months follow-up, n (%)									

1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	31[m]	0	Weight gain success achieved: 15 (48.4)	Critical	VERY LOW
≥50% increase in estimated annual rate of weight gain compared to pre-treatment at 40 to 52 months follow-up, n (%)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	31[m]	0	Weight gain success achieved: 9 (29.0)	Critical	VERY LOW
Neurological outcomes (1 prospective, phase II single-arm clinical trial, 1 retrospective analysis of a phase II clinical trial)									
Clinically evident stroke, n (%) at 24 to 29 months follow-up									
1 retrospective analysis of a phase II clinical trial (lonafarnib monotherapy) Ullrich et al 2013	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Pre-treatment: 4 (15) (average stroke frequency per year: 1.75 [range 1 to 3]) Follow-up): 2 (7.69) (average stroke frequency per year: 0.25 [range not reported]) The authors stated that *"one child with a history of strokes died of a stroke after 5 months on the study. None of the 3 other patients who had reported clinical strokes at trial entry experienced recurrent TIA or stroke during treatment…one patient with no known history of clinically evident stroke and no prior neuroimaging studies experienced acute hemiparesis accompanied by headache and increased fatigue"*[m]	Important	VERY LOW

Brain infarcts on MRI, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Pre-treatment: 5 (14) Follow-up: 3 (8.1) (2 patients developed new infarcts and 1 had infarcts pre-treatment and while on treatment; 4 patients with brain infarcts at baseline did not develop additional infarcts during treatment)	Important	VERY LOW
TIA in children with a history of strokes, n (%) at 24 to 29 months follow-up									
1 retrospective analysis of a phase II clinical trial (lonafarnib monotherapy) Ullrich et al 2013	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4	0	Pre-treatment: 3 (75) Follow-up: 0 (0)	Important	VERY LOW
TIA, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Pre-treatment: NR Follow-up: 3 (8.1) developed new TIAs (1 of these patients also experienced a new infarct)	Important	VERY LOW
Number of children with headaches, n (%) at 24 to 29 months follow-up									
1 retrospective analysis of a phase II clinical trial (lonafarnib monotherapy)	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	25	0	Pre-treatment (n=26): 15 (58) (average headache frequency per week: 0.9) Follow-up (n=25): 7 (28) (average headache frequency per week: 0.37, indicating a 41% reduction in headache frequency); the authors reported that there were no new	Important	VERY LOW

Ullrich et al 2013							patients experiencing headaches during the study *Difference in number of children with headaches from pre-treatment to follow-up: p=0.005*		
Average frequency of headache per week at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	NR	0	Pre-treatment: 1.2 Follow-up: 0.81	Important	VERY LOW
Recurrent or new onset of seizures, n (%) at 24 to 29 months follow-up									
1 retrospective analysis of a phase II clinical trial (lonafarnib monotherapy) Ullrich et al 2013	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	25	0	Pre-treatment (n=26): 4 (15) Follow-up (n=25): 0 (0); the authors stated that *"no patient experienced recurrent or new onset of seizures during the study period"*	Important	VERY LOW
Audiological outcomes (1 prospective, phase II single-arm clinical trial)									
Sensorineural hearing, ≥10 dB improvement in median low-frequency sensorineural hearing, n (%) at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	18	0	Pre-treatment (n=NR): the authors stated that *"Sensorineural hearing was in the normal or low-normal range in both ears for all assessable patients"* Follow-up: improvements in the better-hearing ear (n=18; p=0.008) and poorer-hearing ear (n=16; p=0.002); the authors reported that, clinically, 8 (44%) children experienced ≥10 dB improvement in	Important	VERY LOW

