Summary of risk management plan for Zokinvy (lonafarnib)

This is a summary of the risk management plan (RMP) for Zokinvy (lonafarnib). The RMP details important risks of Zokinvy, how these risks can be minimised, and how more information will be obtained about Zokinvy' s risks and uncertainties (missing information).

Zokinvy's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zokinvy should be used.

This summary of the RMP for Zokinvy should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zokinvy's RMP.

I. The medicine and what it is used for

Lonafarnib is indicated for the treatment of patients 12 months of age and older a genetically confirmed diagnosis of Hutchinson-Gilford Progeria Syndrome or a processing-deficient Progeroid Laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.

Further information about the evaluation of Zokinvy's benefits can be found in Zokinvy's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/zokinvy

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of lonafarnib, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, in the SmPC and PIL addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of lonafarnib, these measures are supplemented with additional risk minimisation measures mentioned below under relevant important risks.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of lonafarnib is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of lonafarnib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of lonafarnib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of Important Risks and Missing Information for Lonafarnib

List of important risks and missing information	
Important identified risks	Diarrhoea, nausea, and vomiting Drug interaction with loperamide Increased AST/ALT
Important potential risks	Drug Interaction with parenterally administered midazolam and other sensitive CYP3A or CYP2C19 substrates Drug interaction with weak CYP3A4 inhibitors Drug interaction with P-gp substrates Drug interaction with select* HMG CoA reductase inhibitors
Missing information	None

*Only lovastatin, simvastatin, and atorvastatin are contraindicated due to CYP3A metabolism

II.B Summary of important risks

Table 2 Summary of Important Risks

Important Identified Risk: Diarrhoea, nausea, and vomiting	
Evidence for linking the risk to the medicine	Gastrointestinal toxicity is a well-known side effect of lonafarnib and have been seen in studies evaluating lonafarnib for other disease states (**Error! Reference source not found.**2008, **Error! Reference source not found.**2015). As found with other molecular-targeted compounds, diarrhoea can be managed by discontinuation of therapy or by use of antidiarrheal drugs. Gastrointestinal adverse reactions (vomiting [85.7%], diarrhoea [77.8%], nausea [38.1%]) were the most frequently reported adverse reactions.
Risk factors and risk groups	Several organs are not affected by premature aging including the gastrointestinal tract (**Error! Reference source not found.**2016). Risk factors for GI disorders among children include a previous history of GI symptoms, children of parents with GI disorders, childhood abuse, anxiety, food allergies, and traveling to foreign countries (**Error! Reference source not found.**2010, **Error! Reference source not found.**1995, **Error! Reference source not found.**2017).
Risk minimisation measures	Routine risk minimisation measures: The SmPC states that the dose of loperamide should not exceed 1 mg daily.

	The SmPC also states: Electrolyte abnormalities (hypermagnesaemia, hypokalaemia, hyponatraemia) have been reported. The severity of gastrointestinal adverse reactions, especially during the first 4 months of treatment, should be closely monitored. When gastrointestinal adverse reactions occur, monitoring the patient's weight, caloric consumption, and fluid volume intake should be done on a regular basis. In some cases, persistent diarrhoea can result in hypovolaemia, which should be treated by infusion or orally. Prevention of treatment of vomiting and/or diarrhoea with an anti-emetic and/or anti-diarrhoeal medicinal product can be considered. For patients who have increased their dose to 150 mg/m^2 twice daily and are experiencing repeated episodes of vomiting and/or diarrhea resulting in dehydration or weight loss, the dose of lonafarnib can be lowered to the starting dose of 115 mg/m^2 twice daily. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL).
Important Identified Risk: Increased AST/ALT	
Evidence for linking the risk to the medicine	Increased alanine aminotransferase was recorded for 14 (50.0% of patients) ProLon1 patients. Of the patients with increased alanine aminotransferase, 11 (78.6%) patients experienced a Grade 1 increase (defined as greater than ULN to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times baseline if baseline was abnormal), 1 (7.1%) patient experienced a Grade 2 increase (defined as >3.0 to 5.0 times ULN if baseline was normal; >3.0 to 5.0 x baseline if baseline was abnormal), and 2 (14.3%) patients experienced a Grade 3 increase (defined as >5.0 to 20.0 x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal).Increased aspartate aminotransferase was recorded for 18 (64.32%) of ProLon1 patients. Of these patients, 17 (94.4%) patients experienced a Grade 1 increase (defined as greater than ULN to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times baseline if baseline was abnormal) and 1 (5.6%) patient experienced a Grade 3 increase (defined as >5.0 to 20.0 x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal).
Risk factors and risk groups	Liver disease
Risk minimisation measures	Routine risk minimisation measures: The SmPC states increased liver enzymes, such as aspartate aminotransferase or alanine aminotransferase, have been reported. Signs and symptoms of reduced liver function should be assessed on a consistent basis. Liver function should be measured annually or at the onset of any new or worsening signs or symptoms of liver dysfunction. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL)
Important Identified Risk: Drug interaction with loperamide	
Evidence for linking the risk to the medicine	When lonafarnib was co-administered with loperamide in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased loperamide (single 2 mg oral dose) C_{max} by 214% and AUC by 299%. In the ProLon1 (BCH 07-01-007), 13 subjects received loperamide either

