# Post-Authorisation Safety Study Protocol

## A Registry of Patients Treated with Fintepla

## FINTEPLA® (fenfluramine)

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| Study No.: | ZX008-2101 (EP0218) |
| EU PAS No.: | EUPAS105358 |
| Sponsor: | Zogenix International, Ltd. (a wholly owned subsidiary of UCB Biosciences, Inc.) |
| Protocol edition No.: | 6.0 |
| Date of protocol edition: | 04 June 2025 |

# Post-authorisation Safety Study (PASS) – Study ZX008-2101 – A Registry of Patients Treated with Fintepla

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| **Study title:** | A Registry of Patients Treated with Fintepla |
| **Protocol edition No.** | 6.0 |
| **Date of protocol edition** | 04 June 2025 |
| **EU PAS No.** | EUPAS105358 |
| **Active substance** | Fenfluramine (ATC code: [redacted]) |
| **Medicinal product** | Fintepla (fenfluramine) |
| **Product reference** | European Union (EU) marketing authorisation number:<br>EU/1/20/1491/001<br>EU/1/20/1491/002<br>EU/1/20/1491/003<br>EU/1/20/1491/004 |
| **Procedure No.** | EU procedure number:<br>EMEA/H/C/003933 |
| **Marketing Authorisation Holder** | UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Bruxelles,<br>Belgium<br>(After MAH Transfer EC Decision on 12 April 2023. Previously Zogenix ROI Limited) |
| **Joint PASS** | No |
| **Research question and objectives** | The primary objective of this study is to assess the long-term cardiac safety of fenfluramine as prescribed in routine clinical practice for fenfluramine approved indications.<br>The secondary objectives of this study are:<br>• To assess the occurrence of growth retardation, if any, in patients treated with fenfluramine in routine clinical practice for fenfluramine approved indications.<br>• To describe patients' ECHO monitoring for patients treated with fenfluramine in routine practice for fenfluramine approved indications.<br>• To assess the primary and secondary objectives mentioned above for all patients treated with fenfluramine enrolled in the registry. |
| **Countries of study** | It is expected that the study will be performed in at least five European countries (including UK, Germany, Austria, Italy, Spain, and France). |

# Marketing Authorisation Holder

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| **Marketing Authorisation Holder** | UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Brussels,<br>Belgium<br>(After MAH Transfer EC Decision on 12 April 2023.<br>Previously Zogenix ROI Limited) |
| **Marketing Authorisation Holder contact person:** | [redacted]<br>UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Brussels,<br>Belgium<br>Mail to: [redacted] |

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# 2 List of Abbreviations

| Abbreviation or Term | Definition |
|---|---|
| 5-HT | 5 hydroxytryptamine |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AED | Antiepileptic drug |
| ANOVA | Analysis of variance |
| ATC | Anatomical therapeutic chemical |
| BAZ | BMI-for-age z-score |
| BMI | Body mass index |
| CCI | Charlson Comorbidity Index |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| [redacted] | |
| CRF | Case report form |
| CRO | Contract Research Organisation |
| DRG | Diagnosis-related group |
| DS | Dravet Syndrome |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| GEP | Good Epidemiological Practice |
| [redacted] | |
| GLP | Good Laboratory Practices |
| GP | General practitioner |
| GPP | Good Pharmacoepidemiology Practices |
| GVP | Good Pharmacovigilance Practice |
| HAZ | Height-for-age z-score |
| HCP | Healthcare professional |
| [redacted] | |
| HMA | Heads of Medicines Agencies |
| ICD | International Classification of Diseases |
| ICF | Informed consent form |
| ICH | International Conference of Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEA | International Epidemiological Association |
| IEC | Independent ethics committee |
| IQR | Interquartile range |

| Abbreviation or Term | Definition |
|---|---|
| IRB | Institutional Review Board |
| ISPE | International Society for Pharmacoepidemiology |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| LAZ | Length-for-age z-score |
| LGS | Lennox-Gastaut syndrome |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| mSS | modified Safety Set |
| NCMP | Nordic Classification of Medical Procedures |
| NCSP | Nordic Classification of Surgical Procedures |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| OR | Odds ratio |
| PAH | Pulmonary arterial hypertension |
| PAS | Post-authorisation study |
| PASS | Post-authorisation safety study |
| PedsQL | Pediatric Quality of Life Inventory () questionnaires |
| [redacted] | |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| PT | Preferred term |
| RMP | Risk Management Plan |
| RWD | real-world data |
| [redacted] | |
| SADR | Serious adverse drug reaction |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SDV | Source data verification |
| SE | Status epilepticus |
| SGA | Small for gestational age |
| SmPC | Summary of Product Characteristics |
| [redacted] | |
| SOC | System organ class |
| SOP | Standard operating procedure |
| SS | Safety Set |
| SSAR | Safety Signal Assessment Report |
| STROBE | STrengthening the Reporting of OBservational studies in Epidemiology |
| SUDEP | Sudden unexpected death in epilepsy |
| [redacted] | |
| TTE | transthoracic ECHO |

| Abbreviation or Term | Definition |
|---|---|
| UK | United Kingdom |
| US | United States |
| VABS | Vineland Adaptive Behavior Scale |
| VHD | Valvular heart disease |
| WAZ | Weight-for-age z-score |
| WHO | World Health Organization |
| WHZ | Weight-for-height z-score |

# 3 Responsible Parties

| Study contacts | Contact Name/Address | Contact details |
|---|---|---|
| **Sponsor** | Zogenix International, Ltd.<br>The Pearce Building, West Street,<br>Maidenhead, Berkshire SL6 1RL, UK | |
| **Clinical Development** | [redacted]<br>Clinical Development/Study Lead<br>UCB Biosciences Inc.<br>4000 Paramount Parkway, Suite [redacted]<br>Morrisville, NC 27560, USA | |
| **Real-World Evidence** | [redacted]<br>Real World Evidence Strategy Lead<br>UCB Pharma S.A.,<br>Bath Road Slaugh,<br>SL1 3WE, UK | |
| **Medical Affairs** | [redacted]<br>Medical Affairs Lead<br>UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Brussels, Belgium | |
| **Marketing Authorisation Holder contact person** | [redacted]<br>Regulatory Science Lead<br>UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Brussels, Belgium | |
| **Patient Benefit Risk and Medical Safety** | [redacted]<br>Benefit Risk Lead<br>UCB Pharma S.A.,<br>Bath Road,<br>Slough, SL1 3WE, UK | |
| **EU QPPV** | [redacted]<br>Head International PV and QPPV<br>UCB Pharma S.A.,<br>Allée de la Recherche 60,<br>B-1070 Brussels, Belgium | |
| **Contract Research Organisation (CRO)** | Parexel International (IRL) Limited, One Kilmainham Square, Inchicore Rd, Dublin 8, D08, FP5V, Dublin - Ireland | |
| **Principal/Coordinating Investigator** | A list of all principal/coordinating investigator for each country, where requested by local regulations, are available on request | |

# 4 Abstract

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|---|---|
| **Study Title** | A Registry of Patients Treated with Fenfluramine |
| **Study No.** | ZX008-2101 (EP0218) |
| **Protocol Edition No. and Date** | Version 6.0<br>04 June 2025 |
| **Rationale and Background** | Fenfluramine (Fintepla®) oral solution has been approved in the United States (US), European Union (EU), and the United Kingdom (UK) since 2020 for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older (as an add-on therapy in the EU and UK). In 2022, Fintepla was approved in Japan as a treatment for (epileptic) seizures associated with DS as an add-on therapy to anti-epileptic medicines in patients 2 years of age and older whose seizures are not controlled by other anti-epileptic medicines. The program was additionally successful in supporting a supplemental New Drug Application (sNDA) in the US (approved by the Food and Drug Administration [FDA] in March 2022), a Marketing Authorization extension variation in the EU and UK (approved by the European Medicines Agency [EMA] in January 2023, and by the Medicines and Healthcare products Regulatory Agency [MHRA] in July 2023), and a Partial Change Application in Japan (approved by the Pharmaceuticals and Medical Devices Agency [PMDA] in March 2024) in patients 2 years of age and older with Lennox-Gastaut syndrome (LGS) (as an add-on therapy in EU, UK, and Japan). It is anticipated that in the future Fintepla might be developed and approved for additional forms of rare paediatric epilepsies e.g., CDKL-5 Deficiency Disorder.<br><br>The efficacy and safety of fenfluramine in children and young adults with DS have been established in 3 pivotal, randomised, multi-centre, placebo-controlled studies [1,2]. The efficacy of fenfluramine in children and adults aged 2 to 35 years has been established for LGS in a global multi-centre, randomized, placebo-controlled phase 3 trial (NCT03355209), which demonstrated that fenfluramine significantly reduced the frequencies of seizures associated with a drop and generalized tonic-clonic seizures, and did not worsen executive function (e.g., self-control, attention, working memory) [3,4].<br><br>DS and LGS are rare, severe and treatment-resistant developmental and epileptic encephalopathies of childhood-onset associated with increased mortality rates compared to the general population [5,6].<br><br>DS is a characterised by medically intractable seizures. Onset of the first seizure typically occurs in the first year of life (usually at 5 to 8 months of |

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| | age) in otherwise healthy infants. It often consists of prolonged, unilateral, or generalised clonic seizure provoked by fever [5,7]. The incidence of DS is estimated to range from one in 20,000 to one in 40,000 [5,8]; in the European Union, DS affects fewer than 1 in 20,000 people [9] and recent research suggests it may affect one out of every 15,700 live births in the United States, which is in line with the lower bound of the original estimate [10]. DS is responsible for 7% of the severe epilepsies starting before the age of 3 [7]. In addition to the intractable seizures that define DS, the condition has wide-ranging comorbidities including hypotonia, speech delay, temperature dysregulation, nocturnal seizures, autistic traits, sleep issues, frequent infections, blood abnormalities, and some psychiatric issues [11-13].<br><br>LGS is always manifested by a triad of symptoms; (1) multiple types of intractable seizures including tonic, atonic, myoclonic, tonic-clonic and atypical absence seizures that may cause sudden falls, also known as drop attacks [6,14], (2) presence of slow spike-and-wave pattern and fast rhythm poly-spikes on electroencephalography (EEG), and (3) cognitive dysfunction with developmental, intellectual and behavioural impairments [14]. The onset of LGS occurs mostly in children between 3 and 5 years of age, with the entire triad of symptoms developing throughout childhood [6].<br><br>LGS incidence is estimated to range from 0.1 to 0.28 per 100,000 population, with an overall prevalence of about 26 per 100,000 people, and with males slightly more affected than females. It is responsible for 1 to 2% of all epilepsies and 2 to 5% of all childhood epilepsies [15,16]. Most (70-80%) cases of LGS have a known cause, including abnormal brain development, congenital infections, West syndrome, and trauma [17]. Patients with LGS have 14 times higher mortality rates than the general population and limited treatment options that include dietary therapy, surgery or device and antiepileptic drug (AED) [18].<br><br>Fenfluramine was approved in Europe in the 1960s and in North America and other countries in the 1970s as an appetite suppressant for the treatment of obesity in adults. Fenfluramine was withdrawn from worldwide markets in the late 1990s due to its reported association with cardiac valve abnormalities [19-21], as well as reported cases that associated the development of primary pulmonary hypertension with the medication [22-24]. Information on long-term safety of fenfluramine at a mean dose of 0.34 (0.12–0.90) mg/kg/day is provided from an open-label study in Belgium that followed two cohorts with a total of 21 patients treated with fenfluramine for DS, some of whom were treated for more than 27 years, and did not report any unusual safety events [25-27]. In addition, no valvular heart disease (VHD) or pulmonary arterial |

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| | hypertension (PAH) events have been reported in the interim analysis of the long-term, open-label study of fenfluramine at 0.2 to 0.7 mg/kg/day in 330 patients with DS treated for a median treatment duration of 631 days [28,29]. An international, multicenter, open-label extension trial of patients treated with fenfluramine for up to 36 months (NCT03936777) strongly supports the continued, long-term safety and favourable benefit-risk profile of fenfluramine for the adjunctive treatment of seizures associated with DS.<br><br>This observational registry will provide data to further assess the long-term utilisation and safety of fenfluramine as prescribed in routine clinical practice for approved fenfluramine indications, with a focus on characterising and quantifying the important potential risk of VHD and the important identified risk of PAH (PAH was previously considered an important potential risk for fenfluramine, but the totality of the available evidence including post-marketing surveillance has led to PAH becoming an important identified risk). In addition, the registry will provide data to characterise and quantify the important potential risk of growth retardation. Moreover, the data collected on the frequency of echocardiographic monitoring will also contribute to assessing the effectiveness of risk minimisation measures. These above-mentioned objectives will be assessed in patients treated with fenfluramine approved indications as well as for all patients treated with fenfluramine enrolled in the registry. |
| **Research Question and Objectives** | ***Primary Objective***<br>The primary objective of this registry is to assess the long-term cardiac safety of fenfluramine as prescribed in routine clinical practice for fenfluramine approved indications.<br>***Secondary Objectives***<br>The secondary objectives of this study are:<br>• To assess the occurrence of growth retardation, if any, in patients treated with fenfluramine in routine clinical practice for fenfluramine approved indications.<br>• To describe patients' ECHO monitoring for patients treated with fenfluramine in routine practice for fenfluramine approved indications.<br>• To assess the primary and secondary objectives mentioned above for all patients treated with fenfluramine enrolled in the registry |
| **Study Design** | ***Registry***<br>• The objectives will be addressed via a prospective observational, multi-country, longitudinal cohort study (a registry) of patients treated with fenfluramine hydrochloride oral solution, conducted at centres |

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| | prescribing fenfluramine in routine practice (in European countries (including UK, Germany, Austria, Italy, Spain, and France).<br>• The enrolment period will be five years from the registry start date in the first participating country.<br>• The study period will be ten years from the registry start date in the first participating country.<br>• Patients will be followed up until six months after the end of fenfluramine treatment, loss to follow-up, death, or end of study period (defined as last patient last visit), whichever occurs first.<br>• The maximum follow-up period in the registry for the first patient included will be ten years.<br>• The maximum follow-up period in the registry for the last patient included will be five years.<br>• Current users (e.g., continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product) will also be included (see Section **9.2.2**), and the registry follow-up will add to any previous follow-up time while being treated with fenfluramine.<br><br>***External Reference (Primary Objective only)***<br>The incidence rate of VHD and PAH in the general population younger than 40 years old is expected to be extremely low [30]. Echocardiographic surveillance in this age group is rarely done and is performed only in very specific cases where medically indicated (e.g., treatment with specific chemotherapies known to have a cardiac effect or driven by clinical signs). Children and young adults with DS or other rare epilepsies treated with other drugs are not routinely monitored via echocardiographic surveillance. Consequently, in view of the low background risk and in the absence of a suitable comparator group, an external reference will be used to benchmark the incidence rates observed in the registry.<br>Background risks will be obtained via electronic healthcare databases to assess the incidence rate of valvulopathy, VHD, and PAH in the:<br>• General population within the same age range as the registry population (Cohort 1)<br>• General population within the same age range as the registry population, with the exclusion of patients with congenital cardiac malformation (Cohort 2)<br><br>Background incidence rates will be assessed over the same study period as the registry. This assessment will be performed only if at least one case of valvulopathy, VHD, and PAH is observed in the registry. |

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| **Population** | ***Registry***<br>Below, inclusion and exclusion criteria are applicable for all participating countries, except Germany. Inclusion and exclusion criteria required for Germany are listed in **Annex I German -Specific Eligibility Criteria**.<br>• Inclusion criteria:<br>o Patients being treated with fenfluramine.<br>o Either new users of fenfluramine or current users (e.g., continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product).<br>o Patients treated at centres/by physicians prescribing fenfluramine in routine practice (expectedly neuro-paediatricians, paediatricians, or neurologists with experience in the treatment of epilepsy). In some countries, only patients prescribed fenfluramine according to the summary of product characteristics (SmPC) may be included, in accordance with local regulations.<br>o Provided informed consent or assent, as required by local regulations.<br>• Exclusion criteria:<br>o Evidence of congenital cardiac malformation.<br>***External Reference (Primary Objective only)***<br>• Inclusion criteria:<br>o Ages <40 years old during each year of the study period.<br>• Exclusion criteria:<br>o Cohort 1 (see Section **10.1.1.2.1**): <12 months of available data in the medical records prior to fulfilling the inclusion criteria<br>o Cohort 2 (see Section **10.1.1.2.2**): <12 months of available data in the medical records prior to fulfilling the inclusion criteria Evidence of congenital cardiac malformation (International Classification of Diseases 10th edition [ICD-10] codes: Q20-24) |
| **Variables** | ***Registry***<br>***Primary Outcomes***<br>• Valvulopathy:<br>o Presence of a new finding, and at least one grade increase from the baseline of: ≥mild aortic or ≥moderate mitral regurgitation or ≥moderate tricuspid or ≥moderate pulmonary valve regurgitation seen on transthoracic ECHO (TTE)<br>o The findings also need to be confirmed by repeat TTE<br>• VHD:<br>o Presence of ≥mild aortic or ≥moderate mitral regurgitation seen on transthoracic echocardiogram (TTE) |

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| | ○ The findings also need to be confirmed by repeat TTE<br>○ Plus, one of the following:<br>▪ Physical signs or symptoms attributable to valve disease<br>▪ A structural lesion of the aortic or mitral valve (e.g., thickening)<br>▪ A restriction of valve movement of the aortic or mitral valve<br>▪ Abnormal left ventricular (LV) systolic function with depressed left ventricular ejection fraction (LVEF <50%)<br>▪ LV dilatation<br>▪ Left atrial enlargement<br>• PAH:<br>○ Pulmonary artery systolic pressure (PASP) ≥35 mmHg on echocardiogram [33]<br>Cases for the above events will be validated and ascertained by an external independent validation committee.<br>***Secondary Outcomes***<br>• Growth retardation<br>○ Growth will be assessed based on clinical diagnosis of retardation according to physician judgment.<br>○ As complementary information, anthropometric measurements (length/height and weight) at baseline and during follow-up will be collected and assessed based on standardised growth indicators.<br>• Echocardiographic monitoring characteristics (performed at baseline, frequency during treatment, frequency after drug discontinuation)<br>***Registry Main Other Variables***<br>• Patient demographics<br>• Epilepsy diagnosis and medical history<br>• Epilepsy Treatment history<br>• Anthropometric measurements (e.g., length/height and weight)<br>• Fenfluramine treatment characteristics (e.g., start date, treatment characteristics before inclusion if any, dose, frequency of administration)<br>• Fenfluramine treatment discontinuation or withdrawal (e.g., stop date and reason)<br>• Other antiepileptic medications than fenfluramine, if any (e.g., drug name, start and stop dates)<br>• Concomitant significant non-pharmacological epilepsy treatments<br>• Concomitant medications other than antiepileptics (e.g., drug class and number)<br>• Convulsive seizure activity |