							average low-frequency sensorineural hearing		
Sensorineural hearing, ≥10 dB improvement in median high-frequency sensorineural hearing, n at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Unchanged in both ears for the 5 assessable patients	Important	VERY LOW
Conductive hearing loss at low frequency, n at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	NR	0	Pre-treatment (n=23): 21 Follow-up (n=NR): the authors reported that *"no change was detected in low-frequency hearing in the poorer- or better-hearing ears"* The authors also reported that *"From a clinical perspective, no ear changed by ≥10 dB"*	Important	VERY LOW
Conductive hearing loss at high frequency, n at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	NR	0	Pre-treatment (n=23): 7 Follow-up (n=NR): the authors reported that *"median hearing thresholds were significantly different for high-frequency conductive hearing in the poorer-hearing ear (p = 0.01) but not in the better-hearing ear"*, but the direction of effect was not reported The authors also reported that *"From a clinical perspective, no ear changed by ≥10 dB"*	Important	VERY LOW
Bone structure (2 prospective, phase II single-arm clinical trials)									
Skeletal rigidity,[0] median at 24 to 29 months follow-up (benefit indicated by increase in values]									

1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	0	The authors reported that treatment with lonafarnib *"led to median percent increases at the four radial sites tested* [i.e. 4%, 20%, 50% and 66%] *of 40-50% in axial rigidity, 170-228% in flexural rigidity, and 167-229% in torsional rigidity"* Findings at the 20% (n=11), 50% (n=10), and 66% (n=9) radial sites were similar, with the improvements pre-treatment vs follow-up reported to be statistically significant (p=0.007 to p=0.03)	Important	VERY LOW
Percent increase or decrease in SSI at the 20% radial site,º median (range) at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	22	0	9% increase (17% decrease to 193% increase) *Change compared to pre-treatment p=0.002*	Important	VERY LOW
Percent increase or decrease in SSI at the 50% radial site,º median (range) at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13	0	9% increase (13% decrease to 30% increase) *Change compared to pre-treatment p=0.06*	Important	VERY LOW
Percent increase or decrease in SSI at the 66% radial site,º median (range) at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	10	0	35% increase (3% decrease to 138% increase) *Change compared to pre-treatment p=0.01*	Important	VERY LOW

Gordon et al 2012									
Load bearing capacity – bending rigidity [EI] (N●M^2) at 4% radial site,^{p} median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 695 (353 to 994) Follow-up: 855 (696 to 1,076) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
Load bearing capacity - bending rigidity [EI] (N●M^2) at 20% radial site,^{p} median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 891 (567 to 1,187) Follow-up: 1,131 (722 to 1,289) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
Load bearing capacity - bending rigidity [EI] (N●M^2) at 50% radial site,^{p} median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 785 (529 to 1,100) Follow-up: 952 (827 to 1,192) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
Load bearing capacity - axial rigidity [EA] (MN) at 4% radial site,^{p} median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 2.32 (1.44 to 2.83) Follow-up: 2.66 (2.34 to 3.14) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW

(triple therapy) Gordon et al 2016									
Load bearing capacity - axial rigidity [EA] (MN) at 20% radial site,[p] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 2.18 (1.60 to 2.76) Follow-up: 2.70 (2.24 to 3.17) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
Load bearing capacity - axial rigidity [EA] (MN) at 50% radial site,[p] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 2.14 (1.51 to 2.98) Follow-up: 2.78 (2.23 to 3.26) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
Load bearing capacity - torsional rigidity [GJ] (N●M^4) at 4% radial site,[p] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 754 (416 to 1,095) Follow-up: 868 (711 to 1,087) *Difference compared to pre-treatment p=0.0003*	Important	VERY LOW
Load bearing capacity - torsional rigidity [GJ] (N●M^4) at 20% radial site,[p] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 925 (593 to 1,233) Follow-up: 1,148 (739 to 1,312)	Important	VERY LOW

clinical trial (triple therapy) Gordon et al 2016							*Difference compared to pre-treatment p<0.001*		
Load bearing capacity - torsional rigidity [GJ] (N●M^4) at 50% radial site,[p] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23 to 24	0	Pre-treatment: 798 (536 to 1,121) Follow-up: 961 (850 to 1,203) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
aBMD (total body), n at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	25	0	>3% increase:[q] 11 >3% decrease: 4 No significant change: 10 *Percent change from pre-treatment to follow-up: p=0.15*	Important	VERY LOW
aBMD (whole body), g/cm^2 at 40 to 52 months follow-up[r] (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	31	0	Pre-treatment 0.49 Follow-up 0.54 *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
aBMD height-adjusted Z-score (whole body), at 40 to 52 months follow-up[r] (benefit indicated by increase in values)									
1 prospective, phase II	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	Pre-treatment: -2.75 (-3.20 to -2.10) Follow-up: -2.11 (-2.80 to -1.20)	Important	VERY LOW

