European Post-Authorization Registry for RAVICTI® in Partnership with E-IMD (RRPE)

Sponsor: Horizon Pharma

EIMD
European registry and network for Intoxication type Metabolic Diseases

European Post-Authorization Registry for RAVICTI® in Partnership with E-IMD (RRPE)

Aims/objectives

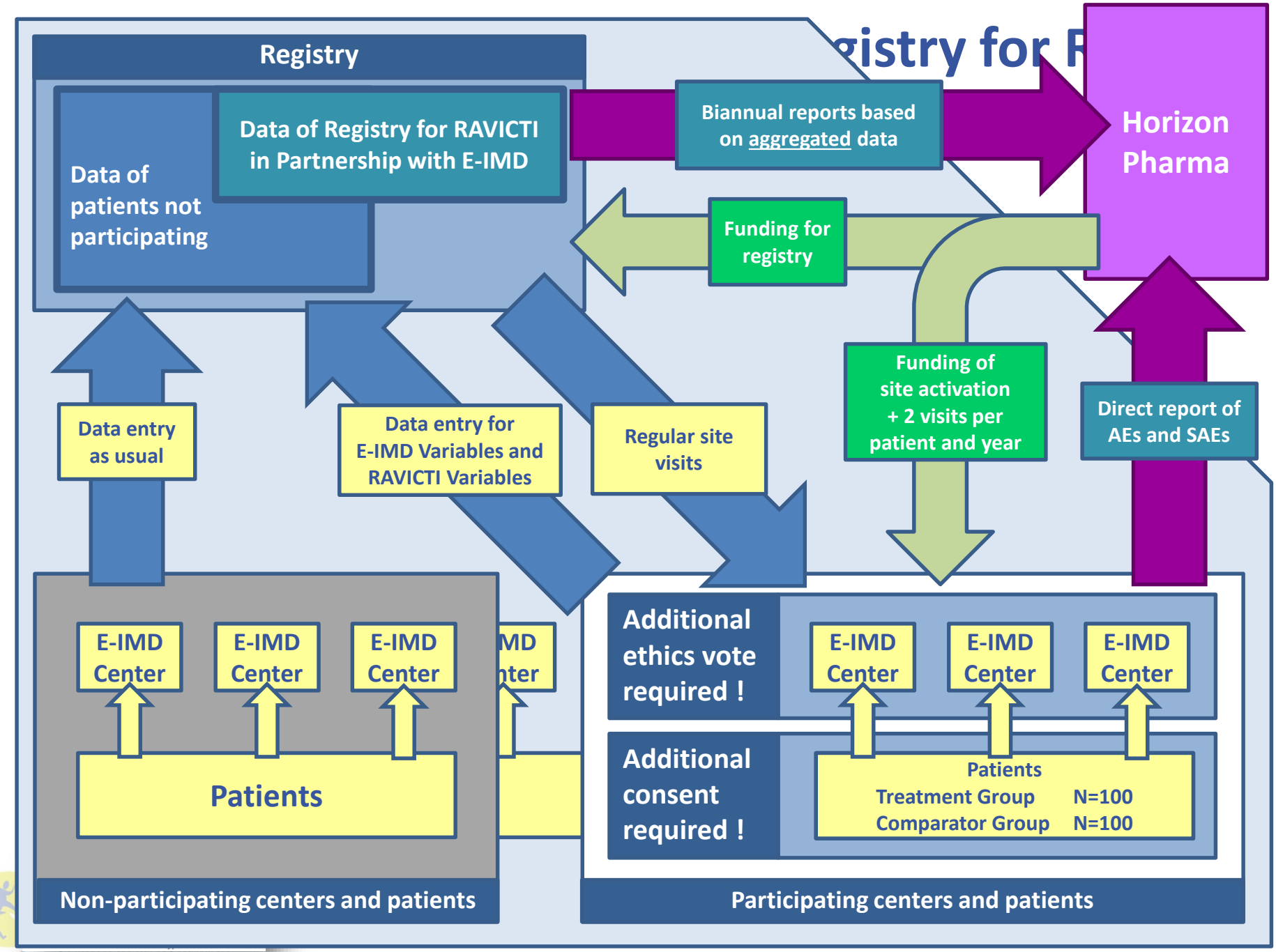
Implementing the post authorization safety study (PASS) for the evaluation and characterization of the safety profile of RAVICTI (Glycerol Phenylbutyrate) and tracking long-term outcomes in UCD patients treated with RAVICTI to fulfil an EMA post-authorization measure

