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Title	European Post-Authorization Registry for RAVICTI® (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) Study Number: HZNP-RAV-401
Protocol Version Identifier	V3.0
Date of last version of the protocol	29 Nov 2016
EU PAS Register number	Study not registered The study protocol will be entered in the register before the start of data collection
Active substance	Glycerol phenylbutyrate ATC code: A16AX09
Medicinal product	RAVICTI
Product reference	HC/003822
Procedure number	EMEA/H/C/003822
Marketing Authorization Holder(s)	Horizon Pharma Ireland Ltd.
Joint PASS	No
Research question and objectives	The Registry is established to further evaluate and characterize the safety profile of RAVICTI and track long-term outcomes in UCD patients treated with RAVICTI to fulfill an EMA post-authorization measure (PAM).
Country(ies) of study	E-IMD centers in the following countries have signaled interest in participation: Austria, Belgium, Croatia, Denmark, France, Germany, Italy, Poland, Portugal, Spain, Switzerland and the UK pending an approved protocol (see Annex 1).
Author	[redacted]

Marketing Authorization Holder(s)

Marketing authorization holder(s)	Horizon Pharma Ireland Ltd. Connaught House, 1st Floor 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
MAH contact person	[redacted]

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2 List of Abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
ARG	Arginase 1
ASAT	Aspartate aminotransferase
ASL	Argininosuccinate lyase
ASS	Argininosuccinate synthetase 1
BSID	Bayley Scales of Infant Development
BV	Baseline Visit
CHMP	Committee for Medicinal Products for Human Use
cm	Centimetre
CPS	Carbamoyl phosphate synthetase 1
d	Day
°C	Degree Celsius
EEA	European Economic Area
E-IMD	European Registry and Network for Intoxication Type Metabolic Disease
EMA	European Medicines Agency
EU	European Union
EU5	European Union Five
EV	Emergency Visit
fl	Femtolitre
FV	Fatal Disease Course Visit
HAC	Hyperammonemic crisis
HHH	Hyperornithinemia–Hyperammonemia–Homocitrullinuria
g	Gramm
GFR	Glomerular filtration rate
GPB	Glycerol phenylbutyrate
GVP	Good Pharmacovigilance Practice
ICD	International Statistical Classification of Diseases and Related Health Problems
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IEC	Independent ethics committee
im	Intramuscular
in	Intranasal
IQ	Intelligence Quotient
iv	Intravenous
kg	Kilogram
l	Litre
MAH	Marketing Authorization Holder
MCV	Mean corpuscular volume
mcg	Microgram
ml	Millilitre
µmol	Micromole
n	Number
NAGS	N-acetylglutamate synthetase
NIH	National Institutes of Health
nl	Nanolitre
OTC	Ornithine transcarbamylase

PAA	Phenylacetate
PAGN	Phenylacetylglutamine
PAM	Post-authorization measure
PBA	Phenylbutyrate
po	Per os
pr	per rectal
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PV	Pharmacovigilance
RV	Regular Visit
SAE	Serious adverse event
SAP	Statistical analysis plan
sc	Subcutaneous
SD	Standard deviation
SmPC	Summary of the Product Characteristics
SPSS	Statistical Package for the Social Sciences
top	Topical
UCD	Urea cycle disorder
UCDC	Urea Cycle Disorders Consortium
UK	United Kingdom
US	United States
UV	Unscheduled Visit
WBC	White blood cell count
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale of Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

3 Responsible Parties

MAH / Sponsor of the PASS	Horizon Pharma Ireland Ltd. Connaught House, 1st Floor 1 Burlington Road Dublin 4 D04 C5Y6 Ireland The Registry is based on collaboration between Horizon Pharma Ireland Ltd. (MAH) and the European Registry and Network for Intoxication Type Metabolic Diseases ("E-IMD"). The collaborative approach taken jointly by the MAH and E-IMD will use the established E-IMD UCD disease registry and amend the existing E-IMD data collection by additional data elements pertaining to specific research questions regarding the safety of RAVICTI. The E-IMD consists of a network of collaborating partners from various clinical centers of excellence and patient support groups across Europe. A contract has been established between the MAH and the E-IMD, which determines the tasks and responsibilities of the MAH and the E-IMD, deliverables and reporting of study results, as well as the ownership of data,
Collaborating partner	The European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)
Principal Investigator	A principal investigator will be selected after a final protocol has been agreed by the PRAC.
Coordinating investigator	The selection of the coordinating investigator and study sites will depend on various factors including availability of a final protocol which has been agreed by the PRAC. E-IMD centers in the following countries have signaled interest in participation: Austria, Belgium, Croatia, Denmark, France, Germany, Italy, Poland, Portugal, Spain, Switzerland and the UK pending an approved protocol (see Annex 1).
Data Management and Data Analysis:	Central study office of E-IMD at: Center for Pediatric and Adolescent Medicine Division for Neuropediatrics and Metabolic Medicine Im Neuenheimer Feld 430 D – 69120 Heidelberg
Horizon Pharma Pharmacovigilance Responsible Contact	[redacted]
Author of the protocol	[redacted]

4 Abstract

Title	European Post-Authorization Registry for RAVICTI® (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) Study Number: HZNP-RAV-401
	Version: 3.0; Date: 29 Nov 2016
	Author: [redacted]
Rationale and Background	Urea Cycle Disorders (UCD) are rare, inborn defects in the metabolism of waste nitrogen caused by a deficiency in one of six enzymes or two mitochondrial transport proteins involved in the production of urea, resulting in accumulation of toxic levels of ammonia in the blood (hyperammonemia). Severe deficiencies may lead to death or to severe neurological injury. The main goal of medical management of UCD patients is to prevent chronic or acute hyperammonemic states leading to central nervous system damage. This requires restriction in dietary protein intake, amino acid supplementation and the use of nitrogen scavenging agents if diet alone does not adequately control patients. Liver transplantation in selected patients may cure the enzyme defect but does not reverse neurological damage. RAVICTI is a nitrogen binding drug, which contains glycerol phenylbutyrate (GPB), which is a prodrug of phenylbutyrate (PBA), approved in the EU on 27 November 2015 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003822/human_med_001939.jsp&mid=WC0b01ac058001d124. GPB is hydrolyzed by lipases to PBA and PBA is metabolized to phenylacetate (PAA). PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN), which is excreted by the kidneys. In the EU/ European Economic Area (EEA), RAVICTI is indicated for use as adjunctive therapy for chronic management of adult and pediatric patients ≥2 months of age with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Clinical trials of RAVICTI in the target UCD population included 114 patients across 4 short-term and 3 long-term clinical studies. The clinical development program did not include pregnant or lactating females and patients with renal impairment. Furthermore only a limited number of patients have been exposed to RAVICTI for a long-term period (i.e., > 1 year). Therefore the safety profile of RAVICTI in these patient populations and long-term safety including the aspect of potential PAA toxicity has been recognized as missing information during the European Authorization procedure and Horizon Pharma is committed to conduct a post-authorization registry to collect additional data. Furthermore in a 2-year carcinogenicity study in Sprague-Dawley® rats, there were statistically significant increases in the incidence of various treatment-related tumors. A scientific advisory panel of independent experts concluded that none of the findings in rats suggested a substantive cancer risk to UCD patients who would be given RAVICTI and most findings were considered rodent specific with no relevant counterpart in humans. Carcinogenicity was therefore considered a potential risk in the European

	Authorization Procedure and Horizon Pharma committed to follow up on this potential risk in the Registry.
Research Questions and Objectives	The Registry is established to further evaluate and characterize the safety profile of RAVICTI and track long-term outcomes in UCD patients treated with RAVICTI. The registry also includes a comparator group equal in size to the study group treated with alternative nitrogen scavenging medication other than RAVICTI. In all other relevant characteristics (age group, severity of the UCD and gender for OTC patients), the comparator group will be adequately matched to the study group. The Registry is set up to: • Collect relevant long-term safety data in patients with UCDs treated with RAVICTI; • Collect information on incidence rate and type of cancer in patients with UCDs treated with RAVICTI; • Collect information on potential PAA toxicity in patients with UCDs treated with RAVICTI; • Collect safety information in patients with UCDs and concurrent renal impairment treated with RAVICTI; • Evaluate pregnancy outcomes in children born to female patients exposed to RAVICTI during pregnancy or children exposed during lactation; and • Collect the data specified above also in an adequately matched comparator group equal in size to the study group thereby allowing to evaluate long-term safety in patients with UCDs treated with RAVICTI as compared to patients treated with alternative nitrogen scavenging medication other than RAVICTI, specifically: o Compare incidence rate of adverse events in patients treated with RAVICTI and patients in the comparator group o Compare incidence rate of cancer in patients treated with RAVICTI and patients in the comparator group o Compare safety information collected in patients with renal impairment treated with RAVICTI to patients with renal impairment treated with comparator medication o Compare pregnancy outcomes in children born to female patients exposed to RAVICTI to outcomes in children born to female patients exposed to comparator drugs during pregnancy or children exposed during lactation.
Study Design	This is a multi-center, prospective, non-interventional registry conducted by E-IMD in collaboration with Horizon Pharma designed to collect data on safety and outcomes in patients with UCDs on treatment with RAVICTI or patients with UCDs treated with alternative nitrogen scavenging medication other than RAVICTI. The Registry uses observational methods to prospectively collect uniform data on specified outcomes in patients with UCDs in order to monitor the long-term safety of RAVICTI following granting of the centralized marketing authorization.
Population	Adult and pediatric patients with a confirmed diagnosis of UCD in whom treatment with RAVICTI or alternative nitrogen scavenging medication other than RAVICTI had been initiated.
Variables	The registry will collect demographic data as well as comprehensive data on the initial presentation, diagnostic process, medical history and family history at baseline. Additional data on the current overall health status, organ-specific disease