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| | • Echocardiogram dates and findings; characteristics in case of abnormalities<br>• Growth retardation clinical diagnosis and characteristics<br>• AE/ADR<br>***External Reference Outcomes (Primary Objective only)***<br>• Diagnoses of valvulopathy (ICD-10 codes: I34.x, I35.x, I36.x, I37.x, I38, I39)<br>• Diagnoses of VHD (ICD-10 codes: I34.x, I35.x)<br>• Diagnoses of PAH (ICD-10 codes: I27.0, I27.2) |
| **Data Sources** | ***Registry***<br>The current assumption is that mainly neuro-paediatricians or physicians who specialise in paediatrics or neurology with experience in the treatment of epilepsy will be included; however, specialties of prescribing physicians will be checked after fenfluramine launch based on routine practice. A feasibility assessment will be run as a first step to identify suitable sites for this study.<br>Physicians will be informed about and encouraged to participate in the fenfluramine registry as part of the fenfluramine Risk Management Plan (RMP) educational materials.<br>In order to maximise site participation and to ensure that the diversity of prescribers and settings is reflected, physicians will be identified and contacted via different possible and complementary approaches.<br>• Centres already participating in existing rare epilepsy like DS registries or research networks (e.g., [redacted])<br>• Other reference centres in the treatment of rare paediatric epilepsies<br>• Academic or community hospitals with physicians specialised in the treatment of rare epilepsies.<br>• Investigators in fenfluramine clinical trials<br>• Sites with physicians participating in Access Programs or Compassionate Use Programs<br>• Sponsor's and contract research organisation's networks<br>• Country-specific lists of physicians and physician panels<br>• Patient Advocacy Groups<br>Data specific to the needs of this registry will be collected prospectively, at inclusion (baseline) and every 6 months (±1 month) for the first 2 years and annually (±2 months) thereafter, at fenfluramine discontinuation, and at 6 months after fenfluramine discontinuation. It is expected that the participating sites will report the findings (images and reports) of the |

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| | echocardiographic assessment even if it was performed in another hospital or centre.<br>If sites are participating in an existing registry, data overlapping with the study variables could be extracted from the registry where possible to avoid any additional burden to the investigators.<br>It is expected that, subject to market availability, the study will be performed in at least five European countries (including UK, Germany, Austria, Italy, Spain, and France).<br>***External Reference (Primary Objective only)***<br>Electronic healthcare databases will be used. Databases need to cover a large part of a country's population and, at best, be national. Databases also need to include clinical diagnosis data. Although some databases might include some echocardiographic information for some patients, a limitation will be that most of the time, no echocardiographic details will be available, and identification of events will rely on clinical diagnosis codes.<br>Based on potential participating countries in the registry which will be selected in accordance with the launch plan and on availability of suitable data sources, candidate databases include the following:<br>**UK:** [redacted]<br>The [redacted] is the National Health Service's (NHS) observational and interventional research service in the UK and is jointly funded by the NHS National Institute for Health Research (NIHR), and the Medicines and Healthcare Products Regulatory Agency (MHRA). The [redacted] is composed of anonymised longitudinal medical records from primary care providers in the UK since 1987. It includes more than 20 million patient lives, with more than 5 million currently registered and active patients. The patient population captured in the database is broadly representative of the demographic breakdown of the UK population. Diagnosis information is recorded in Read-OXMIS format. The [redacted] data set, which allows the same patient to be tracked in secondary care, where both inpatient and outpatient diagnoses are captured.<br>[redacted]<br>Diagnoses will be obtained from the [redacted] which contains nationwide primary and secondary International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes from all hospital inpatient and outpatient visits in Sweden.<br>**Spain:** [redacted]<br>The Health Improvement Network, is a large European database of anonymized Electronic Health Records. These anonymized data are transmitted by a network of voluntary physicians. [redacted] database |

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| | consists of datasets obtained from 7 European countries (France, United Kingdom, Spain, Italy, Germany, Belgium, and Romania). The database gets updated in near real-time and data can be delivered monthly. Data are fully anonymized and General Data Protection Regulation (GDPR)-compliant. The dataset in Spain captures data from 2.9 million patients collected from approximately 300 medical centers, 2000 general practitioners, and 2400 specialty physicians.<br>**France:** [redacted]<br>The [redacted] includes the [redacted] which is the [redacted] database, and the [redacted] which is the national hospitalisation database (based on diagnoses-related groups). It includes information from the three main social insurance systems in France and covers 98.8% of the French population [34]. The [redacted] includes information on all healthcare expenses, including outpatient visits, dispensed medication, procedures, chronic conditions, as well as hospital admission diagnoses and procedures, and date of death, on an individual level. It includes diagnoses (ICD-10 codes) for chronic diseases and discharge diagnoses (ICD-10 codes) for hospitalisations.<br>[redacted]<br>The [redacted] is based on claims data from statutory health insurance providers and currently includes information on about 20 million persons who have been insured with one of the participating providers since 2004. In addition to demographic data, [redacted] contains information on drug prescriptions, outpatient and inpatient services and diagnoses. All diagnoses are recorded using the ICD-10, German Modification (ICD-10-GM). Per data year, there is information on approximately 17% of the general population from all geographical regions of Germany.<br>**Italy:** [redacted] Research and Health Foundation) is an administrative database, previously referred to as the [redacted] database it includes data on demographic variables, reimbursed prescription drugs, inpatient and outpatient diagnoses and procedures (ICD-9 codes), and in hospital mortality (date of death). The [redacted] database covers approximately 5.5 million inhabitants (approximately 10% of entire Italian population) from several regions in Italy. The database is representative of the Italian population in terms of age, sex, and geographical distribution. The data collection began in 2012 for most individuals and the data lag is 9 to 12 months. |
| **Study Size** | The purpose of the study is descriptive. Therefore, no formal sample size or power calculation is necessary. The safety context of the study requires that the sample size be sufficient to detect a signal, if any. The external |

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| | reference will be used to benchmark the results from the registry and, due to the different sources of data, no comparative analyses will be conducted.<br>***Registry***<br>• VHD is rare in the general population below 40 years of age. Under a hypothesis of a 0.5% frequency of pathologic mitral or aortic regurgitation as assessed via echocardiography [35], 600 patients would be needed to yield a 95.1% probability that at least one case of VHD would be detected. In other words, if no events of VHD are observed among 600 patients treated with fenfluramine for DS or other potential future indications, then this will rule out a risk associated to their fenfluramine exposure equal to or greater than the background risk of 0.5%.<br>• Other studies (though not based on echocardiography) found even smaller frequency estimates in the general 0 to 39-year-old population (lowest observed incidence rate being 2.5/100,000 person-years for mitral regurgitation in the 25 to 29 age group; highest observed incidence rate being 11.8/100,000 person-years for aortic regurgitation in the 35 to 39 age group [30]). With 600 patients, the probability to observe at least one event under the hypothesis that the incidence rate is equal to these rates is:<br>o 1.5% for a 2.5/100,000 person-years background rate (see above)<br>o 6.8% for a 11.8/100,000 person-years background rate (see above)<br>Consequently, observing one case of VHD among 600 patients can occur with a non-negligible probability if the true incidence rate is in the range of the published background rates.<br>• PAH is a rare condition and its overall frequency is expected to be as low as 2.5 to 7.1 per million subjects in Europe [36], and the risk in adult obese patients treated with fenfluramine for weight loss for more than 12 years in the period before the late 1990s has been estimated to be 1 in 10,000 patients [37].<br>• Based on this figure 30,000 patients would be needed to yield a 95% probability to detect at least one PAH event. However, this number of patients is much higher than the expected number of DS fenfluramine users for a long period of time (see market forecasts below) and thus will not be used to address the study size.<br>The final number of patients in the study will depend on the actual market uptake, including the number of prescribing sites, and the rate of site and patient participation. |

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| | ***External Reference (Primary Objective only)***<br>The background risks of non-congenital aortic or mitral VHD and of PAH are expected to be rare [30,36], as reported above. In each country and each database, the full population of patients aged up to 40 years old will serve to assess the denominator for this analysis. |
| **Data Analysis** | ***Registry***<br>The analyses will be descriptive. Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. Categorical variables will be described as the total number and relative percentage per category. 95% confidence intervals (CIs) will be calculated when relevant. There will be no imputation of missing data.<br>Incidence rates will be calculated by dividing the number of new cases (up to the first event) of valvulopathy, VHD, or PAH by the number of person-years at risk. Person-years or person-days for an individual will be defined as the total number of days/years of fenfluramine exposure and will be calculated over the follow-up period as defined above (patient time at risk ending at the date of the first valvulopathy, VHD, or PAH event, the final dose of fenfluramine, death, or data cut-off).<br>There will be two analysis sets to address the objectives of the registry, depending on whether or not we specifically target the patients who are treated with fenfluramine for an approved indication:<br>• Safety Set (SS): Patients enrolled in the registry who are treated with fenfluramine for approved indication. For growth retardation, only patients under 18 will be included.<br>• modified Safety Set (mSS): All patients enrolled in the registry who are treated with fenfluramine<br>Subgroup analysis: Subgroup analyses will be performed depending on the final sample size and data availability for the primary, and secondary, outcomes.<br>Sensitivity analysis: Valvulopathy, VHD, and PAH incidence rates will be also calculated as person-years or person-days for an individual defined as the total number of days/years of fenfluramine exposure plus an additional 6 months (in line with fenfluramine patient leaflet) and will be calculated over the follow-up period as defined above (patient time at risk ending at the date of the outcome of interests, the final dose of fenfluramine plus 6 months, death, or data cut-off).<br>***External Reference (Primary Objective only)***<br>The analyses will be descriptive. Results will be presented by database only due to the different nature of each database. Incidence rates will be calculated by dividing the number of new cases of valvulopathy, VHD, or PAH by the number of person-year at risk. The number of person-year at risk will be calculated over the study period. |

| | |
|---|---|
| | <u>Benchmark of cardiac events incidence rate on background incidence rates</u><br>If greater than zero, the incidence rate observed in the registry will be benchmarked against the incidence rates observed in the external reference. The background rates will also be checked against literature data for any change or new trend in the incidence rate of valvulopathy, VHD, or PAH in the general population below the age of 40 years old. |
| **Milestones** | • PRAC approval: Q3 2022<br>• Start of data collection: Q2 2023<br>• End of data collection: [redacted]<br>• Final study report: [redacted]<br>Progress reports will be communicated as part of the Periodic Safety Update Reports (PSUR) and will include information on participating countries, patient count data to evaluate the success of recruitment and descriptive statistics on patients' baseline demographic and clinical characteristics.<br>The marketing authorisation holder (MAH) will monitor enrolment and will keep the Pharmacovigilance Risk Assessment Committee (PRAC) informed of progress of the registry at regular intervals. If enrolment is lower than anticipated, the MAH will consider and implement any mitigation strategy that might be considered in order to increase the recruitment level in the context of the overall usage of the product within the European Union. The MAH will also monitor the retention of patients and will undertake all reasonable efforts and methods to minimise loss to follow-up.<br>Timelines are conditional on the actual date of market entry in each country. |

# 5 Amendments and Updates

## 5.1 Amendment 6.0 (04 June 2025)

The overall rationale for this protocol amendment is:

- To adjust the enrolment period from 3 to 5 years.
- To adjust the maximum follow-up period for the last patient enrolled from 7 to 5 years.
- To clarify the definition of primary outcome and adjust the primary objective accordingly.
- To clarify the list of countries participating in the study

Other minor editorial and non-substantive changes are not listed in the table below.

| Sections of protocol changed | Summary of amendment/update | Reason |
|---|---|---|
| **6 Milestones** | The estimated dates for the interim safety analyses have been adjusted to reflect the new enrolment period.<br>A line was added to list an additional ECHO monitoring report to be delivered by [redacted] focusing on the analysis relevant to the ECHO monitoring. | To reflect the adjustment in the enrolment period from 3 to 5 years.<br>To address PRAC recommendation. |
| **7 Rationale and Background**<br>**7.3 Risk of Valvular Heart Disease and Pulmonary Arterial Hypertension Associated with Fenfluramine**<br>**7.3.1 Background** | The bullet points listing VHD and PAH as primary safety outcomes to focus on were deleted. | VHD and PAH are the primary outcomes of the primary objective, and not part of the objective itself. |
| **8 Research Questions and Objectives**<br>**8.1 Primary Objective** | The bullet points listing VHD and PAH as primary safety outcomes to focus on were deleted. | VHD and PAH are the primary outcomes of the primary objective, and not part of the objective itself. |

| Sections of protocol changed | Summary of amendment/update | Reason |
|---|---|---|
| **9 Registry Research Methods**<br>**9.1 Registry Study Design**<br>**9.1.1 Registry Overview** | The list of countries participating in the study has been clarified. | The list of countries participating in the study is limited to European countries. |
| **9.1.2 Registry Duration and Follow-up** | The enrolment period was adjusted from 3 to 5 years and the maximum follow-up period for the last patient enrolled was adjusted from 7 to 5 years. | To improve recruitment and maximize the number of patients in the study. |
| **9.3 Variables**<br>**9.3.1 Primary Outcome Definition and Variables**<br>**9.3.1.1 Primary Outcome Definition** | The "main outcome definition" of the incidence of VHD was clarified and renamed to encompass "valvulopathy" as well as VHD. | To use medical language that would comprehensively capture both right-sided and left-sided cardiac valves. The term "valvulopathy" would not only capture cases involving valves that are on the left side of the heart (≥mild aortic or ≥moderate mitral valve regurgitation), as per FDA case definition for fenfluramine-induced valvulopathy, but also cases involving valves of the right side of the heart (≥moderate tricuspid or ≥moderate pulmonary valve regurgitation). |
| **9.3.1.1 Primary Outcome Definition** | The "sensitivity analysis definition" was deleted from this section | Sensitivity analysis is now described in detail in Section 9.7.9. |
| **9.3.1.2 Primary Outcome Variables** | The variables of Cardiac ECHO findings to be collected in case of valvulopathy, VHD, or PAH event of interest were clarified. | To align with the definition of the primary outcomes. |

| Sections of protocol changed | Summary of amendment/update | Reason |
|---|---|---|
| **9.4 Data Sources** | The term "repeat ECHO" was clarified. | To clarify that "repeat ECHO" is defined as the next available ECHO that is performed either at the next scheduled observational data collection point or for the specific purpose of confirming the findings in the original ECHO. ECHOs performed on the same day due to image quality or technical issues are not considered to be confirmatory "repeat" ECHOs. |
| **9.7 Data Analysis**<br>**9.7.3 Descriptive Statistics** | A sentence was added to mention that in the final report, study results will also be presented side-by-side with study results from EP0217 (US) and EP0222 (Japan). | To address PRAC recommendation. |
| **9.7.4 Primary Outcome Analyses**<br>**9.7.4.1 Measure of valvulopathy, VHD, and PAH Incidence** | Valvulopathy was added as a primary outcome to be collected and for which the incidence will be calculated. | To reflect the changes made in definition of the primary outcomes. |
| **9.7.5 Secondary Outcomes Analyses**<br>**9.7.5.2 Identification of Potential Risk Factors for valvulopathy, VHD, PAH, and Growth Retardation** | Valvulopathy was added as a variable for which potential risk factors will be identified. | To reflect the adjustment in the enrolment period from 3 to 5 years. |
| **9.7.6 Interim Safety Analysis** | The first interim safety analysis has been adjusted to reflect the new enrolment period. | To reflect the adjustment in the enrolment period from 3 to 5 years. |

| Sections of protocol changed | Summary of amendment/update | Reason |
|---|---|---|
| **9.7.8 Subgroup Analyses** | The analysis of the sub population consisting of patients completed the entire follow-up vs patients with shorter observation periods has been modified. | To reflect the adjustment in the maximum follow-up period for the last patient enrolled from 7 to 5 years. |
| | A description of the analysis relevant to the ECHO monitoring to be presented in an ECHO monitoring report ([redacted]- has been added. | To describe the statistical analysis relevant to the ECHO monitoring. |
| **9.7.9 Sensitivity analyses** | The purpose of the sensitivity analysis was clarified as regard to the changes in the primary outcome definitions.<br>Valvulopathy was added as an outcome for which the incidence will also be calculated as person-years or person-days. | To reflect the changes made in definition of the primary outcomes. |
| **9.9.2 External Comparator** | Valvulopathy was added as a variable for which the background risk will be evaluated. | To reflect the changes made in definition of the primary outcomes. |
| **10 External Reference Research Methods for Primary Objective only** | Valvulopathy was added as a variable for which the background incidence rate will be assessed. | To reflect the changes made in definition of the primary outcomes. |
| **10.2 Variables**<br>**10.2.1 Primary Outcome** | The codes used to identify the incident cases of valvulopathy, VHD, or PAH were adjusted. | To reflect the changes made in definition of the primary outcomes. |
| **10.5 Data Management** | Valvulopathy has been added as a variable to be described. | To reflect the changes made in definition of the primary outcomes. |

| Sections of protocol changed | Summary of amendment/update | Reason |
|---|---|---|
| **10.6 Data Analysis**<br>**10.6.1.1 Incidence of Events of Interest** | Valvulopathy has been added to Table 5 as one of the primary endpoints for which the incidence rate should be calculated. | To reflect the changes made in definition of the primary outcomes. |
| **ANNEX II**<br>**LIST OF STANDALONE DOCUMENTS** | The Vineland Adaptive Behavior Scale (VABS) and Pediatric Quality of Life Inventory (PedsQL) questionnaires were added as available standalone documents. | The neurocognitive functions and psychomotor development as measured by the VABS and the quality of life as measured by the PedsQL questionnaires are secondary outcomes specific to France. |

## 5.2 Amendment 5.0 (09 April 2024)

The overall rationale for this protocol amendment is to:

- Reflect that pulmonary arterial hypertension (PAH) is now characterized as an important identified risk and no longer considered an important potential risk.

  Based on the previously reported cardiotoxicity associated with fenfluramine at doses used for obesity, PAH was considered an important potential risk to evaluate for ZX008, and no subject in any clinical study with treatment up to 3 years developed PAH at any time. However, during a recent safety signal assessment report (SSAR) (with DLP of 14 Jan 2024) available evidence from nonclinical studies, clinical studies, registries that collect safety data (post-marketing surveillance), spontaneous reports, and relevant information from published literature was extensively reviewed, and the totality of the available evidence presented in the SSAR has led to PAH becoming an important identified risk.
- Reflect that [redacted] The Health Improvement Network, a large European database of anonymized Electronic Health Records, is now the database that will capture data from patients in Spain instead of [redacted].
- Clarify that the end of study is the last patient last visit.