	intermittently or regularly throughout the trial to prevent or treat diarrhoea. Of these, 7 subjects experienced constipation in response to prophylactic loperamide administration.
Risk factors and risk groups	Patients taking lonafarnib and loperamide.
Risk minimisation measures	Routine risk minimisation measures: The SmPC states: When lonafarnib was co-administered with loperamide in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased loperamide (single 2 mg oral dose) Cmax by 214% and AUC by 299%. The dose of loperamide should not exceed 1 mg daily. In the event more than 1 mg of loperamide daily is to be administered, the dose should be slowly increased with caution as needed to treat diarrhoea. The SmPC also states that patients experiencing diarrhoea and treated with the anti-diarrhoeal loperamide should be monitored for adverse reactions associated with increased exposure to loperamide. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy PD(PL).
Important Potential Risk: Drug Interaction with parenterally administered midazolam and other sensitive CYP3A or CYP2C19 substrates	
Evidence for linking the risk to the medicine	A Phase 1, open-label, single-centre, two-period, single-sequence, multi-drug-drug interaction study in healthy subjects has been completed to evaluate the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose midazolam, a sensitive CYP3A substrate, and in parallel, the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose fexofenadine, a sensitive P-gp substrate. A total of 17 subjects enrolled and completed the study. The results of the study indicate that lonafarnib is a weak inhibitor of P-gp. Based on the findings of this study, sensitive substrates of P-gp with a narrow therapeutic index should be monitored closely during concomitant administration with lonafarnib and ritonavir. In vitro data suggest lonafarnib may inhibit P-gp, as the presence of lonafarnib resulted in a 95.3% inhibition P-gp in Caco-2 clone cell monolayers using digoxin as a probe substrate. An IC_{50} assessment was performed, resulting in an IC_{50} of 0.740 µM. Based on these results, an in vivo confirmatory DDI study was required. In this study, a single 180 mg fexofenadine dose will be administered on 2 separate occasions, with and without multiple-dose lonafarnib. The lonafarnib dose used will be 100 mg twice daily and is expected to maximise steady-state lonafarnib exposures while staying below the maximum tolerated dose. Lonafarnib is a potent in vivo CYP3A mechanism-based inhibitor and, when given concomitantly with either lovastatin, simvastatin or atorvastatin, is expected to increase the plasma concentrations of these statins. This results in an increased risk of myopathy including rhabdomyolysis. *Sensitive CYP3A substrates* When lonafarnib was co-administered with midazolam in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased midazolam (single 3 mg oral dose) C_{max} by 180% and AUC by 639%. This interaction thereby increases the risk of extreme sedation and respiratory depression. *Sensitive CYP2C19 substrates*