	manifestations and interventions including physical examination, laboratory tests and neuropsychological tests, medication and diet will be collected at baseline and in subsequent follow-up visits. Follow-up visits will encompass regular patient visits as well as unscheduled visits and emergency visits e.g., hospitalization due to hyperammonemic crisis (HAC). The registry will collect a specific set of variables for evaluating the impact of other medications with RAVICTI with special consideration of adverse drug reactions, carcinogenicity and exposure during pregnancy and lactation. This specific set of variables will also be collected in the comparator group for any alternative nitrogen scavenging medication other than RAVICTI. A detailed list of variables is included in the protocol.
Data Sources	Participating investigators will enter the data in the electronic registry record forms provided by the E-IMD. The E-IMD routinely collects data for all enrolled patients at least annually and at time points in between, if the patient is seen as standard of care during regular visits for the treatment of UCD or unscheduled visits for any other condition or the patient experiences a hyperammonemic crisis and is seen as an emergency visit or during hospitalization. At the time of enrolment, health-related baseline data will be collected. During participation in the Registry, information pertaining to the variables described above will be collected as available. Results of age-appropriate neuropsychological testing will be recorded according to the E-IMD registry protocol. For additional safety data, which will be collected for the RAVICTI post marketing surveillance, participating investigators will be asked to complete the respective information including reason for the visit, information on RAVICTI treatment, and safety data (adverse events [AE], pregnancy, lactation) during each regular visit and any additional unscheduled or emergency visit. This information will also be collected in the comparator group for any alternative nitrogen scavenging medication other than RAVICTI.
Study Size	Approximately 200 patients are planned to be enrolled in the Registry split in equal parts between the study group and the comparator group. The number of anticipated patients is based on the estimated prevalence of the orphan indication (UCD) and assumptions regarding the availability of RAVICTI at E-IMD sites. All UCD patients treated with RAVICTI or alternative nitrogen scavenging medication other than RAVICTI are eligible to enroll in the Registry. In order to minimize bias in the selection of patients, participating investigators are encouraged to consecutively enroll all patients treated with RAVICTI who consent and meet the selection criteria. Recruitment period is planned for 3 years. Eligible patients will be enrolled in the Registry and followed for up to 10 years.
Data Analysis	Health-related personal data concerning treatment and clinical condition of individual patients will be collected at a baseline visit (BV), and prospective regular visits (RV) or during unscheduled/emergency visits (UV/EV) per E-IMD patient registry protocol. Regular visits collect data from visits that are performed at least annually as standard care for the metabolic condition (UCD). Regular visits may occur more frequently if medically indicated. Unscheduled visits (UV) are all other visits that are not directly related to the treatment of the UCD. Visits for the acute management of impending metabolic decompensation (including hyperammonemic crisis [HAC]) are recorded

<table>
<tr><td></td><td colspan="2">as emergency visits (EV).

A formal statistical analysis plan (SAP) that will provide details of all analyses and presentation of data will be approved prior to data analysis.

Descriptive statistics will comprise the number (n) of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and n and percent for categorical variables.

Analysis population:

Data will be presented for UCD patients enrolled in the Registry and partaking in the surveillance of RAVICTI or the comparator group. Data of UCD patients not receiving RAVICTI will only be presented if consent for participating in the comparator group is given. Furthermore data other than specified will not be presented. Additional subgroups may also be examined, as deemed appropriate (pediatric versus adult, UCD type, etc.).

Disposition data will be summarized with descriptive statistics and presented in listings. Demographic and clinical data will be summarized with descriptive statistics and presented in listings.

Post-baseline values and/or change from baseline in the outcome variables will be summarized with descriptive statistics, and, where appropriate, graphical presentations. Differences in outcome variables between RAVICTI and comparator group will be further evaluated by use of generalized linear mixed models (continuous and dichotomous endpoints) as well as hazard models for dichotomous and, when adequate, multinomial endpoints.</td></tr>
<tr><td rowspan="7">Milestones</td><td>Milestone</td><td>Planned Date</td></tr>
<tr><td>Study Protocol to be agreed by EMA, Horizon Pharma, and E-IMD – 6 months</td><td>Mid 2016</td></tr>
<tr><td>Final Study Protocol to be Implemented – 6 months</td><td>End 2016</td></tr>
<tr><td>Start of data collection</td><td>Planned for 2017 (of note: start of data collection will depend on the availability of a final protocol, the approval by national health authorities and independent ethics committees, the availability of RAVICTI in the respective country and the consent of the participating patients)</td></tr>
<tr><td>End of data collection</td><td>End 2029</td></tr>
<tr><td>Patient Recruitment for 3 years after agreement of Study Protocol and Completion of Study implementation</td><td>End 2019</td></tr>
<tr><td>Study progress reports as referred to in Article 107m(5) of Directive 2001/83/EC</td><td>Not requested</td></tr>
</table>

	Interim report(s) of study results: E-IMD to provide tables and listings according to PSUR	Every 6 months
	End of the agreed period of 10 years of follow-up	End 2029
	Final Report of study results to be provided to the EMA	End July 2030

5 Amendments and Updates

None

6 Milestones

The Registry study is based on the collaboration between Horizon Pharma and the E-IMD. As agreed with the European Medicines Agency (EMA), Committee for Medicinal Products for Human Use CHMP/ Pharmacovigilance Risk Assessment Committee (PRAC), the study encompasses (a) 3 years of patient enrolment, followed by (b) 10 years of follow-up of the enrolled patients. The E-IMD will provide tables and listings to Horizon Pharma according to the Periodic Safety Update Report (PSUR) writing cycle, i.e. every six month. A final report is planned after the last patient enrolled in the Registry has completed 10 years observation period.

The defined milestones and corresponding timeframe for deliverable are set forth in the table below.

Milestone	Planned Date
Study Protocol to be agreed by EMA, Horizon Pharma, and E-IMD – 6 months	Mid 2016
Final Study Protocol to be Implemented – 6 months	End 2016
Start of data collection	Planned for 2017 (of note: start of data collection will depend on the availability of a final protocol, the approval by national health authorities and independent ethics committees, the availability of RAVICTI in the respective country and the consent of the participating patients)
End of data collection	End 2029
Patient Recruitment for 3 years after agreement of Study Protocol and Completion of Study implementation	End 2019
Study progress reports as referred to in Article 107m(5) of Directive 2001/83/EC	Not requested
Interim report(s) of study results: E-IMD to provide tables and listings according to PSUR	Every 6 month s
End of the agreed period of 10 years of follow-up	End 2029
Final Report of study results to be provided to the EMA	End July 2030

7 Rationale and background

Urea Cycle Disorders (UCD) are inborn defects in the metabolism of waste nitrogen caused by a deficiency in one of six enzymes or two mitochondrial transport proteins involved in the production of urea, resulting in accumulation of toxic levels of ammonia in the blood (hyperammonemia) and the brain of affected patients.

UCDs affect all age groups, and may begin at any age (e.g., neonatal, infantile, childhood, adolescence, or adulthood). Published estimates of the incidence of UCDs vary, regardless of the country in which the estimates are based. Available data indicate that UCDs are very rare disorders; e.g., a 2013 publication which represented collaboration between United States (US) and European experts and utilized data from both the National Institutes of Health (NIH) -sponsored Urea Cycle Disorders Consortium (UCDC) Longitudinal Study and the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) estimated the incidence of UCDs to be approximately 1 in 35,000 births (Summar 2013).

The most important clinical manifestations of UCDs are attributable to hyperammonemia. The severity and timing of UCD presentation vary according to the severity of the deficiency, which may range from mild to severe depending on the specific enzyme or transporter deficiency, and the specific mutation in the relevant gene, as well as other non-genetic factors. UCD patients may present in the early neonatal period with a catastrophic illness; or at any point in childhood, or even adulthood, after a precipitating event such as infection, trauma, surgery, pregnancy/delivery, or change in diet (Summar 2003). Acute hyperammonemic episodes at any age carry the risk of encephalopathy and resulting neurologic damage, sometimes fatal; but even chronic, sub-critical hyperammonemia can result in impaired cognition (Gropman 2007). UCDs are therefore associated with a significant incidence of neurological abnormalities including cognitive impairment and developmental disabilities over all ages (Tuchman 2008, Krivitzky 2009). UCD patients with neonatal-onset disease are especially likely to suffer cognitive impairment (Krivitzky 2009) and death (Summar 2008) compared with patients who present later in life.

The main goal of medical management of UCD patients is to prevent chronic or acute hyperammonemic states leading to central nervous system damage. This requires restriction in dietary protein intake, amino acid supplementation and the use of nitrogen scavenging agents if diet alone does not adequately control patients. Liver transplantation in selected patients may cure the enzyme defect but does not reverse neurological damage.

RAVICTI is a nitrogen binding drug, which contains glycerol phenylbutyrate (GPB), which is a prodrug of phenylbutyrate (PBA). GPB is hydrolyzed by lipases to PBA and PBA is metabolized to phenylacetate (PAA). PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN), which is excreted by the kidneys. In the EU/EEA RAVICTI is indicated for use as adjunctive therapy for chronic management of adult and pediatric patients ≥2 months of age with UCDs including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase 1 (ASS), argininosuccinate lyase (ASL), arginase 1 (ARG) and ornithine translocase deficiency (synonym, hyperornithinaemia-hyperammonemia homocitrullinuria syndrome or HHH syndrome) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and sometimes dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free caloric supplements) depending on the daily dietary protein intake needed to promote growth and development.

Due to the low incidence and low prevalence of the UCDs, RAVICTI is classified as an orphan medicinal product for the treatment of UCD in the EU/EEA. RAVICTI was approved for marketing in

the EU/EEA in November 2015. Clinical trials in the target UCD population included 114 patients with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH syndrome across 4 short term and 3 long-term clinical studies. Due to the rarity of UCD it was unfeasible to conduct studies in significantly larger populations and only a limited number of patients have been exposed to RAVICTI for a long term period (i.e. > 1 year) so far. Furthermore the clinical development program did not include pregnant or lactating females and patients with renal impairment. Therefore the safety profile of RAVICTI in these patient populations and long-term safety has been recognized as missing information during the European Authorization procedure and Horizon Pharma is committed to conduct a post-authorization registry to collect additional data.