single-arm clinical trial (triple therapy) Gordon et al 2016							*Difference compared to pre-treatment p<0.001*		
aBMD (lumbar spine), n at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	25	0	>3% increase:[q] 11 >3% decrease: 7 No significant change: 7 *Percent change from pre-treatment to follow-up: p=0.33*	Important	VERY LOW
aBMD (spine), g/cm^2 at 40 to 52 months follow-up[r] (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment: 0.44 Follow-up: 0.52 *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
aBMD height-adjusted Z-score (spine), at 40 to 52 months follow-up[r] (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	Pre-treatment: -1.68 (-2.50 to -0.80) Follow-up: -0.74 (-1.30 to -0.10) *Difference compared to pre-treatment p=0.001*	Important	VERY LOW
aBMD (hip), n at 24 to 29 months follow-up (benefit indicated by increase in values)									
1 prospective,	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	25	0	>3% increase:[q] 11 >3% decrease: 4	Important	VERY LOW

phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012							No significant change: 10 *Percent change from pre-treatment to follow-up: p=0.03*		
vBMD at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	NR	0	The authors stated that radius vBMD was normal pre-treatment and at follow-up, but no further details were reported	Important	VERY LOW
vBMD at 4% radial site,[s] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	24	0	Pre-treatment: 0.73 (0.67 to 0.83) Follow-up: 0.89 (0.86 to 1.55) *Difference compared to pre-treatment p<0.001*	Important	VERY LOW
vBMD at 20% radial site,[s] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	24	0	Pre-treatment: 1.20 (1.08 to 1.32) Follow-up: 1.30 (1.24 to 1.76) *Difference compared to pre-treatment p=0.*006	Important	VERY LOW
vBMD at 50% radial site,[s] median (IQR) at 40 to 52 months follow-up (benefit indicated by increase in values)									

1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	23	0	Pre-treatment: 1.20 (1.08 to 1.36) Follow-up 1.34 (1.25 to 1.76) *Difference compared to pre-treatment p=0.001*	Important	VERY LOW
Fracture incidence, n (%) at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	25	0	Pre-treatment: 3 (12) Follow-up: 2 (8)	Important	VERY LOW
Number of children with new fractures, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Appendicular: 6 (16) Skull: 3 (8)	Important	VERY LOW
Extraskeletal calcifications (positive by X-ray), n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	32	0	Pre-treatment: 11 (34.4) Follow-up: 21 (65.6) *Difference compared to pre-treatment p=0.006* The authors reported that *"calcifications were also observed as calcific skin eruptions in 3 participants* [who] *demonstrated*	Important	VERY LOW

							these at baseline, and 7 participants exhibited new eruptions while on triple therapy"		
Number of children with new dislocations, n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Hip: 3 (8) Shoulder: 3 (8)	Important	VERY LOW
Plasma progerin (1 cohort study)									
Progerin changes (% change) at 4 months follow-up									
1 cohort study (Trial 1: lonafarnib monotherapy) Gordon et al 2023	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	25	0	48% decrease during the dosing period using 115 mg/m^2 lonafarnib *Difference compared to baseline (i.e. before commencement of the current trial) (p<0.0001)*	Important	VERY LOW
Progerin changes (% change) up to 2.2 years follow-up									
1 cohort study (Trial 1: lonafarnib monotherapy) Gordon et al 2023	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	22 to 25	0	The authors stated that *"For each of the 5 remaining patient visits where lonafarnib dose was 150 mg/m^2, average decreases from baseline* [i.e. before commencement of the current trial] *ranged between 50% and 62% (n=22–25 patients, all P<0.0001)"*[t]	Important	VERY LOW
Progerin changes (% change) at 6 months follow-up									
1 cohort study (Trial 2: triple therapy) Gordon et al 2023	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	13	0	41% decrease *Difference compared to baseline (i.e. before commencement of the current trial) (p=0.0018)*	Important	VERY LOW
Progerin changes (% change) up to 3.5 years follow-up									

