FINAL STUDY REPORT/EP0220

Title:	A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome and Lennox-Gastaut Syndrome
European Post-Authorization Study (PAS) register number	EUPAS48741
Investigational product:	FINTEPLA® (fenfluramine)
Indication:	Dravet Syndrome and Lennox-Gastaut Syndrome
Development phase:	Phase 4
Brief description:	Cross-sectional, multicountry, noninterventional survey conducted through an anonymous web questionnaire among physicians who prescribe fenfluramine in European countries.
Sponsor:	UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium
Study initiation date:	30 Aug 2022
Study completion date:	05 Dec 2024
Report date:	02 Apr 2025
GCP compliance statement:	This study was conducted in compliance with Good Clinical Practice (GCP), including archiving of essential study documents.

Confidentiality Statement

PRINCIPAL INVESTIGATOR SIGNATURE

Not Applicable.

NON-INTERVENTIONAL

POST-AUTHORIZATION SAFETY STUDY (PASS)

FINAL STUDY REPORT

PASS INFORMATION

Title	A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome and Lennox-Gastaut Syndrome
Date of last version of the final study report	02 Apr 2025
European Post-Authorization Study (PAS) register number	EUPAS48741
Active substance	Fenfluramine (anatomical therapeutic chemical code: N03AX26)
Medicinal product	FINTEPLA® (fenfluramine) oral solution
Product reference	EU marketing authorization number: EU/1/20/1491/001 EU/1/20/1491/002 EU/1/20/1491/003 EU/1/20/1491/004
Procedure number	EU procedure number: EMEA/H/C/003933
Marketing authorization holder	UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium
Joint PASS	No
Research question and objectives	<u>Primary objectives:</u> • Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow up • Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational material on echocardiogram follow up <u>Secondary objectives:</u> • Assess the physician-reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine • Assess the awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management
Countries of study	Austria, France, Germany, Italy, Spain, and United Kingdom

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder	UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium
MAH contact person	PPD

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1 ABSTRACT

Title

A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome and Lennox-Gastaut Syndrome

Keywords

Fenfluramine, FINTEPLA®, noninterventional study, Post-Authorization Safety Study (PASS), effectiveness of educational materials

Rationale and background

Fenfluramine (FINTEPLA®, UCB Pharma SA, Bruxelles, Belgium) oral solution is a prescription treatment for seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other antiepileptic medicines in patients 2 years of age and older. Patients on fenfluramine are to be monitored via regular echocardiograms to detect any early signs of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH). As an additional risk minimization measure, educational materials are communicated to fenfluramine prescribers and to patients/caregivers. In addition, off-label use for weight management is considered as missing information in the risk management plan and is also addressed in the physician educational material. This is in addition to the implementation of the Controlled Access Program (CAP) to prevent off-label use of fenfluramine for weight management.

This observational study assesses the effectiveness of these additional risk minimization measures.

Research question and objectives

The EP0220 study aimed to assess the effectiveness of the fenfluramine educational materials in terms of the key process indicators, which refer to awareness, knowledge, and self-reported compliance with respect to the safety messages conveyed in these materials.

Primary objectives:

- Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow up
- Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational material on echocardiogram follow up

Secondary objectives:

- Assess the physician-reported distribution of educational materials to patients/carers by physicians routinely prescribing fenfluramine
- Assess the awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management

Study design

This study consisted of a noninterventional, cross-sectional survey among physicians prescribing fenfluramine in routine practice in selected European countries. The survey was a structured

questionnaire containing close-ended questions. It was conducted online using a secure electronic data collection platform.

Setting

This study was sponsored by Zogenix International Limited, a wholly owned subsidiary of UCB Biosciences, Inc., and outsourced/conducted by United BioSource LLC®.

The data are reported in 2 waves; wave 1 included data from Germany which are presented in the interim Study Report dated 27 Apr 2023, and wave 2 included data from all the participating countries (including Germany) which are presented in this final study report.

Participant and study size, including dropouts

For this final analysis, 705 Invitation Letters to complete the survey were distributed to physicians and 157 (23.1%) physicians accessed the survey using a unique code (All Respondents Set). Of those, 119 (75.8%) physicians were eligible to participate in the study while 38 (24.2%) physicians were not eligible. Of the 119 eligible physicians, 118 (99.2%) physicians completed the survey and were included in the Completed Survey Set.

Variables and data sources

Variables related to the physicians' characteristics included questions related to physician demographics, practice information, and fenfluramine prescribing patterns. Variables associated with the primary objectives included questions related to awareness, knowledge, and self-reported compliance domains. Variables associated with the secondary objectives included questions related to knowledge and self-reported compliance domains.

Physician responses to the survey were analyzed to calculate the percentage of correct responses to individual questions and average percentages for questions related to each of the primary and secondary objectives. The success criteria for the effectiveness of the additional risk minimization measures were defined as ≥80% of physicians providing correct answers to all survey questions related to the primary objectives' variables.

Results

Participants

Overall, survey data from 118 physicians were included in the analysis. The majority of the physicians (82/118 [69.5%]) were pediatric neurologists and worked in a university hospital (84/118 [71.2%]).

The physicians had prescribed fenfluramine most commonly to patients aged 2 to 11 years (79/118 [66.9%]). The majority of the physicians (85/118 [72.0%]) had prescribed fenfluramine for the first time ≥6 months before completing the survey and a total of 52/118 (44.1%) physicians for the last time <3 months before completing the survey.

Primary objectives

In the final analysis, the percentage of physicians providing correct responses to all 9 questions supporting the primary objectives was 20.3% (24/118; 95% CI: 13.5 to 28.7). The mean percentage of correct responses to any questions supporting the primary objectives per survey participant was 84.7% (95% CI: 82.5 to 86.8).

Awareness variable domain: 85.6% of physicians (101/118) confirmed to have received and 84.7% of physicians (100/118) read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine, and 82.2% of physicians (97/118) correctly identified the type of available Fintepla educational materials for fenfluramine.

Knowledge variable domain: 95.8% of physicians (113/118) correctly indicated the potential risks associated with higher than approved doses of fenfluramine. However, the proportions of physicians who correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11) was 50.0% (59/118; 56.8% [21/37] in Austria/Germany and 46.9% [38/81] in countries other than Austria/Germany). The data were reported separately for Austria/Germany and rest of the countries as the correct answer to Question 11 was updated in Protocol Amendment 1 post data collection in Austria/Germany.

A total of 77.1% (91/118) physicians correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine.

Self-reported compliance variable domain: 93.2% of physicians (110/118) identified echocardiogram as the correct regular monitoring that should be performed during treatment with fenfluramine. Also, 94.1% of physicians (111/118) correctly identified the need for appropriate monitoring and follow up if an echocardiogram indicates pathological valvular changes or suspicion of PAH and 99.2% of physicians (117/118) understood the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine.

Secondary objectives

In the final analysis, the mean percentage of correct responses to any questions supporting the secondary objectives per survey participant was 64.2% (95% CI: 59.3 to 69.1), whereas the percentage of physicians who provided correct responses to all 4 questions supporting the secondary objectives was 22.9% (27/118; 95% CI: 15.7 to 31.5).

Knowledge variable domain: 95.8% of physicians (113/118) confirmed that they would not prescribe fenfluramine for weight management and 50.0% of physicians (59/118) correctly identified the content related to weight management included in the educational materials.

Self-reported compliance variable domain: 50.8% of physicians (60/118) reported that they had provided the dedicated educational materials and the latest version of the package leaflet to patients/caregivers who may initiate fenfluramine, and 60.2% of physicians (71/118) were aware that they should have informed patients/caregivers about the negative benefit-risk of fenfluramine off-label use for weight management.

