A non-interventional Post Authorization Safety Study (PASS) to evaluate long-term safety of Orfadin treatment in hypertyrosinemia type 1 (HT-1) patients in standard clinical care

Title	A non-interventional Post Authorization Safety Study (PASS) to evaluate long-term safety of Orfadin treatment in hypertyrosinemia type 1 (HT-1) patients in standard clinical care
Protocol version identifier	Sobi.NTBC-005
Date of last version of protocol	25 November 2016 (Version 2.1 Non-substantial Amendment) 22 September 2015 (Version 2.0 Substantial Amendment) 19 December 2013 (Version 1.2 Non-substantial amendment) 3 July 2013 (Version 1.1 Non- substantial amendment) 9 April 2013 (Version 1.0 original Protocol)
EU PAS register number	ENCEPP/SDPP/3636
Active substance	ATC code: A16A X04, other alimentary tract and metabolism products Nitisinone, 2-[2-nitro-4-(trifluoromethyl)benzoyl] cyclohexane-1,3-dione
Medicinal product	Orfadin capsules, 2 mg, 5 mg, 10 mg, 20 mg and Orfadin oral suspension 4 mg/ml
Product reference	EU/1/04/303/001-003
Procedure number	EMEA/H/C/000555
Marketing authorization holder	Swedish Orphan Biovitrum International AB, SE-112 76 Stockholm, Sweden
Joint PASS	No
Research question and objective	The primary objective is to assess long-term safety of Orfadin used in standard clinical practice to treat patients with HT- 1.
Countries of study	The study will be started in Italy, France, Germany, Spain and UK. The following countries will follow; Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, Iceland, Liechtenstein and Norway.
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promptly notified.

Marketing authorization holder

Marketing authorization holder	Swedish Orphan Biovitrum International AB SE-112 76 Stockholm, Sweden
MAH contact person	[redacted] Regulatory Affairs Manager Swedish Orphan Biovitrum [redacted] SE-112 76 Stockholm T: +46 8 697 20 00

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2 List of abbreviations

Abbreviation	Term
AE	Adverse event
AFP	Alfa-fetoprotein
IEC	Independent ethics committee
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract research organization
eCRF	electronic Case Report Form
FAH	Fumarylacetoacetate hydrolase
HT-1	Hereditary tyrosinemia type 1
ICF	Informed consent form
MAH	Market authorization holder
PMS	Post-marketing surveillance program
p-Phe	Plasma phenylalanine
PSUR	Periodic Safety Update Report
p-Tyr	Plasma tyrosine
SA	Succinylacetone
SAE	Serious adverse event
Sobi	Swedish Orphan Biovitrum

3 Responsible parties

The parties specified below are responsible for the conduct of the study.

Study Contacts	Contact Name/Address	Telephone/Fax Number & Email
Sponsor	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm, Sweden	T: +46 8 697 20 00
Medical Director	[redacted] Medical Director Swedish Orphan Biovitrum SE-112 76 Stockholm, Sweden	[redacted]
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Study Project Manager	[redacted] Clinical Program Leader Swedish Orphan Biovitrum SE-112 76 Stockholm, Sweden	[redacted] T: +46 8 697 20 00
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Contract Research Organization (CRO)	Administrative set-up locally	Administrative set-up locally
Main Author	[redacted] Clinical Program Leader Swedish Orphan Biovitrum SE-112 76 Stockholm, Sweden	[redacted] T: +46 8 697 20 00
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4 Abstract