Furthermore in cancer patients who received PAA intravenously reversible clinical manifestations suggestive of neurotoxicity (e.g., nausea, vomiting, and somnolence) have been reportedly associated with phenylacetate (PAA) levels ranging from 499-1285 mcg/ml. Although these have not been seen in the clinical trials involving UCD patients, neurotoxicity associated with high PAA levels may present a potential risk. The aspect of potential PAA toxicity has been recognized as missing information during the European Authorization procedure and Horizon Pharma is committed to collect additional data.

In a 2-year carcinogenicity study in Sprague-Dawley® rats (Study WIL-671007), oral administration of GPB at 0.07, 0.21, and 0.65 g/kg/day to males and 0.1, 0.3, and 0.9 g/kg/day to females resulted in treatment-related neoplasms (pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma, thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, cervical schwannoma, uterine endometrial stromal polyp, and combined polyp or sarcoma). A scientific advisory panel of independent experts was assembled to evaluate the rat tumor findings and provide input on their clinical relevance and risk for UCD patients. The panel unanimously concluded that none of the findings in rats suggested a substantive cancer risk to UCD patients who would be given GPB (EPL Report 917-002). Carcinogenicity was therefore considered a potential risk in the European Authorization Procedure and Horizon Pharma committed to follow up on this potential risk in the Registry.

This Registry, a PAM, is being established to collect data on the above described missing information and potential risks thus permitting to further evaluate and characterize the safety profile of RAVICTI and track long-term outcomes in UCD patients.

8 Research Question and Objectives

The Registry is being conducted to characterize the demographics and clinical course of the patient population diagnosed with UCD on treatment with RAVICTI thereby gaining further knowledge on the long term safety profile of RAVICTI in UCD patients. It thereby addresses the aspects identified as missing information or potential risks during the marketing authorization procedure in the EU/EEA.

In particular, the EU registry will estimate the incidence rate of adverse events, including the incidence rate and type of cancer in the patient population, and the incidence rate of potential PAA toxicity during a follow up period of 10 years for enrolled patients.

Furthermore the EU registry will document the clinical course in patients underrepresented in the clinical trial program, i.e. patients with renal impairment as well as the use during pregnancy and lactation in patients treated with RAVICTI if these events occur.

The registry will also document the clinical course of a comparator group adequately matched (by age group, disease onset during or after the newborn period and gender for OTC patients) to the study group receiving alternative nitrogen scavenging medication other than RAVICTI. In the case of urea cycle disorders, the most reliable single variable for classification of severity is the onset type. In the

case of ornithine transcarbamylase deficiency, the most frequent urea cycle disorder, the sex of the patient is of similar importance due to X-linked inheritance of the disease. Onset type in this case is dichotomous and means either onset of disease specific symptoms in the neonatal period ("early onset" group), which generally is associated with a more severe disease course, or after the neonatal period ("late onset" group), which is associated with a less severe disease course. These two variables will serve as foundation of group specific comparisons, adequately separating more severe from less severe cases. Further covariates which will be duly considered are (1) the initial peak plasma ammonia level at disease onset, since plasma ammonia levels above 500 µmol/l pose a high risk for irreversible neuronal damage, (2) therapy escalation defined as treatment with more than one nitrogen scavenging drug and (3) developmental delay. All of these covariates also indicate the disease severity. Propensity scores may be used to control the success of the matching process, thus ensuring the comparability of both groups.

The objective of this registry is to further characterize the safety profile of RAVICTI with particular emphasis on the following aspects:

- Collect relevant long-term safety data in patients with UCDs treated with RAVICTI;
- Collect information on incidence rate and type of cancer in patients with UCDs treated with RAVICTI
- Collect information on potential PAA toxicity in patients with UCDs treated with RAVICTI;
- Collect safety information in patients with renal impairment in patients with UCDs treated with RAVICTI;
- Evaluate pregnancy outcomes in children born to female patients exposed to RAVICTI during pregnancy or children exposed during lactation; and
- Collect the data specified above also in an adequately matched comparator group equal in size to the study group thereby allowing to evaluate long-term safety in patients with UCDs treated with RAVICTI as compared to patients treated with alternative nitrogen scavenging medication other than RAVICTI, specifically:
    - Compare incidence rate of adverse events in patients treated with RAVICTI and patients in the comparator group
    - Compare incidence rate of cancer in patients treated with RAVICTI and patients in the comparator group
    - Compare safety information collected in patients with renal impairment treated with RAVICTI to patients with renal impairment treated with comparator medication.
    - Compare pregnancy outcomes in children born to female patients exposed to RAVICTI to outcomes in children born to female patients exposed to comparator drugs during pregnancy or children exposed during lactation.

9 Research Methods

9.1 Study design

This is a multi-center, prospective, non-interventional, registry conducted in partnership with the E-IMD designed to collect data on safety and outcomes in patients with UCDs on treatment with RAVICTI. The same data will be collected in a comparator group adequately matched (by age group, severity of UCD and gender for OTC patients) to the study group receiving alternative nitrogen scavenging medication other than RAVICTI.

The Registry uses observational methods to prospectively collect data on specified outcomes in patients with UCDs in order to monitor the long-term safety of RAVICTI.

The E-IMD registry has established standardized follow-up examinations of children and adults with UCD. Patients are followed using a standardized assessment schedule including basic data, family history, age at diagnosis, first symptoms, characterization of urea cycle disease subtype, frequency and

duration of hospitalization, medical and developmental history, physical and neurological examination, and neuropsychological tests (see www.e-imd.org).

The RAVICTI registry extends the existing E-IMD (www.e-imd.org) project on UCD. The existing data collection is augmented by collection of additional data to gather information from patients with characteristics not previously studied or underrepresented in the clinical program for RAVICTI and characterize the demographics and clinical course of the patient population diagnosed with UCD and on treatment with RAVICTI.

Patients enrolled in this Registry will provide a specific set of health-related personal data at baseline and attend regular office visits or unscheduled or emergency visits at the participating treatment sites to facilitate data collection, as indicated in section "Data analysis". The registry is planned with a 3-year recruitment and a 10-year observation period and is planned to include about 100 patients receiving RAVICTI and 100 patients receiving an alternative nitrogen scavenging medication.

9.2 Setting

9.2.1 Study population

Inclusion and exclusion criteria

The registry will enroll adult and pediatric patients who fulfill one of the following criteria:

- Confirmed diagnosis of UCD in whom treatment with RAVICTI had been initiated or
- Confirmed diagnosis of UCD in whom treatment with alternative nitrogen scavenging medication other than RAVICTI had been initiated.

Informed consent to participate and to provide health related data by the patient or legal representative according to applicable law will be obtained.

No other inclusion or exclusion criteria apply.

All UCD patients treated with RAVICTI or alternative nitrogen scavenging medication other than RAVICTI are eligible to enroll in this registry. In order to minimize bias in the selection of patients, participating investigators are encouraged to consecutively enroll all patients treated with RAVICTI who consent and meet the selection criteria.

Patient follow up and replacement of patients

It is planned to follow up on all enrolled patients for 10 years irrespective of whether they belong to the RAVICTI group or the comparator group. According to past experience of the E-IMD registry on average two visits per patient per year can be expected for patients not treated with RAVICTI by only recording data from visits that are part of standard clinical care (i.e. without scheduling additional exclusive study visits), making two visits per year a reasonable aim for both study groups.

Patients receiving RAVICTI at any time-point during the 3 year recruitment will be considered "RAVICTI" patients from the time-point they received RAVICTI even if these patient switch to another therapy during the further course of the study.

Patients who receive alternative nitrogen scavenging medication during the entire study period only, will be considered as "COMPARATOR" patients.

Patients starting in the comparator group, who switch to RAVICTI treatment during the 3 year recruitment period will be evaluated and followed up as "RAVICTI" patients and an additional "COMPARATOR" patient will be recruited as replacement to achieve the target patient number at the end of the recruitment period.

Patients in the comparator group, who switch to "RAVICTI" treatment during the 10 year-follow up period will be considered as "RAVICTI" patients from the time of switch onwards and followed up until end of the study period. However these patients will not be replaced by recruiting an additional "COMPARATOR" patient.

Medical care

The proposed registry has been developed in collaboration with the E-IMD. The E-IMD has been set up with the principal objective to promote access to rapid diagnosis and the best up-to-date care for patients with a UCD. The E-IMD has therefore identified the provision of "European evidence-based consensus care protocols" as one of its main activities. All centers participating in the RAVICTI registry are, or will be, members of the E-IMD and thus with the declared commitment to implement the consensus based standard of care treatment. The adherence to and consistency with the consensus treatment guidelines is a key characteristic of the E-IMD network centers and a cornerstone of their daily patient care.

With this adherence to the consensus treatment guidelines, conduct of the RAVICTI registry exclusively in collaboration with the E-IMD will ensure comparable and consistent treatment based on the European consensus guideline. Treatment guidelines published by the E-IMD network (Häberle et al 2012) cover all relevant areas including the management of acute hyperammonemia, dietary management and pharmacotherapy, both in the acute crisis and long term setting. UCD treatments (diet, other pharmacotherapy) will be documented and presented in the interim and final study reports.

Thus, although the actual treatment schemes of individual patients inevitably vary due to highly individual disease severity and concomitant patient needs, the pledge to adhere to the standard of care as established by the European consensus guideline is uniform and characteristic for all E-IMD centers and will support the comparability between patients receiving RAVICTI or other treatments and also across different participating countries.