1 cohort study (Trial 2: triple therapy) Gordon et al 2023	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	12 to 13	0	At subsequent follow-up visits, the authors stated that *"average progerin remained significantly decreased from baseline* [i.e. before commencement of the current trial] *by 35% to 47% (n=12–13 patients, visits 3–5, P=0.0015–0.0058)"*	Important	VERY LOW
Progerin changes (% change) up to 7.6 years follow-up									
1 cohort study (Trial 2: lonafarnib monotherapy extension) Gordon et al 2023	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	10	0	Differences in average progerin between triple therapy and lonafarnib monotherapy: p=0.99	Important	VERY LOW
Progerin changes (% change) at 2.4 years follow-up									
1 cohort study (Trial3: lonafarnib monotherapy after triple therapy) Gordon et al 2023	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	26	0	36.7% decrease *Difference compared to baseline (i.e. before commencement of the current trial (p<0.0001)*	Important	VERY LOW
Safety (2 prospective, phase II single-arm clinical trials)[u]									
Lonafarnib toxicity – mild (grade 1) or moderate (grade 2),[v] n at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Gastrointestinal: 49 Constitutional: 53 Organ function: 24 Low absolute leukocyte count: 43 Metabolic: 50 Other: 3	Important	VERY LOW
Lonafarnib toxicity – mild (grade 1) or moderate (grade 2),[w] n at 40 to 52 months follow-up									
1 prospective, phase II	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Gastrointestinal: 41 Constitutional: 41 Organ function: 34	Important	VERY LOW

single-arm clinical trial (triple therapy) Gordon et al 2016							Metabolic: 10 Other: 2		
Lonafarnib toxicity - severe (grade 3) or potentially life threatening (grade 4),[x] n at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	Gastrointestinal: 6 [grade 3] Constitutional: 1 [grade 4] Organ function: 2 [grade 3] Metabolic: 5 [grade 3]	Important	VERY LOW
Lonafarnib toxicity -severe (grade 3),[y] n at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Gastrointestinal: 1 Organ function: 4	Important	VERY LOW
Post-zoledronic acid infusion toxicity (first 48 hours) – mild (grade 1) to moderate (grade 2), n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Abdominal: 3 (8.1) Chills: 1 (2.7) Dehydration: 1 (2.7) Diarrhoea: 1 (2.7) Fatigue: 3 (8.1) Fever: 12 (32.4) Flu-like syndrome: 1 (2.7) Headache: 3 (8.1) Hypocalcaemia: 4 (10.8) Muscle/joint/body pain: 11 (29.7) Nausea: 1 (2.7) Neuropathy: 1 (2.7) Vomiting: 5 (13.5)	Important	VERY LOW

Post-zoledronic acid infusion toxicity (first 48 hours) – severe (grade 3), n (%) at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	Hypocalcaemia: 1 (2.7)	Important	VERY LOW
Pravastatin toxicity at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy) Gordon et al 2016	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	The authors stated that *"There were no pravastatin-related side effects identified"*	Important	VERY LOW
Lonafarnib toxicity leading to discontinuation at 24 to 29 months follow-up									
1 prospective, phase II single-arm clinical trial (lonafarnib monotherapy) Gordon et al 2012	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	The authors reported that *"therapy was well tolerated, and no child came off study because of toxicity"*	Important	VERY LOW
Triple therapy toxicity leading to discontinuation at 40 to 52 months follow-up									
1 prospective, phase II single-arm clinical trial (triple therapy)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	37	0	The authors reported that *"therapy was well tolerated, and no participant came off study due to treatment-related toxicity"*	Important	VERY LOW

Gordon et al 2016									

Abbreviations
aBMD: areal bone mineral density; cm: centimetre; dB: decibel; DBP: diastolic blood pressure; ECG: electrocardiogram; g: gram; IQR: interquartile range; kg: kilogram; LV: left ventricular; LVH: left ventricular hypertrophy; m: metre; MRI: magnetic resonance imaging; n: number; NR: not reported; QTc: corrected QT interval; s: second; SBP: systolic blood pressure; SSI: strength strain index; TIA: transient ischaemic attack; vBMD: volumetric bone mineral density.