Title	A non-interventional Post Authorization Safety Study (PASS) to evaluate long-term safety of Orfadin treatment in hypertyrosinemia type 1 (HT-1) patients in standard clinical care
Rationale and background	Orfadin® (nitisinone) was approved by the EMA (European Medicines Agency) 21 February 2005 for the treatment of HT-1, which is a multisystemic disease affecting the liver, kidneys and peripheral nerves. The only other treatment available for this fatal condition is liver transplantation. As required by the Committee for Medicinal Products for Human Use (CHMP), a post-marketing surveillance (PMS) program to monitor hepatic, renal, hematological, neurological and ophthalmic status in all patients treated with Orfadin has been ongoing since the approval of Orfadin. To date, data has been collected and summarized in the Periodic Safety Update Reports (PSUR) for approximately 400 patients. At the annual re-assessment in 2009 the CHMP concluded that the benefit-risk balance was positive. However, Swedish Orphan Biovitrum Sobi was requested to continue to collect data and to report the results in the annual PSURs. The present non-interventional PASS will replace the ongoing PMS. The transition will be gradual, starting in 2013 in countries with the largest number of HT-1 patients (France, UK, Germany, Italy and Spain). The protocol for this study is developed in accordance with the guidance for the format and content of the protocol of a non-interventional PASS (**1**). The protocol will be published in the EU PAS register.
Research question and objectives	The primary objective is to assess long-term safety of Orfadin used in standard clinical practice to treat patients with HT-1.
Study design	This is a long-term non-interventional, non-comparative, multicenter PASS to collect retrospective and prospective longitudinal data in the normal clinical setting where HT-1 patients are treated. Data will be collected from patients receiving Orfadin at the time of market authorization 21 February 2005 (index date) as well as patients starting treatment after this date. No data will be collected for the period prior to the index date. The patients will be followed as long as they are treated or to the planned end of the study September 2019. Data will be captured at least once every year. However, investigators will be encouraged to collect and report data following each routine patient visit. The chosen design is acceptable for a study with the primary objective of assessing long-term safety of Orfadin used in HT-1 patients under standard clinical care
Population	HT-1 patients on Orfadin treatment in standard clinical care at study entry as well as patients diagnosed and starting Orfadin treatment during the time of the study.

Variables	The primary endpoints are occurrence of adverse events (AEs) related to hepatic, renal, ophthalmic, hematological or cognitive, developmental function, respectively. The following secondary endpoints will be assessed: • Occurrence of liver transplantation or death • Occurrence of death • Occurrence of liver transplantation • Occurrence of hepatic malignancy • Occurrence of other malignancies • Occurrence of incorrect administration of the oral suspension formulation of Orfadin • Occurrence of other AEs • Discontinuation of Orfadin treatment • Laboratory investigations (Plasma tyrosine (p-Tyr), Plasma phenylalanine (p-Phe), Plasma, serum or dry blood spot concentrations of succinylacetone (SA), Urinary SA, Plasma alfa-fetoprotein (AFP) • Treatment and Diet compliance • Extent of exposure (daily dose of Orfadin, plasma,serum or dry blood spot concentrations of nitisinone) • Overall clinical condition
Data sources	Prospective and retrospective post authorization safety data since the EU approval of Orfadin 21 February 2005 will be collected in this study. The patients' hospital case records will be the source for all data. The investigators will verify the transfer of relevant prospective data to the electronic Case Report Form (eCRF) designed for the study. Retrospective data collected in the ongoing PMS for patients participating in this PASS study will be imported to a web-based data entry tool for review of accuracy by the treating physician. Additional retrospective safety data will be obtained from Sobi's safety data base when available. The rational for using this additional retrospective data is to minimize selection bias when estimating event rates.
Study size	The sample size is not based on any formal calculation. All HT-1 patients receiving Orfadin treatment are eligible for entry.
Data analysis	There will be 2 sets of data analyzed: • The complete set including all patients receiving Orfadin at the index date (21 February 2005) or starting thereafter • The subset of patients having their first dose of Orfadin on the index date or later. For the complete set, the analyses of primary and secondary endpoints will reflect events occurring and assessments made after the index date. Duration of exposure prior to the index date will be ignored when estimating event rates. As the complete set thus will ignore exposure as well as events prior to the index date the subset of patients who starts treatment with Orfadin after the index date will inform more reliable on the safety profile after the first initiation of Orfadin treatment. For this set of patients the entire duration of treatment will be used when estimating event rates.
Milestones	The study will start in September 2013 and end in September 2019 with a final report prepared in April 2020. Safety data will be presented in the annual PSURs during the study period.