Study sample

- **Ravicti group:** UCD patients receiving RAVICTI (n=100)
- **Comparator group:** UCD patients receiving other nitrogen scavengers (n=100)

Study period

- **3 years:** patient recruitment (can be extended if recruitment goals are not met within 3 years)
- **10 years:** follow-up, half-yearly interim reports to the EMA


Registry
Data of patients not participating
Data of Registry for RAVICTI in Partnership with E-IMD
Biannual reports based on aggregated data
Horizon Pharma
Funding for registry
Funding of site activation + 2 visits per patient and year
Direct report of AEs and SAEs
Data entry as usual
Data entry for E-IMD Variables and RAVICTI Variables
Regular site visits
E-IMD Center
E-IMD Center
E-IMD Center
Patients
Non-participating centers and patients
Additional ethics vote required !
Additional consent required !
E-IMD Center
E-IMD Center
E-IMD Center
Patients
Treatment Group N=100
Comparator Group N=100
Participating centers and patients

RRPE Timeline

Actions	Timeframe
Decision of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) on the study protocol	Protocol accepted by EMA on the 1st of December 2016
Decision of the local IRB of the first study site (Heidelberg)	Protocol accepted by local IRB on the 2nd of January 2017
Update of E-IMD registry and forms	Registry overhaul completed on the 22nd of May 2017
Start of enrolment	Enrolment for comparator group started as of November 2017
Market release of Ravicti	Ravicti introduced into the European market by SOBI, starting with Germany in the first quarter of 2018 Other European countries will follow later that year
End of the agreed period of 10 years of follow-up	Mid 2030
Final report to be provided to the EMA	End July 2031

RRPE Activation of Study Sites

Actions	Tasks
Feasibility assessment	• Communicate interest to central study site in Heidelberg • Sign confidentiality agreement (provided by Horizon according to tentative marketing plan of Ravicti) • Assess study protocol for feasibility (provided by Horizon according to tentative marketing plan of Ravicti)
Negotiation of compensation	• Each site negotiates directly and confidential with Horizon on the compensation for study participation (site activation fee and compensation for up to two study visits per patient per year) • Obtain a calculation from your institutional R&D department based on the study protocol as basis for negotiation
Ethics vote	• Obtain vote of local IRB (Heidelberg will provide an English template to be adapted to local context)
Registry study agreement	• Sign the registry study agreement as negotiated with Horizon
Site activation	• Heidelberg will make a conference call and inform on correct implementation of the study procedures
Study implementation	• Enrolment of new and existing patients on the protocol • Entering of complete datasets into the registry • Timely sending of AE/SAE forms to Horizon Pharmacovigilance • Receive internal routine monitoring visits by central study site (Heidelberg)

RRPE – Site Status and Current Patient Enrollment

Site Status	
Confidentiality Agreement (CDA) executed	17 / 20
Feasibility awaiting completion by sites	5 / 20
Feasibility completed and returned	12 / 20
Clinical Trial Agreement (CTA) issued	11 / 20
Clinical Trial Agreement (CTA) executed	1 / 20

Current Patient Enrollment	
Subjects Enrolled in RAVICTI Group	4 / 19
Subjects Enrolled Comparator Group	15 / 19
Subjects Enrolled Switchover	1 / 19
Subjects Complete	0 / 19
Subjects Withdrawn	0 / 19

RRPE – RAVICTI Launch and Reimbursement

RAVICTI launched and reimbursed							Reimbursed on individual patient basis		Pricing and reimbursement in process	
2017	UK	DK	NL	SE	IT	ES				
2018	DE	AT	FI	IRE			CH	PT	FR	BE

RRPE – Geographical Coverage of Prospective Study Sites

Countries	Cities
Austria	Innsbruck
Belgium	Antwerp, Brussels
Croatia	Zagreb
Denmark	Copenhagen
France	Lille, Paris
Germany	Heidelberg
Italy	Rome, Padova
Poland	Warsaw
Portugal	Porto
Spain	Barcelona, Palma de Mallorca
Switzerland	Zurich
UK	London, Manchester