Summary of Risk Management Plan for Lonapegsomatropin Ascendis Pharma Powder and Solvent for Solution for Injection in cartridge (Lonapegsomatropin)

This is a summary of the risk management plan (RMP) for Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge. The RMP details important risks of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information).

The summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge should be used.

This summary of the RMP for Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current risks will be included in updates of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge is authorised for growth failure in children and adolescents aged 3 up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency, [GHD]) (see SmPC for the full indication). It contains lonapegsomatropin as the active substance and it is given by subcutaneous route of administration.

Further information about the evaluation of the benefits of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge can be found in the EPAR for Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge, 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/lonapegsomatropin-ascendis-pharma.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge, together with measures to minimise such risks and the proposed studies for learning more about the risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC 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 so 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment 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 Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge 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 Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge. Potential risks are where 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).

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Neoplasms (benign, malignant, unspecified) Diabetes mellitus type 2 Medication errors
Missing information	Long-term safety (including adverse drug reactions potentially related to mPEG exposure)

II.B Summary of Important Risks

Important Potential Risk: Neoplasms (benign, malignant, unspecified)	
Evidence for linking the risk to the medicine	Despite theoretical concerns about the effect of GH on tumour development, a review of various clinical and epidemiological studies, examining the relationship between GH treatment and cancer risk in terms of de novo malignancy, recurrence, and secondary neoplasm, demonstrated that there is no clear evidence of a causal relationship between GH treatment in patients with GH deficiency and tumour development. Nonetheless, a small number of studies have reported that childhood cancer survivors who have received GH treatment have a small increased risk of de novo cancer and second malignant neoplasm.
Risk factors and risk groups	GH treatment may, in the case of cancer survivors, increase an individual's risk of developing cancer by increasing the risk of recurrence or secondary malignancy.

Important Potential Risk: Neoplasms (benign, malignant, unspecified)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8.* *In order to inform patients of this risk, corresponding text is also present in the package leaflet.* *There is a contraindication in section 4.3 of the SmPC.* *According to section 4.4 of the SmPC, in patients with previous malignant disease, special attention should be given to signs and symptoms of relapse. Patients with pre-existing tumours or GHD secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process.* *In order to warn patients about this risk, corresponding text is also present in the package leaflet.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *A prospective, non-interventional, long-term, safety study of patients treated with Lonapegsomatropin Ascendis Pharma.* See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Diabetes mellitus type 2	
Evidence for linking the risk to the medicine	Studies investigating the effects of GH on glucose metabolism have demonstrated that GH may increase glucose production through gluconeogenesis and glycogenolysis from the liver and kidney. Patients with acromegaly and human individuals exposed to high doses of GH showed markedly increased gluconeogenesis activity in the liver and kidney. Recently, a review article summarised the available data on glucose metabolism in children with GHD. It was concluded that the reported impact of GHD *per se* on glucose metabolism is quite homogeneous, with the majority of studies reporting no significant difference in metabolic parameters between GHD children and controls. Conversely, GH proves to be more frequently associated with a subtle form of insulin resistance.
Risk factors and risk groups	Risk factors included patients with predisposing risk factors for diabetes mellitus type 2, such as obesity, family history of diabetes, Turner syndrome, Prader-Willi syndrome, or glucocorticoid treatment. The development of diabetes mellitus type 2 was not associated with the dose or duration of GH treatment.