5 Amendments and updates

There are three non- substantial amendments, dated 3 July 2013, 19 December 2013 and 25 November 2016. One substantial amendment dated 22 September 2015.

6 Milestones

The study will run over a period of 6 years. Planned dates for initiation, safety reports during the study period, completion and final report are shown below.

Milestone	Planned date
Start of data collection	September 2013
End of data collection	September 2019
Periodic Safety Update Report (PSUR) 11	Data cut-off February 2014
PSUR 12	Data cut-off February 2015
PSUR 13	Data cut-off February 2016
PSUR 14	Data cut-off February 2017
PSUR 15	Data Cut off February 2018
PSUR 16	Data Cut off February 2019
PSUR 17, Final report of study results	April 2020

7 Rationale and background

HT-1 is an ultra-orphan disease. There are fewer than 1,000 patients known worldwide. HT-1 is caused by a defect in fumarylaceoacetate hydrolase (FAH), the final enzyme in the pathway of the degradation of tyrosine. As a result, toxic metabolites are formed, primarily in the liver and kidneys. One of the metabolites is succinylacetone (SA) and can be readily detected in plasma or urine of affected (untreated) patients. This is a pathognomic test for the diagnosis of HT-1. Tyrosine levels in plasma might be raised by 0-30 %. The liver is often the most severely affected organ. Acute liver failure already during the first months of life is common. If the disease is untreated, patients will develop cirrhosis and liver nodules, potentially resulting in liver cancer, hepatocellular carcinoma (HCC). Alfa-fetoprotein (AFP) is a marker of liver regeneration and is often elevated in newly diagnosed patients due to ongoing liver damage by formation of the toxic tyrosine metabolites. It could also signal development of malignancy. Patients can present with acute, subacute or chronic forms of HT-1. Patients with the acute form

generally present with liver failure before the age of 6 months. The subacute form is somewhat less severe, but will usually result in liver disease before one year of age, whereas the chronic form mainly results in liver cirrhosis and/or kidney disease. Newborn screening has been implemented in some regions, but is still lacking in most parts of Europe.

Before 1991, treatment of HT-1 was based on diet to lower tyrosine intake, and eventually liver transplantation. However, the prognosis was generally very poor (2 van Spronsen 1994, 3 Larochelle 2012). In 1991 an open-label study with nitisinone was initiated.

Nitisinone is an enzymatic competitive inhibitor of one of the enzymes of the tyrosine catabolic pathway, developed for the treatment of hereditary tyrosinemia type 1 (HT-1). By inhibiting 4-hydroxyphenylpyruvate dioxygenase, an enzyme which precedes FAH, nitisinone prevents the accumulation of the toxic intermediates maleylacetoacetate and Fumarylacetoacetate as well as SA. Successful treatment leads to rapid decrease in plasma and urine SA to levels below the limit of quantitation. Following this, other liver parameters such as transaminases, AFP and bilirubin will normalize. The liver echogram will usually also improve. However, late initiation of treatment cannot rectify all liver damage and the risk of developing liver malignancy remains elevated.

For patients treated with Orfadin the following common adverse reactions have been reported; thrombocytopenia, leucopenia, granulocytopenia, conjunctivitis, corneal opacity, keratitis, photophobia and eye pain. Elevated levels of tyrosine have been associated with the eye related adverse events due to the fact that tyrosine at high concentrations in the eye can crystalize. It is important to maintain a low tyrosine and phenylalanine diet to control tyrosine levels. It has also been hypothesized that increased tyrosine levels can lead to negative effects on neurocognition (4 Thimm 2012).