Discussion

Although the Protocol-defined success criterion for effectiveness of the additional risk minimization measures was not met in the final analysis, the data confirm that the physicians had access to and read the educational materials and the implementation of the CAP was successful. Reasons for not reaching the Protocol-defined success criterion could be a potential lack of knowledge regarding the long-term Fintepla patient registry (likely because it had not been launched in Spain and Italy at the time of the survey). Additionally, prescribers selecting a higher than recommended frequency for echocardiogram monitoring during fenfluramine treatment could have also contributed to missing this target. However, these results show that the

educational materials were successful at raising awareness about the requirement for regular echocardiogram monitoring and that the minimum frequency is likely to be met.

Based on this final analysis, the physicians were well aware of the risks of VHD and PAH as a high level of compliance with echocardiogram monitoring after initiating fenfluramine treatment was reported. Physicians also understand their role to inform patients/caregivers about these risks. However, the educational materials seem partially successful in educating physicians about echocardiograms to exclude any pre-existing VHD/PAH prior to and during fenfluramine treatment. The ongoing distribution of the updated educational material is an opportunity to re-emphasize the risk minimization measures, the role of physicians, and the importance of these activities. The benefit-risk balance for the use of Fintepla in patients with Dravet syndrome and Lennox-Gastaut Syndrome remains unchanged. UCB will continue to implement new measures to achieve its goal of educating both prescribers and patients/caregivers on identified VHD/PAH risks.

Marketing Authorization Holder(s)

UCB Pharma S.A.,

Allée de la Recherche 60,

B-1070 Bruxelles,

Belgium

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT	5-hydroxytryptamine
CAP	Controlled Access Program
DLP	Data lock point
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
GVP	Good Pharmacovigilance Practice
MAH	Marketing Authorization Holder
PAH	Pulmonary arterial hypertension
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SSAR	Safety signal assessment report
VHD	Valvular heart disease

3 INVESTIGATORS

Not applicable because of the nature of the study (online survey).

4 OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Title/Role in Study
UCB Biosciences, Inc. 4000 Paramount Parkway, Suite PPD Morrisville, NC 27560 USA	Sponsor
PPD, Medical Affairs Lead UCB Pharma S.A. (France) Immeuble Défense Ouest 420, rue d'Estienne d'Orves F – 92700 Colombes	Medical Affairs
PPD, Regulatory Science Lead UCB Pharma S.A. (France) Immeuble Défense Ouest 420, rue d'Estienne d'Orves F – 92700 Colombes	MAH Contact Person
PPD, Benefit Risk Lead UCB Pharma Ltd., 208 Bath Road, Slough, SL1 3WE UK	Patient Benefit Risk and Medical Safety
PPD, Real World Evidence Lead UCB Pharma Ltd., 208 Bath Road, Slough, SL1 3WE UK	Real World Evidence Lead
PPD, Development Physician UCB Biosciences, Inc. 4000 Paramount Parkway, Suite PPD Morrisville, NC 27560 USA	Development Physician
PPD UCB Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium	PPD

QPPV=Qualified Person Responsible for Pharmacovigilance

5 MILESTONES

Important study milestones are described below.

Milestones	Planned dates	Actual dates	Comments
Protocol approval by IEC/IRB PRAC	Q3 2022	27 Jul 2022	–
Registration in the EU PAS register	Q3 2022	31 Aug 2022	–
Earliest market entry (Germany)	Q1 2021	Feb 2021	–
Start of data collection	Q3 2022	30 Aug 2022	–
Interim report of study results	Estimated Q3 2023	27 Apr 2023	End of data collection for interim analysis: 22 Dec 2022
End of data collection	Estimated Q1 2025	05 Dec 2024	For whole study

IEC=Institutional Ethics Committee; IRB=Institutional Review Board; PAS=Post-Authorization Study; PRAC=Pharmacovigilance Risk Assessment Committee; Q=quarter

6 RATIONALE AND BACKGROUND

Fenfluramine (FINTEPLA®, UCB Pharma SA, Bruxelles, Belgium) is indicated for the treatment of seizures associated with Dravet syndrome (US, EU, UK, and Japan) and Lennox-Gastaut syndrome (US, EU, UK, and Japan) as an add-on therapy to other antiepileptic medicines in patients 2 years of age and older (EMA, Fintepla SmPC, 2024).

Fenfluramine is a serotonin-releasing agent, and thereby stimulates multiple 5-HT receptor subtypes through the release of serotonin (EMA, Fintepla SmPC, 2024). It may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. The precise mode of action of fenfluramine in Dravet syndrome is not known.

Fenfluramine was approved in Europe in the 1960s as an appetite suppressant for the treatment of obesity in adults but was withdrawn from the market in the late 1990s due to its association with cardiac valve abnormalities (Wong et al, 1998; Connolly et al, 1997) and the development of PAH (Pouwels et al, 1990; McMurray et al, 1986; Douglas et al, 1982). Fenfluramine has now been developed and approved in the US (Jun 2020), EU (Dec 2020), UK (Aug 2021), and in Japan (Sep 2022) with a specific dosing scheme for the treatment of seizures associated with Dravet syndrome in children aged 2 to 17 years and adults. The program was additionally successful in supporting a supplemental New Drug Application in the US (approved by the Food and Drug Administration in Mar 2022), a Marketing Authorisation Application in the EU and UK (approved by the EMA in Jan 2023 and by the Medicines and Healthcare products Regulatory Agency in Jul 2023), and a Partial Change Application in Japan (approved by the Pharmaceuticals and Medical Devices Agency in Mar 2024) in patients 2 years of age and older with Lennox Gastaut syndrome. A Phase 3 clinical study evaluating fenfluramine in CDKL5 Deficiency Disorder has been initiated. Since 2022, Fintepla has been approved in various countries other than US, EU, UK, and Japan.

Patients on fenfluramine treatment are to be monitored via regular echocardiograms per the SmPC to detect any early signs of VHD or PAH. As an additional risk minimization measure, educational materials are communicated to fenfluramine prescribers and to patients/caregivers. In addition, off-label use for weight management is considered as missing information in the risk management plan and is also addressed in the physician educational material. This is in addition to the implementation of the CAP to prevent off-label use of fenfluramine for weight management.

This observational study assesses the effect of these additional risk minimization measures by describing the awareness, knowledge, and compliance of fenfluramine prescribers to the physician-specific educational material (Protocol Annex III), as well as the distribution of the patient/caregiver educational material (Protocol Annex IV) by the physicians.

In this study, data were collected 12 to 18 months after the implementation of educational materials in each country. Given that market entry date in Germany was earlier than in other countries, the data were collected in 2 waves; the first wave included Germany (reported in the interim study report dated 27 Apr 2023, final data collection date: 22 Dec 2022) and the second wave includes all study countries (Austria, France, Germany, Italy, Spain, and UK). The survey was launched in 4 waves: wave 1 in Germany, wave 2 in Austria, wave 3 in the UK and Italy, and wave 4 in Spain and France. This final study report presents the data collected in all 4 waves.

7 RESEARCH QUESTION AND OBJECTIVES

The study aims to assess the effectiveness of the fenfluramine educational materials in terms of the key process indicators, which refer to awareness, knowledge, and self-reported compliance with respect to the safety messages conveyed in these materials. The study objectives are as follows:

Primary objectives:

- Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow up
- Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational material on echocardiogram follow up

Secondary objectives:

- Assess the physician-reported distribution of educational materials to patients/carers by physicians routinely prescribing fenfluramine
- Assess the awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management

8 AMENDMENTS AND UPDATES

The original protocol was issued on 27 Jun 2022. There were 2 amendments to the study protocol.