1 Risk of bias: very serious limitations due to non-consecutive and incomplete inclusion of participants, and it was unclear whether statistical analyses were appropriate as p-values did not reflect adjustments for multiple comparisons.
2. Indirectness: serious indirectness due to the lack of a comparator group.
3. Risk of bias: serious limitations due to non-consecutive and incomplete inclusion of participants.
4. Risk of bias: very serious limitations due to non-consecutive and incomplete inclusion of participants, and unclear statistical analyses.
5. Risk of bias: very serious limitations due to non-consecutive and incomplete inclusion of participants, no adjustment for multiple comparisons, and the potential for overlap in patients as some may have participated in more than one contributing trial.

a Carotid-femoral pulse wave velocity was measured using the propagation time of the pressure pulse from the carotid to femoral arteries.
b The authors stated that carotid-femoral pulse wave velocity was 3.5 times greater than published paediatric normal values in these 18 patients, indicating high arterial stiffness and low distensibility.
c Only 23 of 32 patients were assessable as nine patients had malfunction with ECG-to-ultrasound communication and were therefore not included in the analysis.
d A patient was considered improved in echodensity of the deep common carotid artery adventitia 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.
e Echodensity analyses included two patients who did not have follow-up echodensity measurements and were counted as echodensity failures.
f There was a discrepancy in the numbers reported in the table, which indicated n=32, but this did not reflect the 5% stated.
g There was a discrepancy in the numbers reported in the text (n=14) and table (n=16) and we have reported the number stated in the table.
h The authors stated that *"5 patients were too young to tolerate baseline assessment. End-of-therapy assessment showed no plaque; therefore baseline was assumed negative".*
i Elevated blood pressure was defined as at or above the 95th percentile.
j Weight gain before study enrolment was estimated using least squares regression for the prior year's data. A patient was considered improved in rate of weight gain if they experienced either a 10% annualised increase in rate of weight gain compared to pre-study entry, or if annualised change in weight converted from decreasing pre-study entry to increasing on-treatment. Rates of weight change were estimated by the slope of patient-specific least squares regressions versus age using data collected within the year prior to study entry and data collected during treatment.
k Further details on fold change were not provided and it was therefore unclear how these results should be interpreted
l Ten patients had stable weight (±50%) and six had weight decreases of >50%.
m Four patients were excluded from this analysis a priori due to being under the age of three years, which the authors stated is too young to establish weight gain thresholds.
n The authors reported that CT angiogram showed dense calcification and stenosis of both cervical internal carotid arteries, and follow-up MRI showed a subacute infarction in the left frontal region in the patient with no known history of clinically evident stroke and no prior neuroimaging studies who experienced acute hemiparesis. The authors presumed that baseline cerebrovascular disease in the setting of relative dehydration contributed to the stroke.
o SSI and load-bearing capacity (axial [EA], bending [EI], and torsional [GJ] rigidities) were calculated using pQCT images obtained at serial cross-sections through the radius. These rigidity values reflect the structural properties of the cancellous and cortical bones at 4%, 20%, 50%, and 66% distances from the proximal end.
p vBMD, and load-bearing capacity (axial [EA], bending [EI], and torsional [GJ] rigidities) were calculated using pQCT images obtained at serial cross-sections through the radius. These rigidity values reflect the structural properties of the cancellous and cortical bones at 4%, 20%, 50%, and 66% distances from the distal radial epiphysis. An increase in values indicates benefit.
q A >3% increase from pre-treatment to follow-up was defined as clinically significant.
r Clinically significant >3% increase at one or more sites: 19/25 (76). Decreases at one or more sites: 10/25 (40). The authors reported that *"Seven children experienced both clinically significant losses and gains at different sites. Two children had improvements in all three measured sites: total body, hip, and spine. Ten children had improvements in two of three sites, and seven had improvements in one site only."*
s It was unclear from the paper whether the statistic used was mean or median.