Orfadin (nitisinone) was approved by the EMA (European Medicines Agency) 21 February 2005, and has become standard of care for HT-1 (5 deLaet et al 2013). At the time of approval, the Committee for Medicinal Products for Human Use (CHMP) required the market authorization holder (MAH) to conduct a post-marketing surveillance (PMS) program to monitor hepatic, renal, hematological, neurological and ophthalmic status in all patients treated with Orfadin. The purpose of the PMS was to stimulate reporting of safety observations in patients treated with Orfadin. A questionnaire collecting safety data and additional data on demographics, dosing, as well as data on nitisinone, SA and tyrosine plasma concentrations was to be completed by all treating physicians in 27 European countries to date. Data obtained was to be summarized and included in the PSURs. To date, data has been collected from approximately 400 patients.

Although the CHMP concluded that the benefit-risk balance was positive during the annual re-assessment in 2009, and removed the conditional approval of the marketing authorization, the MAH (presently Swedish Orphan Biovitrum (Sobi)) was requested to continue to collect data and to report the results in the yearly PSURs.

The scope of the present non-interventional PASS is to collect prospective and retrospective safety data since the EU approval of Orfadin 21 February 2005. It will replace the ongoing PMS. The transition will be gradual, starting 2013 in countries with the largest number of HT-1 patients (France, UK, Germany, Italy and Spain).

The protocol for this study is developed in accordance with the guidance for the format and content of the protocol of a non-interventional PASS (1). The protocol will be published in the EU PAS register.

The collected safety data will be reported in the annual PSUR.

8 Research question and objectives

The primary objective is to assess long-term safety of Orfadin used in standard clinical practice to treat patients with HT-1.

9 Research methods

9.1 Study design

This is a long-term non-interventional, non-comparative, multicenter PASS to collect retrospective and prospective longitudinal data in the normal clinical setting where HT-1 patients are treated. Data will be collected from patients receiving Orfadin at the time of market authorization 21 February 2005 (index date) as well as patients starting treatment after this date. No data will be collected for the period prior to the index date. The patients will be followed as long as they are treated or to the planned end of the study September 2019. Data will be captured at least once every year. However, investigators will be encouraged to collect and report data following each routine patient visit. The chosen design is acceptable for a study with the primary objective of assessing long-term safety of Orfadin used in HT-1 patients under standard clinical care.

9.2 Setting

All HT-1 patients on Orfadin treatment in standard clinical care at study entry as well as patients diagnosed and starting Orfadin treatment during the time of the study will be included and followed-up at least annually for several years. No specific exclusion criteria will be applied. Hence, the study population will be highly representative of the source population.

Baseline data may only be available for patients diagnosed and put on Orfadin treatment during the study period.

9.3 Variables

9.3.1 Primary endpoints

The primary endpoints are occurrence of Adverse Events (AE) related to hepatic, renal, ophthalmic, hematological or cognitive, developmental function, respectively. Management and

reporting of adverse events/adverse reactions related to these functions are described in Section 11.

9.3.2 Secondary endpoints

9.3.2.1 Occurrence of liver transplantation or death

Prospective information on occurrence of liver transplantation or death will be managed and reported as described in Section 11. Retrospective information on Orfadin treated patients with liver transplantation or deceased before initiation of this study will be collected from Sobi's safety data base.

9.3.2.2 Occurrence of death

Prospective information on occurrence of death will be managed and reported as described in Section 11. Retrospective information on Orfadin treated patients deceased before initiation of this study will be collected from Sobi's safety data base.

9.3.2.3 Occurrence of liver transplantation

Prospective information on occurrence of liver transplantation will be managed and reported as described in Section 11. Retrospective information on patients with liver transplantation during Orfadin treatment, but no longer on treatment at the time of initiation of this study will be collected from Sobi's safety data base.

9.3.2.4 Occurrence of hepatic malignancies

Occurrence of hepatic malignancies will be separately captured as an Adverse Event and managed and reported as described in Section 11.