- **Amendment 1.0** (20 Oct 2023): Upon interim analysis on the data collected in Germany (report dated 27 Apr 2023), it was assessed that the option to the knowledge Question 11 "considering the patient for eligibility for the long-term patient safety registry" was not an essential requirement for physicians to initiate treatment with fenfluramine. Before continuing the survey in other countries, the response options for Question 11 were therefore made clearer and limited to medical conditions. The question's option for Question 11 (Variable 6) "Should be considered for eligibility for the long-term patient safety registry" was deleted (Protocol Annex VI). Though not reported in the interim study report, data for Austria were collected and analyzed under the original protocol.
- **Amendment 2.0** (09 Apr 2024): Based on the totality of the available evidence presented in the SSAR (DLP of 14 Jan 2024), PAH was characterized as an important identified risk and no longer considered an important potential risk (Protocol Section 5).

9 RESEARCH METHODS

9.1 Study design

The study objectives were addressed through a noninterventional, cross-sectional survey among physicians prescribing fenfluramine in routine practice in selected European countries. The survey was a structured questionnaire containing close-ended questions, where the response format was either the selection of a single response or selection of several responses, as appropriate. It was conducted online using a secure electronic data collection platform.

The study was conducted in selected European countries after the launch of fenfluramine and the distribution of the educational materials to physicians (Protocol Table 2). The data were collected 12 to 18 months after the implementation of educational materials in each country, ie, depending on the country-specific market entry date for fenfluramine and related distribution of the educational material. Given that market entry date in Germany was earlier than in other countries, the data were collected in 2 waves; the first wave included Germany (reported in the interim study report dated 27 Apr 2023, final data collection date: 22 Dec 2022), and the second wave includes all study countries. Of note, in this study, the survey was launched in 4 waves: wave 1 in Germany, wave 2 in Austria, wave 3 in the UK and Italy, and wave 4 in Spain and France. This final study report includes data collected in all 4 waves.

This PASS was conducted according to the guideline on GVP, Module VIII (EMA/813938/2011 Rev 3, 2017) and according to the GVP Module XVI (EMA/204715/2012 Rev 2, 2017).

9.2 Setting

This study was sponsored by Zogenix International Limited a wholly owned subsidiary of UCB Biosciences, Inc. and outsourced/conducted by United BioSource LLC®.

The study consisted of a survey conducted online using a secure electronic data collection platform. The survey was launched (and study data collected) in 4 waves (wave 1 in Germany, wave 2 in Austria, wave 3 in the UK and Italy, and wave 4 in Spain and France) at 12 to 18 months after the implementation of Fintepla educational materials in each country (Feb 2021 in Germany). The data were collected in 2 waves: wave 1 included data from Germany (presented in the interim study report dated 27 Apr 2023) and wave 2 included data collected in all 4 waves, presented in this final study report.

9.3 Participants

The target population was physicians practicing in selected countries who prescribed fenfluramine at least once (Protocol Section 9.2.3). It was anticipated that these physicians were neuropediatricians or physicians specializing in pediatrics or neurology with experience in the treatment of epilepsy (eg, epileptologists). These specialties were targeted based on the SmPC, which indicates that fenfluramine treatment is to be initiated by physicians with experience in the treatment of epilepsy. Furthermore, fenfluramine is to be prescribed and dispensed through a CAP, which should limit the population to that described above. Recruitment strategy for physicians varied among countries mainly depending on whether CAP portal registration was required or not for physicians prescribing fenfluramine because not all countries had a CAP portal implemented and the supply was controlled via other means.

In countries where a CAP portal registration was required for physicians prescribing fenfluramine (Austria, France, Germany, Italy, and UK), physicians having prescribed fenfluramine at least once were targeted through the CAP portal. All physicians who registered in the CAP portal and provided consent to be contacted were approached to participate in the survey.

In countries where a CAP portal was not implemented (Spain), any physician having prescribed fenfluramine at least once was identified and contacted through several possible and complimentary approaches that included the following:

- Network and reference centers in the treatment of rare pediatric epilepsies

- Investigators in fenfluramine studies
- Sponsor's network
- Country-specific commercial lists of physicians and physician panel

9.3.1 Inclusion and exclusion criteria

Physicians who met each of the following inclusion criteria were eligible to participate in the study (there were no exclusion criteria):

- Physicians who prescribed fenfluramine at least once
- Physician's primary country of practice was among selected study country
- Provided informed consent for using the survey data

9.4 Variables

9.4.1 Physicians' characteristics

Variables related to the following physician's characteristics were collected (Protocol Section 9.3.1):

- Years of practice
- Primary specialty
- Practice setting
- Country of practice
- Fenfluramine prescribing patterns
  - Number of patients treated with fenfluramine
  - Time since first prescription of fenfluramine
  - Time since last prescription of fenfluramine

Please refer to Protocol Annex V for the detailed survey questionnaire.

9.4.2 Variables associated with the primary objectives

The variables associated with awareness and knowledge of the educational materials on the requirement of echocardiogram follow up by physicians routinely prescribing fenfluramine are listed in Table 9-1.

Table 9-1: Variables associated with awareness and knowledge of educational materials on the requirement of echocardiogram follow up

Variable	Variable content	Variable Domain	Survey Question
Variable 1	Receipt of the educational materials.	Awareness	4
Variable 2	Reading of the educational materials.	Awareness	5
Variable 3	Knowledge of the 2 types of educational materials available.	Awareness	6
Variable 4	Known risk of VHD and PAH associated with higher than approved doses of fenfluramine.	Knowledge	8
Variable 5	Knowledge that periodic echocardiography must be performed when treating Dravet syndrome and LGS patients with fenfluramine.	Knowledge	14
Variable 6	Knowledge that prior to initiating treatment with fenfluramine, all patients must undergo an echocardiogram to establish a baseline and to exclude any pre-existing VHD or PAH.	Knowledge	11

LGS=Lennox-Gastaut Syndrome; PAH=pulmonary arterial hypertension; VHD=valvular heart disease
Data source: Protocol Section 9.3.2

The variables related to the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational materials on the requirement of echocardiogram follow up are listed in Table 9-2.

Table 9-2: Variables related to self-reported compliance with recommendations provided in the educational materials on the requirement of echocardiogram follow up

Variable	Variable content	Variable Domain	Survey Question
Variable 7	Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter during fenfluramine treatment.	Self-reported compliance	12
Variable 8	If an echocardiogram indicates pathological valvular changes or PAH or if treatment with fenfluramine is stopped because of pathological changes in the heart valves or PAH, appropriate monitoring and follow up should be provided.	Self-reported compliance	15
Variable 9	Patients and carers should be informed about the need for echocardiography assessments before and during fenfluramine treatment due to important potential safety risks associated with fenfluramine.	Self-reported compliance	16

PAH=pulmonary arterial hypertension
Data source: Protocol Section 9.3.2

Please refer to Protocol Annex V for the detailed survey questionnaire.

9.4.3 Variables associated with the secondary objectives

The variable related to the physician-reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine is listed in Table 9-3.

Table 9-3: Variable related to physician-reported distribution of educational material to patients/carers

Variable	Variable content	Variable Domain	Survey Question
Variable 10	Distribute dedicated educational materials to patients/carers and latest version of package leaflet.	Self-reported compliance	7

Data source: Protocol Section 9.3.2

The variables related to the awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management are listed in Table 9-4.

Table 9-4: Variables related to awareness, knowledge, and self-reported compliance of educational material on prevention of off-label use for weight management

Variables	Variable content	Variable Domain	Survey Question
Variable 11	Fenfluramine should not be prescribed or used for weight management.	Knowledge	9
Variable 12	Inform patients/caregivers about the negative benefit-risk use of fenfluramine in weight management.	Self-reported compliance	10
Variable 13	If you suspect that fenfluramine might be used to control the weight of other people, patients/caregivers should be reminded that fenfluramine should only be taken by the person for whom it was prescribed and not by anyone else.	Knowledge	13

Data source: Protocol Section 9.3.2

Please refer to Protocol Annex V for the detailed survey questionnaire.