Other minor editorial and non-substantive changes such as updates to the List of Abbreviations and to the approval status of Fintepla are not listed in the table below.

| Sections of protocol changed | Summary of amendment/ update | Reason |
|---|---|---|
| **Throughout the protocol** | Pulmonary arterial hypertension (PAH) is now characterized as an important identified risk and no longer considered an important potential risk. | Available evidence from nonclinical studies, clinical studies, registries that collect safety data (post-marketing surveillance), spontaneous reports, and relevant information from published literature renders PAH an important identified risk. |
| **Throughout the protocol** | Last patient last visit has been defined as the end of study. | To clarify that the end of study is the last patient last visit. |
| **Synopsis**<br><br>**10.3 Data Sources**<br>**Table 4. Availability of Key Variables in the Proposed Data Sources**<br><br>**10.3.4 Spain:** [redacted] | [redacted] was changed with [redacted] The Health Improvement Network, to capture data from patients in Spain. | To ensure efficient patient data capture in Spain, UCB decided to change [redacted] |

# 6 Milestones

| Milestone | Planned Date |
|---|---|
| Study protocol approved by PRAC | Q3 2022 |
| Registration of protocol in the HMA-EMA Catalogue of RWD (previously EU PAS register) | Q4 2022 |
| Start of data collection (first patient first visit) | Q2 2023 |
| End of data collection (last patient last visit) | [redacted] |
| Progress reports | At the time of PSUR submission |
| ECHO monitoring report | [redacted] |
| Interim safety update reports | • Estimated [redacted] the first interim report will be delivered [redacted] after the start of data collection.<br>• Estimated [redacted] The second interim report will be delivered [redacted] after the first report. |
| Final report of study results | [redacted] |

Abbreviations: EMA=European Medicines Agency; HMA=Heads of Medicines Agencies; PRAC=Pharmacovigilance Risk Assessment Committee; RWD=real-world data

# 7 Rationale and Background

## 7.1 Fenfluramine

Fenfluramine (Fintepla®) oral solution has been approved in the United States (US), European Union (EU), and the United Kingdom (UK) since 2020 for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older (as an add-on therapy in the EU and UK). In 2022, Fintepla was approved in Japan as a treatment for (epileptic) seizures associated with DS as an add-on therapy to anti-epileptic medicines in patients 2 years of age and older whose seizures are not controlled by other anti-epileptic medicines. The program was additionally successful in supporting a supplemental New Drug Application (sNDA) in the US (approved by the Food and Drug Administration [FDA] in March 2022), a Marketing Authorization extension variation in the EU and UK (approved by the European Medicines Agency [EMA] in January 2023, and by the Medicines and Healthcare products Regulatory Agency [MHRA] in July 2023), and a Partial Change Application in Japan (approved by the Pharmaceuticals and Medical Devices Agency [PMDA] in March 2024) in patients 2 years of age and older with Lennox-Gastaut syndrome (LGS) (as an add-on therapy in EU, UK, and Japan). It is anticipated that in the future Fintepla might be developed and approved for additional forms of rare paediatric epilepsies e.g., CDKL-5 Deficiency Disorder.

Fenfluramine is a serotonin-releasing agent, and thereby stimulates multiple 5-hydroxytryptamine (5-HT) receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors**,** and also by acting on the sigma-1 receptor. Fenfluramine is currently indicated for the treatment of seizures associated with DS or LGS as an add-on therapy to other antiepileptic medicines in patients 2 years of age and older [38]. The precise mode of action of fenfluramine in treating seizures in patients with DS or LGS is not known.

The efficacy and safety of fenfluramine in children and young adults with DS have been established in three pivotal, randomised, multi-centre, placebo-controlled studies [1,2].

The efficacy of fenfluramine in children and adults aged 2 to 35 years has been established for LGS in a global multi-centre, randomized, placebo-controlled phase 3 trial (NCT03355209), which demonstrated that fenfluramine significantly reduced the frequencies of seizures associated with a drop and generalized tonic-clonic seizures, and did not worsen executive function (e.g., self-control, attention, working memory) [3,4].

## 7.2 Rare epilepsies

### 7.2.1 Dravet Syndrome

#### 7.2.1.1 Description of Dravet Syndrome

DS, previously known as severe myoclonic epilepsy of infancy, is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 [39]. Typical features include febrile onset of seizures, progressive neurological and motor impairments, photosensitivity, and drug resistance [5].

The diagnosis of DS is based on clinical signs and symptoms, though the presence of a mutation in the *SCN1A* gene is considered a likely, though not definitive, marker for the disorder [5,40,41]. Onset of the first seizure typically occurs in the first year of life (usually at 5 to 8 months of age) in otherwise healthy infants, and most often consists of prolonged, unilateral or generalised, clonic seizures provoked by fever [5,7,42]. These patients typically have poor response that may include worsening seizures to standard antiepileptic drugs (AEDs), in particular, sodium channel antagonist medications [5].

After the first year, other types of seizures often begin to occur with high frequency and include 1) convulsive seizures consisting of generalised clonic seizures, generalised tonic-clonic seizures, or alternating unilateral clonic seizures (in the youngest patients, they often evolve into status epilepticus [SE]); 2) myoclonic seizures (appearing between the ages of 1 and 5 years); 3) atypical absences (appearing at different ages between 4 months and 6 years or later); 4) focal seizures with or without secondary generalisation (appearing between the ages of 4 months and 4 years); or 5) rarely, tonic seizures [5]. Individuals with DS are at high risk for SE that often results in injury and hospitalisation [7].

Patients with DS usually experience a progressive disturbance in cerebral function that leads to significant impairment of psychomotor, behavioural, and neurological development [5]. Developmental delay and stagnation usually become apparent within the second year of life and are followed by cognitive impairment and neurobehavioral disorders. Although cognitive impairment in some children may stabilise around 6 years of age, the degree of cognitive and other neurological impairment appears to correlate, at least partially, with the frequency of seizures, and has been hypothesised to occur because of repeated cerebral hypoxia and possibly neuroinflammation [43].

Patients with DS were noted to have reduced height and weight growth trend, as well as a subset with endocrine dysfunction evidenced by low IGF-1 and testosterone levels [44].

The mortality risk in DS is high, with sudden unexpected death in epilepsy (SUDEP) being the most commonly reported cause of death. In a 2017 survey, SUDEP comprised 56% of reported deaths in patients with DS at 2 peak age ranges: 1 to 3 years of age and after 18 years of age [13]. A Dravet-specific SUDEP rate of 9.32 per 1000 person-years has been reported [41], which is 6-fold higher than that reported in the general population of patients with epilepsy [45]. A meta-analysis of cohort and case studies that described 177 unique cases of fatal DS found that SUDEP caused 49% and SE caused 32% of the deaths [46]. Attempts to

address possible publication bias by first excluding case reports and then further excluding 1 cohort study that reported only cases of SE had only minor impacts on the resulting distribution. Regardless of the cause of death, a majority (73%) of the patients described had not yet reached the age of 10 years at the time of the fatal outcome.

A survey of caregivers for 274 European patients with DS found that tonic-clonic seizures were the most common seizure type experienced; approximately 45% of the patients had more than 4 tonic-clonic seizures per month, despite treatment with a mean of 3 and as many as 6 AEDs [47]. One-third of the patients had required emergency treatment for SE in the prior year.

Although understanding of DS has evolved since it was originally described, seizures continue to be intractable in a majority of patients, and neurodevelopmental outcomes are generally poor [48].

#### 7.2.1.2 Epidemiology of Dravet Syndrome

The incidence of DS has been estimated to range from 1 in 20,000 to 1 in 40,000 [5,8]. In the European Union (EU), DS has been reported to affect fewer than 1 in 20,000 people [9], and studies in Sweden, Norway, and Spain published between 2015 and 2019 found that the prevalence ranged from 0.1 to 0.2 per 10,000 population [49-51]. DS is responsible for 7% of the severe epilepsies starting before the age of 3 years [7].

#### 7.2.1.3 Current Standard of Care for Dravet Syndrome

Currently, no treatment algorithm exists for DS as recommended by the International League Against Epilepsy or any other similar medical entity. Drugs approved with specific indications for the treatment of DS are fenfluramine, stiripentol, and cannabidiol [52]. Cross et al note that important treatment goals are to attain optimal seizure control, minimise side effects, provide prompt rescue treatment to avoid SE, and, importantly, avoid conditions that may aggravate the condition, including use of sodium channel antagonist AEDs as well as environmental factors known to trigger seizures in the population, such as hyperthermia [48]. They propose a treatment protocol that includes valproate as first-line therapy, and, once the diagnosis is clear and continued seizures are observed, augmentation with any of several potential drug therapies: stiripentol (with or without clobazam), cannabidiol, or fenfluramine. They also suggest, as alternative second-line therapies, ketogenic diet, clobazam, topiramate, bromide, and vagal nerve stimulation. Some clinicians recommend clobazam as first-line therapy and consider cannabidiol to be a third-line option [52].

Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin are not recommended in DS because they often exacerbate seizures [53]. A multivariate binomial logistic regression analysis of data from a cohort that included 116 patients with DS found that duration of use of these medications independently predicted worse cognitive outcome.

### 7.2.2 Lennox-Gastaut Syndrome

#### 7.2.2.1 Description of Lennox-Gastaut Syndrome

LGS is a rare, paediatric-onset developmental and epileptic encephalopathy in which the epileptic activity itself may directly contribute additional cognitive and behavioural impairments over those expected from the underlying aetiology alone and that suppression of epileptic activity might minimize this additional impairment [54].

The diagnosis of LGS includes clinical signs combined with typical EEG features. The clinical presentation of LGS is always characterized by a triad of symptoms; (1) multiple types of intractable seizures with onset prior to 18 years [55], including tonic, atonic, myoclonic, tonic-clonic and atypical absence seizures that may cause sudden falls, also known as drop attacks [6,14], (2) presence of slow spike-and-wave pattern and fast rhythm poly-spikes on electroencephalography (EEG), and (3) cognitive dysfunction with developmental, intellectual and behavioural impairments [14]. The onset of LGS occurs mostly in children between 3 and 5 years of age, with the entire triad of symptoms developing throughout childhood [6].

Nearly all patients with LGS have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: 5% of patients die, 80% to 90% continue having seizures into adulthood, and most have cognitive and behavioural problems [56].

#### 7.2.2.2 Epidemiology of Lennox-Gastaut Syndrome

LGS incidence is estimated to range from 0.1 to 0.28 per 100,000 population, with an overall prevalence of about 26 per 100,000 people, and with males slightly more affected than females. It is responsible for 1 to 2% of all epilepsies and 2 to 5% of all childhood epilepsies [15,16]. Most (70-80%) cases of LGS have a known cause, including abnormal brain development, congenital infections, West syndrome, and trauma [17]. Patients with LGS have 14 times higher mortality rates than the general population and limited treatment options that include dietary therapy, surgery or device and antiepileptic drug (AED) [18].

#### 7.2.2.3 Current Standard of Care for Lennox-Gastaut Syndrome

Due to the heterogeneity in aetiology, pathophysiology, and type of seizures experienced by patients with LGS, many different treatments are used [14], often with little success and a high rate of drug resistance.

Valproic acid represents one of the first-line options in the treatment of LGS. Other AEDs may be considered and added: lamotrigine, topiramate, clobazam, rufinamide, felbamate or cannabidiol [14,57]. The use of carbamazepine, oxcarbazepine, eslicarbazepine, tiagabine, and phenytoin in LGS is not recommended due to the potential risk of aggravation of drop attacks with a myoclonic component [17].

Because patients with LGS experience a range of different seizure types and underlying aetiologies, the condition is notoriously difficult to treat [17,58], and seizures in LGS are

usually not fully controlled with currently available antiepileptic drug treatments [59]. Initial treatment for LGS is usually monotherapy with one of the currently approved AEDs. If this is not successful, which is the most common case, a second agent is usually added, although some physicians will prescribe the second drug as monotherapy [58,60]. Where possible, no more than two AEDs should be used concomitantly. Non-pharmacological therapies, including resective surgery, the ketogenic diet, vagus nerve stimulation, and callosotomy, should be considered for use alongside AED therapy from the outset of treatment [17].

## 7.3 Risk of Valvular Heart Disease and Pulmonary Arterial Hypertension Associated with Fenfluramine

### 7.3.1 Background

Cases of valvulopathy and VHD, some severe or even fatal, were reported in adults taking fenfluramine for the treatment of obesity in doses of 60 to 120 mg per day, usually in combination with phentermine [19-21].

At the time of the 1997 post-marketing cases of valvulopathy related to fenfluramine or dexfenfluramine with or without phentermine in obese patients, the United States (US) Food and Drug Administration (FDA) decided that, because minimal degrees of regurgitation (i.e., trace or mild mitral regurgitation (MR) or trace aortic regurgitation (AR) are relatively common in the general population, these are not generally considered abnormal. Therefore, these lesser degrees of regurgitation were excluded from the agency's 1997 case definition of fenfluramine- or dexfenfluramine-associated valvulopathy, which requires documented mild or greater aortic regurgitation OR moderate or greater mitral regurgitation. This case definition of valvulopathy was used by the US FDA as a search criterion to screen cases in its database, based solely on the regurgitation jet observed on the echocardiogram (ECHO) without any associated clinical or other findings seen on the ECHO. However, in order to diagnose clinically relevant valvular heart disease (VHD), the patient must have additional findings: a heart murmur, symptoms of VHD, valve thickness, restriction of valve movement, left ventricular dysfunction, or left atrial enlargement.

Based on the history in adult obese populations at higher doses, VHD is considered an important potential risk for fenfluramine [61].

Fenfluramine is one of over 16 different compounds that has been purported to be associated with PAH [62]. Rare cases of PAH, some severe or even fatal, have been reported in adults taking fenfluramine for the treatment of the historical indication for obesity in doses of 60 to 120 mg per day [22-24].

Some information on the long-term safety of fenfluramine at a mean dose of 0.34 (0.12–0.90) mg/kg/day is provided from an open-label study in Belgium that followed 2 cohorts with a total of 21 patients treated with fenfluramine for DS, some of whom were treated for more than 27 years, and did not report any outstanding safety events [25-27].

In addition, no VHD or PAH events have been reported in an ongoing study of fenfluramine at 0.2 to 0.7 mg/kg/day in 330 patients treated for a median duration of treatment of 631 days [28,29].

More recently, cases of PAH and VHD have been identified during routine post-marketing surveillance.

Based on the previously reported cardiotoxicity associated with fenfluramine at doses used for obesity of 60 to 120 mg/day (i.e., 2 to 4 times higher than the proposed maximum daily dose), PAH and VHD were an important potential risk to evaluate for ZX008, and no subject in any clinical study with treatment up to 3 years developed PAH or VHD at any time. However, during Safety Signal Assessments (with Data Lock Point of 14 Jan 2024 and 15 August 2024), available evidence from nonclinical studies, clinical studies, registries that collect safety data (post-marketing surveillance), spontaneous reports, and relevant information from published literature was extensively reviewed, and UCB have now recategorized the risk of PAH and VHD to an Important Identified Risk.

Furthermore, an international, multicentre, open-label extension trial of patients treated with fenfluramine for up to 36 months (NCT03936777) strongly supports the continued, long-term safety and favourable benefit-risk profile of fenfluramine for the adjunctive treatment of seizures associated with DS.

### 7.3.2 Fenfluramine Animal Data

Some in vitro studies have suggested a possible role of serotonin or agonist activity of norfenfluramine in cardiac valve disease. However, in vivo studies using animal models have not been able to reliably demonstrate any effect on cardiac valves [63]. No changes in the mitral or aortic valves were noted in the Good Laboratory Practices (GLP)-compliant juvenile rat toxicity studies performed by Zogenix, even at fenfluramine doses that caused mortality (20 mg/kg/day).

Additionally, no changes in the mitral or aortic valves were noted at any dose level in the GLP-compliant, 13-week rat toxicity study performed by Zogenix.

### 7.3.3 Fenfluramine Clinical Trial Data

The DS fenfluramine clinical development programme includes a prospectively defined, long-term, longitudinal cardiovascular study of the function and structure of the heart valves, focusing on signs of VHD and PAH. Safety assessment in the ZX008 clinical programme includes serial colour Doppler ECHO monitoring for VHD (valvulopathy) and PAH. Study 1603, a thorough QT study in healthy adult subjects, was also conducted.

No VHD, as measured by valve function and observations of valve structure, or PAH, as measured by pulmonary pressure, has developed in any subject in the reported DS trials, nor, in fact, has any VHD or PAH developed in any patient in the programme to date. Normal non-pathologic trace and mild mitral regurgitation and trace aortic regurgitation were observed at very low rates consistent with what has been reported in the literature, with no patients progressing to VHD; most of these findings were transient and fluctuated between absent and

trace regurgitation during the study. The point prevalence rates of trace mitral and aortic regurgitation were equal to or lower than the incidence rates reported in normal healthy developing children [38,64].

### 7.3.4 Fenfluramine SmPC Precautions for Use Regarding Cardiac Monitoring

Due to reported cases of VHD that may have been caused by fenfluramine at higher doses used to treat adult obesity, cardiac monitoring must be performed using echocardiography. Prior to starting treatment, patients must undergo an ECHO to establish a baseline prior to initiating treatment and exclude any pre-existing VHD or pulmonary hypertension. ECHO monitoring should be conducted every 6 months for the first 2 years and annually thereafter. If an ECHO indicates pathological valvular changes, a follow-up ECHO should be considered at an earlier timeframe to evaluate whether the abnormality is persistent. If pathological abnormalities on the ECHO are observed, it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist [38].

### 7.3.5 Fenfluramine Controlled Access Programme

A controlled access programme has been created to 1) prevent off-label use in weight management in obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking fenfluramine [38].

## 7.4 Potential Risk of Growth Retardation Associated with Fenfluramine

### 7.4.1 Background

Appetite suppression is a known effect of fenfluramine caused by its mechanism of action as a centrally acting serotonergic agent. Increased serotoninergic transmission in the centres of feeding behaviour in the hypothalamus suppress appetite, leading to decreased food intake and malnutrition, which could ultimately impact physical development based on chronic suboptimal caloric intake [61].

Appetite suppression and decrease in weight have been observed in the DS population treated with fenfluramine at lower doses than for the treatment of obesity in adults in the 1960s and 1970s at doses of 60 to 120 mg per day. As weight loss can impact growth and development, growth retardation is considered an important potential risk [61].

Abnormal growth in height and weight were reported in a cohort of 64 children with DS who were at least 2 years of age. The children were treated with a mean of 2.9 antiseizure medications but were not being treated with fenfluramine or with any hormonal treatment. When the height and weight measurements were compared with growth curves from the US Centers for Disease Control and Prevention, the resulting z-scores showed that for every year the children's ages increased, the height z-score decreased by 0.10 ($p \leq 0.001$) and the weight z-score decreased by 0.09 ($p \leq 0.01$) [44].

The growth data collected in the registry will be interpreted in the context of the published dataset from patients with DS or LGS [44].

### 7.4.2 Fenfluramine Clinical Trial Data

In the controlled trials of children and young adults with DS, 34.4% of fenfluramine-treated patients had decreased appetite, compared to 8.3% of patients on placebo; approximately 18.9% of fenfluramine-treated patients had a decrease in weight ≥7% from their baseline weight, compared to 2.4% of patients on placebo [38]. A recent analysis of z-scores for height and weight in patients with DS who participated in an open-label extension of two clinical trials reported that at least 12 months of treatment with 0.2 to 0.7 mg/kg/day of fenfluramine had minimal impact on the patients' height and weight, which at baseline and at the end of 12 months (n=279) and 24 months (n=128) [65] were similar to measures in published data for the DS population [44].

### 7.4.3 Fenfluramine SmPC Precautions for Use Regarding Decreased Appetite and Weight Loss

As fenfluramine can cause decreased appetite and weight loss, the patient's weight should be monitored. A benefit-risk evaluation should be undertaken prior to commencing treatment with fenfluramine in patients with a history of anorexia nervosa or bulimia nervosa [38].

## 7.5 Study Rationale

Based on the history, profile, and clinical programme of fenfluramine, the risk management plan (RMP) of fenfluramine includes the following important risks to be further characterised:

- Valvular heart disease
- Pulmonary arterial hypertension
- Growth retardation

Therefore, this observational registry is proposed to further assess the long-term utilisation and safety of fenfluramine as prescribed in routine practice in patients with DS and LGS and other potential future approved indications with a focus on characterising and quantifying the important risk of VHD and PAH. This registry will also provide data to characterise and quantify the important potential risk of growth retardation.