	When lonafarnib was co-administered with the CYP2C19 substrate omeprazole in healthy adult subjects, multiple dose lonafarnib (75 mg twice daily for 5 consecutive days) increased omeprazole (single 40 mg oral dose) C_{max} by 28% and AUC by 60%.
Risk factors and risk groups	Concomitant administration of lonafarnib with sensitive CYP3A or CYP2C19 substrates and strong or moderate CYP3A inhibitors or inducers, including herbal supplements.
Risk minimisation measures	Routine risk minimisation measures: The SmPC states that concomitant use of strong CYP3A inhibitors are contraindicated. Concomitant use of medicinal products that are predominately metabolised by CYP3A4, such as midazolam, lovastatin, simvastatin and atorvastatin are contraindicated. The SmPC states that patients requiring parenteral midazolam for a surgical procedure should discontinue lonafarnib for 14 days before and 2 days after administration of midazolam. The SmPC states that patients taking medicinal products that are CYP2C19 substrates should be monitored during this period for potential adverse reactions, with dose adjustments made, as necessary. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL).
Important Potential Risk: Drug interaction with weak CYP3A4 inhibitors	
Evidence for linking the risk to the medicine	Lonafarnib is a potent in vivo CYP3A mechanism-based inhibitor and, when given concomitantly with either lovastatin, simvastatin or atorvastatin, is expected to increase the plasma concentrations of these statins. This results in an increased risk of myopathy including rhabdomyolysis. No interaction studies have been conducted with a weak CYP3A inhibitor. No dose adjustment is considered necessary; however, if the concomitant use of a weak CYP3A inhibitor induces a persistent toxicity, the dose of lonafarnib should be reduced by 50% and QTc monitoring is recommended. When lonafarnib was co-administered with ketoconazole, a strong CYP3A inhibitor, in healthy adult subjects, ketoconazole (200 mg for 5 doses) increased lonafarnib (single dose of 50 mg) C_{max} by 270% and AUC by 425%. This may lead to an increased risk of adverse reactions.
Risk factors and risk group	Concomitant administration of lonafarnib with weak CYP3A inhibitors.
Risk minimisation measures	Routine risk minimisation measures: The SmPC states that if the concomitant use of a weak CYP3A inhibitor induces a persistent toxicity, the dose of lonafarnib should be reduced by 50% and QTc monitoring is recommended The SmPC also states that the patient should resume the BSA indicated dose of lonafarnib 14 days after the toxicity has fully resolved or discontinuation of the weak CYP3A inhibitor. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL).
Important Potential Risk: Drug interaction with P-gp substrates	

Evidence for linking the risk to the medicine	A Phase 1, open-label, single-centre, two-period, single-sequence, multi-drug-drug interaction study in healthy subjects has been completed to evaluate the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose midazolam, a sensitive CYP3A substrate, and in parallel, the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose fexofenadine, a sensitive P-gp substrate. A total of 17 subjects enrolled and completed the study. The results of the study indicate that lonafarnib is a weak inhibitor of P-gp. Based on the findings of this study, sensitive substrates of P-gp with a narrow therapeutic index should be monitored closely during concomitant administration with lonafarnib and ritonavir. In vitro data suggest lonafarnib may inhibit P-gp, as the presence of lonafarnib resulted in a 95.3% inhibition P-gp in Caco-2 clone cell monolayers using digoxin as a probe substrate. An IC_{50} assessment was performed, resulting in an IC_{50} of 0.740 µM. Based on these results, an in vivo confirmatory DDI study was required. In this study, a single 180 mg fexofenadine dose will be administered on 2 separate occasions, with and without multiple-dose lonafarnib. The lonafarnib dose used will be 100 mg twice daily and is expected to maximise steady-state lonafarnib exposures while staying below the maximum tolerated dose. When lonafarnib was co-administered with the P-glycoprotein substrate fexofenadine in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased fexofenadine (single 180 mg oral dose) C_{max} by 21% and AUC by 24%. When lonafarnib is co-administered with P-glycoprotein substrates (*e.g.*, digoxin, dabigatran) where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce the dose of the P-glycoprotein substrate in accordance with its approved product labelling.
Risk factors and risk groups	Concomitant administration of lonafarnib with P-gp substrates.
Risk minimisation measures	Routine risk minimisation measures: The SmPC states when lonafarnib was co-administered with the P-glycoprotein substrate fexofenadine in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased fexofenadine (single 180 mg oral dose) C_{max} by 21% and AUC by 24%. When lonafarnib is co-administered with P-glycoprotein substrates (*e.g.*, digoxin, dabigatran) where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce the dose of the P-glycoprotein substrate in accordance with its approved product labelling. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL).
Important Potential Risk: Drug interaction with select HMG CoA reductase inhibitors	
Evidence for linking the risk to the medicine	A Phase 1, open-label, single-centre, two-period, single-sequence, multi-drug-drug interaction study in healthy subjects has been completed to evaluate the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose midazolam, a sensitive CYP3A substrate, and in parallel, the effects of multiple-dose lonafarnib on the pharmacokinetics of single-dose fexofenadine, a sensitive P-gp substrate. A total of 17 subjects enrolled and completed the study. The results of the study indicate that lonafarnib is a weak inhibitor of P-gp. Based on the findings of this study, sensitive substrates of P-gp with a narrow therapeutic index should be monitored closely during concomitant administration with lonafarnib and ritonavir. Lonafarnib is a potent in vivo CYP3A mechanism-based inhibitor and, when given concomitantly with either lovastatin, simvastatin or atorvastatin, is