9.5 Data sources and measurement

In this study, primary data collection was conducted through a web-based questionnaire for physicians prescribing fenfluramine in routine practice (Protocol Section 9.4). The questionnaire was developed in English and translated for each of the selected countries; physicians completed the questionnaire in their local language. The questionnaire contained a set of standard questions (approximately 10 minutes to complete) validated through pilot interviews with at least 1 physician from the Sponsor in each of the selected countries as part of the user acceptance testing phase. In the questionnaire, questions could not be skipped without choosing an answer option and there was no option to click back to previous questions to adjust the answers; physicians were not contacted to clarify or revise their responses.

Physicians who provided consent during the CAP portal registration process to be contacted in the future regarding fenfluramine studies were approached to complete the survey (Protocol Section 10.1). In countries where a CAP portal was not implemented, physicians were

identified and contacted through other approaches to complete the survey (Section 9.3). Physicians were informed of the purpose and procedures of the survey and, as part of the survey screening questions, were asked to provide their consent for the use of their survey data.

Physicians were sent an initial e-mail invitation to participate and a minimum of 2 reminder communications could have been sent (Protocol Section 9.6.1). Physicians with an incomplete survey were encouraged to complete their forms through e-mail and/or phone reminders. No incentive payments were made to the physicians.

Physicians were provided a unique link to access the online data collection forms and were tracked through a unique identifier that was inactivated after use to minimize exposure bias and fraud (SAP Section 5.1). If a respondent completed more than 1 survey, only the results from the first completed survey were to be included in the analyses.

Each physician had ultimate responsibility for the self-reporting of all data entered and ensuring that they were accurate, complete, consistent, legible, and timely (contemporaneous) (Protocol Section 9.6.1).

All study data were collected and processed to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (Protocol Section 10.2). No participant-identifying information were collected and the data collected were pseudonymized (anonymous to study staff and MAH).

9.6 Bias

To reduce information bias, survey questions were close-ended to avoid errors in interpreting free text during analysis (Protocol Section 9.9). Additionally, the unique code provided to respondents during the recruitment process in order to gain access to the survey, was inactivated after use to minimize exposure bias and fraud (SAP Section 5.1).

9.7 Study size

For the study, it was estimated that approximately 1780 physicians could potentially prescribe fenfluramine within the target EU countries (SAP Section 3; Protocol Table 2). A conservative assumption was that at 12 to 18 months after launch in the participating countries and after receiving the educational materials, approximately 356 physicians (20% of the above) will have prescribed fenfluramine at least once.

The response rate was expected to be 20% to 25% in this population of specialized physicians treating a rare disease, therefore leading to an expected number of 80 physicians as minimum required sample size for the final completed study. For larger countries (eg, Germany or France), 10 to 30 responses were targeted. An additional 10 to 20 responses were targeted for the UK.

Based on the predefined target levels, Protocol Table 2 presents the precision around proportions of physicians reporting awareness, knowledge, or self-reported compliance according to different sample sizes. Based on approximately 80 physicians completing the survey (final analysis) and a predefined success criteria target of 80%, the precision around the proportion of physicians reporting awareness, knowledge, or self-reported compliance would be approximately 71.2% to 88.8%.

The final number of physicians in the study was dependent on the actual market uptake including the number of prescribing sites and the rate of sites participation.

9.8 Data management

All study data were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (Protocol Section 10.2). Data are pseudonymized and no participant-identifying information were collected.

A web-based EDC system was used as an integrated, transparent tool to collect and manage the survey data (Protocol Section 9.6.1). Data in the EDC system was kept in a central location on secure servers, meets approved, established standards for the security of health information, and had built-in edit checks and validations (Protocol Section 9.8).

9.9 Statistical methods

9.9.1 Analysis sets

The following analysis sets were used in the final analysis:

- All Respondent Set: includes unique respondents who had accessed the survey using the unique code. These respondents were used as the denominator for percentages in survey administration statistics and in the survey eligibility results analysis.
- Completed Survey Set: includes only eligible respondents with completed surveys. A "Completed" survey is defined as a survey from a respondent who answered all questions/items associated with the primary objective.

9.9.2 Main summary measures

Statistical analyses were primarily descriptive in nature and 95% CIs (inferential statistics) were calculated for primary and secondary endpoints to generalize the results to the entire targeted population (SAP Section 5.1). No formal hypothesis was tested. All analyses were performed at the respondent level.

Counts and percentages were calculated for each question/item in the questionnaire. All CIs around the percentages for the correct responses were exact binomial 2-sided 95% CIs calculated according to the method of Clopper-Pearson (Clopper and Pearson, 1934).

Decimal places for descriptive statistics applied the following rules:

- "n" was an integer
- Mean, SD, and median used 1 additional decimal place compared with the original data
- Minimum and maximum had the same number of decimal places as the original value

9.9.3 Main statistical methods

9.9.3.1 Participant disposition

Respondent eligibility (Questions 1, 2, and 3) were analyzed by country using descriptive statistics in the All Respondent Set (SAP Section 5.2).

The following survey administration statistics were reported:

- Number of invitations sent
- Number of invitations undeliverable
- Number of reminder letters sent
- Number and percentages of respondents based on the number of invitations minus number of invitations undeliverable
- Number of eligible respondents based on the number of all respondents
- Number of completed surveys based on the number of eligible surveys
- Number of incomplete surveys
- Number of surveys ineligible or eligibility questions incomplete

9.9.3.2 Baseline characteristics

Respondent characteristics were reported for the completed survey population using descriptive statistics for the survey questions related to physician characteristics (Questions 17 to 22) (SAP Section 6.1). For Question 20.1 (How many patients have you prescribed fenfluramine for each of the following age groups?), the distribution for the number of patients treated for Dravet syndrome was reported for each age group separately. If a respondent completed Question 20.1 for at least 1 age group and had missing values for another age group, the missing value was imputed by "Not prescribed for this age group."

9.9.3.3 Analysis of primary objectives

Primary endpoint analyses were performed in the Completed Survey Set (SAP Section 5.3.1). Descriptive statistics were used to summarize the awareness, knowledge, and self-reported compliance to messaging in the educational materials on the requirement of echocardiogram follow up by physicians routinely prescribing fenfluramine, based on the variables with corresponding survey questions as outlined in Section 9.4.2.

For each question, the proportion of physicians who provided correct answer was calculated with 95% CIs. In addition, the number of correct answers was calculated for the primary objective questions and reported using descriptive statistics (number and percentages of respondents who answered 0, 1, 2, etc. questions correctly). The 95% CIs were provided for the proportion of respondents who provided the correct response to all questions associated with the primary objective. The average number and percentages of correct answers were computed on respondent level and summarized by descriptive statistics. The percentages of correct responses were defined as the number of correct responses divided by the total number of items in the primary endpoint. The 95% CIs for the number and percentages of correct answers were calculated based on a normal distribution function.

The percentages of correct responses overall (over all questions and respondents) were also provided. Because of the possible correlations of the responses within the respondents, no CIs were calculated for this measure.

The percentage of physicians who provided correct answers to all questions related to each of the primary objectives' individual domain, namely awareness (Questions 4, 5, and 6), knowledge (Questions 8, 11, and 14), and self-reported compliance (Questions 12, 15, and 16), were also computed and reported with 95% CIs.

The success criteria for the effectiveness of the additional risk minimization measures were defined as ≥80% of physicians providing correct answers to all survey questions related to the primary objectives' variables.