Key routine risk minimisation measures within the summary of product characteristics (SmPC) include instruction for:

- ECHO assessment to confirm absence of VHD and PAH prior to fenfluramine treatment initiation
- ECHO monitoring during use of fenfluramine and 3-6 months after discontinuation of fenfluramine

Data on the extent and frequency echocardiographic monitoring will be collected within this observational study and contribute to assess the effectiveness of risk minimisation measures.

The above-mentioned objectives of this study will be assessed in patients treated with fenfluramine approved indications as well as for all patients treated with fenfluramine in routine clinical practice.

# 8 Research Questions and Objectives

## 8.1 Primary Objective

The primary objective of this registry is to assess the long-term cardiac safety of fenfluramine as prescribed in routine clinical practice for fenfluramine approved indications.

## 8.2 Secondary Objectives

The secondary objectives of this registry are:

- To assess the occurrence of growth retardation, if any, in patients treated with fenfluramine in routine clinical practice for fenfluramine approved indications
- To describe patients' ECHO monitoring for patients treated with fenfluramine in routine practice for fenfluramine approved indications
- To assess the primary and secondary objectives mentioned above for all patients treated with fenfluramine enrolled in the registry

The present protocol describes the research methods used for the Registry in Section **9** and for the External Reference (Registry Primary Objective only) in Section **10**

# 9 Registry Research Methods

## 9.1 Registry Study Design

### 9.1.1 Registry Overview

The objectives of the Registry will be addressed via an observational, multi-country, cohort study (a registry) of patients treated with fenfluramine hydrochloride oral solution, conducted at centres prescribing fenfluramine in routine practice (expectedly physicians specializing in paediatrics or neurology – e.g., neuro-paediatricians, paediatricians, or neurologists – with experience in the treatment of epilepsy) in European countries (including UK, Germany, Austria, Italy, Spain, and France).

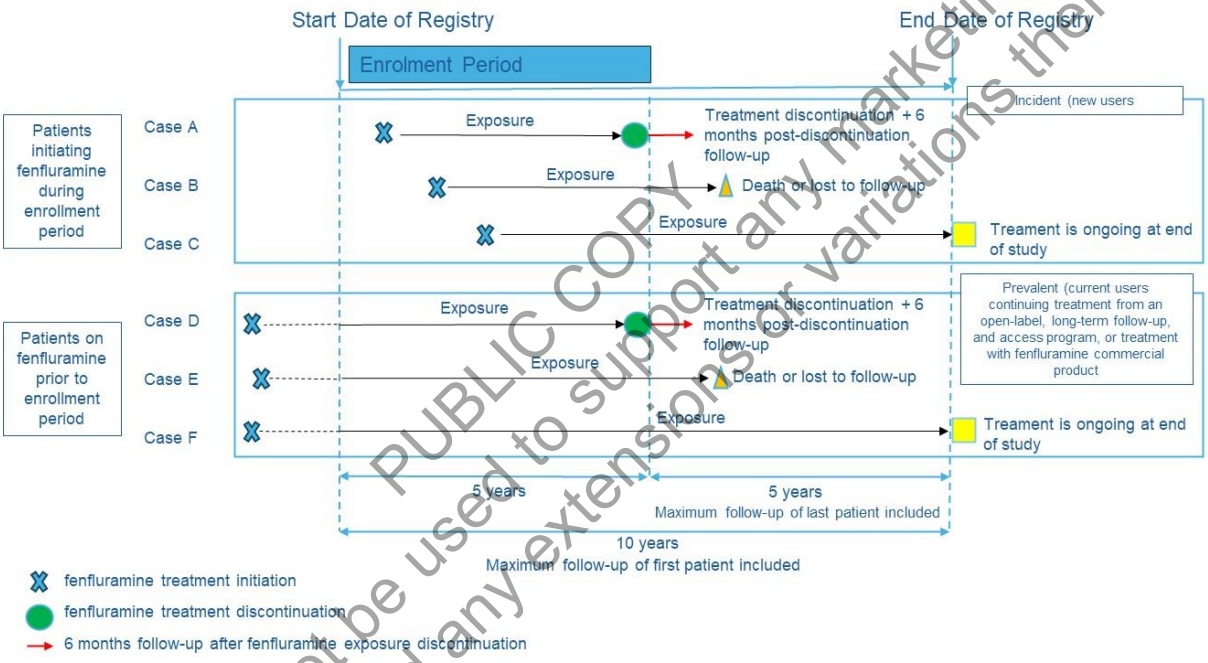
### 9.1.2 Registry Duration and Follow-up

The enrolment period will begin from the registry start date in the first participating country and span over five years, conditional of approval of the protocol by the European Medicines Agency (EMA) for European countries and Institutional Review Board (IRB) for all countries. The registry is planned to last ten years from the first patient first visit to the last

patient last visit; therefore, the maximum follow-up period for the last patient enrolled in the registry will be five years, and the maximum follow-up period will be ten years for the first patient enrolled.

Participation of each patient in the registry will begin at cohort enrolment (Day 1), and the patient will be followed for up to six months after discontinuation of fenfluramine treatment, loss to follow-up, death, or end of the study period (end of study is last patient last visit), whichever occurs first. Two groups of patients will be included in the registry: incident users (new users) and prevalent users (current users continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product); the registry follow-up will add to any previous follow-up time while being treated with fenfluramine. Study design schematic is presented in **Figure 1**.

**Figure 1. Study Design Schematic**




## 9.2 Setting

### 9.2.1 Study Sites

The current assumption based on fenfluramine SmPC and the implementation of a controlled access programme is that mainly neuro-paediatricians and paediatricians or neurologists with experience in the treatment of epilepsy will be included in the study. In some countries, it is possible that maintenance prescriptions will be written by a local general practitioner or family physician under the supervision of the responsible neurologist to ensure care continuity in case of geographical distance to the specialised care centre. In this situation, every effort

will be made to ensure data collection as per study protocol and avoid any potential duplication or loss of information.

Physicians will be informed about and encouraged to participate in the fenfluramine registry as part of the fenfluramine RMP educational materials.

Physicians will be identified and contacted via different possible and complementary approaches due to the heterogeneity of care settings across planned participating countries with fenfluramine approved indications:

- Centres contributing to existing disease registry as [redacted] e.g., in Italy where a large number of sites contribute to [redacted].
- Reference sites of existing networks such as [redacted] - a European Reference Network for rare and complex epilepsies [redacted] where a few of all the above centres may participate in the European Countries, but not the UK.
- Reference centres in the treatment of rare paediatric epilepsies, e.g., Network in France of reference and competence centres labelled by the Ministry of Health.
- Academic or community hospitals with physicians specialised in the treatment of rare epilepsies, e.g., in Germany, Spain, and the UK.
- Investigators in fenfluramine clinical trials.
- Sites with physicians participating in fenfluramine Access Programs/Compassionate Use Programs.
- Country-specific commercial lists of physicians and physician panels.
- Sponsor's and contract research organisation's (CRO) network.
- Prescribers entering the FINTEPLA Controlled Access Programme portal who give their permission to be contacted for future Post-authorisation safety study (PASS) studies.

Every effort will be made to develop the present registry in collaboration with existing registries and networks (e.g., [redacted]) as recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to optimise patient recruitment, leverage any existing data collection, and minimise the burden of reporting sites.

The number of potential sites in each country will be determined through a feasibility assessment as part of the site qualification process. This is a first estimate, and the planned number of enrolled sites (overall and by country) will depend on the registry's effective start-up date, fenfluramine market uptake, the number of patients treated with fenfluramine for approved indications initiating treatment with fenfluramine at each site, and overall site interest in participation. To represent variations in current real-world patterns of care, where possible, sites will be selected based on geographic region, institution size and type (e.g.,

academic vs community). These considerations will be considered when analysing the results of the study.

### 9.2.2 Study Population Selection Criteria

Both patients who start fenfluramine within the study setting and have no prior use of fenfluramine (incident/new user) and those who began using fenfluramine before enrolment in the registry (prevalent/current users) will be included in the study.

Patient selection is based on the inclusion and exclusion criteria listed below. Patients who meet each of the inclusion criteria and none of the exclusion criteria are eligible to participate in the registry.

Below, inclusion and exclusion criteria are applicable for all participating countries, except Germany. Inclusion and exclusion criteria required for Germany are listed in **Annex I German -Specific Eligibility Criteria**.

#### 9.2.2.1 Inclusion Criteria

To be included in the study, the patients must fulfil the following criteria:

- Patients being treated with fenfluramine
- Either new users of fenfluramine or current users (e.g., continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product)
- Patients treated at centres/by physicians prescribing fenfluramine in routine practice (expectedly neuro-paediatricians, paediatricians, or neurologists with experience in the treatment of epilepsy). In some countries, only patients prescribed fenfluramine according to the SmPC may be included, in accordance with local regulations.
- Provided informed consent or assent, as required by local regulations

#### 9.2.2.2 Exclusion Criteria

- Evidence of congenital cardiac malformation

### 9.2.3 Patient Recruitment and Retention

All consecutive, eligible patients treated with fenfluramine who meet inclusion/exclusion criteria and agree to participate will be enrolled in the study. The marketing authorisation holder (MAH) will monitor enrolment and will inform the PRAC on progress with the registry. Progress reports will be communicated as part of the Periodic Safety Update Reports and will include information on the current status of recruitment and the proportion of patients lost-to-follow-up to evaluate the success of recruitment. In addition, the MAH will discuss within each progress report whether measures must be implemented to enhance recruitment or/and to reduce the proportion of patients lost-to-follow up. If required, possible measures will be presented and discussed in each progress report. If the recruitment of patients in the

registry is lower than anticipated, the MAH will consider and implement mitigation strategies to increase the recruitment rate in the context of the overall usage of the product.

The MAH will also monitor the retention of patients and will undertake all reasonable efforts and methods to minimise loss to follow-up. In any circumstances, every effort consistent with the standard of care will be made to keep track of the patients and obtain information about the patients' health status and reason for study withdrawal other than lost to follow-up (through, for example, repeated phone calls, emails, contact to relatives, contact to other health care professionals managing the patients), such efforts will be documented.

### 9.2.4 Withdrawal Criteria

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and without giving a reason. Any withdrawal will be fully documented in the eCRF and source documents. Discontinuation from the study for any other reasons (e.g., lost to follow-up, death) will also be recorded in the eCRF.

A patient must be withdrawn from the study if:

- The patient and/or his or her legal representative (if applicable) withdraw(s) his or her consent (defined as a patient and/or his or her legal representative [if applicable] who explicitly take(s) back his or her consent).
- The investigator considers it, for study compliance reasons, in the patient's best interests that he or she be withdrawn.

If the patient withdraws consent for disclosing future information, no additional data should be collected. However, the sponsor may keep and continue to use any data collected before the withdrawal of consent date.

### 9.2.5 Study Treatment(s)

This study is strictly observational; the assignment of patients to fenfluramine or any drug will not be determined in advance by the protocol and will be clearly separated from the decision to include the patients in the study. Physicians will determine visits schedule according to routine practice and fenfluramine prescription to patients. It is anticipated that fenfluramine will be prescribed by neuro-paediatricians, paediatricians, or neurologists with experience in treating epilepsies. Patients treated with fenfluramine initiating treatment during the enrolment period or prior to enrolment (e.g., continuing treatment from an open-label, long-term follow-up or from an Access Program) will be included in the registry. There is no prohibited concomitant medication as part of this study, and all data collected on treatment regimens and visits will be documented in the eCRF.

### 9.2.6 Study Plan

Before study initiation, the protocol will be submitted for review and approval by an institutional review board (IRB) or independent ethics committee (IEC) as applicable in each country. For patients younger than 18 years old, the informed consent must be obtained from the legal representative according to local laws before participation in the registry and/or

assent as necessary per local regulations. Paediatric patients should be informed to the most appropriate extent possible about the registry in language and terms suitable for their age to ensure understanding.

Patient eligibility will be assessed against the registry inclusion and exclusion criteria. After inclusion and obtention of written informed consent/assent from the patient or legal representative as per local regulations, registry-related procedures will begin. Patient data from source documents will be recorded in an electronic Case Report Form (eCRF).

The planned assessments and the scheduled observational data collection timepoints are summarised in **Table 1**. Only data documented in patients' medical records during usual care will be collected. As the study is observational, this will not change the patient-HCP relationship, nor influence the HCP's drug prescription or therapeutic management of the patient. Moreover, no additional laboratory tests or HCP assessments will be required as part of this study. The HCP will determine the schedule of patient visits and ECHOs according to the local standard of care and fenfluramine SmPC guidance. The latter recommends echocardiographic surveillance prior to fenfluramine treatment initiation, then every six months for the first two years and annually afterwards.

The main variables to be collected include but are not limited to: demographic data, relevant medical and treatment history, anthropometric measurements, fenfluramine treatment data, comorbidities and concomitant medications, ECHO dates and findings with characteristics in case of abnormality, growth retardation clinical diagnosis and characteristics, convulsive seizure activity, AEs/ADRs, and patient status, which will be entered into the eCRF. Data timepoints include baseline data collection, then data specific to the needs of this registry will be collected prospectively each time an echocardiographic surveillance is performed. Then, it will be recommended that cumulative data are collected at a minimum of 6-month intervals (± 1 month) during the first two years of participation in the registry and annually (± 2 months) thereafter, as well as at fenfluramine discontinuation and at 6 months after fenfluramine discontinuation.

The patient will be followed at six months after discontinuation of fenfluramine treatment in order to collect the same variables recorded during fenfluramine treatment visits (except fenfluramine treatment characteristics). This duration after treatment discontinuation is in line with post-treatment ECHO data from the ZX008 clinical programme, available published trial data in adult obese patients using fenfluramine [66], and the fenfluramine patient leaflet.

## Table 1. Study Data Collection Schedule

| Assessments | Baseline Observational Data Collection Point | Observational Data Collection Point during fenfluramine treatment[a] | Observational Data Collection Point at fenfluramine discontinuation | Observational Data Collection Point six months following fenfluramine discontinuation |
|---|---|---|---|---|
| Informed consent/assent | X | | | |
| Inclusion/exclusion criteria | X | | | |
| Demographics | X | | | |
| Anthropometric measurements (i.e., weight, length/height) | X | X | X | X |
| Epilepsy diagnosis and medical history | X | | | |
| Antiepileptic treatment history | X | | | |
| Fenfluramine treatment characteristics | X | X | X | |
| Reason for fenfluramine discontinuation | | | X | |
| Other antiepileptic pharmacological treatment(s) characteristics (e.g., stiripentol, clobazam, valproate, phenobarbital, carbamazepine) | X | X | X | X |
| Other significant non-pharmacological epilepsy treatments (e.g., ketogenic diet, vagal nerve stimulation) | X | X | X | X |
| Concurrent medical conditions | X | X[b] | X[b] | X[b] |
| Concomitant pharmacological treatments other than antiepileptics: number per therapeutic class | X | X | X | X |
| Characteristics of concomitant pharmacological treatment(s) other than antiepileptics | | X[b] | X[b] | X[b] |
| Convulsive seizure activity | X | X | X | X |
| Echocardiogram date and findings; characteristics in case of abnormality | X | X | X | X |
| Growth retardation clinical diagnosis | X | X | X | X |
| AE/ADR | X | X | X | X[c] |
| Patient status and if applicable date of death, lost to follow-up, withdrew consent | | X | X | X |

Abbreviations: AE = adverse event; ADR = adverse drug reaction
[a] Cumulative data collection every six months (± 1 month) for the first two years and annually (± 2 months) thereafter.
[b] To be evaluated in case of VHD, PAH, clinical growth retardation diagnosis or AE/ADR event.
[c] To be evaluated only for VHD and PAH as AE/ADR.

## 9.3 Variables

### 9.3.1 Primary Outcome Definition and Variables

#### 9.3.1.1 Primary Outcome Definition

Valvulopathy is a general term that broadly refers to any abnormality affecting any of the four heart valves and can include structural abnormalities, functional impairments, or both. Valvular heart disease is a clinically relevant valvulopathy which may need intervention and proper management. Fenfluramine-induced valvulopathy mainly affects the left-sided heart valves (i.e., aortic and mitral).

In order to harmonize the overall data from all geographies (EU, US and the rest of the world), the incidence of valvulopathy, together with the incidence of VHD and the incidence of PAH will be the primary outcomes.

The primary outcomes will be assessed via routine echocardiographic surveillance established for patients treated with fenfluramine. The VHD definition in the study is aligned with the FDA case definition for fenfluramine-induced valvulopathy [19] (i.e., ≥mild aortic regurgitation or ≥moderate mitral valve regurgitation) and focuses on the clinically relevant aortic and mitral valves conditions as well as the echocardiographic criteria of severity for VHD [31] and the guidelines on the management of VHD [32] from the European Society of Cardiology. The valvulopathy assessment will include all four cardiac valves. The detailed definitions for valvulopathy, VHD, and PAH are as below.

Cases of valvulopathy, VHD, and PAH events will be validated and ascertained by an external independent validation committee (i.e., Clario), composed of cardiologists with expertise in reading ECHOs:

- Valvulopathy:
  - Presence of a new finding, and at least one grade increase from the baseline of: ≥mild aortic or ≥moderate mitral regurgitation or ≥moderate tricuspid or ≥moderate pulmonary valve regurgitation seen on transthoracic ECHO (TTE)
  - The findings also need to be confirmed by repeat TTE (see Section 9.4).
- VHD:
  - Presence of ≥mild aortic or ≥moderate mitral regurgitation seen on transthoracic echocardiogram (TTE)
  - The findings also need to be confirmed by repeat TTE (see Section 9.4)
  - Plus, one of the following:
    - Physical signs or symptoms attributable to valve disease
    - A structural lesion of the aortic or mitral valve (e.g., thickening)
    - A restriction of valve movement of the aortic or mitral valve
    - Abnormal left ventricular (LV) systolic function with depressed LVEF (<50%)

  - LV enlargement/dilatation
  - Left atrial enlargement
- PAH:
  - Pulmonary artery systolic pressure (PASP) ≥35 mmHg on TTE [33]

#### 9.3.1.2 Primary Outcome Variables

Primary outcome variables for all patients will include but not be limited to:

- Date of ECHO
- Grade (absent/trace, mild, moderate, severe) of valve regurgitation and affected valves (aortic, mitral, pulmonary, tricuspid)
- Presence or absence of elevated PASP (equal to or more than 35 mm Hg)
- Valvular or any other abnormality reported on baseline ECHO

These variables will be collected at baseline, every 6 months for the first 2 years and annually thereafter, at fenfluramine discontinuation, and at 6 months after fenfluramine discontinuation.