9.3.2.5 Occurrence of other malignancies

Occurrence of malignancies will be captured as an Adverse Event and managed and reported as described in Section 11.

9.3.2.6 Occurrence of incorrect administration of the oral suspension formulation of Orfadin

Preventive measures have been taken to minimize the risk for medication errors and therefore the potential for medication errors with Orfadin oral suspension formulation is considered low. However, possible types of medication errors could be:

- The suspension is not properly re-suspended before use.
- The wrong oral dispenser is used.
- The incorrect dose is withdrawn into the dispenser.

- The dose is not given immediately after being withdrawn into the dispenser.
- The oral dispenser is not adequately rinsed after use.

Incorrect handling and administration of the oral suspension formulation of Orfadin will be captured and reported as a medication error according to the procedures for reporting Adverse Events.

9.3.2.7 Occurrence of other adverse events

Occurrence of AEs other than those related to hepatic, renal, ophthalmic, hematological or cognitive functions will also be managed and reported as described in Section 11.

9.3.2.8 Discontinuation of Orfadin treatment

Treatment interruption or discontinuation will be recorded in the electronic Case Report Form (eCRF). The reason for treatment discontinuation will be given as death, liver transplantation or other reason which will be specified.

9.3.2.9 Laboratory investigations

Plasma, serum,or dry blood spot and/or urine concentrations of SA, and p-Tyr, p-Phe, p-AFP will recorded in the eCRF. Values judged as clinically significant by the investigator should be reported as AEs. If a clinically significant laboratory value is associated with a symptom or diagnosis, the symptom or diagnosis should be captured as an AE.

9.3.2.10 Treatment and diet compliance

The investigator's assessment of treatment compliance and compliance with diet restrictions will be recorded in the eCRF.

9.3.2.11 Extent of exposure

Exposure to Orfadin is captured in the eCRF in terms of daily dose, plasma, serum or dry blood spot concentration of nitisinone and duration of treatment. The accuracy of the exposure information, collected from the patient's medical record, is sufficient for assessment of long-term safety of Orfadin in standard clinical practice.

9.3.2.12 Overall clinical condition

The investigator's assessment of the patient's overall clinical condition will be rated as good, poor or very poor in the eCRF.

9.4 Data sources

Prospective and retrospective post authorization safety data since the EU approval of Orfadin 21 February 2005 will be collected in this study. The patients' hospital case records will be the source for all data.

The investigators will verify the transfer of relevant prospective data to the eCRF designed for the study.

Retrospective data collected in the ongoing PMS for patients participating in this PASS study will be imported to a web-based data entry tool for review of accuracy by the treating physician. Additional retrospective safety data will be obtained from Sobi's safety data base when available. The rational for using this additional retrospective data is to minimize selection bias when estimating event rates.

9.5 Study size

The sample size is not based on any formal calculation. All HT-1 patients meeting the inclusion criteria are eligible for entry. Approximately 300 to 500 patients may be included in the study.

The precision of the incidence estimates for any of the events defined in the primary endpoints is shown below for various sample sizes and incidence rates.

Assumed incidence	Number of patients	Width of two-sided 95% confidence interval for incidence (using normal approximation)
20%	500	7.0
	400	7.8
	300	9.0
10%	500	5.2
	400	5.8
	300	6.8
5%	500	3.8
	400	4.2
	300	5.0
2%	500	2.4
	400	2.8
	300	3.2

9.6 Data management

A web based data entry tool will be used in this study. The tool allows the investigator to enter data to the eCRF designed for the study. Each person involved in data entry at each study center will have an individual username and password to allow record traceability. Individual access applications will be handled by a central function within Sobi.

Prospective data will be captured in an eCRF to be completed for each patient at least once yearly. Retrospective patient data collected during the PMS will be imported to the web-based data entry tool for review of accuracy by the treating physician. All data will be downloaded on a

regular basis and when required. Downloaded data and programs used for analysis will be stored and archived in Sobi's Clinical Data Repository.