9.9.3.4 Analysis of secondary objectives

Secondary endpoints were analyzed similarly to the primary endpoints using the Completed Survey Set (SAP Section 5.4.1.1). However, because of the definition of the Completed Survey Set, there was the possibility of missing values in the survey responses associated with the secondary endpoint.

Descriptive statistics were used to summarize the physician-reported distribution of educational material to patients/caregivers, and the awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management. This was based on the variables with corresponding survey questions as outlined in Section 9.4.3.

For each question, the number of respondents who completed the specific survey question and the proportion of physicians who provided the correct answers were calculated and reported with 95% CIs. The denominator for the calculation of percentages was the number of nonmissing survey responses. In addition, the number of correct answers was calculated for the secondary objective questions and reported using descriptive statistics. For the derivation of the number of correct responses, missing survey responses were counted as an incorrect response. The 95% CIs were provided for the proportion of respondents who provided the correct response to all questions associated with the secondary objective. The average number and percentage of correct answers was computed on the respondent level and summarized by descriptive statistics. The percentages of correct responses were defined as the number of correct responses divided by the total number of items in the secondary objective. For the average number and percentage of correct responses, missing responses were counted as an incorrect response. The 95% CIs for the number and percentages of correct answers were calculated based on a normal distribution function.

The proportion of physicians who provided correct answers to the questions related to each of the secondary objectives' individual domain, namely knowledge (Questions 9 and 13) and self-reported compliance (Questions 7 and 10), were also computed and reported with 95% CIs. For the analysis of the number of correct responses by domain, missing responses were counted as an incorrect response.

9.9.4 Methods used to examine subgroups and interactions

Subgroup analyses for the primary and secondary endpoints were performed in the final analysis for the following subgroups:

- EU vs non-EU countries (UK)
- Physician specialty (pediatrician, pediatric neurologist, neurologist, other)
- Last fenfluramine prescription date (<3 months, 3 to 5 months, ≥6 months, I do not recall)

The respondents from all countries were combined. For each subgroup, 95% CIs were calculated without adjustments for multiplicity. Therefore, subgroup differences, based on nonoverlapping CIs, were interpreted with care, especially for the individual survey questions.

9.9.5 Missing values

No imputation methods were applied to replace missing data (Protocol Section 9.7.8).

9.9.6 Sensitivity analyses

Sensitivity analyses were performed for the final analysis for this study. The responses to questions associated with the primary and secondary endpoints were compared between survey completers as defined in the completed survey population and eligible respondents who did not complete the survey to analyze the possible bias from excluding noncompleted surveys from the main analysis.

9.9.7 Amendments to the SAP

The following change was made to the SAP-defined analyses:

- The proportion of physicians who provided correct answers to the questions regarding prevention of off-label use (Questions 9, 10, and 13) was also calculated and reported with 95% CIs.

9.10 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 are extensively described in the data management plan and the SAP (Protocol Section 9.8).

The development of the Protocol and SAP followed internal SOPs, which included detailed rounds of review. Quality control of the statistical programming also followed the appropriate SOPs.

The EDC system meets approved, established standards for the security of health information and was validated. To ensure that participant data (as well as other confidential data) remained secure and intact, appropriate SOPs and quality control processes that addressed participant data security were followed. The EDC system also had built-in edit checks and validations.

10 RESULTS

The results of the final analysis are presented in this section. Individual answers are provided in Listing 1 (screening questions, respondent eligibility, and time to complete survey), Listing 2 (responses to Questions 4 to 16), and Listing 3 (responses to Questions 17 to 22).

10.1 Participants

Overall, 705 Invitation Letters to complete the survey were distributed to physicians, of which 24 (3.4%) Invitation Letters were returned as undeliverable (Table 10-1).

A total of 157 (23.1%) physicians accessed the survey using a unique code (All Respondents Set); of whom, 38 (24.2%) were not eligible to participate in the study.

- A total of 133/157 (84.7%) physicians had prescribed fenfluramine at least once (Question 1) and 23/157 (14.6%) physicians provided informed consent for using their survey data (Question 3) (Table 10-2).
- A total of 14/157 (8.9%) physicians were discontinued from participation in the survey. Respondents were counted as discontinued if they opened the survey and did not answer all eligibility questions without being identified as ineligible in a previous question.

Of note, Question 3 ("Do you provide informed consent for using the survey data?") was removed in the survey system during the conduct of the study and the question was captured in the consent form within the eCRF. For this reason, 96/157 (61.1%) of the respondents did not provide a response for this question as the question was no longer available (Table 10-2).

Of the 119/157 eligible respondents, 118 respondents completed the whole survey and were included in the Completed Survey Set (Table 10-1, Listing 2, and Listing 3). One of the 119 eligible respondents (Listing 3) did not answer all questions but was counted as completer because the respondent answered all questions associated with the primary objective (definition of Completed Survey Set, see Section 9.9.1.

Table 10-1: Survey administration statistics (All Respondents Set)

Parameter	Austria	France	Germany	Italy	Spain	United Kingdom	Overall
Number of Invitation Letters distributed	11	73	287	110	187	37	705
Number of Invitation Letters returned as undeliverable	0	2	5	8	7	2	24
Number of Reminder Letters distributed	18	53	504	0	169	64	808
Number of Reminder Letters returned as undeliverable	0	2	4	0	5	2	13
Number of respondents screened for participation (All Respondents) [a], n (%)	7 (63.6)	34 (47.9)	64 (22.7)	7 (6.9)	32 (17.8)	13 (37.1)	157 (23.1)
Eligible respondents [b]	6 (85.7)	33 (97.1)	31 (48.4)	7 (100.0)	29 (90.6)	13 (100.0)	119 (75.8)
Completed survey [c]	6 (100.0)	32 (97.0)	31 (100.0)	7 (100.0)	29 (100.0)	13 (100.0)	118 (99.2)
Did not complete the survey [c]	0	1 (3.0)	0	0	0	0	1 (0.8)
Respondents not eligible [b, d]	1 (14.3)	1 (2.9)	33 (51.6)	0	3 (9.4)	0	38 (24.2)

n=number
[a] Number of unique respondents who accessed the survey. Percentage was based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[b] Percentage was based on the number of all respondents.
[c] Percentage was based on the number of eligible respondents.
[d] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.
Data source: Table 1.1

Table 10-2: Survey participant eligibility results (All Respondents Set)

Question	Austria (N=7) n (%)	France (N=34) n (%)	Germany (N=64) n (%)	Italy (N=7) n (%)	Spain (N=32) n (%)	United Kingdom (N=13) n (%)	Overall (N=157) n (%)
Question 1: Have you prescribed fenfluramine at least once?							
Yes	6 (85.7)	33 (97.1)	45 (70.3)	7 (100.0)	29 (90.6)	13 (100.0)	133 (84.7)
No [a]	0	0	10 (15.6)	0	0	0	10 (6.4)
Discontinued	1 (14.3)	1 (2.9)	9 (14.1)	0	3 (9.4)	0	14 (8.9)
Question 3: Do you provide informed consent for using the survey data?							
Yes	0	0	23 (35.9)	0	0	0	23 (14.6)
No [a]	0	0	14 (21.9)	0	0	0	14 (8.9)
N/A Question has been removed from the survey [b]	6 (85.7)	33 (97.1)	8 (12.5)	7 (100.0)	29 (90.6)	13 (100.0)	96 (61.1)
Question not asked [c]	0	0	10 (15.6)	0	0	0	10 (6.4)
Discontinued	1 (14.3)	1 (2.9)	9 (14.1)	0	3 (9.4)	0	14 (8.9)

N=total number of respondents; n=number of respondents; N/A=not applicable
Note: Respondents were counted as discontinued if they opened the survey and did not answer all eligibility questions without being identified as ineligible in a previous question. Once respondents were counted as discontinued, they were counted as discontinued in all subsequent eligibility questions.
[a] Ineligible to participate in the survey.
[b] Question 3 ("Do you provide informed consent for using the survey data?") was removed in the survey system during the conduct of the study and the question was captured in the consent form within the eCRF.
[c] Question not asked due to previous question termination.
Data source: Table 1.2

10.2 Descriptive data

Of the 118 physicians included in the Completed Survey Set, all but 2 physicians spent ≥5 years working in medical practice and 21/118 (17.8%) physicians had spent >25 years. The majority of the physicians (82/118 [69.5%]) were pediatric neurologists and worked in a university hospital (84/118 [71.2%]) (Table 10-3).