In case of valvulopathy, VHD or PAH event of interest (≥35 mmHg) occurs as defined above (see Section **9.3.1.1**), the following variables to characterise the event to be collected will include (but will not be limited to):

- Cardiac ECHO findings, including:
  - ≥mild aortic or ≥moderate mitral regurgitation or ≥moderate tricuspid or ≥moderate pulmonary valve regurgitation
  - Restricted valve motion, or and/or structural lesion (e.g., valve thickening)
  - Presence of left ventricular abnormalities:
    - Abnormal left ventricular (LV) systolic function with depressed left ventricular ejection fraction (LVEF <50%)
    - LV dilatation
    - Left atrial enlargement
  - Interventricular septal flattening
  - Elevated right heart/pulmonary artery pressure
- Presence of VHD and PAH symptoms, and if symptomatic, description of symptoms
- Presence of VHD and PAH signs, and if signs, description of signs
- Outcome of VHD and PAH (including medical or interventional therapy, hospitalisation, discontinuation of treatment, death, no change in fenfluramine)
- Additional pertinent ECHO results, if any

- Additional pertinent laboratory test results will be collected in the MAH safety database if available

- Concurrent medical conditions, including:
  - Hypertension
  - Mitral valve prolapse (including severity grade of prevalent valve disease)
  - History of rheumatic heart disease
  - Bicuspid aortic valve (including severity grade of prevalent valve disease)
  - Marfan syndrome
  - Reversal of shunt with ventricular septal defect, atrial septal defect, patent foramen ovale, or patent ductus arteriosus
  - Mitral valve disease (including severity grade of prevalent valve disease)
  - Aortic valve disease (including severity grade of prevalent valve disease)
  - Sleep apnoea
  - Sickle cell disease
  - Chronic obstructive pulmonary disease (COPD)
- Characteristics of concomitant pharmacological treatment(s) other than antiepileptics
  - Drug name
  - Start and stop dates
- Exposure to other drugs or biological products, including ergotamine, other prescription and non-prescription drugs, and dietary supplements

### 9.3.2 Secondary Outcome Definitions and Variables

#### 9.3.2.1 Secondary Outcome Definitions

##### 9.3.2.1.1 Clinical Diagnosis of Growth Retardation

Growth retardation will be based on the clinical diagnosis of growth retardation according to physician judgment for patients <18 years old within the registry.

##### 9.3.2.1.2 Standardised Growth Indicators

As complementary information, standardised growth indicators will be calculated based on length/height and weight measurements for age and sex in patients to assess potential growth retardation in patients <18 years old within the registry.

The following standardised growth indicators will be calculated and monitored in patients <18 years in the registry:

- Length/height-for-age z-score (LAZ/HAZ)
- Weight-for-age z-score (WAZ)
- Weight-for-height z-score (WHZ)
- BMI-for-age z-score (BAZ)

To assess the occurrence of patients with potential growth retardation, the number of patients with more than 2 standard deviations (SDs) below the mean for age and sex (i.e., below the -2 z-score line) on the UK-WHO growth charts, for each growth indicator abovementioned will be calculated at each data collection timepoint (see **Table 1**).

In addition, the mean (SD) of the z-scores abovementioned will be compared with published mean (SD) z-scores of other populations of patients <18 years old with DS or another potential approved indication, but not treated with fenfluramine (see further details in analysis Section **9.7.5**).

#### 9.3.2.2 Secondary Outcome Variables

##### 9.3.2.2.1 Growth Retardation

Secondary outcomes variables related to growth retardation for all patients include but are not limited to:

- Diagnosis of growth retardation according to physician judgment
- Weight
- Length/height
- Body mass index (calculated based on length/height and weight)

These variables will be collected at baseline, every 6 months (± 1 month) for the first 2 years and annually (± 2 months) thereafter, at fenfluramine discontinuation, and 6 months after fenfluramine discontinuation.

In case of growth retardation according to physician judgment, the variables collected to characterise the growth retardation will include but are not limited to:

***Growth retardation functional exploration test assessments***

- Performance and results of growth functional exploration tests, if ordered (e.g., IGF1, IGFBP-3, growth hormone, sex hormones), as performed in routine practice:
  - Date of laboratory assessment
  - Laboratory test finding (abnormal, normal)
  - Result and unit for result

***Any known causes other than fenfluramine that can affect growth***

- Adverse outcomes affecting size at birth:
  - Preterm birth (birth <37 weeks of gestation),
  - Small for gestational age (SGA) (birth weight <10$^{th}$ centile for their gestational age)
  - Low birth weight (birth weight <2500g)
- Chronic systemic disease: e.g., anaemia, growth hormone deficiency, inflammatory bowel disease, celiac disease, chronic renal disease, congenital heart disease, diarrhoea, pulmonary disease
- Genetic disease: e.g., Turner syndrome, Prader-Willi, Noonan syndrome
- Malignancy: e.g., osteosarcoma of the lower limbs
- Endocrine disease: e.g., achondroplasia, acquired growth hormone deficiency, congenital growth hormone deficiency, congenital hypothyroidism, intrauterine growth deficiency, primary nutritional deficiency

***All concomitant treatments, including those potentially related to growth retardation***

- Pharmacological treatment for growth retardation
  - Drug name
  - Start and stop dates
- All other pharmacological treatments, including but not limited to those treatments known to cause short stature (e.g., corticosteroids, attention-deficit/hyperactivity disorder medications):
  - Drug name
  - Start and stop dates

These variables will be collected at each observational data collection timepoint from growth retardation clinical diagnosis as defined in Table 1. Study Data Collection Schedule.

#### 9.3.2.2.2 Echocardiographic Monitoring Characteristics

Echocardiographic monitoring will be collected prospectively starting at baseline until 6 months after fenfluramine discontinuation, including the following variables:

- Date of every echocardiographic monitoring

### 9.3.3 Fenfluramine Treatment Characteristics

Treatment characteristics of fenfluramine will be collected prospectively starting at baseline until fenfluramine discontinuation, including the following variables:

- Start and stop dates
- Treatment duration will be derived from initiation date (index date) and discontinuation date
- Initial dose in mg/kg/day
- Maintenance daily dose
- Frequency of administration
- Any fenfluramine treatment change in terms of dose or frequency of administration, including fenfluramine treatment discontinuation
    - Date of change(s)
    - Reason for change(s) (e.g., new onset comorbidities, AEs, death, patient/parent's decision)

### 9.3.4 Other Variables Collected for All Patients

The variables in this section will be collected for all patients enrolled in the registry.

#### 9.3.4.1 Collected at Baseline

##### 9.3.4.1.1 Epilepsy Diagnosis Information and Disease Characteristics

- Epilepsy diagnosis associated with fenfluramine prescription
- Date of epilepsy disease diagnosis confirmation (e.g., DS, LGS)
- Date and result of genetic test to confirm epilepsy diagnosis, if performed
- Date of first epilepsy symptoms onset
- Convulsive seizures type and frequency
- Antiepileptic treatment history:
    - Date of first antiepileptic treatment
    - Last prescribed anti-epileptic treatments before fenfluramine initiation
    - Number of previous antiepileptic treatments
    - Number of anti-epileptic drugs being prescribed when fenfluramine treatment was initiated

#### 9.3.4.1.2 Patient Characteristics

- Demographics (e.g., sex, age at inclusion in the registry)
- Anthropometrics (i.e., weight and height or length)
- Mid-parental height, defined as child's projected adult height based on the heights of the parents
- Medical history:
  - Personal history of VHD and/or PAH diagnosis
  - Family history information
    - Maternal and paternal family history of VHD or PAH
    - Maternal and paternal family history of blood clotting disorders or pulmonary embolism
    - Immediate family history of growth retardation
- Concurrent medical conditions, including:
  - Hypertension
  - Mitral valve prolapse (including severity grade of prevalent valve disease)
  - History of rheumatic heart disease
  - Bicuspid aortic valve (including severity grade of prevalent valve disease)
  - Marfan syndrome
  - Reversal of shunt with ventricular septal defect, atrial septal defect, patent foramen ovale, or patent ductus arteriosus
  - Mitral valve disease (including severity grade of prevalent valve disease)
  - Aortic valve disease (including severity grade of prevalent valve disease)
  - Sleep apnoea
  - Sickle cell disease
  - Chronic obstructive pulmonary disease (COPD)

### 9.3.4.2 Collected at Baseline and at observational data collection timepoints

Observational data collection timepoints are defined in Table 1. Study Data Collection Schedule.

#### 9.3.4.2.1 Fenfluramine Treatment Characteristics

Treatment characteristics of fenfluramine will be collected prospectively starting at baseline until fenfluramine discontinuation as described in Section 9.3.3.

#### 9.3.4.2.2 Other Antiepileptic Treatment(s) Characteristics

- Antiepileptic treatment exposure other than fenfluramine (treatment at baseline and during the study) (e.g., stiripentol, clobazam, valproate, phenobarbital, carbamazepine, levetiracetam, cannabidiol, topiramate)
    - Drug name(s)
    - Start and end dates
    - Dose
    - Reason for treatment discontinuation/withdrawal
- Other significant non-pharmacological epilepsy treatments (e.g., ketogenic diet, vagal nerve stimulation)
    - Treatment name(s)
    - Start and end dates

#### 9.3.4.2.3 Concomitant Pharmacological Treatments

- Concomitant pharmacological treatments (other than antiepileptics including ergotamine, i.e., prescription and non-prescription drugs, and dietary supplements):
    - Therapeutic class (e.g., psychotropic treatment)
    - Number of drug(s) per therapeutic class

#### 9.3.4.2.4 Convulsive Seizures Activity

- Convulsive seizures activity characteristics
    - Change in seizure frequency from last data collection timepoint (increased, decreased, no change)
    - Change in seizure severity since last data collection timepoint
    - Change in seizure duration from last data collection timepoint
    - Return to baseline quicker after seizure/improvement in postictal state

### 9.3.4.3 Collected at Each Data Collection Timepoint during Follow-up

#### 9.3.4.3.1 Patient Status

- Patient status (e.g., death, lost to follow-up and the reason for lost to follow-up, withdrew consent)
- If applicable: date of death, primary cause of death, date of loss to follow-up, date of consent withdrawal, or reason for consent withdrawal

## 9.4 Data Sources

Medical information will be recorded in patients' medical records during every clinic visit and each time an echocardiographic surveillance is performed (according to fenfluramine SmPC: every six months for the first two years and annually thereafter; according to fenfluramine patient leaflet; if fenfluramine treatment is stopped, an ECHO should be conducted 6 months after the last dose). Patients' medical record information and any relevant diagnostic reports are the source documents for study data collection.

Findings need to be confirmed by repeat ECHO, defined as the next available ECHO that is performed either at the next scheduled observational data collection point or for the specific purpose of confirming the findings in the original ECHO. ECHOs performed on the same day due to image quality or technical issues are not considered to be confirmatory 'repeat' ECHOs.

Clinical information recorded in patients' medical record and/or diagnostic reports will be abstracted and entered into the case report form (CRF) in the electronic data capture (EDC) system at inclusion (baseline) and then according to the schedule presented in **Table 1**.

Each CRF will have a unique number within the study (Patient Identification). Each site will maintain a Patient Identification list linking the patient to the Patient Identification within the study. Only the treating investigator and/or authorised personnel will be able to identify the patient based on the Patient Identification list, which will be held only at the site.

The MAH will be the 'Controller' of personal data collected for the study. The MAH, as data controller, will take appropriate steps to ensure that personal data are protected.

When possible, in order to adequately manage EDC entry, sites are encouraged to enter data in the EDC within seven days of a patient's data collection timepoint. Data collection requirements for safety events, which need to be reported to Zogenix (acquired by and is a wholly owned subsidiary of UCB, Inc) within specified timelines, are detailed in Section **12.3**.

It is expected that the participating sites will report the findings (images and reports) of the echocardiographic assessment even if it was performed in another hospital or centre.

If sites are participating in an existing registry, data overlapping with the study variables could be extracted from the registry where possible to avoid any additional burden to the investigators.

Monitoring visits to each site will be conducted by the assigned clinical research associate as described in the monitoring plan. The monitoring plan will be developed and available prior to the start of monitoring. The CRFs and patient's corresponding original medical records (source documents) will be fully available for review by the MAH's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and review by independent ethics committee (IEC)/institutional review board (IRB).

## 9.5 Study Size

The purpose of the study is descriptive. Therefore, no formal sample size or power calculation is necessary. The sample size is based on both practical and statistical considerations. The safety context of the study requires that the sample size be sufficient to detect a signal, if any. The study will aim to enrol approximately 600 patients treated with fenfluramine, who are either current fenfluramine users (continuing treatment from an open-label, long-term follow-up or from an Access Program) or initiating treatment with fenfluramine. The final number of patients in the study will depend on the actual market uptake, including the number of prescribing sites, and the rate of sites and patient participation.

Valvular heart diseases are rare in the general population below 40 years of age. Under a hypothesis of a 0.5% frequency of pathologic mitral or aortic regurgitation as assessed via echocardiography [35], 600 patients would be needed to yield a 95.1% probability that at least one case of VHD would be detected (based on a binomial distribution). In other words, if no events of VHD are observed among 600 patients with DS or other potential approved fenfluramine indication then this will rule out a risk associated to fenfluramine exposure equal to or greater than the background risk of 0.5%.

Other studies (though not based on echocardiography) found even smaller frequency estimates in the general 0 to 39 year-old population (lowest observed incidence rate being 2.5/100,000 person-years for mitral regurgitation in the 25 to 29 age group; highest observed incidence rate being 11.8/100,000 person-years for aortic regurgitation in the 35 to 39 age group[30]). With 600 patients, the probability to observe at least one event under the hypothesis that the incidence rate is equal to these rates is:

- 1.5% for a 2.5/100,000 person-years background rate (see above)
- 6.8% for a 11.8/100,000 person-years background rate (see above).

Consequently, observing one case of VHD among 600 patients can occur with a non-negligible probability if the true incidence rate is in the range of the published background rates.

Pulmonary arterial hypertension is a rare condition and its overall frequency is expected to be as low as 2.5 to 7.1 per million subjects in Europe [36] and the risk in adult obese patients treated with fenfluramine for weight loss for more than 12 years in the period before the late 1990s has been estimated to 1 in 10,000 patients [37]. Based on this figure 30,000 patients would be needed to yield a 95% probability to detect at least one PAH event. However, this number of patients is much higher than the expected number of fenfluramine users for a long period of time (see market forecasts below) and thus will not be used to address the study size.

## 9.6 Data Management

A data management plan will be prepared and will detail the data management and data handling procedures (**Annex II. List of Standalone Documents**).

In order to ensure completeness and quality of the ECHO data, ECHO performance date and results will be mandatory fields in the electronic data collection platform, and the data management plan will include automatic edit checks on these items as well as manual queries, as needed. Additionally, to ensure that ECHOs are not only documented when an event is observed, the mandatory field of the eCRF collecting Data on ECHO performance will include the response options: 'ECHO was performed and revealed a medical finding', 'ECHO was performed and did not reveal a medical finding', and 'ECHO was not performed/documented at this visit'. Further, full ECHO reports and images will be collected.

### 9.6.1 Data Collection

Data required by the protocol will be collected in an electronic (e)CRFs and entered into a validated data management system that is compliant with all regulatory requirements. The web-based EDC system aims to serve as an integrated, transparent tool to collect and manage data and track study progress at the centre and patient level. Data in the EDC system are kept in a central location.

Each study investigator has ultimate responsibility for the collection and reporting of all data entered in the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed prior to database lock by the study investigator or by an authorised staff member to attest that the data contained in the eCRFs are correctly recorded. The CRO will inform sites when it is time for eCRF sign-off to occur.

In the present case, the source documents are the patient medical charts and, therefore, data collected in the eCRFs should match the data in the charts.

### 9.6.2 Data Monitoring

Site staff will be trained by the CRO to perform the chart abstraction, including data entry and how to retrieve and respond to data queries in the EDC system. It is assumed that all sites will be able to complete data entry into the eCRFs via the EDC system.

The CRO will supervise and perform site management and monitoring as described in the study-specific monitoring plan. All participating sites will only have access to view and enter the data for their own patients. Only data required by the protocol for the purposes of the study should be collected.

Quality control mechanisms (e.g., verification of data completeness, validations, and edit checks), which will be automated at time of data entry, will be built into the EDC. Queries will be generated by the CRO for resolution by site staff within the EDC system.

The EDC system will have built-in methods for data validation (e.g., drop down lists, value range controls, and standardised response formats) to minimise data entry errors; however, a data cleaning method will be employed to correct inconsistencies or errors that were not captured during data entry (e.g., outliers or conflicting data). Data queries will be identified on an ongoing basis during data collection. Queries will be generated for site completion within the EDC system. Sites will receive a regular e-mail notifying them of any new or outstanding queries; frequency of e-mail notification will be defined in the Data Management Plan. Sites will have approximately five business days to complete queries following e-mail notification. As database lock approaches, the duration to resolve queries may be fewer than five business days. Formal source data verification (SDV) will be performed as relevant according to the study-specific monitoring plan.

### 9.6.3 Record Keeping

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator must keep the investigator's set of documents in accordance with national requirements on archiving of medical records, including site agreement, the identity of all participating patients (sufficient information to link records, e.g., eCRFs and medical charts), source documents, detailed records of patient disposition (e.g., signed informed consent), and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator for the length of time specified in local regulations, or in the Site Contract Agreement (whichever time period is longer).

If the investigator becomes unable for any reason (e.g., retirement or relocation) to continue to retain study records for the required period, the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or to an independent third party arranged by the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

## 9.7 Data Analysis

### 9.7.1 Statistical Analysis Plan

The planned statistical analyses are summarised in Sections **9.7.3** to **9.7.8** and will be described in detail in a stand-alone statistical analysis plan (SAP).

The SAP will include tables, listings, figure shells to be populated during the final data analysis and details of changes in the planned analysis post-protocol finalisation if applicable. It will also provide a description of the methods to deal with missing data, censoring and procedures to control potential sources of bias and their influence on the results.

All analyses will be conducted in accordance with the study objectives, SAP, and applicable guidelines. Statistical methods will be driven, in part, by the final sample size and the number of events. Results will be rounded to 1 decimal place; therefore, percentages may not always

add up to 100. Standard deviation and 95% confidence intervals (CIs) will be calculated when relevant.

### 9.7.2 Statistical Analysis Sets

There will be two analysis sets to address the objectives of the registry, depending on whether or not we specifically target the patients who are treated with fenfluramine for an approved indication:

- modified Safety Set (mSS): Patients enrolled in the registry who are treated with fenfluramine for approved indications. For growth retardation, only patients under 18 will be included.
- Safety Set (SS): All patients enrolled in the registry who are treated with fenfluramine.

### 9.7.3 Descriptive Statistics

Descriptive statistics will be used to summarise registry data in tables, listings, and figures as appropriate. Continuous variables will be described with summary statistics such as n, mean, standard deviation, median, first quartile, third quartile, minimum and maximum values. For each categorical variable, the frequency and percentage in each category will be reported. Percentages will be calculated using the specified denominator in the table. The frequency and percentage of patients with missing data for each data point will be presented. Confidence intervals (CI) of 95% will be calculated when relevant.

As per protocol, descriptive analyses only will be performed for each interim safety analysis and for the final report at the end of the study (i.e., last patient last visit). In the final report, the study results will also be presented side-by-side with study results from EP0217 (US) and EP0222 (Japan).

### 9.7.4 Primary Outcome Analyses

#### 9.7.4.1 Measure of valvulopathy, VHD, and PAH Incidence

This study will primarily assess VHD and PAH incidence among patients exposed to fenfluramine and summarise the data collected for those with reported valvulopathy, VHD, and PAH using counts and percentages for the mSS (patients treated with fenfluramine for approved indication). The proportion of patients with new cases of valvulopathy, VHD, and PAH will be reported with their corresponding 95% confidence interval as part of the descriptive analysis. An external reference will be used to provide the background risks in the general population of the cardiovascular events of interest as described in detail in Section **10**.