The completed eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, without written permission from Sobi. Investigators access to the eCRFs is restricted to the patients under their care.

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The database lock will be approved by relevant study personnel and all edit accesses will be removed.

The data management process will be documented in the Data Management Plan (DMP).

AE(s)/ Serious adverse event (s) (SAE) reported will be entered into Sobi safety data base.

9.7 Data analysis

9.7.1 General

All analyses will be based on the combined prospectively and retrospectively collected data as described in previous section.

All enrolled patients will be included in the statistical analyses and descriptive analyses will primarily be conducted to summarize the data. No imputation of missing data will be conducted. However in case of an extended amount of missing data the impact of this will be discussed.

9.7.2 Data sets to be analyzed.

There will be 2 sets of data analyzed

- The complete set including all patients receiving Orfadin at the index date (21 February 2005) or starting thereafter
- The subset of patients having their first dose of Orfadin on the index date or later.

For the complete set, the analyses of primary and secondary endpoints will reflect events occurring and assessments made after the index date. Duration of exposure prior to the index date will be ignored when estimating event rates.

As the complete set thus will ignore exposure as well as events prior to the index date the subset of patients who starts treatment with Orfadin after the index date will inform more reliable on the safety profile after the first initiation of Orfadin treatment. For this set of patients the entire duration of treatment will be used when estimating event rates.

9.7.3 Statistical analyses.

Demographics and other patient characteristics will be presented descriptively.

The proportion of patients who experience events defined in the primary endpoints and the associated two-sided 95% confidence intervals will be calculated as well as incidence rate expressed as frequency of events per cumulative exposure expressed in patient years.

The AEs will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) and tabulated by seriousness, system organ class and preferred term. Both the total number of events and the number of patients reporting each event at least once will be tabulated as well as incidence rate per patient years on Orfadin treatment.

Laboratory data will be summarized using descriptive statistics.

Exposure will be summarized descriptively. Time on Orfadin treatment will be presented and may also be divided into dose categories.

Compliance to medication and diet will be summarized using descriptive statistics.

Time to liver transplantation or death from start of Orfadin treatment will be analyzed applying Kaplan-Meier methodology. This analysis will only be conducted on the subset of patients who initiated treatment after the index date.

9.8 Quality control

Collection of data will follow the standard clinical practice in treatment of the patient. The source for all collected data will be the patients' medical records. It is the responsibility of the treating physician to ensure completion and to review and approve all eCRFs. At all times, the treating physician has the final responsibility for the accuracy and authenticity of all patient data entered into the eCRFs. The web-based data entry tool includes logical checks to prevent data entry errors. Data inconsistencies outside the logical checks will be managed by queries directly to the site which will be monitored until resolution within the entry tool. Issues that arise and that are not possible to resolve within the entry tool will be managed by a site review. Data will be validated on an ongoing basis, and at the time for data extraction for the yearly PSUR, a specific validation process will be applied. All validation of data will be described in detail in the DMP.

9.9 Limitations of the research methods

An uncontrolled study design is the only feasible design in this non-intervention study since a comparator group cannot be introduced in a study population where all patients are treated with Orfadin and this treatment cannot be substituted. Accordingly, the study design carries the general limitations inherent in an uncontrolled design regarding statistical analyses, interpretation, generalizability and conclusiveness. In addition, missing data may introduce bias in the estimates and no imputation of missing data is planned. The potential bias caused by missing data applies in particular to the retrospective data.

The chosen design is deemed acceptable for a study with the primary objective to assess long-term safety of Orfadin used in HT-1 patients under standard clinical care. A strength of the study with this safety objective is that a majority of all patients in the EEA with HT-1 will be followed during long term treatment.

9.10 Other aspects

The relevant aspect of the study is covered by previous sections.

