SUMMARY OF THE RISK MANAGEMENT PLAN FOR WAYLIVRA

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

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

This summary of the RMP for WAYLIVRA 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 ones will be included in updates of WAYLIVRA's RMP.

I. The medicine and what it is used for

WAYLIVRA is authorised for use as an adjunct to diet for the treatment of adult patients with genetically confirmed FCS (see SmPC for the full indication). It contains volanesorsen as the active substance and it is given as 300 mg in 1.5 mL injected subcutaneously once weekly using a single-use prefilled syringe.

Further information about the evaluation of WAYLIVRA's benefits can be found in WAYLIVRA'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/waylivra).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of WAYLIVRA, together with measures to minimise such risks and the proposed studies for learning more about WAYLIVRA's 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 the case of WAYLIVRA, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 WAYLIVRA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of WAYLIVRA 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 WAYLIVRA. 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.

List of important risks and missing information	
Important identified risks	Thrombocytopenia Injection site reactions
Important potential risks	Immunogenicity Hepatotoxicity Nephrotoxicity
Missing information	Use in pregnancy and lactation Use in patients with hepatic impairment Use in patients with severe renal impairment Long-term safety Use in elderly

II.B Summary of Important Risks

Important Identified Risk: Thrombocytopenia	
Evidence for linking the risk to the medicine	Clinical Studies CS6, CS16, CS7 and CS2.
Risk factors and risk groups	Patients with thrombocytopenia (< 140 × 10^9/L)
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC: This risk minimisation measure is addressed in Sections 4.2, 4.3, 4.4 and 4.8. Prescription only medicine. PL: Sections 2 and 4. <u>Additional risk minimisation measures</u> Educational materials will be available for potential prescribers, patients and carers and will include information on participation in the

	WAYLIVRA™ Product Registry. The distribution of educational materials will be linked to product distribution from a centralized warehouse for all of Europe and this will enable the Company to have visibility to ordering pharmacies. The product will be shipped along with the Prescriber Kit containing educational materials for the treating physician, dispensing pharmacist and the patient/carer, and with each shipment.
Additional pharmacovigilance activities	<u>Enhanced Pharmacovigilance</u> The following thrombocytopenia-associated events are considered adverse events of special interest (AESI): • Platelet count reduction to < 50×10^9/L with or without bleeding events. • Serious bleeding events associated with death, life-threatening nature, or hospitalisation. Enhanced pharmacovigilance practices will be implemented during the collection, collation, assessment and reporting of thrombocytopenia associated events. All thrombocytopenia-associated events will be actively followed up to achieve a complete dataset for each case. A targeted questionnaire for post-marketing AE reports (spontaneous and organised data collection sources) will be implemented to solicit case details for all reports of thrombocytopenia or platelet count declines. ICSRs of thrombocytopenia AESIs will be expedited to the regulatory authorities within 15 calendar days. Thrombocytopenia-associated events will be reviewed on a monthly basis individually and cumulatively and aggregate safety data will be comprehensively analysed and discussed in PBRERs on an ongoing basis. WAYLIVRA™ Product Registry

Important Identified Risk: Injection site reactions	
Evidence for linking the risk to the medicine	Clinical Studies CS6, CS7.
Risk factors and risk groups	Potential risk factors for injection site reactions: sites where pressure or rubbing may occur from clothing. This medicinal product should not be injected into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC Section 4.2 and 4.8. PL Section 4.
Additional pharmacovigilance activities	Enhanced Pharmacovigilance with active follow-up with targeted questionnaire. Comprehensive evaluation in PBRER. WAYLIVRA™ Product Registry

Important Potential Risk: Immunogenicity	
Evidence for linking the risk to the medicine	Clinical Studies CS6, CS16, CS7 and CS17.

Risk factors and risk groups	WAYLIVRA is contraindicated in patients with a history of hypersensitivity to volanesorsen.
Risk minimisation measures	SmPC Sections 4.4. PL Section 4.
Additional pharmacovigilance activities	Enhanced Pharmacovigilance with active follow-up with targeted questionnaire. Comprehensive evaluation in PBRER. WAYLIVRA™ Product Registry

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical Studies CS6, CS16 and CS7.
Risk factors and risk groups	None identified
Risk minimisation measures	SmPC Section 4.4. PL Sections 2 and 4.
Additional pharmacovigilance activities	Enhanced Pharmacovigilance with active follow-up with targeted questionnaire. Comprehensive evaluation in PBRER. WAYLIVRA™ Product Registry

Important Potential Risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Clinical Studies CS6, CS16 and CS7.
Risk factors and risk groups	None identified
Risk minimisation measures	SmPC Section 4.4. PL Sections 2 and 4.
Additional pharmacovigilance activities	Enhanced Pharmacovigilance with active follow-up with targeted questionnaire. Comprehensive evaluation in PBRER. WAYLIVRA™ Product Registry

Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC: Use in Use in pregnancy and breast feeding is discussed in Section 4.6. PL: Section 2. Prescription only medicine.
Additional pharmacovigilance activities	WAYLIVRA™ Product Registry

Missing Information: Use in Patients with Hepatic Impairment	
Risk minimisation measures	Routine risk minimisation measures SmPC: Use in hepatic impaired patients is discussed in Sections 4.2 and 5.2. Prescription only medicine.
Additional pharmacovigilance activities	WAYLIVRA™ Product Registry

Missing Information: Use in Patients with Severe Renal Impairment	
Risk minimisation measures	Routine risk minimisation measures SmPC: Use in renal impaired patients is discussed in Sections 4.2 and 5.2. Prescription only medicine.
Additional pharmacovigilance activities	WAYLIVRA™ Product Registry

Missing Information: Long-term Safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	WAYLIVRA™ Product Registry

Missing Information: Use in Elderly	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Use in elderly patients is discussed in Sections 4.2, 5.1, and 5.2. Prescription only medicine.
Additional pharmacovigilance activities	WAYLIVRA™ Product Registry

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation:

WAYLIVRA™ Product Registry

Purpose of study: The WAYLIVRA™ Product Registry will enroll patients with FCS prescribed WAYLIVRA. Data on platelet monitoring and dose adjustments and incidence of

thrombocytopenia and bleeding events will be collected for each patient, and periodic safety evaluations will be provided to the EMA in interim annual registry reports and the PBRER.

This registry will enroll patients treated with WAYLIVRA and will monitor the incidence and risk of thrombocytopenia (and any bleeding outcomes associated with thrombocytopenia), as well as adherence with platelet monitoring and dose adjustment requirements in the SmPC. The registry will also monitor hepatotoxicity, renal toxicity, severe injection site reactions, immunogenicity/immunological events, safety in elderly patients, safety in patients with renal or hepatic impairment, outcomes in WAYLIVRA-exposed pregnancies, and the long-term safety profile of WAYLIVRA. Efficacy outcomes in terms of triglyceride reduction and clinical outcomes of pancreatitis events will also be monitored. All enrolled patients will be prospectively followed to collect data while they are on treatment with WAYLIVRA and for twelve months following treatment termination. The registry will exist for the commercial life of the drug. The registry will also aim to collect targeted retrospective FCS disease data from the patient's medical history prior to registry enrollment.

Information on the registry will be included in educational materials for prescribers and patients. These will be available to all prescribers and will also be available to pharmacists and clinic staff (e.g., nurses, counsellors) and will provide information on the objectives of the registry, the importance of the registry, which is being conducted at the request of the CHMP as a Condition of the Marketing Authorisation.

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

Not applicable.