The incidence rate of valvulopathy, VHD, and PAH will be calculated according to the conventions described in **Table 2**. The incidence of each outcome will be expressed per person-year of exposure and calculated as the number of patients with an event of interest, divided by the number of person-years at risk, i.e., the summed person-years of fenfluramine exposure. The number of person-years at risk will be calculated over the study period. Only new cases will be included in the numerator; patients with existing valvulopathy, VHD,

and/or PAH prior to enrolment will be excluded from the analysis population, and patients who initially experience valvulopathy, VHD, and/or PAH after enrolment will be counted only once in the numerator (i.e., worsening outcomes will not be counted as new cases).

Person-years will be calculated by dividing person-days by 365. Person-days for an individual will be defined as the total number of days of fenfluramine exposure (patient time at risk ending at the date of the first valvulopathy, VHD, or PAH event, the final dose of fenfluramine, death, or data cut-off). For each incidence rate, 95% CIs will be calculated using exact methods. The incidence rates observed in the registry, if greater than zero, will be benchmarked against the incidence rates observed in the external reference (see Section **10**).

**Table 2. Calculation of Outcome Incidences for valvulopathy, VHD, and PAH**

| Outcome | Numerator | Denominator |
|---|---|---|
| Valvulopathy | Number of new valvulopathy cases during the time interval | Summed person-years of fenfluramine exposure during the time interval among patients without pre-existing valvulopathy (patient time at risk ending at the date of the first valvulopathy event, the final dose of fenfluramine, death, or data cut-off). |
| VHD | Number of new VHD cases during the time interval | Summed person-years of fenfluramine exposure during the time interval among patients without pre-existing VHD (patient time at risk ending at the date of the first VHD event, the final dose of fenfluramine, death, or data cut-off). |
| PAH | Number of new PAH cases during the time interval | Summed person-years of fenfluramine exposure during the time interval among patients without pre-existing PAH (patient time at risk ending at the date of the first PAH event, the final dose of fenfluramine, death, or data cut-off). |

Abbreviations: PAH = pulmonary arterial hypertension; VHD = valvular heart disease

### 9.7.5 Secondary Outcomes Analyses

#### 9.7.5.1 Analysis of the Occurrence of Growth Retardation

##### 9.7.5.1.1 Clinical Diagnosis of Growth Retardation

The occurrence of growth retardation will be based on the clinical diagnosis of growth retardation according to physician judgment in patients aged <18 years with DS, or any other potential future fenfluramine approved epilepsy indication (e.g. LGS) (mSS). The proportion of patients aged <18 years with clinically diagnosed growth retardation will be calculated using the numerator and denominator presented in Table 3 and reported with 95% CIs.

##### 9.7.5.1.2 Standardised Growth Indicators

International standardised growth indicators will be used to flag patients aged <18 years within the registry with potential growth problems using the UK-WHO growth charts. These charts describe how children should grow under optimal conditions and are not intended to be used as a sole diagnostic instrument for growth retardation but as a tool to assess the overall clinical impression of a child's growth. Potential deviations from normal growth will be evaluated by calculating the growth velocity overtime against standardised growth indicators that consider both child's age and sex. These analyses will be undertaken using measurements collected at each data collection timepoint (see **Table 1**).

Growth charts present reference lines called z-scores lines, also known as standard deviation (SD) scores. These z-scores are used to determine how far a child's measurement deviates from the mean (average) in the reference population. As boys and girls grow with different velocities and sizes, the length/height, weight, and BMI measurements will be plotted on growth charts in the Boys years growth chart or Girls years growth chart. Depending on whether the child will lie down for measurement of length or stand for measurement of height, the length or height-forage z-score (LAZ/HAZ) will be calculated.

Most of the growth indicators do not strictly follow a normal distribution, but present right skewed distributions. Right skewness has the effect of making distances between positive z-scores increase progressively the farther away they are from the median, while distances between negative z-scores decrease progressively. Due to that, WHO Growth Standards and the 2007 WHO Growth references introduced a revision of the LMS method proposed by Cole to accommodate the distributions of the different anthropometric measurements.

To obtain the z-score for a given measurement, the following equation will be used:

If L≠0:

$$\mathrm{Z-score} = \frac{\left(\frac{\mathrm{Value}}{\mathrm{M}}\right)^{\mathrm{L}} - 1}{\mathrm{L} \times \mathrm{S}}$$

If L=0:

$$Z - score = \frac{\ln\left(\frac{Value}{M}\right)}{S}$$

Where L, M and S are taken from the growth chart:

- M = median
- L = power in the Box-Cox transformation
- S = generalized coefficient of variation

To calculate the z-scores according to the LMS method, data from the growth chart that includes L, M, and S values by age (in completed years) and gender will be transferred into a SAS® dataset to be merged with the eCRF data to derive the below z-scores.

As age is recorded in completed years, the reference value used from the growth table will be the value for that age.

The following standardised growth indicators will be assessed:

- Length/height-for-age z-score (LAZ/HAZ)
- Weight-for-age z-score (WAZ)
- Weight-for-height z-score (WHZ)
- BMI-for-age z-score (BAZ)

For each child, the LAZ/HAZ, WAZ, WHZ and BAZ will be calculated using the above formula and means (SD) will be calculated for the overall population of children in the registry.

For each growth indicator, binary variables will be generated to identify children with more than 2 SD below the mean (i.e., below the –2 z-score line) on the UK-WHO growth charts according to the conventions described in Table 3. For each frequency, 95% CIs will be calculated using exact methods. To maximise model fit, all available and valid measurements will be used in the trend analysis, which will be performed using a linear mixed regression model with a random intercept and slope. Further details will be provided in the separate SAP.

Additionally, for each growth indicator, the mean (SD) z-scores of patients <18 years enrolled in this registry will be compared with published mean (SD) z-scores of patients <18 years with DS or another potential approved indication, but not treated with fenfluramine. Particularly, the registry z-scores will be compared with those reported in a study conducted in the US among 68 children with DS not treated with fenfluramine [44], which is, to the best of our knowledge, the only published study of this type; registry z-scores will also be compared with those reported in all future relevant published studies. The comparison of the mean (SD) z-scores will be performed using a two-sample t-test.

**Table 3. Calculation of the Proportions (95% CIs) of Patients <18 Years with Growth Retardation and Below the -2 Z-score Line on the UK-WHO Growth Charts for Each Growth Indicator**

| Binary Outcomes | Numerator | Denominator |
|---|---|---|
| Growth retardation | Number of patients aged <18 years with clinical diagnosis of growth retardation according to physician judgment | All patients aged <18 years within the registry |
| LAZ/HAZ <-2 z-score | Number of patients aged <18 years whose LAZ/HAZ is below the –2 z-score line on the UK-WHO growth charts - <18 years | Number of patients aged <18 years with a valid LAZ/HAZ |
| WAZ <-2 z-score | Number of patients aged <18 years whose WAZ is below the –2 z-score line on the UK-WHO growth charts - <18 years | Number of patients aged <18 years with a valid WAZ |
| WHZ <-2 z-score | Number of patients aged <18 years whose WHZ is below the –2 z-score line on the UK-WHO growth charts - <18 years | Number of patients aged <18 years with a valid WHZ |
| BAZ <-2 z-score | Number of patients aged <18 years whose BAZ is below the –2 z-score line on the UK-WHO growth charts - <18 years | Number of patients aged <18 years with a valid BAZ |

Abbreviations: BAZ = BMI-for-age Z-score; LAZ = Length-for-Age Z-score; HAZ = Height-for-Age Z-score; SD = standard deviation; WAZ = Weight-for-age Z-score; UK = United Kingdom; WHO = World Health Organization; WHZ = Weight-for-height Z-score

#### 9.7.5.2 Identification of Potential Risk Factors for valvulopathy, VHD, PAH, and Growth Retardation

If sample size allows, further analyses will be undertaken based on the mSS to examine the impact of fenfluramine exposure duration, daily weight-adjusted exposure, cumulative exposure, and identification of other potential risk factors associated with the possible development of:

- Valvulopathy
- VHD
- PAH
- Growth retardation

For each of the above outcomes or the combination of valvulopathy, VHD, and PAH if number of events is low, analyses will compare patients with the outcome to those without the outcome to help understand the risk factors that may influence the development of valvulopathy, VHD, PAH, and growth retardation in patients exposed to fenfluramine. Only variables collected in all patients participating in the European Union Fenfluramine Registry will be included in the model.

For categorical potential risk factors, differences between patients with and without the outcome of interest will be examined using Fisher's Exact tests or chi-squared tests. For continuous potential risk factors, differences between patients with and without the outcome of interest will be analysed using t-tests or analysis of variance (ANOVA) models. Continuous variables may also be categorised into clinically meaningful groupings and analysed as categorical variables to ease the results' interpretation. Appropriate controls will be applied for time-varying continuous variables.

For each outcome event, or the combination of valvulopathy, VHD, and PAH if number of events is low, (presence or absence of an event), univariate models for each exposure variable (exposure duration, daily weight-adjusted exposure, and cumulative exposure) and each baseline characteristic identified as potential predictors of the outcome will be constructed. For each model, an unadjusted odds ratio (OR) will be reported, along with the corresponding 95% confidence interval and p-value. Although formal correction for multiple testing is not planned, individual confidence intervals and p-values will not be displayed or reported without indication of the number of individual models tested.

Regression models (univariate and/or multivariate) will be employed only if the number of events permits. For regression analysis, to account for exposure varying over time, a generalised mixed model approach will be used. For variables that change over time, such as exposure, individual measurements at each data collection time point will be used. The logged observation time will be used as an offset variable, and the model will use the appropriate distribution (i.e., binomial or Poisson) and a logit link.

#### 9.7.5.2.1 Potential Risk Factors for development of valvulopathy, VHD, and PAH

If sample size allows the following potential risk factors may be included in analyses, as appropriate:

- Fenfluramine exposure duration
- Daily weight-adjusted fenfluramine exposure
- Cumulative fenfluramine exposure
- Age
- Sex
- Body mass index
- Family history of VHD, PAH, blood clotting disorders, or pulmonary embolism
- Exposure to antiepileptic drugs
- Concurrent medical conditions, including hypertension, mitral valve prolapse, history of rheumatic heart disease, bicuspid aortic valve, Marfan syndrome, reversal of shunt (with ventricular septal defect, atrial septal defect, patent foramen ovale, or patent ductus arteriosus), mitral valve disease, aortic valve disease, sleep apnoea, sickle cell disease, and COPD

Some variables will not be included in regression models to identify potential risk factors; however, they will be summarised. These data will include the following:

- Characteristics of exposure to other drugs such as exposure to biological products, other prescription and non-prescription drugs, dietary supplements, and vaccines

#### 9.7.5.2.2 Potential Risk Factors for Growth Retardation

If sample size allows, the following potential risk factors for growth retardation may be included in analyses, as appropriate:

- Fenfluramine exposure duration
- Daily weight-adjusted fenfluramine exposure
- Cumulative fenfluramine exposure
- Family history of growth retardation
- Stiripentol exposure

As is described in Section **9.3.2.2**, some data will be collected only from patients with clinically diagnosed growth retardation. These variables will not be included in regression models to identify potential risk factors; however, they will be summarised descriptively for patients with diagnosed growth retardation. These data will include the following:

- Performance and results of growth functional exploration tests if ordered (e.g., IGF1, IGFBP-3, Growth Hormone, sexual hormones)

- Pharmacological treatment for growth retardation
- Any known causes other than fenfluramine that can affect growth (Section **9.3.2.2**)
- Characteristics of exposure to drugs other than antiepileptics

#### 9.7.5.3 Assessment of ECHO Performance and Results

An assessment of ECHO results over time will be performed for all patients serving as their control (intraindividual control). ECHO results assessed at baseline will serve as a benchmark for the successive ECHO results, and any changes will be described and reported.

In addition, the following variables will be estimated:

- Number and percentage of patients with ECHOs at the following timepoints: at baseline prior to fenfluramine treatment initiation and every 6 months for the first 2 years and annually thereafter. To evaluate the results, different windows will be considered around the timepoints above (e.g., ±2 months). Windows will be defined in the SAP.
- Number and percentage of patients with ECHOs performed according to SmPC (baseline, every six months for the first 2 years and annually thereafter) with the number of ECHOs expected to be performed during fenfluramine treatment for each patient as denominator.

### 9.7.6 Interim Safety Analysis

There will be two interim safety analyses at the following time points:

- After 5 years of data collection (i.e., at the planned end of enrolment)

The appropriate date for the second interim report will be determined after the first report has been assessed. Descriptive baseline and safety outcome analyses will be undertaken on the study population present in the registry for each interim analysis and full analyses including risk factors analysis according to the SAP on the overall study population for the final analysis report.

An ECHO monitoring report will be prepared in [redacted]. This report will focus on the analysis relevant to the ECHO monitoring. It will consist of the following:

- Disposition of the consented patients at the time of the data cut
- Schedule of visits relative to the study timepoint windows
- Echocardiograms by visit
- Number of Echocardiograms per patients: ECHOs performed within study timepoint windows; ECHOs performed between study timepoint windows; total number of ECHOs per patient

The analysis described above will be presented by user group (i.e. prevalent users or new users of Fintepla) and overall.

### 9.7.7 Analysis of AEs/ADRs

All AEs/ADRs and SAEs/SADRs will be recorded in the eCRF by the treating physician or by the site staff and listed with information on the patients' baseline characteristics. Additionally, SAEs/SADRs, SAEs/SADRs with outcome death, and SAEs/SADRs leading to withdrawal from the study will be presented in separate listings.

MedDRA coding version 24.0 or later will be used to classify and tabulate AEs/ADRs. Frequencies (absolute and percentages) across system organ class (SOC), for individual events within those classes and preferred term (PT), will be provided and calculated with 95% CIs. AEs/ADRs will be summarised using counts and percentages for the entire study population and subgroups of interest.

### 9.7.8 Subgroup Analyses

Subgroup analyses will be performed depending on the final sample size and data availability for the primary and secondary outcomes.

Three separate subgroup analyses will be performed: (1) prevalent fenfluramine users will be compared to incident users to document the potential effect of selection bias by 'depletion of susceptible' – an unwanted exclusion from a safety assessment of persons discontinuing treatments following early adverse reactions; (2) population characteristics of patients who completed the entire 5-year follow-up period will be compared to those with shorter observation periods (e.g., 1- and 3-year follow-up periods); and (3) those who are lost-to-follow-up will be compared to those who remained in the study to help identify potential sources of bias.

In addition, the registry data may be summarised and stratified by the following sub populations (if applicable):

- Patients from European countries vs non-European countries
- Patients treated for approved (e.g., DS) vs non-approved indications
- Patients with existing valvulopathy, VHD, and/or PAH prior to enrolment vs those without existing valvulopathy, VHD, and/or PAH prior to enrolment
- Patients with normal growth vs those with evidence of growth retardation
- Patients who are fenfluramine incident users vs prevalent fenfluramine users
- Patients completed the entire 5-year follow-up period vs patients with shorter observation periods
- Patients who are lost-to-follow-up vs those who remained in the registry

### 9.7.9 Sensitivity analyses

The primary objective of this study is to assess the long-term cardiac safety of fenfluramine as prescribed in routine clinical practice for fenfluramine approved indications.

The purpose of the sensitivity analysis is to assess the consistency of the primary analysis on the mSS, when all patients treated with fenfluramine are included in the analysis (i.e., including patients treated with fenfluramine outside of approved indications). The sensitivity analysis will be conducted on all primary and secondary outcomes.

In order to assess VHD and PAH incidence, this study will summarise the data collected for those with reported valvulopathy, VHD, and PAH using counts and percentages for SS (patients treated with fenfluramine for any indication; see Section **9.7.4.1**).

In addition, valvulopathy, VHD, and PAH incidence rates will be also calculated as person-years or person-days for an individual defined as the total number of days/years of fenfluramine exposure plus an additional 6 months (in line with fenfluramine patient leaflet) and will be calculated over the follow-up period as defined above (patient time at risk ending at the date of the outcome of interests, the final dose of fenfluramine plus 6 months, death, or data cut-off).

For each incidence rate, 95% CIs will be calculated using exact methods. The incidence rates observed in the registry, if greater than zero, will be benchmarked against the incidence rates observed in the external reference (see Section **10**).

| Outcome | Numerator | Denominator |
|---|---|---|
| Valvulopathy | Number of new valvulopathy cases during the time interval | Summed person-years of fenfluramine exposure plus 6 months during the time interval among patients without pre-existing valvulopathy (patient time at risk ending at the date of the first valvulopathy event, the final dose of fenfluramine plus 6 months, death, or data cut-off). |
| VHD | Number of new VHD cases during the time interval | Summed person-years of fenfluramine exposure plus 6 months during the time interval among patients without pre-existing VHD (patient time at risk ending at the date of the first VHD event, the final dose of fenfluramine plus 6 months, death, or data cut-off). |
| PAH | Number of new PAH cases during the time interval | Summed person-years of fenfluramine exposure plus 6 months during the time interval among patients without pre-existing PAH (patient time at risk ending at the date of the first PAH event, the final dose of fenfluramine plus 6 months, death, or data cut-off). |

### 9.7.10 Handling of Missing Data

There will be no imputation for missing data in this study; however, the count and percentages of patients with missing values will be reported for both continuous and categorical variables. Further details on the handling of missing data, e.g., partially missing dates, will be described in the SAP.

### 9.7.11 Statistical Software

The analyses will be performed using SAS® statistical software, Version 9.4 or higher. Further details will be provided in the SAP.

## 9.8 Quality Control

The procedures to ensure data quality and integrity, including the accuracy and legibility of the data collected and original documents, extent of source data verification and validation of endpoints, storage of records, and archiving of the statistical programming performed to generate the results will be extensively described in the Data Management Plan and the SAP. Both documents will be stand-alone documents.

Systems with procedures will be implemented to ensure the quality of every aspect of the study.

The development of the protocol and SAP will follow internal standard operating procedures (SOP) of the CRO, which include detailed rounds of review. Quality control of the statistical programming will also follow the CRO's SOPs.

The EDC system meets approved, established standards for the security of health information, is validated, and is 21 CFR Part 11 compliant. To ensure that patient data (as well as other confidential data) remain secure and intact, the CRO will follow SOPs and quality control processes that address patient data security. The EDC system has built-in edit checks and validations and supports electronically generated and manual queries.

Patient confidentiality will be strictly maintained. Access to the EDC system will be regulated via a hierarchical username and password control. Subject data will be pseudonymized through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, or centre-assigned patient identifiers. Only trained site staff will enter data into the eCRFs. Patients' ages in whole years, but not date of birth, will be entered. No patient identifiers used by sites will be entered; rather, the EDC programme will automatically assign a study ID to each patient. The de-identified data as entered into the EDC system will be visible to the CRO and the sponsor, but only centre staff will be able to trace a study ID number back to a patient identity, a necessary measure to allow centre staff to respond to data queries raised by the CRO later.