A total of 26/118 (22.0%) physicians had prescribed fenfluramine to patients of <2 years of age, 79/118 (66.9%) to patients aged 2 to 11 years, 57/118 (48.3%) to patients aged 12 to 18 years, and 43/118 (36.4%) to patients of >18 years.

The majority of the physicians (85/118 [72.0%]) had prescribed fenfluramine for the first time ≥6 months before completing the survey. A total of 52/118 (44.1%) physicians had prescribed fenfluramine for the last time <3 months before completing the survey.

Half of the physicians (59/118 [50.0%]) were familiar with the long-term Fintepla post-authorization safety registry study in EU (ie, Study EP0218) that collects data on the long-term safety of fenfluramine in routine practice and the risks of VHD and PAH, and 31/118 (26.3%) physicians had recruited any patients for it.

For Question 22 (“Did you recruit any patients for the long-term Fintepla registry?”), 1 physician in Italy incorrectly answered Yes though no sites for the registry had yet opened in Italy

Table 10-3: Description of eligible survey participants (Completed Survey Set)

Question	Austria (N=6) n (%)	France (N=32) n (%)	Germany (N=31) n (%)	Italy (N=7) n (%)	Spain (N=29) n (%)	United Kingdom (N=13) n (%)	Overall (N=118) n (%)
Question 17: How many years of practice do you have?							
<5 years	0	1 (3.1)	1 (3.2)	0	0	0	2 (1.7)
5 - 15 years	1 (16.7)	19 (59.4)	10 (32.3)	2 (28.6)	10 (34.5)	9 (69.2)	51 (43.2)
16 - 25 years	5 (83.3)	8 (25.0)	13 (41.9)	3 (42.9)	13 (44.8)	2 (15.4)	44 (37.3)
>25 years	0	4 (12.5)	7 (22.6)	2 (28.6)	6 (20.7)	2 (15.4)	21 (17.8)
Question 18: What is your primary specialty?							
Pediatrician	0	0	3 (9.7)	0	0	0	3 (2.5)
Pediatric neurologist	5 (83.3)	28 (87.5)	20 (64.5)	4 (57.1)	14 (48.3)	11 (84.6)	82 (69.5)
Neurologist	1 (16.7)	4 (12.5)	7 (22.6)	2 (28.6)	15 (51.7)	2 (15.4)	31 (26.3)
Other [a]	0	0	1 (3.2)	1 (14.3)	0	0	2 (1.7)
Question 19: What is your primary practice setting?							
Local hospital	0	1 (3.1)	4 (12.9)	1 (14.3)	0	0	6 (5.1)
Regional hospital	1 (16.7)	1 (3.1)	9 (29.0)	1 (14.3)	1 (3.4)	3 (23.1)	16 (13.6)
University hospital	5 (83.3)	28 (87.5)	8 (25.8)	5 (71.4)	28 (96.6)	10 (76.9)	84 (71.2)
Private hospital	0	0	0	0	0	0	0
Private practice	0	2 (6.3)	0	0	0	0	2 (1.7)
Community-based practice	0	0	5 (16.1)	0	0	0	5 (4.2)
Specialized center	0	0	5 (16.1)	0	0	0	5 (4.2)

Table 10-3: Description of eligible survey participants (Completed Survey Set)

Question	Austria (N=6) n (%)	France (N=32) n (%)	Germany (N=31) n (%)	Italy (N=7) n (%)	Spain (N=29) n (%)	United Kingdom (N=13) n (%)	Overall (N=118) n (%)
Question 20.1: How many patients have you prescribed fenfluramine for in each of the following age groups?							
<2 years							
1-2 patients	1 (16.7)	7 (21.9)	6 (19.4)	4 (57.1)	4 (13.8)	0	22 (18.6)
3-5 patients	0	1 (3.1)	2 (6.5)	0	0	0	3 (2.5)
6-9 patients	0	0	0	0	0	0	0
≥10 patients	0	0	0	0	1 (3.4)	0	1 (0.8)
Not prescribed for this age group	5 (83.3)	24 (75.0)	23 (74.2)	3 (42.9)	24 (82.8)	13 (100.0)	92 (78.0)
2-11 years							
1-2 patients	3 (50.0)	10 (31.3)	11 (35.5)	3 (42.9)	7 (24.1)	4 (30.8)	38 (32.2)
3-5 patients	1 (16.7)	9 (28.1)	3 (9.7)	2 (28.6)	6 (20.7)	6 (46.2)	27 (22.9)
6-9 patients	1 (16.7)	4 (12.5)	2 (6.5)	1 (14.3)	1 (3.4)	0	9 (7.6)
≥10 patients	0	2 (6.3)	1 (3.2)	0	2 (6.9)	0	5 (4.2)
Not prescribed for this age group	1 (16.7)	7 (21.9)	14 (45.2)	1 (14.3)	13 (44.8)	3 (23.1)	39 (33.1)
12-18 years							
1-2 patients	3 (50.0)	9 (28.1)	7 (22.6)	3 (42.9)	7 (24.1)	6 (46.2)	35 (29.7)
3-5 patients	0	5 (15.6)	1 (3.2)	2 (28.6)	3 (10.3)	3 (23.1)	14 (11.9)
6-9 patients	0	3 (9.4)	3 (9.7)	0	0	0	6 (5.1)
≥10 patients	0	0	0	0	2 (6.9)	0	2 (1.7)
Not prescribed for this age group	3 (50.0)	15 (46.9)	20 (64.5)	2 (28.6)	17 (58.6)	4 (30.8)	61 (51.7)
>18 years							
1-2 patients	0	5 (15.6)	9 (29.0)	1 (14.3)	7 (24.1)	2 (15.4)	24 (20.3)

Table 10-3: Description of eligible survey participants (Completed Survey Set)