t At 8 months (4 months after transitioning from 115 to 150 mg/m^2 dosing) (n=25): p=0.06; the authors stated that *"at each of the 4 subsequent trial visits, progerin was significantly decreased while taking 150 mg/m^2 of lonafarnib over the 115 mg/m^2 dose (n=22–25 patients, all P<0.05). There were no significant differences between average progerin at the 8-month 150 mg/m^2 visit and subsequent visits at the same drug dose (n=22–25 patients, all P≥0.05)".*

u Per patient count is once for that patient's highest toxicity grade, but patients could experience more than one type of toxicity. (e.g. for gastrointestinal toxicities, patients could experience diarrhoea, vomiting, dehydration, constipation and dyspepsia).

v Gastrointestinal (diarrhoea, vomiting, constipation, and dyspepsia); constitutional (fatigue, nausea, anorexia, and fever); organ function (elevated AST, ALT and alkaline phosphatase); low absolute leukocyte count (low white blood cell count, low absolute neutrophil count, and low haemoglobin); metabolic (hypermagnesemia, hyperkalaemia, hypokalaemia, hyponatremia, hypocalcaemia, hypercalcaemia, depressed serum bicarbonate, hypoglycaemia, and hyperglycaemia); other (granuloma, perineal oedema, Raynaud's phenomenon).

w Gastrointestinal (diarrhoea, dyspepsia, and vomiting); constitutional (anorexia, fatigue, headache, nausea, and weight loss); organ function (elevated AST, ALT, alkaline phosphatase and CPK, and low ANC, ALC, haemoglobin, platelets and WBC); metabolic (elevated magnesium and potassium, and low CO2 and sodium); other (colitis and dry mouth).

x Gastrointestinal (diarrhoea, vomiting, and dehydration); constitutional (fever); organ function (elevated AST and ALT); metabolic (hypokalaemia, and hypoglycaemia).

y Gastrointestinal (diarrhoea); organ function (elevated ALT).

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Cost effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).

Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Reliability	The ability to get the same or similar result each time a study is repeated with a different population or group.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Single-arm trial	A clinical trial in which all participants receive the experimental intervention of interest. This is especially common in phase I and II trials.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between 2 variables (if an association exists) means that the study is statistically significant. The statistical power of a study is primarily related to the number of people included. If too few people are included, any differences in the outcomes will not be statistically significant.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
Validity	Whether a test or study actually measures what it aims to measure. Internal validity shows whether a study or test is appropriate for the question, for example, whether a study of exercise among gym members measures the amount of exercise people do at the gym, not simply whether people join. External validity is the degree to which the results of a study hold true in non-study situations, for example, in routine NHS practice. It may also be referred to as the generalisability of study results to non-study populations.

References

Included studies

- Gordon LB, Kleinman ME, Miller DT, Neuberg DS, Giobbie-Hurder A, Gerhard-Herman M, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2012;109(41):16666-71.
- Gordon LB, Massaro J, D'Agostino RB, Sr., Campbell SE, Brazier J, Brown WT, et al. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. Circulation. 2014;130(1):27-34.
- Gordon LB, Kleinman ME, Massaro J, D'Agostino RB, Sr., Shappell H, Gerhard-Herman M, et al. Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. Circulation. 2016;134(2):114-25.
- Gordon LB, Shappell H, Massaro J, D'Agostino RB, Sr., Brazier J, Campbell SE, et al. Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. Jama. 2018;319(16):1687-95.
- Gordon LB, Norris W, Hamren S, Goodson R, LeClair J, Massaro J, et al. Plasma Progerin in Patients With Hutchinson-Gilford Progeria Syndrome: Immunoassay Development and Clinical Evaluation. Circulation. 2023;147(23):1734-44.
- Ullrich NJ, Kieran MW, Miller DT, Gordon LB, Cho YJ, Silvera VM, et al. Neurologic features of Hutchinson-Gilford progeria syndrome after lonafarnib treatment. Neurology. 2013;81(5):427-30.

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