Investigators will prescribe RAVICTI and other treatments including nitrogen scavengers other than RAVICTI based on usual clinical practice and actual patient's needs. There will be no restrictions on the medical care or concomitant medication of patients. The registry is strictly observational and will not change the patient/ healthcare provider relationship, nor influence the healthcare provider's management of the patient. Patients who decide to participate should not expect to receive better medical care than other patients with the same disease.

Withdrawal of patients

Patients may decide to discontinue participation at any time without penalty and without affecting future medical care. A patient may be withdrawn from the study prior to completion for any of the following reasons:

- Withdrawal of patient consent; and/or
- Any other reason, such that continuation of the patient's participation is thought by the investigator to be inappropriate.

If a patient withdraws or is withdrawn, the reason should be documented in the registry records.

9.2.2 Study procedures

Site selection

E-IMD members will be informed by the E-IMD Steering committee/Executive Board about participation in the RAVICTI Registry. All participating sites will be trained on the protocol, registry logistics, and the electronic data capture system. Retraining will be conducted as needed. Horizon will obtain and/or confirm independent ethics committee (IEC) on behalf of the participating sites approval for each participating site.

Any E-IMD site should be regarded as being qualified to contribute to the RAVICTI Registry, if minimal number of UCD patients and availability of infrastructure that enables systematic follow-up (including psychometric tests), etc. is confirmed. Qualification of E-IMD sites has been evaluated and approved by the E-IMD steering committee. Qualification criteria include experience of more than five years in the diagnosis, emergency and maintenance treatment as well as long-term follow-up of patients with urea cycle disorders, the availability of an interdisciplinary team including a metabolic specialist, a specialized dietitian, a psychologist, and other healthcare professionals (e.g. physicotherapeutist, occupational therapist, speech therapist), as well as specialized metabolic laboratory and ICU/NICU. Metabolic specialists at E-IMD sites have been trained according to the SSIEM training syllabus and follow evidence-based guidelines developed and published by E-IMD.

Study visits

Baseline Visit (BV)

An initial baseline visit will be scheduled for patients who are considered for study participation at the discretion of the investigator.

Regular Visits (RV) (years 1 to 10)

E-IMD routinely collects data from all inpatient and outpatient visits that are part of standard care of the metabolic condition, such visits are expected to be scheduled at least once per year but can be more frequent if medically indicated.

Unscheduled Visits (UV) and Emergency Visits (EV) including HAC

All other inpatient and outpatient visits that are not directly related to the treatment of the metabolic condition of the patient are recorded as unscheduled visits. Inpatient and outpatient visits for the acute management of impending metabolic decompensations (including HAC) are recorded as emergency visits. If such visits occur, available data from the list below will be collected. All visits will be recorded as sequential study visits in the database.

Fatal Disease Course Visit (FV)

If a patient dies while participating in the registry a final visit gathering data on the cause of death is entered.

Neuropsychological Tests

Neuropsychological tests will be performed according to following schedule:

Testing age	**Tests**
For patients 12 months and older at baseline visit	*choose battery appropriate to current age*
1;0 (1;0 – 1;2) year	BSID-II or III (cognitive scale) + Denver II
2;0 (1;10 – 2;2) years	BSID-II or III (cognitive scale) + Denver II
3;0 (3;0 – 3;2) years	WPPSI-III + Denver II
5;0 (4;6 – 5;6) years	WPPSI-III
8;0 (7;6 – 8;6) years	WISC-IV
15;0 (14;6 – 15;6) years	WISC-IV
18;0 (17;6 – 18;6) years	WAIS-IV

BSID: Bayley Scales of Infant Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale of Children; WAIS: Wechsler Adult Intelligence Scale.

If patients cannot be examined with the test appropriate for age, it should be tried to apply a test for younger age groups.

9.3 Variables

The following table provides an overview on variables collected for all patients enrolled into the study. Data collection for routine E-IMD data and additional variables will be uniformly implemented for all patients; i.e. for all patients who are treated with RAVICTI and all patients treated with a comparator nitrogen scavenger therapy.

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
Demographic Data	**Demographic Data**						
	Age at first symptoms	numeric	discrete	x			
	Age at diagnosis	numeric	discrete	x			
	Gender	categorical (single selection)	male/female	x			
	Race	categorical (single selection)	white/black/asian/mixed/unknown	x			
Presentation of UCD - Diagnosis	**Presentation of UCD - Diagnosis**						
	Mode of diagnosis	categorical (single selection)	newborn screening/selective screening/ high risk family screening/ high-risk population screening/ prenatal screening	x			
	Disease name	categorical (single selection)	nags/cps1/otc/ass/asl/arg1/hhh	x			
	Nucleotid change	string	char(25)	x			
	Protein change	string	char(25)	x			
Presentation of UCD - Initial crisis	**Presentation of UCD - Initial crisis**						
	Symptomatic	categorical (single selection)	yes/no	x			
	First symptoms	categorical (multiple selection)	impaired consciousness/hyperexcitability/ recurrent vomiting/ "sepsis-like" appearance/seizures/ muscular hypotonia/ odour/other	x			
	First symptoms other	string	char(150)	x			
	Ph	numeric	continuous	x			
	Pco2 [kpa]	numeric	continuous	x			
	Standard bicarbonate [mmol/l]	numeric	continuous	x			
	Base excess [mmol/l]	numeric	continuous	x			
	Plasma lactate [mmol/l]	numeric	continuous	x			
	Serum glucose [mmol/l]	numeric	continuous	x			
	Plasma ammonia [µmol/l]	numeric	continuous	x			
	Plasma glutamine [µmol/l]	numeric	continuous	x			
	Plasma citrulline [µmol/l]	numeric	continuous	x			
	Plasma arginine [µmol/l]	numeric	continuous	x			

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	Plasma ornithine [µmol/l]	numeric	continuous	x			
	Plasma argininosuccinate [µmol/l]	numeric	continuous	x			
	Other symptoms leading to the diagnosis	categorical (multiple selection)	feeding problems/hepatic disease/ epilepsy/movement disorder/ mental retardation/psychiatric disease/ renal disease/ bone marrow dysfunction/cardiac disease	x			
	Other symptoms leading to the diagnosis - other	string	char(150)	x			
Family History	**Family History**						
	Family members with same disease (up to 5)	numeric	discrete	x			
	Relationship to patient (1 - 5)	categorical (multiple selection)	mother/father/daughter/son/sister/ brother/cousin/others	x			
Presentation of UCD - Physical/Neurological Examination	**Presentation of UCD - Physical/Neurological Examination**						
	Height [cm]	numeric	continuous	x	x	x	
	Weight [kg]	numeric	continuous	x	x	x	
	Head circumference [cm]	numeric	continuous	x	x		
	Temperature [°c]	numeric	continuous	x	x	x	
	General state of health	categorical (single selection)	normal/abnormal/ not examined	x	x	x	
	Blood pressure	categorical (single selection)	normal/hypotension/ hypertension/not examined	x	x	x	
	Pulses	categorical (single selection)	normal/bradycardia/ tachycardia/not examined	x	x	x	
	Gastrostomy	categorical (single selection)	absent/present/ not examined	x	x		
	Consciousness	categorical (single selection)	normal/somnolence/stupor/ coma/not examined	x	x	x	
	Muscle tone	categorical (single selection)	normal/hypotonia/ hypertonia/not examined	x	x	x	
	Gross motor	categorical (single selection)	normal/abnormal/ not examined	x	x		
	Gross motor milestones	categorical (single selection)	sitting without support/ hands-and-knees crawling/ standing with assistance/ standing alone/ walking with assistance/ walking alone/ none/not examined	x	x		
	Fine motor	categorical (single selection)	normal/abnormal/ not examined	x	x		

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	Movements	categorical (single selection)	normal/abnormal/ not examined	x	x	x	
	Movements - disorders	categorical (multiple selection)	dystonia/chorea/ ataxia/spasticity	x	x	x	
	Movements - disorders severity	categorical (single selection)	mild/moderate/severe	x	x	x	
	Icd10 (up to 10 times)	string	char(8)	x	x	x	
Neuropsychological Tests	**Neuropsychological Tests**						
	Denver [developmental age]	numeric	continuous	x	x		
	BSID [iq]	numeric	continuous	x	x		
	WPPSI [iq]	numeric	continuous	x	x		
	WISC [iq]	numeric	continuous	x	x		
	WAIS [iq]	numeric	continuous	x	x		
Other ammonia scavenging medication	**Other ammonia scavenging medication**						
	Sodium benzoate [mg/day]	numeric	continuous	x	x	x	
	Sodium phenylbutyrate [mg/day]	numeric	continuous	x	x	x	
	Sodium Phenylacetate [mg/day]	numeric	continuous			x	
	Carbamylglutamate [mg/day]	numeric	continuous	x	x	x	
	L-arginine [mg/day]	numeric	continuous	x	x	x	
	L-citrulline [mg/day]	numeric	continuous	x	x	x	
	Metronidazole [mg/day]	numeric	continuous	x	x	x	
	Colistin [mg/day]	numeric	continuous	x	x	x	
Other medication	**Other medication**						
	Other drug name (up to 15)	string	char(150)	x	x	x	
	Other drug dose [mg/d] (1 - 15)	numeric	continuous	x	x	x	
	Other drug route (1 - 15)	categorical (single selection)	po/iv/im/sc/pr/top/in/inhale	x	x	x	
Dietary treatment	**Dietary treatment**						
	Natural protein intake [g/kg/d]	numeric	continuous	x	x	x	
	Protein from aam [g/kg/d]	numeric	continuous	x	x	x	
	Isoleucine [g/kg/d]	numeric	continuous	x	x		
	Leucine [g/kg/d]	numeric	continuous	x	x		
	Valine [g/kg/d]	numeric	continuous	x	x		
	Methionine [g/kg/d]	numeric	continuous	x	x		
Hyperammonemic crisis (HAC)	**Hyperammonemic crisis (HAC)**						
	Ammonia at max metabolic derangement	numeric	continuous			x	