Question	Austria (N=6) n (%)	France (N=32) n (%)	Germany (N=31) n (%)	Italy (N=7) n (%)	Spain (N=29) n (%)	United Kingdom (N=13) n (%)	Overall (N=118) n (%)
3-5 patients	0	3 (9.4)	2 (6.5)	2 (28.6)	6 (20.7)	0	13 (11.0)
6-9 patients	1 (16.7)	0	2 (6.5)	0	1 (3.4)	1 (7.7)	5 (4.2)
≥10 patients	0	0	0	0	1 (3.4)	0	1 (0.8)
Not prescribed for this age group	5 (83.3)	24 (75.0)	18 (58.1)	4 (57.1)	14 (48.3)	10 (76.9)	75 (63.6)
Question 20.2: How long since your first prescription of fenfluramine?							
<3 months	0	5 (15.6)	2 (6.5)	0	0	0	7 (5.9)
3 - 5 months	0	4 (12.5)	8 (25.8)	0	3 (10.3)	0	15 (12.7)
≥6 months	6 (100.0)	21 (65.6)	20 (64.5)	7 (100.0)	18 (62.1)	13 (100.0)	85 (72.0)
I do not recall	0	2 (6.3)	0	0	8 (27.6)	0	10 (8.5)
Missing	0	0	1 (3.2)	0	0	0	1 (0.8)
Question 20.3: How long since your last prescription of fenfluramine?							
<3 months	3 (50.0)	15 (46.9)	16 (51.6)	3 (42.9)	8 (27.6)	7 (53.8)	52 (44.1)
3 -5 months	2 (33.3)	8 (25.0)	7 (22.6)	1 (14.3)	3 (10.3)	1 (7.7)	22 (18.6)
≥6 months	1 (16.7)	6 (18.8)	6 (19.4)	3 (42.9)	10 (34.5)	5 (38.5)	31 (26.3)
I do not recall	0	3 (9.4)	1 (3.2)	0	8 (27.6)	0	12 (10.2)
Missing	0	0	1 (3.2)	0	0	0	1 (0.8)
Question 21: Are you familiar with the long-term Fintepla registry?							
Yes	4 (66.7)	28 (87.5)	9 (29.0)	1 (14.3)	12 (41.4)	5 (38.5)	59 (50.0)
No	2 (33.3)	3 (9.4)	17 (54.8)	4 (57.1)	12 (41.4)	5 (38.5)	43 (36.4)
I do not recall	0	1 (3.1)	4 (12.9)	2 (28.6)	5 (17.2)	3 (23.1)	15 (12.7)
Missing	0	0	1 (3.2)	0	0	0	1 (0.8)

Table 10-3: Description of eligible survey participants (Completed Survey Set)

Question	Austria (N=6) n (%)	France (N=32) n (%)	Germany (N=31) n (%)	Italy (N=7) n (%)	Spain (N=29) n (%)	United Kingdom (N=13) n (%)	Overall (N=118) n (%)
Question 22: Did you recruit any patients for the long-term Fintepla registry?							
Yes	0	21 (65.6)	6 (19.4)	1 (14.3)	2 (6.9)	1 (7.7)	31 (26.3)
No	5 (83.3)	9 (28.1)	21 (67.7)	6 (85.7)	26 (89.7)	11 (84.6)	78 (66.1)
I do not recall	1 (16.7)	2 (6.3)	3 (9.7)	0	1 (3.4)	1 (7.7)	8 (6.8)
Missing	0	0	1 (3.2)	0	0	0	1 (0.8)

N=total number of respondents; n=number of respondents
[a] Verbatim text responses for questions are presented in Listing 3.
Data source: Table 2

10.3 Outcome data

Results from the final analysis are presented in Section 10.4.

10.4 Main results

10.4.1 Results supporting the primary objectives

The survey questions supporting the primary objectives are presented in Table 10-5 together with their correct responses.

- A total of 24/118 (20.3%) physicians (95% CI: 13.5 to 28.7) provided correct responses to all 9 questions linked to the primary objective (Table 10-4).
- The mean percentage of correct responses to any questions supporting the primary objectives per survey participant was 84.7% (95% CI: 82.5 to 86.8).

10.4.1.1 Awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow up

Survey questions 4, 5, and 6 support this primary objective and cover the awareness variable domain (see Table 9-1). Survey questions 8, 11, and 14 support this primary objective and cover the knowledge variable domain.

For each of the Awareness Questions (survey questions 4, 5, and 6), the number of physicians providing the correct response was as follows (Table 10-5):

- A total of 101/118 (85.6%) physicians (95% CI: 77.9 to 91.4) confirmed to have received (Question 4) and 100/118 (84.7%) physicians (95% CI: 77.0 to 90.7) read (Question 5) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine. In Spain and UK, 23/29 (79.3%) and 9/13 (69.2%) physicians, respectively, confirmed to have received the Fintepla educational materials though 24/29 (82.8%) and 11/13 (84.6%) physicians, respectively, confirmed they had read the educational materials. This indicates that it is likely the physicians misunderstood the 2 questions.
- A total of 97/118 (82.2%) physicians (95% CI: 74.1 to 88.6) correctly identified the available Fintepla educational materials for fenfluramine (Question 6).

Correct responses to all 3 Awareness Questions were provided by 85/118 (72.0%) physicians (95% CI: 63.0 to 79.9) (Table 10-4).

For each of the Knowledge Questions (survey questions 8, 11, and 14), the number of physicians providing the correct response was as follows (Table 10-5):

- A total of 113/118 (95.8%) physicians (95% CI: 90.4 to 98.6) correctly identified the potential risks associated with higher than approved doses of fenfluramine (Question 8).
- A total of 59/118 (50.0%) physicians (95% CI: 40.7 to 59.3), (21/37 [56.8%] physicians [95% CI: 39.5 to 72.9] in Austria/Germany and 38/81 [46.9%] physicians [95% CI: 35.7 to 58.3] in countries other than Austria/Germany), correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11, see Table 10-5 for the correct response and Table 3.1 for all response choices offered in the survey). The data are reported separately for Austria/Germany and rest of the countries as the

correct answer to Question 11 was updated in Protocol Amendment 1 post data collection in Austria/Germany.

- A total of 91/118 (77.1%) physicians (95% CI: 68.5 to 84.3) correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine (Question 14, see Table 10-5 for the correct response and Table 3.1 for all response choices offered in the survey).

Correct responses to all 3 Knowledge Questions were provided by 43/118 (36.4%) physicians (95% CI: 27.8 to 45.8) (Table 10-4).

10.4.1.2 Self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational material on echocardiogram follow up

Survey questions 12, 15, and 16 support this objective and cover the self-reported compliance variable domain (see Table 9-2).

For each of the Compliance Questions, the number of physicians providing the correct response was as follows (Table 10-5):

- A total of 110/118 (93.2%) physicians (95% CI: 87.1 to 97.0) identified performing the correct regular monitoring during treatment with fenfluramine (Question 12; echocardiogram).
- A total of 111/118 (94.1%) physicians (95% CI: 88.2 to 97.6) correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or suspicion of PAH (Question 15).
- A total of 117/118 (99.2%) physicians (95% CI: 95.4 to 100.0) correctly identified the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine (Question 16).

Correct responses to all 3 Compliance Questions were provided by 103/118 (87.3%) physicians (95% CI: 79.9 to 92.7) (Table 10-4).

Table 10-4: Summary analysis of responses to questions linked to the primary objectives (Completed Survey Set)