10 Protection of human subjects

This study will comply with ethical and regulatory requirements in each country.

10.1 Conduct of study

This study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (6), the definition for Post-Authorisation Safety Studies in Directive 2001/83/EC Art 1 (7), and its refinement provided in the Guideline of Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies (8).

This study will be conducted in compliance with this protocol and in accordance with the ethical principles for Medical Research Involving Human Subjects in the Declaration of Helsinki (9) and will be consistent with the International Ethical Guidelines for Biomedical Research Involving Human Subjects (10) and applicable parts of the ICH (International Conference on Harmonisation) GCP(Good clinical practice) 11), as well as all other applicable regulatory requirements. This study will be conducted in compliance with the Directive 2001/83/EC Art 107-m for Post Authorisation Safety Studies (7), initiated, managed or financed by a marketing authorisation holder voluntarily, as well as Directive 95/46/EC on data protection (12).

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). The investigator will also ensure that this study is conducted in accordance with the laws and regulations of the country in which the research is conducted.

10.2 Institutional Ethics Committee (IEC) review

The investigator will submit this protocol, informed consent forms (ICF), and any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent) to an IEC, where applicable. The investigator will not begin any study activities until approval from the IEC has been documented and provided as a letter to the investigator. If required, the Principal Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also

responsible for promptly informing the EC of any protocol amendments. Any subsequent changes to the IEC submitted study documents, including amendments, will require resubmission and reapproval by the IEC prior to implementation, with the exception of those necessary to reduce immediate risk to study subjects. It is the responsibility of the investigator to ensure that all interactions with IEC are conducted in accordance with current governmental regulations.

10.3 Informed consent

It is the responsibility of the investigator to give each patient (or the patient's representative) prior to any study-related activities, full and adequate verbal and written information in local language regarding the study, including aims, methods, objectives, study activities/procedures, the possible risks/hazards involved in participation, data protection, and alternatives of the study. The investigator must utilize the most current Sponsor and IEC approved ICF for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

Patients may decline the invitation and refuse consent without giving a reason and without prejudice to any treatment that is proposed. The patients must be informed about their right to withdraw from the study at any time.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The written patient information and/or consent form must not be changed without prior agreement with Sobi. Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IEC.

10.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number (as allowed by local law). This means that patient names are not included in data sets, any form, or biological sample that are transmitted to the Sponsor or submitted to IEC, laboratory, or CRO.

10.5 De-identification of patient data

Patient data will be anonymized through design of data entry fields that do not permit the entry of identifying information such as center-assigned patient identifiers. Site staff only will enter data into eCRFs. Patient's date of birth or partial date of birth if required by local regulations, will be entered in the system and age as whole years will be presented.. No patient identifiers

used by centers will be entered; rather patients will be assigned a study-specific identification number (ID). The anonymized data, as entered into the EDC system, will be visible to the CRO and Sponsor, but only center staff will be able to trace a case ID back to a patient identity, a necessary measure to allow center staff to respond to data queries raised later. Detailed explanation of data protection and patient confidentiality measures will be included in each application for local ethics approval. Where necessary, these will include country-specific measures.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations. Only authorized persons will have access to identifiable personal details, if required for data verification. The investigator is responsible for retrieval of information from personal medical records.

In any presentations or in publications of the results of the study, the patient's identities will remain anonymous and confidential. If the Sponsor, its designee(s), and various government health agencies should inspect the records of the study, every effort will be made to keep the patient's personal medical data confidential.

10.6 Sponsor documents

The investigator agrees that all information received from the Sponsor, including but not limited to this protocol, eCRFs, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11 Management and reporting of adverse events/adverse reactions

11.1 Definitions

11.1.1 Adverse event

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

AEs include the following:

- Abnormal test findings, as specified below.

- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Progression/worsening of underlying disease.