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	[µmol/l]						
	Suspected triggers for hac	categorical (multiple selection)	gastroenteritis/pneumonia/meningitis/ upper respiratory tract infection/ urinary tract infection/ other infection/vaccination/change in diet/ change in precursor-free amino acid mixtures/ pregnancy/delivery/ suspected nonadherence to treatment/ new dosage of previous medication/ new medication implemented to treatment			x	
Laboratory Tests	**Laboratory Tests**						
	Ammonia [µmol/l]	numeric	continuous	x	x	x	
	Glutamine [µmol/l]	numeric	continuous	x	x	x	
	Glutamic acid [µmol/l]	numeric	continuous	x	x	x	
	Citrulline [µmol/l]	numeric	continuous	x	x	x	
	Arginine [µmol/l]	numeric	continuous	x	x	x	
	Alanine [µmol/l]	numeric	continuous	x	x	x	
	Glycine [µmol/l]	numeric	continuous	x	x	x	
	Isoleucine [µmol/l]	numeric	continuous	x	x	x	
	Leucine [µmol/l]	numeric	continuous	x	x	x	
	Valine [µmol/l]	numeric	continuous	x	x	x	
	Phenylalanine [µmol/l]	numeric	continuous	x	x	x	
	Lysine [µmol/l]	numeric	continuous	x	x	x	
	Ornithine [µmol/l]	numeric	continuous	x	x	x	
	Creatinine [µmol/l]	numeric	continuous	x	x	x	
	Cystatin C	numeric	continuous	x	x	x	
	Gfr [ml/min/1.73 m2]	numeric	continuous	x	x	x	
	Alat [u/l]	numeric	continuous	x	x	x	
	Asat [u/l]	numeric	continuous	x	x	x	
	Potassium [mmol/l]	numeric	continuous	x	x	x	
	Sodium [mmol/l]	numeric	continuous	x	x	x	
	Haemoglobin [g/dl]	numeric	continuous	x	x	x	
	Mcv [fl]	numeric	continuous	x	x	x	
	Wbc [/nl]	numeric	continuous	x	x	x	
	Platelets [/nl]	numeric	continuous	x	x	x	
Additional Variables for RAVICTI - Drug application	**Additional Variables for RAVICTI - Drug application**						
	RAVICTI total daily dose [mg/day]	numeric	continuous	x	x	x	x
	RAVICTI frequency	numeric	discrete	x	x	x	x
	RAVICTI start date [dd/mm/yyyy]	string	char(10)	x	x	x	x
	RAVICTI stop date	string	char(10)	x	x	x	x

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	[dd/mm/yyyy]						
	Action with RAVICTI	categorical (single selection)	withdrawn/dose reduced/dose increased/ dose not changed/unknown	x	x	x	x
	Action with RAVICTI - explanation	string	char(150)	x	x	x	x
Additional Variables for Sodium benzoate - Drug application	**Additional Variables for Sodium benzoate - Drug application**						
	Sodium benzoate total daily dose [mg/day]	numeric	continuous	x	x	x	x
	Sodium benzoate frequency	numeric	discrete	x	x	x	x
	Sodium benzoate start date [dd/mm/yyyy]	string	char(10)	x	x	x	x
	Sodium benzoate stop date [dd/mm/yyyy]	string	char(10)	x	x	x	x
	Action with Sodium benzoate	categorical (single selection)	withdrawn/dose reduced/dose increased/ dose not changed/unknown	x	x	x	x
	Action with Sodium benzoate - explanation	string	char(150)	x	x	x	x
Additional Variables for Sodium phenylbutyrate - Drug application	**Additional Variables for Sodium phenylbutyrate - Drug application**						
	Sodium phenylbutyrate total daily dose [mg/day]	numeric	continuous	x	x	x	x
	Sodium phenylbutyrate frequency	numeric	discrete	x	x	x	x
	Sodium phenylbutyrate start date [dd/mm/yyyy]	string	char(10)	x	x	x	x
	Sodium phenylbutyrate stop date [dd/mm/yyyy]	string	char(10)	x	x	x	x
	Action with Sodium phenylbutyrate	categorical (single selection)	withdrawn/dose reduced/dose increased/ dose not changed/unknown	x	x	x	x
	Action with Sodium phenylbutyrate - explanation	string	char(150)	x	x	x	x
Additional Variables for - AE/SAE due to nitrogen scavenging medication	**Additional Variables for - AE/SAE due to nitrogen scavenging medication**						
	Putative adverse event due to nitrogen scavenger	categorical (single selection)	RAVICTI/sodium benzoate/ sodium phenylbutyrate	x	x	x	x
	Putative adverse events since last visit (up to 6)	numeric	discrete	x	x	x	x
	Last dose of nitrogen scavenging medication prior to event (1-6)	numeric	continuous	x	x	x	x
	Adverse event severity (1-6)	categorical (single	non serious/ serious	x	x	x	x

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
		selection)					
	Adverse event description (1-6)	categorical (single selection)	abdominal pain/nausea/diarrhoea/headache/ flatulence/decreased appetite/vomiting/ fatigue/abnormal skin odour/other	x	x	x	x
	Adverse event description - other (1-6)	string	char(150)	x	x	x	x
	Adverse event startdate [dd/mm/yyyy] (1-6)	string	char(10)	x	x	x	x
	Adverse event stopdate [dd/mm/yyyy] (1-6)	string	char(10)	x	x	x	x
	Adverse event outcome (1-6)	categorical (single selection)	recovered without sequelae/ recovered with sequelae/ recovering/not recovered/ patient died/unknown	x	x	x	x
	Adverse event causality (1-6)	categorical (single selection)	reasonable possibility that event was caused by nitrogen scavenger/ no reasonable possibility that event was caused by nitrogen scavenger	x	x	x	x
	Adverse event action with nitrogen scavenger (1-6)	categorical (single selection)	withdrawn/dose reduced/dose increased/ dose not changed/unknown	x	x	x	x
	Alternative cause (if not nitrogen scavenger attributed)	string	char(150)	x	x	x	x
	Pregnancy of patient	categorical (single selection)	no/yes/not applicable/unknown	x	x	x	x
	Reported term	numeric	discrete	x	x	x	x
	Discontinuation from European Post-Authorisation Registry for RAVICTI	categorical (single selection)	yes/no	x	x	x	x
	Discontinuation from European Post-Authorisation Registry for RAVICTI - reason	string	char(150)	x	x	x	x
Additional Variables for Carcinogenicity	**Additional Variables for Carcinogenicity**						
	Malignant neoplasm	categorical (single selection)	yes/no	x	x	x	x
	Malignant neoplasm - description icd10	string	char(8)	x	x	x	x
	Malignant neoplasm - description free text	string	char(150)	x	x	x	x
Fatal Disease Course	**Fatal Disease Course**						
	Day of death [dd/mm/yyyy]	string	char(10)				x
	Cause of death	categorical (single selection)	brain edema/epileptic state/fatal aspiration/ acute cardiac failure/acute liver failure/ necrotizing pancreatitis/mass				x

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
			bleeding/ severe infectious disease/uremia/other causes				
	Other death cause ICD10	string	char(8)				x
Additional Variables for Pregnancy exposure	**Additional Variables for Pregnancy exposure**						
	Pregnancy Outcome	categorical (single selection)	spontaneous vaginal delivery/ induced vaginal delivery/ extraction (vacuum, forceps)/ cesarean Section/ intentional abortion/ spontaneous abortion - stillbirth	(x)	(x)	(x)	(x)
	Spontaneous abortion, stillbirth - causality	string	Char(150)	(x)	(x)	(x)	(x)
	Sex of child	categorical (single selection)	male/ female	(x)	(x)	(x)	(x)
	Gestational Age	numeric	discrete	(x)	(x)	(x)	(x)
	Birth weight	numeric	continuous	(x)	(x)	(x)	(x)
	Birth length	numeric	continuous	(x)	(x)	(x)	(x)
	Head circumference	numeric	continuous	(x)	(x)	(x)	(x)
	APGAR Score [10 min]	numeric	discrete	(x)	(x)	(x)	(x)
	RAVICTI exposure during pregnancy	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	RAVICTI exposure during pregnancy – cumulative weeks in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median RAVICTI dose in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	RAVICTI exposure during pregnancy – cumulative weeks in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median RAVICTI dose in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	RAVICTI exposure during pregnancy – cumulative weeks in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median RAVICTI dose in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium benzoate exposure during pregnancy	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Sodium benzoate exposure during pregnancy – cumulative weeks in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median Sodium benzoate dose in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium benzoate exposure during pregnancy – cumulative weeks in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	Median Sodium benzoate dose in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium benzoate exposure during pregnancy – cumulative weeks in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median Sodium benzoate dose in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium phenylbutyrate exposure during pregnancy	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Sodium phenylbutyrate exposure during pregnancy – cumulative weeks in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median Sodium phenylbutyrate dose in 1. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium phenylbutyrate exposure during pregnancy – cumulative weeks in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median Sodium phenylbutyrate dose in 2. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Sodium phenylbutyrate exposure during pregnancy – cumulative weeks in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Median Sodium phenylbutyrate dose in 3. Trimester	numeric	continuous	(x)	(x)	(x)	(x)
	Maternal medical problems during pregnancy	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Maternal medical problems during pregnancy – free text	string	char(150)	(x)	(x)	(x)	(x)
	Maternal medical problems during pregnancy – ICD10	string	char(8)	(x)	(x)	(x)	(x)
	Congenital abnormalities (including fetal malformations and neoplasms)	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Congenital abnormalities (including fetal malformations and neoplasms) – free text	string	char(150)	(x)	(x)	(x)	(x)
	Congenital abnormalities (including fetal malformations and neoplasms) – ICD10	string	char(8)	(x)	(x)	(x)	(x)