Important Potential Risk: Diabetes mellitus type 2	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8.* *In order to inform patients of this risk, corresponding text is also present in the package leaflet.* *According to section 4.4 of the SmPC, growth hormonemay reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes mellitus, glucose intolerance, or additional risk factors for diabetes mellitus should be monitored closely during lonapegsomatropin therapy.* *In order to warn patients about this risk, corresponding text is also present in the package leaflet.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *A prospective, non-interventional, long-term, safety study of patients treated with Lonapegsomatropin Ascendis Pharma..* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Lonapegsomatropin is indicated for growth failure in children and adolescents aged 3 up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency, [GHD]). The recommended starting dose of lonapegsomatropin is 0.24 mg somatropin/kg body weight, given once weekly. The amount and concentration of lonapegsomatropin is always expressed in terms of mg somatropin referring to the content of the somatropin moiety and not including mPEG-linker in order to prevent medication errors when patients switch from daily somatropin therapy. As requested by the Committee for Medicinal Products for Human Use (CHMP), medication errors are to be considered an important potential risk in order to further characterise any adverse clinical outcome which might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product.
Risk factors and risk groups	Patients not being given sufficient information on how to administer the product may be at higher risk.

Important potential risk: Medication errors	
Risk minimisation measures	Routine risk minimisation measures: *According to section 4.2 of the SmPC, treatment should be initiated and monitored by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. The amount and concentration of lonapegsomatropin is always expressed in terms of mg somatropin referring to the content of the somatropin moiety and not including mPEG-linker in order to prevent medication errors when patients switch from daily somatropin therapy. The posology and administration should be individualised for each patient. The recommended starting dose of Lonapegsomatropin Ascendis Pharma is 0.24 mg somatropin/kg body weight, given once weekly. Lonapegsomatropin Ascendis Pharma is intended to be administered after reconstitution of the powder for solution for injection with the enclosed solvent. Lonapegsomatropin Ascendis Pharma should be administered by means of the GH Auto-Injector.* *The patient and caregiver should receive training to ensure understanding of the administration procedure by means of the device in order to be allowed to (self)-inject lonapegsomatropin.* *In order to warn patients about this risk, corresponding text is also present in the package leaflet.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *A prospective, non-interventional, long-term, safety study of patients treated with Lonapegsomatropin Ascendis Pharma.* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety (including adverse drug reactions potentially related to mPEG exposure)	
Risk minimisation measures	Routine risk minimisation measures: *None.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures:

Missing information: Long-term safety (including adverse drug reactions potentially related to mPEG exposure)	
	None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *A prospective, non-interventional, long-term, safety study of patients treated with Lonapegsomatropin Ascendis Pharma.* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lonapegsomatropin Ascendis Pharma powder and solvent for solution for injection in cartridge.

II.C.2 Other Studies in Post-Authorisation Development Plan

A prospective, non-interventional, long-term, safety study of patients treated with Lonapegsomatropin Ascendis Pharma.

Purpose of the study:

The overarching goal of this study is to further characterise the potential long-term safety risks of Lonapegsomatropin Ascendis Pharma in patients treated with Lonapegsomatropin Ascendis Pharma under real-world conditions in the post-marketing setting.

Primary Objectives:

- To evaluate the occurrence of neoplasms (benign, malignant and unspecified), and diabetes mellitus type 2 in patients treated with Lonapegsomatropin Ascendis Pharma.

Secondary Objectives:

- To evaluate the occurrence of renal, hepatic, immunologic and neurologic adverse events in patients treated with Lonapegsomatropin Ascendis Pharma.
- To evaluate the occurrence of medication errors in patients treated with Lonapegsomatropin Ascendis Pharma.
- To characterise IGF-1 response to therapy.
- To compare the occurrence of neoplasms (benign, malignant and unspecified) in patients treated with Lonapegsomatropin Ascendis Pharma with historical data from literature of paediatric patients with GHD treated with daily somatropin in the registries of NordiNet/ANSWER.
- To compare the occurrence of diabetes mellitus type 2 in patients treated with Lonapegsomatropin Ascendis Pharma with historical data from literature of paediatric patients with GHD treated with daily somatropin in the GeNeSIS registry.

Exploratory objective

- To assess effectiveness by measurement of near adult height (for those who reach near adult height during the course of the study)*

*Near adult height can be defined as:

Height velocity < 2 cm/year over at least 9 months **and**

- Chronological age > 16 years (males) or > 15 years (females) **or**
- Bone age > 16 years (males) and > 15 years (females)