	expected to increase the plasma concentrations of these statins. This results in an increased risk of myopathy including rhabdomyolysis.
Risk factors and risk groups	Concomitant administration of lonafarnib with select HMG CoA inhibitors.
Risk minimisation measures	Routine risk minimisation measures: Lonafarnib is a potent *in vivo* CYP3A mechanism-based inhibitor and, when given concomitantly with either lovastatin, simvastatin or atorvastatin, is expected to increase the plasma concentrations of these statins. This results in an increased risk of myopathy including rhabdomyolysis. Therefore, concomitant use of lonafarnib and lovastatin, simvastatin and atorvastatin are contraindicated. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL).

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There is one study which is considered to be a Category 2 study.

Protocol submission date: No later than September 30th, 2022

Study title:

Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Processing Deficient Progeroid Laminopathy (PDPL)

Rationale and study objectives:

HGPS and processing deficient PL (PDPL) are rare genetic disorders characterised by the presence of aging-associated symptoms, including lack of subcutaneous fat, alopecia, swollen veins, growth retardation, age spots, joint contractures, osteoporosis, cardiovascular pathology, and death due to heart attacks and strokes in childhood (**Error! Reference source not found.**2019).

Currently, lonafarnib is the only FDA-approved drug for the treatment of HGPS and processing deficient PLs in patients one year of age and older. Farnesyltransferase inhibitor lonafarnib demonstrated survival benefits in two clinical trials (**Error! Reference source not found.** 2014, **Error! Reference source not found.** 2018). Post-marketing safety data on lonafarnib would be valuable given the potential for lifelong treatment with lonafarnib. This study is intended to collect long-term data on safety and effectiveness of lonafarnib, and patient-reported HRQoL among patients with HGPS and PDPL, which is designated as a post-authorisation safety study (PASS) commitment for European Medicines Agency (EMA).

The overall objective of this study is to evaluate the long-term safety and effectiveness of lonafarnib treatment among patients with HGPS or a processing-deficient PL in real-world clinical care settings and assess important identified and potential risks, and missing information

Primary objective

Among patients with HGPS or a processing-deficient PL managed in a real-world setting:

- Characterise safety events during treatment with lonafarnib including AEs, SAEs, and AESIs including vomiting, diarrhoea, nausea, abdominal pain, constipation, fatigue, upper respiratory tract infection, decreased weight, decreased appetite, and dehydration.

Secondary objectives

- Describe the overall survival
- Evaluate the incidence of MACEs
- Assess HRQoL
- Describe concomitant use of medications that may interact with lonafarnib (loperamide, parenterally administered midazolam and other sensitive cytochrome P450, family 3, subfamily A (CYP3A) or cytochrome P450 2C19 (CYP2C19) substrates, weak cytochrome P450 3A4 (CYP3A4) inhibitors, P-glycoprotein (P-gp) substrates, and select 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors) and occurrence of safety events
- Describe occurrence of increased aspartate transaminase (AST)/ alanine aminotransferase (ALT)
- Describe use of lonafarnib among patients with severe hepatic impairment

II.C.2 Other studies in post-authorisation development plan

There are no additional studies in the post-authorisation development plan.