Category	Variable Label	Data type	Values	BV	RV	UV/EV	FV
	Neonatal period	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Neonatal period – free text	string	char(150)	(x)	(x)	(x)	(x)
	Neonatal period – ICD10	string	char(8)	(x)	(x)	(x)	(x)
	Death in newborn period	categorical (single selection)	Yes/ no	(x)	(x)	(x)	(x)
	Death in newborn period – free text	string	char(150)	(x)	(x)	(x)	(x)
	Death in newborn period – ICD10	string	char(8)	(x)	(x)	(x)	(x)
Additional Variables for - AE/SAE of children due to pregnancy and-or lactation exposure to nitrogen scavenging medication	**Additional Variables for - AE/SAE of children due to pregnancy and-or lactation exposure to nitrogen scavenging medication**						
	Putative adverse event due to pregnancy and-or lactation exposure to nitrogen scavenger	categorical (single selection)	RAVICTI/sodium benzoate/ sodium phenylbutyrate	x	x	x	x
	Exposure to scavenger due to breastfeeding	categorical (single selection)	Yes/ no	x	x	x	x
	Cumulative months of scavenger exposure due to breastfeeding	numeric	continuous	x	x	x	x
	Median dose of scavenger during breast feeding period	numeric	continuous	x	x	x	x
	Age of child [month]	numeric	continuous	x	x	x	x
	Putative adverse events since last visit (up to 6)	numeric	discrete	x	x	x	x
	Adverse event severity (1-6)	categorical (single selection)	non serious/ serious	x	x	x	x
	Adverse event description - (1-6)	string	char(150)	x	x	x	x
	Adverse event startdate [dd/mm/yyyy] (1-6)	string	char(10)	x	x	x	x
	Adverse event stopdate [dd/mm/yyyy] (1-6)	string	char(10)	x	x	x	x
	Adverse event outcome (1-6)	categorical (single selection)	recovered without sequelae/ recovered with sequelae/ recovering/not recovered/ patient died/unknown	x	x	x	x
	Adverse event causality (1-6)	categorical (single selection)	reasonable possibility that event was caused by pregnancy and-or lactation related exposure to nitrogen scavenger/ no reasonable possibility that event was caused by pregnancy and-or lactation related exposure to nitrogen scavenger	x	x	x	x
	Alternative cause (if not nitrogen scavenger attributed)	string	char(150)	x	x	x	x

9.4 Data Sources

This registry will use available data documented at the participating site for the enrolled patient during each patient contact as specified above. Participating investigators will select the data during the visits from the patient's medical record including physician's or nurse's notes, consultancy reports, discharge summaries, laboratory sheets, etc. Data as described above will be entered during the patient visits in the electronic registry record forms provided by the E-IMD.

The E-IMD routinely collects data for all enrolled patients at least annually and at time points in between, if the patient is seen as standard of care or the patient experiences a hyperammonemic crisis and is seen as an emergency patient.

Health-related information pertaining to the variables described above will be collected as available during the patient's participation in the registry. Results of age-appropriate neuropsychological testing will be recorded according to the E-IMD registry protocol. For additional safety data, which will be collected for the RAVICTI post marketing surveillance (RAVICTI or comparator group), participating investigators will be asked to complete the respective information including reason for the visit, information on RAVICTI or comparator treatment, and respective safety data (AE, pregnancy, lactation) during each regular and any additional unscheduled or emergency patient visit. Safety related data will be collected in the comparator group for alternative ammonia scavenging medication other than RAVICTI using the same approach and tools.

9.5 Study Size

Approximately 200 patients are planned to be enrolled in the Registry, divided equally in study and comparator group. The number of anticipated patients is based on the estimated prevalence of the orphan indication (UCD) and assumptions regarding the availability of RAVICTI at E-IMD sites.
The study will aim to expand the database for the safety profile and the incidence rates will be summarized for each arm for adverse events, cancer (including types) and pregnancies. All UCD patients treated with RAVICTI or another nitrogen scavenger (comparator group) are eligible to enroll in the Registry. For the comparator group E-IMD sites may participate from countries where RAVICTI is not yet commercially available in order to increase the recruitment capacity. A list of E-IMD centers which have already expressed interest in participating in the study is provided in Annex 1.

Recruitment period is planned for 3 years. Eligible patients will be enrolled in the Registry and followed for up to 10 years.

9.6 Data Management

Health-related personal data concerning treatment and clinical condition of individual patients will be collected at baseline, and prospective regular, unscheduled and emergency visits per E-IMD patient registry protocol.

Medical diagnoses will be coded according to ICD 10. Adverse events will not be coded according to a medical dictionary but entered by the investigator from a predefined list (common AE) or as verbatim information of the medical diagnosis. Drugs used to treat the UCD will not be coded but entered according to pre-specified drug categories.

9.7 Data Analysis

Statistical analysis will be performed using the recent version of SPSS and recent version of R environment for statistical computing and graphics. Continuous variables will be described by main summary statistics: number of patients, number of missing values, mean, standard deviation, minimum, 25th percentile (quartile 1), median, 75th percentile (quartile 3), and maximum. Qualitative variables will be described by absolute and relative frequencies or contingency tables, where appropriate. String variables containing free text entries will be listed.

Analysis population: Data will be presented for UCD patients enrolled in the Registry and partaking in the surveillance of RAVICTI. Data of UCD patients not receiving RAVICTI will be presented for those patients who provide consent for participating in the comparator group. Additional subgroups may also be examined, as deemed appropriate (pediatric versus adult, UCD subtype, etc.).

Disposition data will be summarized with descriptive statistics and presented in listings. Demographic and clinical data will be summarized with descriptive statistics and presented in listings. Post-baseline values and/or change from baseline in the outcome variables will be summarized with descriptive statistics, and, where appropriate, graphical presentations.

Onset of disease is used to dichotomize the sample into “early onset” (high disease severity) and “late onset” (low disease severity) groups. Onset type will thus serve as foundation of group specific comparisons, adequately separating more severe from less severe cases. Further covariates considered for group comparison are the initial peak plasma ammonia level at disease onset, and therapy escalation evaluating the use of nitrogen scavengers.
According to the mentioned covariates, the following groups will be compared:

- Onset type: Early vs. late onset
- Peak ammonium level: < 500 µmol/L and >500 µmol/L plasma ammonium
- Therapy escalation: Benzoate vs. phenylbutyrate (sodium phenylbutyrate or glycerol-phenylbutyrate) vs. benzoate plus phenylbutyrate (sodium phenylbutyrate or glycerol-phenylbutyrate)
- Pediatric versus adult
- UCD subtype

The use of these variables is based on previous European and international studies confirming that they are robust and particularly relevant for differentiating different degrees of severity in UCD patients (Kölker et al. 2015; Posset et al. 2016).

Following the above mentioned strategy, endpoint variables are investigated by use of statistical models comparing RAVICTI and UCD patients not receiving RAVICTI. Depending on the scale of variables, linear mixed and generalized linear mixed models for continuous and dichotomous response variables will be accessed to analyze subgroup differences and interactions. To estimate hazard rates and potential problems due to censored data, hazard models for dichotomous and, when adequate, multinomial response variables were evaluated. No meta-analysis or multiple treatment comparison analysis is planned. Multiple imputation of missing values will not be applied. Due to the observational aim of this study, no sensitivity analysis is indicated and power analysis could be applied post-hoc.

9.8 Quality Control:

The E-IMD consortium employs a web-based, secured data collection. The server is located at the University Hospital Heidelberg, the main coordinator of this study (Central Study Office).

The names of the participants and all other confidential information are subject to medical confidentiality and the statutory data protection provisions. Participant data are forwarded to the central database of the study only in key-coded form.

The main coordinator of the study has access to the key-coded data of all participants. The study centers have access only to the data of the participants under their management. Access to the database is restricted to the study physicians and is protected by a personal password generated by the study coordinator, which must be changed by the responsible employees at regular intervals. All data sent via the internet are cryptographically encoded. Thus, no-one apart from the sender (study center) and the recipient (Central Study Office) has access to readable data. The server with the database is protected by a professional security concept. Neither the data transmission nor the central database contains any identifying data, only the key-code.

The E-IMD registry has been used since 2011 for collecting longitudinal observational data of intoxication type metabolic disease. It was developed for this specific task, has been continually improved and already proved its capabilities by providing data for several scientific publications. The data is entered by qualified staff supervised by metabolic experts with long standing experience in using the E-IMD interface.

Wherever possible the registry verifies data already upon entry by checking valid ranges. Additionally prior to each analysis and at regular intervals in between, the entered data is checked for plausibility by qualified study physicians at the study center in Heidelberg and queries are issued as needed. The study centers are informed at regular intervals about the completeness of entered datasets and motivated to close gaps in their data.

Prior to any enrollment in the registry, the MAH will audit the study center at Heidelberg in order to assess data collection, cleaning, and storage practices and systems to ensure compliance with agreed procedures and data security requirements. The MAH may re-audit the center at Heidelberg periodically thereafter to ensure that any prior audit findings have been effectively resolved and ensure ongoing compliance. In addition the study center at Heidelberg will conduct periodic site audits of selected collaborating study centers to ensure that agreed procedures are duly followed. Any major or critical findings from these site audits will be communicated to the MAH. The center at Heidelberg and the MAH will assess the impact of the findings on subjects' rights and safety and data quality and act accordingly to secure corrections and compliance.

9.9 Limitations of the research methods

This registry study is being performed to generate longitudinal safety data in patients with UCD treated with RAVICTI. It is expected to provide further insight into the long term safety of RAVICTI. Furthermore it may generate safety signals or hypotheses on the safety profile of RAVICTI.