## 9.9 Limitations of the Research Methods

This study aims to evaluate the long-term utilisation and safety of fenfluramine in patients treated for DS, LGS, or other potential future approved indications according to the product labelling in a real-world setting. This study's limitations are inherent to non-interventional study design and rare disease study; potential limitations and proposed strategies to address them include the following:

### 9.9.1 Sample Size

The main limitation of this study is the size of the population expected to be exposed to fenfluramine in Europe, along with the rarity of the cardiovascular outcomes of interests. As aforementioned, DS is a rare syndrome with an estimated prevalence ranging from 1 in 20,000 to 1 in 40,000 in the general population. Although there is currently no cure for DS, a multitude of treatments and diets aiming to reduce seizures are available; therefore, only a limited number of patients may be prescribed fenfluramine. Furthermore, VHD and PAH are rare in the general population; hence, the number of patients exposed to fenfluramine and develop VHD, or PAH is anticipated to be very low. Though these adverse events have been previously reported in adult patients exposed to significantly higher doses of fenfluramine when formerly approved for weight loss; as of today, to the best of our knowledge, there have been no reports of VHD or PAH in patients exposed to fenfluramine for the treatment of DS in clinical studies. Of note, PAH was previously considered an important potential risk for fenfluramine, but the totality of the available evidence including post-marketing surveillance has led to PAH becoming an important identified risk. The benefit-risk profile of fenfluramine for the adjunctive treatment of seizures associated with DS or LGS remained favourable.

To achieve a sample size large enough and provide clinically meaningful data, the target sample size was calculated using both practical and statistical considerations. Although, several factors may impact patient recruitment, notably fenfluramine market launch and uptake in the different European countries and other non-European countries, continuous monitoring of patient recruitment at the site and country levels will allow the rapid deployment of mitigation strategies in response to any challenges. Such plans will be discussed by the MAH and the PRAC. They may include the initiation of additional sites within participating countries and/or expanding the study into other countries. Pre-established collaborations with an existing registry and network (i.e., [redacted]) will facilitate the recruitment of patients and help achieve the target sample size.

### 9.9.2 External Comparator

The registry only includes exposed patients. A limitation of the research method might be the use of an external comparator to evaluate the background risks of valvulopathy, VHD, and PAH in the general population (denominator). However, ECHOs are typically performed for diagnosing or monitoring certain heart conditions. Patients with an ECHO test are generally either healthy (athletes) or may have a heart condition, and therefore may not be representative of the general population. As ECHOs are not routinely performed in the general population, mitigations strategies are limited. Nonetheless, to minimise selection bias and maximise the full population of patients aged up to 40 years old in each country, the

external comparator population will be extracted from various databases, and the incidence rate observed in the registry will be benchmarked against the incidence rates observed in the external reference only if greater than zero.

### 9.9.3 Observational Study Design Limitations

Due to the observational nature of this study and the inherent characteristics of such design, this study may be subject to bias including selection bias, observation bias, variability in local treatment practices, guidelines, and data quality across sites.

Selection bias due to non-consent will be mitigated by providing clear information to patients and legal representative(s) on the importance of the registry and the absence of burden for them. The extent of the selection bias will be monitored via the maintenance of an enrolment log at the site, which will anonymously list all eligible patients, consenting status and characteristics, and inform the implementation of mitigation strategies. Additionally, selection bias due to depletion of susceptible will be investigated in a separate subgroup analysis of prevalent fenfluramine users. The risk analysis will take into consideration both the duration of use and the current use.

Observation of ECHO monitoring may be biased as having the objective itself clearly stated in the registry protocol may influence the physicians' behaviour and prompt them to pay attention that patients have regular ECHO monitoring as stated in Fintepla SmPC and educational material.

Similarly, as described in the Hawthorne effect, the observation of fenfluramine prescriptions in epilepsies other than approved indications might be challenging due to the prospective nature of this study and the knowledge of the physicians of being observed.

Collaborations with existing registry and networks and patient recruitment across various European countries will ensure a diversity of prescribers and patients. The eCRF will be designed to minimise the level of missing data collected at baseline and each follow-up data collection timepoint. Additionally, standardised training and documentation for completing the eCRFs, particularly on the importance of accurately collecting exposure and outcome variables information will be provided to all participating sites.

### 9.9.4 Outcome Misclassification

As requested for pharmacovigilance purposes, the misclassification of the primary study outcomes and patients who are lost to follow-up are anticipated to be minimal in this study. However, to address this potential bias, ECHOs will be interpreted as a change as compared to their baseline or previous exam, and a descriptive comparison of the characteristics of the patients in the analysed population to those who are considered lost to follow-up will be performed. To mitigate outcome misclassification due to diagnostic suspicion bias (i.e., when prejudice or subjective judgment affect a diagnosis) an external independent validation committee will review in a blinded manner all ECHOs (images only) that show evidence of VHD/PAH, and a percentage of normal ECHOs. Though it is not possible to completely remove the diagnostic suspicion bias, the results from the prospective registry study, with

consecutive recruitment of patients and with uniform assessment and measurement throughout the study, should not be unduly impacted by and minimise the risk for diagnostic suspicion bias.

The impact that potential biases will have on the study results is currently unknown. Still, each potential source of bias will be evaluated descriptively, assessed by sensitivity analyses and discussed in the reports.

# 10 External Reference Research Methods for Primary Objective only

If at least one case of valvulopathy, VHD, or PAH is observed in the registry then background incidence rates of valvulopathy, VHD, or PAH will be assessed to provide a benchmark for interpretation of the registry results.

## 10.1 Study Design

This is a retrospective, observational cohort study that will identify incident cases of VHD and PAH in subjects <40 years. Two cohorts will be identified, one of which will reflect the general population (cohort 1) and the other will reflect the general population with the exclusion of subjects with pre-existing congenital VHD or PAH (cohort 2). This study design has been selected to estimate baseline risk of VHD and PAH in the general population using secondary data.

### 10.1.1 Study Population Selection Criteria

Patient selection is based on the inclusion and exclusion criteria listed below. Patients who meet each of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

#### 10.1.1.1 Inclusion Criteria

- Ages <40 years during each year of the study period

#### 10.1.1.2 Exclusion Criteria

##### 10.1.1.2.1 Cohort 1

1. <12 months of available data in the medical record prior to fulfilling the inclusion criteria

##### 10.1.1.2.2 Cohort 2

1. <12 months of available data in the medical record prior to fulfilling the inclusion criteria
2. Evidence of congenital cardiac malformation (ICD-10 codes: Q20-24)

### 10.1.2 Study Periods

#### 10.1.2.1 Study Period

The study period will be data from Start date of the Registry to End date of the Registry (see Section **6**).

#### 10.1.2.2 Index Date

The index date will be the date an individual meets all of the inclusion criteria and none of the exclusion criteria.

#### 10.1.2.3 Baseline Period

The baseline period will run from an individual's first available medical record until the index date (included). A minimum baseline period of 12 months prior to index date is required by the inclusion criteria.

#### 10.1.2.4 Follow-up Period

The follow-up period will run until the end of the study period (i.e., last patient last visit), death, or the date the individual transfers out of the practice or the country or disenrolls from the database (country-specific), whichever occurs first. Incident cases of valvulopathy, VHD, or PAH will be identified during the follow-up period.

## 10.2 Variables

### 10.2.1 Primary Outcome

The primary outcome of this study is incident (new onset) of valvulopathy, VHD, or PAH. Incident cases of valvulopathy, VHD, or PAH will be identified through a diagnosis code indicative of valvulopathy (ICD-10 codes: I34.x, I35.x, I36.x, I37.x, I38, I39), VHD (ICD-10 codes: I34.x, I35.x), or PAH (ICD-10 codes: I27.0, I27.2) during the follow-up period. For sensitivity, restricted definitions utilising ICD-10 codes for valvulopathy and VHD will be provided in the SAP.

### 10.2.2 Demographic Characteristics

- Age at index date
  - Age in years
  - Age bands (<2, 2-4, 5-9, 10-14, 15-19, 20-29, 30-39)
- Sex
  - Male
  - Female

- Sleep apnoea (G47.3), sickle cell disease (D57.x) and chronic obstructive pulmonary disease (COPD) (J41-J44), hypertension (I10-I15), history of rheumatic heart disease (I05.x, I06.x, I07.x, I08.x, I09.1, I09.8), Marfan syndrome (Q87.4), ventricular or atrial septal defect including patent foramen ovale (Q21.x) and patent ductus arteriosus (Q25.0)

### 10.3 Data Sources

The proposed data source for each county based on a feasibility assessment at the time of preparing the protocol is listed in **Table 4** below along with a summary of key variables. At this time, there is sufficient relevant data in each of the proposed sources to conduct this study. However, should there be any changes to any of the proposed sources or any new data sources become available before the database study is initiated (i.e., when the registry study ends), the data source for a specific country may be reconsidered.

## Table 4. Availability of Key Variables in the Proposed Data Sources

| | UK [redacted] | [redacted] | [redacted] (Germany) | [redacted] (Spain) | [redacted] (France) | [redacted] (Italy) |
|---|---|---|---|---|---|---|
| **Size** | 13 Million in [redacted] and 3 Million in [redacted] | Nationwide 10.2 Million | 25 Million (2004-2017) In 2017: 17 million | 2.9 Million patients | Nationwide (66 Million) [redacted] (hospital) 12.8 Million annually | 5.5 Million |
| **Age** | Yes | Yes | Yes | Yes | Yes | Yes |
| **Sex** | Yes | Yes | Yes | Yes | Yes | Yes |
| **Valvulopathy, VHD, & PAH diagnoses** | Yes | Yes | Yes | Yes | Yes | Yes |
| **Comorbidities e.g.,** congenital cardiac malformation | Yes | Yes | Yes | Yes | Yes | Yes |
| **Setting of care (primary or secondary, inpatient or outpatient)** | Primary care only, with referral to specialist or hospital information. Hospital data can be obtained through linkage to [redacted] | Diagnosis: secondary care (inpatient and outpatient care) Prescription: primary and secondary care | Primary, secondary care and inpatient care. Outpatient prescription data. | Primary care /general practitioners, specialists, outpatients, paediatrician, intensive care medicine, neurologists, internal medicine. | Diagnosis: hospital only Prescription: primary and secondary care | Diagnosis: secondary care and inpatient care. Outpatient prescription data. |
| **Lag times for data availability** | [redacted] linkage: ~1 year | ~1 year | ~2 year | ~2 months | ~1 year | ~9-12 months |

Abbreviations: A&E = accident and emergency; [redacted] GP = general practitioner; [redacted] PAH = pulmonary arterial hypertension; [redacted] UK = United Kingdom; VHD = valvular heart disease

### 10.3.1 UK: [redacted]

The [redacted] is the National Health Service's (NHS) observational and interventional research service in the UK and is jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Products Regulatory Agency (MHRA). The [redacted] is composed of anonymised longitudinal medical records from primary care providers in the UK since 1987. It includes more than 20 million patient lives, with more than 5 million currently registered and active patients. The patient population captured in the database is broadly representative of the demographic breakdown of the UK population. Diagnosis information is recorded in Read-OXMIS format. The [redacted] offers a linkage with the [redacted] data set, which allows the same patient to be tracked in secondary care, where both inpatient and outpatient diagnoses are captured.

### 10.3.2 Sweden: [redacted]

The [redacted] covers all inpatient and outpatient care encounters in Sweden from public and private service providers. The medical data include main diagnoses, up to 21 secondary diagnoses, and up to 30 surgical procedures. Diagnoses are coded using ICD-10 and surgical procedures with the Nordic Classification of Surgical/Medical Procedures (NCSP/NCMP). Cost information is not included in the registry, however, DRG codes are. Data collection was initiated in 1964, however, complete coverage was achieved in 1987 for inpatient care and 2001 in outpatient care. At present, the NPR is updated once a year, however, statistics are made available on a monthly basis. The registry does not cover primary care.

### 10.3.3 Spain: [redacted]

[redacted] The Health Improvement Network, is a large European database of anonymized Electronic Health Records. These anonymized data are transmitted by a network of voluntary physicians. [redacted] database consists of datasets obtained from 7 European countries (France, United Kingdom, Spain, Italy, Germany, Belgium, and Romania). The database gets updated in near real-time and data can be delivered monthly. Data are fully anonymized and General Data Protection Regulation (GDPR)-compliant. The dataset in Spain captures data from 2.9 million patients collected from approximately 300 medical centers, 2000 general practitioners, and 2400 specialty physicians. Information available in the Spanish dataset includes patients visits, all information on diagnosis recorded during visits, information on treatment delivered in pharmacy or prescribed during visits, demographic information such as age and gender, information on allergies to molecules, lab test results, medical history of patients, first date of diagnosed and some measurable and personal information (e.g., weight, BP, marital status).

### 10.3.4 France: [redacted]

The [redacted] includes the [redacted] which is the [redacted] database, and the [redacted] which is the national hospitalisation database (based on diagnoses-related groups). It includes information from the three main social insurance systems in France and covers 98.8% of the French population [34]. The [redacted] includes information on all healthcare expenses, including outpatient visits, dispensed medication, procedures, chronic conditions, as well as hospital admission diagnoses and procedures, and date of death, on an individual level. It includes diagnoses (ICD-10 codes) for chronic diseases and discharge diagnoses (ICD-10 codes) for hospitalisations.

### 10.3.5 Germany: [redacted]

[redacted] is based on claims data from statutory health insurance providers and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004. Per data year, there is information on approximately 17% of the general population from all geographical regions of Germany. In addition to demographic data, [redacted] contains information on drug dispensations, outpatient and inpatient services, and diagnoses starting from the year 2004. New data are added on an annual basis. Before data are entered into the [redacted] database, they are pseudonymised and validated through numerous plausibility checks. There is currently a lag of up to two years in data availability.

### 10.3.6 Italy: [redacted]

[redacted] Research and Health Foundation) is an administrative database, previously referred to as the [redacted] database, which includes data on demographic variables, reimbursed prescription drugs, inpatient and outpatient diagnoses and procedures (ICD-9 codes), and in hospital mortality (date of death). The [redacted] database covers approximately 5.5 million inhabitants (approximately 10% of entire Italian population) from several regions in Italy. The database is representative of the Italian population in terms of age, sex, and geographical distribution. The database is governed by the 'CORE' (Collaborative Outcome Research Evaluation) scientific committee, a structure for health research activities with public and private collaborators. The data collection began in 2012 for most individuals and the data lag is 9 to 12 months.

## 10.4 Study Size

The sample of patients identified for the current study will be all those patients in the respective databases who meet the inclusion and exclusion during the study period.

All planned analyses are descriptive in nature with no comparative analyses; therefore, power considerations are not necessary.

## 10.5 Data Management

Upon access to data, an experienced data analyst will ensure all relevant variables are available or created and the inclusion and exclusion criteria for cohort creation correctly applied.

Information on patients diagnosed with valvulopathy, VHD, or PAH will be described using the study variables listed in Section **10.2**, using pre-defined lists of codes as appropriate. Time at risk of developing valvulopathy, VHD; or PAH will be contributed by all patients meeting inclusion and exclusion criteria during the study period and at risk of developing valvulopathy, VHD, or PAH.

## 10.6 Data Analysis

Analyses will be conducted at the end of the study period (after last patient last visit) and will be described in detail in the SAP. The analysis population will comprise all patients who meet the inclusion criteria and none of the exclusion criteria.

Demographic characteristics will be summarised. Unless otherwise specified, summary descriptive statistics (n, mean, standard deviation, median, interquartile boundary values [p25, p75], minimum and maximum values) will be presented for continuous variables, and counts, and percentages will be presented for categorical variables. Results will be rounded to 1 decimal place; therefore, percentages may not always add up to 100%. The frequency and percentage of subjects with missing data for each data point will be presented.

The SAP will define censoring, provide a description of the methods to deal with missing data and procedures to control for potential confounders (e.g., stratification by age categories, gender), and minimise the influence of bias on the results.

### 10.6.1 Descriptive Statistics

The primary outcome events of interest are incident (new onset) valvulopathy, VHD, or PAH. VHD includes aortic valve regurgitation or mitral valve regurgitation, and they will be reported overall as well as separately.

Descriptive summary statistics will be used to characterise patients who experience or do not experience primary outcome events of interest. For continuous variables, n, mean, standard deviation, median, interquartile first and third quartiles (p25, p75), and minimum and maximum values will be presented; for categorical variables, counts and percentages will be reported.

#### 10.6.1.1 Incidence of Events of Interest

The incidence proportion of each event of interest will be calculated as the number of patients who receive the corresponding diagnosis (i.e., primary outcome events) during follow-up (numerator) divided by the total number of patients at risk of the primary outcome events during the study period (denominator). Only new primary outcome events will be included in

the numerator. All persons without records of the corresponding primary outcome event will be included in the denominator.

The incidence rate of each primary outcome event of interest will be calculated as the number of patients who receive the corresponding diagnosis (i.e., aortic valve regurgitation, mitral valve regurgitation, or PAH) during follow-up (numerator) divided by the total number of person-years at risk during the study period (denominator). Only new primary outcome events will be included in the numerator. Person-time from persons without records of the corresponding primary outcome event will be summed up as person-time at risk in the denominator. Time at risk (in years) for each person will be computed from index date until the end of the follow-up period or until the person experiences the new primary outcome event of interest. Time at risk over the study period to compute incidence rate for each primary outcome event will be the sum of time at risk across all persons (**Table 5**).

Additionally, 95% CIs of the incidence proportions and incidence rates will also be reported. Incidence proportions and incidence rates will be reported by calendar year or calendar period (e.g., two- or three-year periods) and by selected patient characteristics (e.g., by 5-year age groups and sex) that are of interest and include numerators greater than 5 patients with diagnosis of the event of interest.

For each calendar year, sum of person-years at risk will be calculated by (sum of time at risk for subjects without incident event of interest (calculated as 31 December [year] or date of leaving database – 1 January [year] for each subject)) + (sum of time at risk for patients with incident event of interest (calculated by date of diagnosis - 1 January [year] for each patient). One year is equivalent to 365 days.

Age-specific and sex-specific incidence proportions and incidence rates will be calculated by stratifying above analyses.

All incidence measures will be calculated separately for mitral regurgitation, aortic valve regurgitation, valvulopathy, VHD, and PAH. Combined measures for VHD and PAH will also be calculated.

**Table 5. Calculation of Primary Outcome Event (valvulopathy, VHD or PAH) Incidence Rates**

| Outcome | Numerator | Denominator |
|---|---|---|
| Aortic valve regurgitation | Number of individual patients with a new diagnosis of aortic valve regurgitation during the study period interval | Summed person-years at risk (person-years without any diagnosis of aortic valve regurgitation) during the study period interval across all persons in the study |
| Mitral valve regurgitation | Number of individual patients with a new diagnosis of mitral valve regurgitation during the study period interval | Summed person-years at risk (person-years without any diagnosis of mitral valve regurgitation) during the study period interval across all persons in the study |
| Valvulopathy | Number of individual patients with a new diagnosis of valvulopathy during the study period interval | Summed person-years at risk (person-years without any diagnosis valvulopathy) during the study period interval across all persons in the study |
| VHD | Number of individual patients with a new diagnosis of VHD during the study period interval | Summed person-years at risk (person-years without any diagnosis of VHD) during the study period interval across all persons in the study |

| Outcome | Numerator | Denominator |
|---|---|---|
| PAH | Number of individual patients with a new diagnosis of PAH during the study period interval | Summed person-years at risk (person-years without any diagnosis of PAH) during the study period interval across all persons in the study |

Abbreviations: PAH = pulmonary arterial hypertension; VHD = valvular heart disease

### 10.6.2 Handling of Missing Data

Missing values and data will not be imputed; however, the number and proportion of individuals with missing values will be reported for both categorical and continuous variables. Further details on the handling of missing data, e.g., partially missing dates, will be described in the SAP.