In addition, signs and symptoms resulting from the following will also be handled according to the same principles as AEs:

- Overdose.
- Abuse.
- Misuse.
- Lack of efficacy
- Pregnancy and breast feeding (see section 11.3)

11.1.2 Serious adverse event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient).

Other medically important AEs that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Serious also includes any other event judged by investigator or company as serious. Any suspected transmission of an infectious agent via nitisinone shall also be considered serious.

11.2 Eliciting and recording adverse event information

All AEs, both Serious and Non-serious, related and not related to nitisinone, reported during the study period will be captured in the study database / safety database.

The investigator is to record the occurrence of any AEs on the eCRF, as noted by the investigator or spontaneously reported by the patient.

At each follow-up registered in the eCRF, the investigator will be asked for the occurrence of any significant deterioration in clinical status of the following parameters occur since the last time the information was provided;

- Hepatic function
- Renal function
- Cognitive, developmental function
- Ophthalmic function
- Hematological status
- Hepatic malignancies
- Other malignancies
- Incorrect administration of the oral suspension formulation of Orfadin

The investigator should complete an AE report form for all reported AEs and/or deterioration in the patient's clinical status.

For each AE, the investigator will be requested to make a causality assessment to determine if there is a reasonable possibility that nitisinone caused the AE, i.e. if the AE is assessed as related or not related to nitisinone and is to be considered an adverse reaction or not.

When an SAE is identified, it shall be reported via sending the AE report from to Sobi (fax number +46 8 697 32 30) or by completion of the AE report in the eCRF, within 24 hours of awareness by the investigator.

11.3 Exposure during pregnancy or via breastfeeding

All events of exposure to nitisinone during pregnancy (female patient or male patient's partner) or via breastfeeding shall be reported to Sobi (+) or entered into the eCRF system within 24 hours of awareness by any study personnel. Pregnancies shall be reported regardless of whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to nitisinone; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy.

11.4 Follow-up of unresolved adverse events

All AEs should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends.

In addition, all serious and non-serious AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over.

11.5 Laboratory safety assessments

Plasma (or serum) and urine concentrations of SA, and plasma tyrosine, phenylalanine and α-fetoprotein will be recorded in the eCRF, if available. Values judged as clinically significant by the investigator should be reported as AEs. If a clinically significant laboratory value is associated with a symptom or diagnosis, the symptom or diagnosis should be captured as an AE.

11.6 Monitoring of the benefit-risk balance

Sobi Drug Safety will regularly review all reported AEs and other Safety data collected for the product, within the study and from any other sources. If any significant new safety information relevant for the treatment of the patients in the study is identified, including any changes in benefit risk balance, Sobi will assess the potential impact on the study protocol and a communication will be issued to all investigators.

12 Plans for disseminating and communicating study results

Safety data collected while the study is ongoing will be communicated in annual PSURs as shown in Section 0. A final report on study completion is planned to April 2020.

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues.

13 References

1 European Medicines Agency (EMA): Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, current version dated 26 September 2012.

2 van Spronsen FJ et al. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994 Nov;20(5):1187-91.

3 Larochelle J et al. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Québec. Mol Genet Metab. 2012 Sep;107(1-2):49-54.

4 Thimm et al. Neurocognitive outcome in patients with hypertyrosinemia type I after long-term treatment with NTBC. J Inherit Metab Dis. 2012 Mar;35(2):263-8

5 de Laet C et al, Recommendations for the management of tyrosinaemia type 1. Orphanet J Rare Dis. 2013 Jan 11;8:8

6 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

7 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001,on the Community code relating to medicinal products for human use, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010.

8 European Medicines Agency (EMA): Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies, current version dated 9 July 2012

9 World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, latest amendment at the 59th WMA General Assembly, Seoul, South Korea, October 2008.

10 Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects. 3rd ed. Geneva: CIOMS

11 ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1) Current Step 4 version dated 10 June 1996. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

12 Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

Annex 1. ENCePP checklist for study protocols