The following limitations apply:

- Study size and power to detect new risks:

By necessity, clinical trials in rare disorders enroll small sample sizes. In combination with high inter-individual variability in clinical course observed in UCD, this diminishes a study's power. This study is not immune to this dual disadvantage given that UCDs are ultra-orphan with an estimated incidence of 1 in 35,000 live births. Considering the number of life births in EU member states (5,229,813 according to Eurostat, as of 2011) an average of 149 newborn patients with UCD in EU member states can be expected (M. Summar et al 2013). In the UCD Consortium longitudinal study (M. Batshaw et al 2014) 26% of patients were symptomatic in the newborn period, 69% of all patients had symptoms at some point and 5% remained asymptomatic. Assuming that these figures are comparable in the EU this results in an estimated number of 38 newborns with symptomatic hyperammonemia per year in

the EU. Regarding the feasibility of detecting new risk in UCDs, an ultra-orphan disease, with 100 patients on RAVICTI there is a 9.5% chance of detecting a rare event of 1/10 of a percent. Increasing the chance of detecting a rare event would exceed the population of UCD patients available to participate in the study. In summary the extremely small number of patients with UCD effectively precludes an increase in the targeted patient numbers above the suggested enrolment of 100 patients treated with RAVICTI plus 100 patients treated with a comparator. As a consequence the power to detect rare new risks is estimated to be inevitably low. However, in general, new risks cannot only be feasibly detected by increasing the number of patients but also by long-term follow-up of individual patients. Since this study follows all patients for a significantly extended period for at least ten years with an estimated average of at least 2 visits per year, the registry should be capable of optimizing the probability of identifying new risks which are caused by long-term exposure to RAVICTI.

- Selection bias regarding disease severity

From data collected in the E-IMD until today, it was noted that patients who are severely ill from UCD are to a lesser extent enrolled into the E-IMD registry than patients with less severe manifestations. Thus the generalisability of data collected in the registry to the entire population may be limited and may not include patients who are critically ill. However, all patients treated with RAVICTI or another nitrogen scavenger therapy are invited to participate in the registry. In order to minimize bias in the selection of patients, the investigators are encouraged to consecutively enroll all patients who consent and meet the selection criteria, regardless of health status, or other considerations. To facilitate awareness for a possible selection bias, a log file will be created, recording age, diagnosis, sex and onset type, the dominating markers for diseases course severity and, if applicable, reason for assent for all eligible patients actively approached for enrollment. The data from the log file will be compared to the subset of patients enrolled on this protocol following the regular reporting cycle thus creating awareness for an emerging selection bias, resulting in adaptations of the recruitment strategy as needed. The inclusion of markers for severity will address the major confounder hurting generalizability. The tracking of reasons for not consenting addresses possibly flawed recruitment strategies. It must be noted that UCD is a rare disorder and the clinical presentation even within a certain subtype includes a range of severity/outcomes. The log file will increase transparency on the characteristics of patients enrolled into the RAVICTI registry compared to all patients who were potentially eligible.

- Follow up period and switch in treatment

It is anticipated that patients may switch treatments with nitrogen scavenging medication (RAVICTI or alternative) during the study period. Considering the limited number of available patients in this orphan indication it was decided to maintain these patients in the follow up evaluation. It is planned to evaluate a patient, who switches treatment and has received RAVICTI at any time point in the study, as “RAVICTI” patient from the time of the start of RAVICTI treatment onwards. This classification scheme will introduce limitations, e.g. the follow up period for these patients may be shorter than for patients assigned to one treatment group during the entire study period. Furthermore long term effects of the previous treatment may carry over to the RAVICTI arm. The group of patients who switched treatment will therefore be assessed for an effect by the switch.
For patients treated with RAVICTI additional AE/SAE reports send directly to Horizon Pharma by the treating physician will be available as an alternative data source, whereas no such reports will be available for the comparator group. Therefore safety related data for the comparator group will stem solely from the E-IMD registry, potentially leading to biased results.

- Missing data

Like all non-interventional studies the registry study collects data that are generated according to the patient’s medical needs upon discretion of the treating physician. Although variables have been selected, which reflect common practice in treating UCD patients, it is likely that some data will be missing during the patient’s participation in the registry, e.g. laboratory test results if they are not required according to the individual treatment plans of the patient. Furthermore it must be considered

that some patients may be lost to follow up, as patients may withdraw from the registry any time or move to another health care provider. Analysis of data will therefore include an estimate whether missing data influence the results of the study.

9.10 Other Aspects

None

10 Protection of Human Subjects

The study will be submitted for review by the responsible IEC of the sites, the national health authorities and the PRAC in the EU/EEA in order to ensure adherence with ethics protection regulations..

The Registry is planned as a non-interventional collection of data that are documented as part of the standard of care for the patient. All medical decisions and interventions will be taken independently from the systematic data collection. No additional interventions are planned.

All procedures in data collection and documentation will ensure that data privacy laws are adhered to: Extracted data are anonymized, with patient identifiers restricted to age and gender. The E-IMD will provide tables and listings and respective analysis results to the MAH in anonymized data outputs which will not permit the identification of the individual participants.

Patients and/or parents families are informed about data access, management, storage and protection. They are informed that all data in the registry are pseudonymized (and what pseudonymization means). Patients and/or parents give written informed consent before inclusion in the E-IMD registry. The informed consent includes an explicit statement that patients/parents allow the E-IMD to provide anonymized data to third parties.

In summary, the well-being and rights of participants is not impacted by participation in the Registry.

11 Management and reporting of adverse events/adverse reactions

Although data regarding putative adverse events and pregnancy/lactation exposure for patients treated with RAVICTI and patients treated in the comparator group is also stored in the registry, the direct reporting of adverse events, serious adverse events and pregnancy/lactation exposure with regard to fulfilling critical timelines in compliance with legal requirements for RAVICTI will remain the sole responsibility of the treating physicians at the various study sites. For this task Horizon Pharmacovigilance will provide suited reporting forms that will be filled in by the treating physician and sent directly to Horizon Pharmacovigilance. The E-IMD registry will help to facilitate this process by making these reporting forms available for download and by integrating a system of automatic warning messages that are triggered when entering data suspicious for an Adverse Event (AE)/Serious Adverse Event (SAE), such as an non-elective hospitalization etc., however none of these measures will assume any of the responsibilities of the treating physician and will remain strictly supportive in nature.

Definition of an AE.
An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Examples of adverse events include one of the following or a combination of two or more of these factors:

- Any unfavorable and unintended sign, symptom, illness, or syndrome;
- Abnormal laboratory values, if judged clinically significant in the opinion of the investigator;

- Worsening (change in nature, severity or frequency) of a concomitant or pre-existing illness;
- An adverse event of the investigational medicinal product, including comparator or concomitant medication;
- Drug interactions;
- An adverse event resulting from an invasive procedure; and/or
- An accident or injury.

Hyperammonemia should be considered an AE if clinically significant unless the Investigator determines that the abnormal result was due to an inaccurate test.

All adverse events fall into one of two categories:
"non – serious" or "serious"

Definition of a suspected adverse reaction
A suspected adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. For the purpose of this registry an adverse event which was judged either by the investigator and/or Horizon Pharma as having a reasonable causal relationship to RAVICTI (see below) will be considered a suspected adverse reaction.

Definition of a SAE
A serious adverse event is any untoward medical occurrence that at any dose (including overdose)

- Results in death; or
- Is life-threatening.

"Life-threatening" means that the patient was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the adverse event, or that they occurred as a consequence of the event.

Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfils any other of the serious criteria.

- Results in persistent or significant disability or incapacity

"Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.

- Is a congenital anomaly or birth defect
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred.

Important medical events that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above, should also usually be considered serious.

A diagnosis of a new cancer/ malignant neoplasm during the course of a treatment will always be considered as medically important (serious) by Horizon Pharma and reported according to the European PV legislation.

Causality
The investigator will provide an assessment of the causal relationship between the event and RAVICTI.

The investigator will primarily apply a binary form of causality assessment:

- Related: There is a reasonable causal relationship between the medicinal product and the adverse event; or
- Unrelated: There is no reasonable causal relationship between the medicinal product and the adverse event.

The investigator should use medical judgment to determine whether he/she assumes a reasonable causal relationship, including into his/her evaluation all relevant factors and factual evidence such as:

- temporal course and latency;
- results from de-challenge or re-challenge;
- pattern of the reaction;
- known pharmacological properties of the product; and
- alternative explanations (e.g. other drugs, medical history, concomitant diseases).

The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Exposure to RAVICTI during pregnancy or lactation

In the event of a pregnancy occurring during the course of this particular study, the patient should be closely followed-up during the entire course of the pregnancy and postpartum period regardless whether the product was continued or withdrawn. Patients will be followed up as long as they agree to participate in the RAVICTI registry. Becoming pregnant is not considered a reason to discontinue from participation (see also section 9.2.1 of the protocol) and therefore the patients will be encouraged to continue in the registry regardless form their decision to continue treatment with RAVICTI during pregnancy. All recommendations described in the Summary of the Product Characteristics (SmPC) during pregnancy and lactation have to be carefully considered.

Parental and neonatal outcomes must be recorded even if they are completely normal and without Adverse Events. Off-spring will be followed by regular adverse event reporting.

Exposure during lactation regardless whether an adverse occurred in the breast fed child will also be recorded.

For documentation of the pregnancy outcome/ exposure during lactation a specific form (annex 3) will be used once at the end of the pregnancy, variables to be recorded are included in the list in chapter 9.3. For documentation of the long term follow-up of relevant children an adapted AE/SAE reporting form will be used, variables to be recorded are included in the list in chapter 9.3.

Reporting of AEs
The E-IMD platform will provide a link to reporting forms. Participating investigators will report within 1 working day upon learning of any adverse events, serious adverse events and pregnancy / lactation by completing the AE or pregnancy/ lactation reporting form and send them via Email or Fax directly to the Horizon Pharmacovigilance contact.