### 10.6.3 Statistical Software

The analyses will be performed using the statistical software SAS®, Version 9.4 or higher (SAS Institute, Cary, NC).

## 10.7 Quality Control

All source code and output will be reviewed by a second SAS programmer, and any inconsistencies or potential errors identified will be discussed and resolved and necessary changes subsequently made to the original programs. All programs will be saved, and the process will be documented.

For countries where external data holders will be carrying out the analyses, extensive quality checks of the results provided will be undertaken, and, if necessary, key analytical programs. Scientific guidance and input into the analyses being performed should be provided to these data holders.

## 10.8 Limitations of the Research Methods

This study is anticipated to have limitations, including but not restricted to those described below.

- As this study will utilise secondary data, information across the data sources for this study are collected for clinical and routine use rather than for research purposes. The identification of patients with valvulopathy, VHD, and PAH will rely on inferences based upon the information appearing on the claims or EMRs. Thus, there is the potential for coding inaccuracies leading to misclassification (e.g., under-reporting) of clinical characteristics.
- It is likely that not all patients in each of the data sources will have complete records, therefore we expect some missing data. Missing data will be described, and any limitations of missing data described in the study report. Furthermore, it is possible that some patients may have had a diagnosis of valvulopathy, VHD, or PAH prior to the study period that are impossible to capture should their full record not be in the respective data source.

- Patients who have not consulted for their symptoms to a physician or to a specialist or hospital reporting to the database, or those not effectively diagnosed for valvulopathy, VHD, or PAH, could not be identified in this study, and therefore incidence may be underestimated.
- Lastly, the characteristics of the study sample may be unique to the source population and may not be generalisable to other populations.

# 11 Protection of Human Subjects

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), and European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Good Pharmacovigilance Practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3).

Detailed patient characteristics of patient subgroups with 5 or less subjects will not be reported in accordance with privacy regulations applied by an increasing number of data source custodians.

## 11.1 Patient Information and Consent

For the registry study, each patient or his/her legally acceptable representative will be provided with information related to the study including specifics related to study participation. This will be documented in an informed consent form (ICF) that is compliant with local regulatory requirements and legal requirements. The ICF used in this study will be approved by the same EC responsible for approval of the protocol at each site. In addition, paediatric assent will be obtained as appropriate according to the patient's age and institutional requirements. The study information will also inform the patient or his/her legally acceptable representative that they have the right to withdraw from the study at any time. They will be informed that if they do withdraw, no further study data will be collected from the time of withdrawal and that their withdrawal will not affect the medical care that they receive. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Prior to any data collection under this protocol, a written informed consent (or assent as applicable) must be signed by the patient or the patient's legally acceptable representative, in accordance with local practice and regulations. A copy of the informed consent/assent form must be given to the patient or patient's legally acceptable representative (as applicable).

If a paediatric patient reaches the age of majority during the study, the patient, if competent to do so, will be required to provide his/her consent to remain in the study and allow for data collection from the date of majority onwards.

For the database component, informed consent is not required. No patient identifiable data will be used as all data will be de-identified, and where required patient-level data will remain at the data source for analyses.

## 11.2 Data Protection

All data collected in this study will be strictly confidential in accordance with applicable data privacy protection laws and regulations.

The eCRF in the EDC system will record subjects only by means of an anonymous, unique ID code assigned by the EDC system to safeguard patient confidentiality. No information such as initials, date of birth, or local case study ID number that could subsequently be used to identify patients will be entered into the EDC system. Only investigators, or site personnel delegated by him/her, will have the possibility of associating the de-identified assigned identification code to a specific subject. Site study staff will be instructed to maintain complete confidentiality of all collected data. The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. By signing the protocol, the institution and/or investigator commit to complying with all related applicable laws and regulations. Summary reports generated from the eCRF will not contain any participant identifying information.

## 11.3 Independent Ethics Committee or Institutional Review Board

With assistance from the CRO, each principal investigator will be responsible for obtaining the necessary approval of the study protocol, protocol amendments, and consent/assent (if needed), and other relevant documents, if applicable, from the central/local IRBs/IECs and for ensuring that the study complies with local legislation relating to data protection and privacy. When local approval is obtained, the documentation indicating the IRB/IEC (if applicable) committee's approval or favourable opinion and the names and qualifications of the committee members must be sent by the principal investigator to the CRO, who will send to the study sponsor before the recruitment process begins.

For each database, any specific protocol review and approval process will be followed (e.g., ISAC for the [redacted] in the UK).

## 11.4 Competent Authorities

The approved protocol will be submitted to regulatory authorities in accordance with the regulations of the countries and participating sites' local clinical research regulatory requirements when applicable.

# 12 Management and Reporting of Adverse Events/Adverse Drug Reactions

## 12.1 Definitions

### 12.1.1 Adverse Events and Events Associated with Special Situations

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

For this study, the medicinal product of interest is fenfluramine.

### 12.1.2 Assessment of Adverse Events

Seriousness and relatedness need to be independently assessed for each AE recorded on the eCRF.

### 12.1.3 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the patient was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (in the child of a patient who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalisation but, when based on appropriate medical judgment, may jeopardise the patient or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events associated with special situations include pregnancy or exposure to medicinal product through breastfeeding and AEs associated with medicinal product overdose, misuse, abuse, medication error, paternal exposure, lack of effect, occupational exposure, quality defect or falsified medicinal product, suspected transmission of an infectious agent via medicinal product. These events associated with special situations are to be captured as AEs but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

Follow-up of SAEs should be attempted up to resolution or, if resolution is unlikely, to stabilisation.

The following hospitalisations are not considered to be SAEs because there is no 'adverse event' (i.e., there is no untoward medical occurrence) associated with the hospitalisation:

- Hospitalisations for respite care
- Hospitalisation planned before informed consent (where the condition requiring the hospitalisation has not changed after study drug administration)
- Hospitalisation for administration of study drug or insertion of access for administration of study drug
- Hospitalisation for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

### 12.1.4 Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study patient known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event

#### 12.1.4.1 Classification of Relatedness

The relationship of each AE to the medicinal product will be recorded on the CRF in response to the following question: Is there a reasonable possibility that the medicinal product caused the AE?

- Yes (related): A causal relationship between the medicinal product and the AE is a reasonable possibility.
- No (not related): A causal relationship between the medicinal product and the AE is not a reasonable possibility.

## 12.2 Monitoring, Recording and Reporting of AEs

### 12.2.1 Monitoring of AEs

It is the investigator's responsibility to monitor AEs. Data on AEs will be obtained at regular site visits, based on the constant survey of the patient's health status by the investigator and on information spontaneously provided by the patient and/or through questioning of the patient.

The investigator should make every effort to obtain all information necessary for appropriate reporting of the event.

For each AE recorded in the AE section of the eCRF, the physician will assess seriousness and relatedness.

### 12.2.2 Recording of AEs

Complete and accurate data on all events experienced for the duration of the recording period will be reported on an ongoing basis.

It is important that each report includes a description of the event, whether it is considered serious (and if so, the criterion satisfied), its duration (onset and resolution dates), its relationship to fenfluramine, any other potential causal factors, any treatment given, or other action taken (including dose modification or discontinuation of fenfluramine) and its outcome.

Physicians should use correct medical terminology/concepts when recording AEs in the AE section of the eCRF. Colloquialisms and abbreviations should be avoided. Only one AE term should be recorded in the event field of the eCRF.

#### 12.2.2.1 Follow-up of AEs

New or updated information will be recorded in the CRF. In case of ongoing AEs and SAEs at end of treatment documentation, the events should be followed-up with reasonable effort until they have been resolved or, if resolution is unlikely, to stabilisation.

### 12.2.3 AE Reporting Period

Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the eCRF.

Once the patient is included in the study, AEs will be collected after enrolment until discontinuation of fenfluramine, except for valvulopathy, VHD, PAH, and growth retardation, which will be collected until the end of the observation period (six months after fenfluramine discontinuation).

### 12.2.4 AE Reporting Procedures

#### 12.2.4.1 Reporting of SAEs

All SAEs, regardless of their relationship to fenfluramine, must be reported on a completed SAE form by e-mail or fax as soon as possible, but no later than 24 hours from when the investigator becomes aware of the event.

Contact details:

| **Countries** | **e-mail** | **Fax number** |
|---|---|---|
| Austria | DS.at@ucb.com | +49 2173 48 2010 |
| France | pharmacovigilance-fr@ucb.com | +33 1 47 29 45 91 |
| Germany | DS.de@ucb.com | +49 2173 48 2010 |
| Italy | DS.it@ucb.com | NA |
| Spain | PVSPAIN@ucb.com | NA |
| United Kingdom | AEReporting@ucb.com | +44 1753 447858 |

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of relatedness.

Initial reports may be followed by detailed descriptions, which may include copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of relatedness, this should also be noted on the follow-up SAE form.

#### 12.2.4.2 Reporting of Related Non-serious AEs/ADRs

Details of all other AEs (i.e., non-serious) will be reported on the CRF and those that are assessed by the investigator as related to fenfluramine will be entered into the MAH's safety database using the data entered into the CRF. It is very important that all information entered into the CRF is as complete as possible at the time the investigator becomes aware of the event and that all relevant information pertaining to the related non-serious AE is entered into the CRF within 7 calendar days from investigator awareness. Follow-up information should also be recorded on the CRF, including any information that changes the investigator's assessment of relatedness.

#### 12.2.4.3 Reporting of Pregnancy

All pregnancies occurring from the date of informed consent signature until six months after the last fenfluramine administration must be recorded in the Pregnancy Report Form.

As soon as possible after becoming aware of the pregnancy, but not later than 24 hours, the investigator has to fill the first sections of the Pregnancy Report Form and send it by e-mail or fax to the contact details provided to the site.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same timeframe and format as other SAEs.

Investigators must actively follow-up and report the outcome of all pregnancies to the MAH. Timelines vary according to the nature of the pregnancy outcome.

#### 12.2.4.4 Reporting to Competent Authorities

Adverse drug reactions (ADRs) and SAEs for fenfluramine will be reported by the MAH to the competent authorities in compliance with local and regional law and established guidance by the MAH or a third party acting on behalf of the MAH. The format of these reports will be dictated by the local and regional requirements. For any adverse reactions occurring after study end, the standard procedures that are in place for spontaneous reporting should be followed.

For ADRs occurring under non-Zogenix products, the investigator should follow the standard procedures that are in place for spontaneous reporting and account for and comply with the local applicable laws and regulations.

### 12.2.5 Evaluation

Reports received on new important safety information will be processed and entered into the MAH's safety database and reviewed on a regular basis. If a potential safety signal is suspected, it will be investigated for further evaluation within the context of benefit risk.

### 12.3 Reporting of Product Complaints without Adverse Events

UCB product complaints without Adverse Events have to be reported by the physicians to UCBCares. A product complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity, Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness or Performance of a product after it has been released and distributed to the commercial market.

Non-UCB product complaints have to be reported as per local regulation.

# 13 Plans for Disseminating and Communicating Study Results

## 13.1 Overview

The sponsor will monitor the data collected while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned.

Any new information that may affect the benefit-risk balance of the medicinal product will be communicated immediately to relevant competent authorities in accordance with Good Pharmacovigilance Practice (GVP).

## 13.2 Study Report

All interim and final reports will be submitted to the regulatory authorities by the Sponsor based on country/region reporting requirements and pursuant to required timeframes. A summary of the final report will also be published on the Heads of Medicines Agencies (HMA)-EMA Catalogue of real-world data (RWD) studies, which replaces the European Union electronic Register of Post-Authorisation Studies (ENCePP - EU PAS Register).

## 13.3 Data Ownership

The data collected in this study are the property of the Sponsor.

Copying or spreading information related to this study without the Sponsor's agreement is prohibited.

## 13.4 Publications

The Sponsor shall have the right to publish such data and information without approval from the sites. The sponsor will establish a uniform procedure for analysing, publishing, and disseminating findings from this study. Co-authors of publications may include participating physicians, the sponsor's personnel, and/or other relevant thought leaders who contribute substantially to the publication.

Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Initiative checklist [67].

The Sponsor intends to prepare publications for peer-review based on this study. The European Medicines Agency will be informed in accordance with the guidelines. In order to allow competent authorities to review in advance the results and interpretations to be published, the MAHs should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

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# ANNEX I
# GERMAN-SPECIFIC ELIGIBILITY CRITERIA

Inclusion criteria specific for conduct of the study in Germany:

To be included in the study, the patients must fulfil the following criteria:

- Patients being treated with fenfluramine **according to one of the approved indications in the EU SmPC**
- Either new users of fenfluramine or current users (e.g., continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product)
- Patients treated at centres/by physicians prescribing fenfluramine in routine practice (expectedly neuro-paediatricians, paediatricians, or neurologists with experience in the treatment of epilepsy). **In Germany**, only patients prescribed fenfluramine according to the **EU** SmPC **can** be included, in accordance with local regulations.
- Provided informed consent or assent, as required by local regulations

Exclusion criteria specific for conduct of the study in Germany:

- Evidence of congenital cardiac malformation
- **Any contraindication listed in section 4.3 of the EU SmPC**

# ANNEX II
# LIST OF STANDALONE DOCUMENTS

- Statistical Analysis Plan
- Data Management Plan
- Declaration and signature page of treating physician
- Study materials specific to France only:
    - Vineland Adaptive Behavior Scale (VABS), Third Edition (Vineland™-3)
    - Pediatric Quality of Life Inventory (PedsQL) questionnaires

# ANNEX III
# ENCEPP CHECKLIST FOR STUDY PROTOCOLS

(Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[a] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[b] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 7;8 |
| 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) | ☒ | ☐ | ☐ | 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |
| 2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 9.2.2; 10.1.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | N/A |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | 8 |

Comments:

| |
|---|
| There is no hypothesis to be tested in this registry study; however, it may generate hypotheses for future studies in this target patient population. |

[a] 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.

[b] Date from which the analytical dataset is completely available.

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g., cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 9.1; 10.1 |
| 3.2 | Does the protocol specify whether the study is based on primary, secondary, or combined data collection? | ☒ | ☐ | ☐ | 9.1;9.4;10.1;10.3 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 8;9.3. 9.7;10.2; 10.6 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | 9.7;10.6.1 |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 12 |

Comments:

| |
|---|
| |

| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 9.2.1;10.1.1; 10.3; |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.1.2;10.1.2 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2.2;10.1.1 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.1.1;10.1;10.3 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.2.2;10.1.1 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.1.2;10.1.2 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.2;10.1.1 |

Comments:

| |
|---|
| |

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.1 | Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3;9.7 |

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.2 | Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3;9.7 |
| 5.3 | Is exposure categorised according to time windows? | ☐ | ☐ | ☒ | N/A |
| 5.4 | Is intensity of exposure addressed? (e.g., dose, duration) | ☒ | ☐ | ☐ | 9.3; 9.7 |
| 5.5 | Is exposure categorised based on biological mechanism of action and considering the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | N/A |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 10 |

Comments:

| |
|---|
| If at least one case of valvulopathy, VHD, or PAH is observed in the registry then background incidence rates of valvulopathy, VHD, or PAH will be assessed to provide a benchmark for interpretation of the registry results. |

| **Section 6: Outcome definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 6.1 | Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 9.3.1;9.3.2;9.3.3 10.2 |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.1;9.3.2;9.3.3 9.7.4;9.7.5;9.7.6 10.2;10.6 |
| 6.3 | Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.1;9.7.4.1 |
| 6.4 | Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☐ | ☒ | N/A |

Comments:

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| **Section 7: Bias** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 7.1 | Does the protocol address ways to measure confounding? (e.g., confounding by indication) | ☐ | ☐ | ☒ | N/A |
| 7.2 | Does the protocol address selection bias? (e.g., healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.7.1; 9.7.9 |
| 7.3 | Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.3.1.1 |

Comments:

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| **Section 8: Effect measure modification** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 8.1 | Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.7.5.2; 9.7.9 |

Comments:

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| **Section 9: Data sources** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 9.1 | Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| | 9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3;9.4 |
| | 9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3.1;9.3.2;9.2.3 9.4;10.2;10.3 |
| | 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.3.4;9.4; 10.2;10.3 |
| 9.2 | Does the protocol describe the information available from the data source(s) on: | | | | |
| | 9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3 |
| | 9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3.1;9.3.2;9.3.3 10.2;10.3 |
| | 9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3.4;10.2 |
| 9.3 | Is a coding system described for: | | | | |
| | 9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | N/A |
| | 9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.7.8;10.2 |
| | 9.3.3 Covariates and other characteristics? | ☐ | ☐ | ☒ | N/A |
| 9.4 | Is a linkage method between data sources described? (e.g., based on a unique identifier or other) | ☒ | ☐ | ☐ | 10.3 |

Comments:

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| **Section 10: Analysis plan** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 10.1 | Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 9.7;10.6 |
| 10.2 | Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5; 10.4 |
| 10.3 | Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7.3;10.6 |
| 10.4 | Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7.9;10.6 |
| 10.5 | Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | N/A |
| 10.6 | Does the plan describe methods for analytic control of outcome misclassification? | ☒ | ☐ | ☐ | 9.7.4 |
| 10.7 | Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7.10;10.6.2 |
| 10.8 | Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | N/A |

Comments:

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| **Section 11: Data management and quality control** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 11.1 | Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6.3;10.5 |
| 11.2 | Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8;10.7 |
| 11.3 | Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 3 |

Comments:

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| **Section 12: Limitations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 12.1 | Does the protocol discuss the impact on the study results of: | | | | |
| | 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.9;10.8 |
| | 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9;10.8 |
| | 12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☐ | ☐ | ☒ | N/A |
| 12.2 | Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☒ | ☐ | ☐ | 9.1.1;9.2.1; 9.5 |

Comments:

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| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 11 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | N/A |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 11 |

Comments:

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| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

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| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g., to regulatory authorities)? | ☒ | ☐ | ☐ | 13 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 13 |

Comments:

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# ANNEX IV
# POST-AUTHORISATION SAFETY/EFFICACY STUDY PROTOCOL AUTHENTICATION AND AUTHORISATION

| | |
|---|---|
| Study title: | A Registry of Patients Treated with Fintepla |
| Study No.: | ZX008-2101 (EP0218) |
| Protocol edition No.: | 6.0 |
| Date of protocol edition: | 04 June 2025 |

This document has been signed electronically. The signatories are listed below.

Clinical Program Director / Study lead

Medical Affairs lead

Real World Evidence (RWE) lead

Qualified person for pharmacovigilance (QPPV):

[redacted]

# Approval Signatures

**Name:** EP0218-protocol-V6.0

**Version:** 5.0

**Document Number:** CLIN-000264790

**Title:** EP0218-protocol-V6.0

**Approved Date:** 05 Jun 2025



| Document Approvals | |
|---|---|
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 04-Jun-2025 15:20:51 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: EEA QPPV<br>Date of Signature: 05-Jun-2025 06:50:25 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Subject Matter Expert<br>Date of Signature: 05-Jun-2025 09:35:43 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Medical<br>Date of Signature: 05-Jun-2025 12:03:17 GMT+0000 |