Horizon Pharma Pharmacovigilance Contact point:

AdverseEvents@horizonpharma.com or Fax: +1-800-860-7836

Every attempt should be made to describe all Adverse Events in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually. The report should be as complete as possible, including details of the current illness and (serious) adverse event, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with RAVICTI.

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) will be documented and sent as a follow up report.

All patients who have adverse events, whether considered causally related to the use of the products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.

Horizon Pharma will identify missing information for each report. Requests for follow up will be sent directly to the investigator. Horizon will require follow up information in regular intervals from the investigators until all queries are resolved or no further information can be reasonably expected.

Reporting to Health Authorities

Cases of adverse events, which are suspected to be causally related to RAVICTI by the investigator and/or Horizon, will be reported in the form of valid individual case safety reports (ICSRs) in line with legal requirements taking account of the interpretive guidance set out in Good Pharmacovigilance Practice (GVP) Module VI to ensure that the ICSRs are reported in accordance with the appropriate timeframes.

12 Plans for disseminating and communicating study results

Each E-IMD member is and shall remain the owner of all data entered by him in the E-IMD registry. Each E-IMD member individually decides to share data for the realization of a specific project such as the European RAVICTI post-authorization registry. For this project, anonymized data which is required for half-yearly reports to the EMA will be provided by E-IMD. However, data ownership will not be transferred.

The E-IMD will provide tables and listings to Horizon Pharma according to the PSUR writing cycle, i.e. every six month. A final report is planned after the last patient enrolled in the Registry has completed 10 years observation period.

With respect to the RAVICTI Registry in Partnership with E-IMD, the MAH shall be provided with a proposed draft of the publication, paper or abstract (or any other material for publication or oral speech) for its comments, which shall be given no later than thirty (30) business days after delivery of such documents to MAH. The E-IMD members shall comply with MAH's requests to delete any references to MAH's confidential or proprietary information and/or MAH work product in any such paper or oral presentation and each of the E-IMD members agrees to withhold publication of same for an additional sixty (60) days in order to permit MAH to obtain patent protection in MAH work product/confidential or proprietary information, if MAH deems it necessary

The final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized before publication; For that purpose the final manuscript will be provided 2 weeks after acceptance for publication.

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Annex 1: List of stand-alone documents:

E-IMD sites with interest in participating in the study

Country	City	Organization
Austria	Innsbruck	Medizinische Universität Universität Innsbruck
Belgium	Antwerp	Universitair Ziekenhuis Antwerpen
Belgium	Brussels	Cliniques Universitaires St Luc, Université Catholique de Louvain, 10 av Hippocrate, B 1200 Bruxelles, Belgium.
Belgium	Brussels	Nutrition and metablism unit, Hôpital Universitaire des Enfants, Reine Fabiola 15, av JJ Crocq, 1020 Bruxelles
Croatia	Zagreb	Sveuciliste u Zagrebu, Mediciniski fakultet
Denmark	Copenhagen	Klinisk Genetisk Afdeling Rigshospitalet
France	Lille	Centre Hospitalier Régional et Universitaire de Lille - CHRU de Lille
France	Paris	Assistance Publique Hopitaux de Paris
Germany	Heidelberg	Universitätsklinikum Heidelberg, Zentrum für Kinder- und Jugendmedizin, Klinik I
Italy	Padova	Azienda Ospedaliera di Padova
Italy	Rome	Ospedale Pediatrico Bambino Gesù, U.O.C. Patologia Metabolica
Poland	Warsaw	Instytut "Pomnik-Centrum Zdrowia Dziecka
Portugal	Porto	Hospital de Sao Joao, EPE
Spain	Badalona	University hospital "German Trias i Pujol"
Spain	Barcelona	Hospital San Joan de Deu
Spain	Palma de Mallorca	Hospital Universitario Son Espases, Carretera de Valdemosa 79, Palma de Mallorca, E-07010, Balearic Islands
Switzerland	Zurich	Kinderspital Zürich, Universitäts-Kinderkliniken, Eleonoren-Stiftung
UK	Birmingham	Birmingham Children's Hospital NHS foundation trust
UK	Manchester	Central Manchester University Hospitals
UK	London	Great Ormond Street Hospital for Children NHS Trust
UK	London	Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery

Annex 2: ENCePP checklist for study protocols

See Next Page

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
European Post-Authorisation Registry for RAVICTI® (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD);

Study reference number:
HZNP-RAV-401

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☒	☐	☐	10
1.1.4 Interim progress report(s)	☒	☐	☐	11
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:
The EU-PAS register number has not yet been assigned, but will be included upon availability of the final protocol

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study is designed as a registry to collect longitudinal safety data from patients treated with RAVICTI in an orphan indication (UCD); the registry will also include a comparator group of matched UCD patients receiving another ammonia scavenger; As such the registry is suitable to describe the safety profile by descriptive statitics. It may identify trends in the safety profile. However, the registry will not formally test a pre-specified hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	15
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	15

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	16
4.2.2 Age and sex?	☒	☐	☐	16
4.2.3 Country of origin?	☒	☐	☐	6
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

Co-morbidity is not routinely collected in the E-IMD registry; the target indication has no seasonality aspects.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

The regisry will report on dose and duration of exposure; these data will be prospectively collected for each enrolled patients. However, the analysis of data is descriptive and will not test for dose or duration responses.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	23-28
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

This registry prospectively collects events of interest (AE, pregnancy outcomes etc.) for patients treated with RAVICTI and UCD patients receiving another nitrogen scavenger. There is no formal testing of the safety endpoints the validity of endpoint measurement was not discussed.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

The safety data collection is designed to collect longitudinal safety data in order to further characterize the safety profile of RAVICTI and compare the outcomes to an adequately matched group of UCD patients treated with other nitrogen scavengers. No confounding factors are pre-defined.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	28

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	28
8.1.3 Covariates?	☒	☐	☐	28
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	23
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23-28
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	29
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	29
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	29
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	28

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

The study size was estimated based on the prevalence of the orphan indication and assumptions made regarding the availability of RAVICTI at E-IMD sites

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	29
10.2 Is the choice of statistical techniques described?	☒	☐	☐	29
10.3 Are descriptive analyses included?	☒	☐	☐	29
10.4 Are stratified analyses included?	☒	☐	☐	29
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	29

Comments:

A comparator group has been added to the protocol to permit the comparison of safety variables between patients treated with RAVICTi and UCD patients receiving an alternative nitrogen scavenger. The comparator group will be matched as far as possible regarding age, gender and disease severity to permit comparison between the two groups. No confounding factors are pre-defined.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	29
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	30
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	30
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	30
12.3 Does the protocol address other limitations?	☒	☐	☐	30

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	31
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	31

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	34

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

Name of the main author of the protocol: [redacted]

Date: / /

Signature: [redacted]

Annex 3: Additional Information

Pregnancy Report Form

Form P – *Pregnancy outcome*

Pat-ID: _____ – _____ Date: _____ /_____ / _____ *[DD/MM/YYYY]*

Signature: _____

- **Only** for patients participating in **RRPE**
- To be filled in once at the end of each pregnancy at baseline (**B**) or regular visit (**V**) or emergency visit (**ER**) or fatal disease course visit (**FD**) as applicable.
- Please evaluate situation **28 days post-partum**

Pregnancy Outcome

☐ Spontaneous vaginal delivery ☐ Unknown

☐ Induced vaginal delivery

☐ Extraction (vacuum, forceps)

☐ Cesarean Section

☐ Intentional abortion

☐ Spontaneous abortion / stillbirth

Causality, if known: _____ [free text]

Gestational age *(fill in also in case of abortion / stillbirth)*

_____ [weeks] ☐ Unknown

Sex of the child

☐ Male ☐ Female ☐ Unknown

Date of birth

____ ____ / ____ ____ ____ ____ [mm/yyyy] ☐ Unknown

Anthropometrics *(also in case of stillbirth if available)*

Birth weight: _____ [g] ☐ Unknown

Birth length: _____ [cm] ☐ Unknown

Head circumference: _____ [cm] ☐ Unknown

Form P – *Pregnancy outcome*

Pat-ID: _____ – _____ Date: _____ /_____ / _____ *[DD/MM/YYYY]*

Signature: _____

RAVICTI® exposure during pregnancy

☐ Yes *(fill in details below)* ☐ Unknown

- ☐ Exposure in 1. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 1. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 2. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 2. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 3. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 3. Trimester: _____ [mg/kg] ☐ Unknown

☐ No

Exposure to Sodium benzoate during pregnancy

☐ Yes, Sodium benzoate *(fill in details below)* ☐ Unknown

- ☐ Exposure in 1. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 1. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 2. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 2. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 3. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 3. Trimester: _____ [mg/kg] ☐ Unknown

☐ No

Exposure to Sodium phenylbutyrate during pregnancy

☐ Yes, Sodium benzoate *(fill in details below)* ☐ Unknown

- ☐ Exposure in 1. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 1. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 2. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 2. Trimester: _____ [mg/kg] ☐ Unknown
- ☐ Exposure in 3. Trimester, cumulative pregnancy weeks: _____ [weeks] ☐ Unknown
- Median dose in 3. Trimester: _____ [mg/kg] ☐ Unknown

☐ No

Form P – *Pregnancy outcome*

Pat-ID: _____ – _____ Date: _____ /_____ / _____ *[DD/MM/YYYY]*

Signature: _____

Maternal medical Problems during pregnancy

☐ No ☐ Unknown

☐ Yes, please describe

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

Congenital abnormalities *(including fetal malformations and neoplasms)*

☐ No ☐ Unknown

☐ Yes, please describe

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

Problems in neonatal period

☐ No ☐ Unknown

☐ Yes, please describe

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

Death in newborn period

☐ No ☐ Unknown

☐ Yes, please describe

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____

_____ [free text] ICD10 _____