	Austria (N=6)	France (N=32)	Germany (N=31)	Italy (N=7)	Spain (N=29)	United Kingdom (N=13)	Overall (N=118)
Number of correct responses, n (%) [95% CI] [a]							
4 correct responses	0	0	1 (3.2)	0	0	0	1 (0.8)
5 correct responses	0	0	1 (3.2)	0	2 (6.9)	0	3 (2.5)
6 correct responses	0	2 (6.3)	3 (9.7)	0	4 (13.8)	3 (23.1)	12 (10.2)
7 correct responses	2 (33.3)	7 (21.9)	9 (29.0)	2 (28.6)	6 (20.7)	6 (46.2)	32 (27.1)
8 correct responses	3 (50.0)	15 (46.9)	9 (29.0)	4 (57.1)	13 (44.8)	2 (15.4)	46 (39.0)
9 correct responses	1 (16.7) [0.4-64.1]	8 (25.0) [11.5-43.4]	8 (25.8) [11.9-44.6]	1 (14.3) [0.4-57.9]	4 (13.8) [3.9-31.7]	2 (15.4) [1.9-45.4]	24 (20.3) [13.5-28.7]
Average number of correct responses, mean (SD) [95% CI] [b]	7.8 (0.75) [7.0-8.6]	7.9 (0.86) [7.6-8.2]	7.5 (1.26) [7.1-8.0]	7.9 (0.69) [7.2-8.5]	7.4 (1.12) [7.0-7.9]	7.2 (1.01) [6.6-7.8]	7.6 (1.05) [7.4-7.8]
Percentage of correct responses, mean (SD) [95% CI] [b]	87.0 (8.36) [78.3-95.8]	87.8 (9.51) [84.4-91.3]	83.9 (14.01) [78.7-89.0]	87.3 (7.67) [80.2-94.4]	82.8 (12.45) [78.0-87.5]	80.3 (11.25) [73.5-87.1]	84.7 (11.70) [82.5-86.8]
Correct response to all Awareness Questions (Questions 4, 5, and 6), n (%) [95% CI] [a]	5 (83.3) [35.9-99.6]	26 (81.3) [63.6-92.8]	27 (87.1) [70.2-96.4]	4 (57.1) [18.4-90.1]	17 (58.6) [38.9-76.5]	6 (46.2) [19.2-74.9]	85 (72.0) [63.0-79.9]
Correct response to all Knowledge Questions (Questions 8, 11, and 14), n (%) [95% CI] [a]	2 (33.3) [4.3-77.7]	12 (37.5) [21.1-56.3]	10 (32.3) [16.7-51.4]	5 (71.4) [29.0-96.3]	10 (34.5) [17.9-54.3]	4 (30.8) [9.1-61.4]	43 (36.4) [27.8-45.8]
Correct response to all Compliance Questions (Questions 12, 15, and 16), n (%) [95% CI] [a]	4 (66.7) [22.3-95.7]	29 (90.6) [75.0-98.0]	25 (80.6) [62.5-92.5]	6 (85.7) [42.1-99.6]	26 (89.7) [72.6-97.8]	13 (100.0) [75.3-100.0]	103 (87.3) [79.9-92.7]
Percentage of correct responses overall, % [c]	87.0	87.8	83.9	87.3	82.8	80.3	84.7

Table 10-4: Summary analysis of responses to questions linked to the primary objectives (Completed Survey Set)

	Austria (N=6)	France (N=32)	Germany (N=31)	Italy (N=7)	Spain (N=29)	United Kingdom (N=13)	Overall (N=118)

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: Correct responses to the question associated with the primary endpoint: Question 4=Yes; Question 5=Yes; Question 6=A and B; Question 8=Valvular heart disease and pulmonary arterial hypertension; Question 11=A, B, and C (Austria/Germany) or A and B (except Austria/Germany) (the responses were different for Austria/Germany and for rest of the countries post Protocol Amendment 1); Question 12=Echocardiogram; Question 14=Every 6 months for the first 2 years and then annually thereafter; Question 15=True; Question 16=The need for echocardiogram monitoring.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentage of correct responses overall was calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 3.2

Table 10-5: Analysis of responses to questions linked to the primary objectives (Completed Survey Set; only correct responses shown)

Question	Austria (N=6) n (%) [95% CI] [a]	France (N=32) n (%) [95% CI] [a]	Germany (N=31) n (%) [95% CI] [a]	Italy (N=7) n (%) [95% CI] [a]	Spain (N=29) n (%) [95% CI] [a]	United Kingdom (N=13) n (%) [95% CI] [a]	Overall (N=118) n (%) [95% CI] [a]
Question 4: Have you received the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?							
Yes	6 (100.0) [54.1-100.0]	29 (90.6) [75.0-98.0]	28 (90.3) [74.2-98.0]	6 (85.7) [42.1-99.6]	23 (79.3) [60.3-92.0]	9 (69.2) [38.6-90.9]	101 (85.6) [77.9-91.4]
Question 5: Have you read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?							
Yes	6 (100.0) [54.1-100.0]	26 (81.3) [63.6-92.8]	28 (90.3) [74.2-98.0]	5 (71.4) [29.0-96.3]	24 (82.8) [64.2-94.2]	11 (84.6) [54.6-98.1]	100 (84.7) [77.0-90.7]
Question 6: Which Fintepla educational materials for fenfluramine are available?							
Risk management information for prescribers AND Important information for patients and caregivers	5 (83.3) [35.9-99.6]	30 (93.8) [79.2-99.2]	28 (90.3) [74.2-98.0]	6 (85.7) [42.1-99.6]	20 (69.0) [49.2-84.7]	8 (61.5) [31.6-86.1]	97 (82.2) [74.1-88.6]
Question 8: Do you know the potential risks associated with higher than approved doses of fenfluramine?							
Valvular heart disease and pulmonary arterial hypertension	6 (100.0) [54.1-100.0]	32 (100.0) [89.1-100.0]	26 (83.9) [66.3-94.5]	7 (100.0) [59.0-100.0]	29 (100.0) [88.1-100.0]	13 (100.0) [75.3-100.0]	113 (95.8) [90.4-98.6]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (Austria/Germany)							
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension AND Should be considered for eligibility for the long-term patient safety registry	3 (50.0) [11.8-88.2]	–	18 (58.1) [39.1-75.5]	–	–	–	21 (56.8) [39.5-72.9]

Table 10-5: Analysis of responses to questions linked to the primary objectives (Completed Survey Set; only correct responses shown)

Question	Austria (N=6) n (%) [95% CI] [a]	France (N=32) n (%) [95% CI] [a]	Germany (N=31) n (%) [95% CI] [a]	Italy (N=7) n (%) [95% CI] [a]	Spain (N=29) n (%) [95% CI] [a]	United Kingdom (N=13) n (%) [95% CI] [a]	Overall (N=118) n (%) [95% CI] [a]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (other than Austria/Germany)							
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension	–	15 (46.9) [29.1-65.3]	–	5 (71.4) [29.0-96.3]	12 (41.4) [23.5-61.1]	6 (46.2) [19.2-74.9]	38 (46.9) [35.7-58.3]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (overall)							
Number not missing	N=6	N=32	N=31	N=7	N=29	N=13	N=118
Selected correct response [b]	3 (50.0) [11.8-88.2]	15 (46.9) [29.1-65.3]	18 (58.1) [39.1-75.5]	5 (71.4) [29.0-96.3]	12 (41.4) [23.5-61.1]	6 (46.2) [19.2-74.9]	59 (50.0) [40.7-59.3]
Did not select correct response	3 (50.0)	17 (53.1)	13 (41.9)	2 (28.6)	17 (58.6)	7 (53.8)	59 (50.0)
Question 12: Which monitoring do you perform regularly during treatment with fenfluramine?							
Echocardiogram	5 (83.3) [35.9-99.6]	32 (100.0) [89.1-100.0]	28 (90.3) [74.2-98.0]	6 (85.7) [42.1-99.6]	26 (89.7) [72.6-97.8]	13 (100.0) [75.3-100.0]	110 (93.2) [87.1-97.0]
Question 14: During fenfluramine treatment, echocardiogram monitoring should be conducted:							
Every 6 months for the first 2 years and then annually thereafter	5 (83.3) [35.9-99.6]	28 (87.5) [71.0-96.5]	20 (64.5) [45.4-80.8]	6 (85.7) [42.1-99.6]	24 (82.8) [64.2-94.2]	8 (61.5) [31.6-86.1]	91 (77.1) [68.5-84.3]
Question 15: If an echocardiogram indicates pathological valvular changes or suspicion of pulmonary arterial hypertension, then appropriate monitoring and follow-up should be provided in accordance with local guidelines:							
True	5 (83.3) [35.9-99.6]	29 (90.6) [75.0-98.0]	28 (90.3) [74.2-98.0]	7 (100.0) [59.0-100.0]	29 (100.0) [88.1-100.0]	13 (100.0) [75.3-100.0]	111 (94.1) [88.2-97.6]
Question 16: You should inform the patients/caregivers about the following before and during fenfluramine treatment:							
The need for echocardiogram monitoring	6 (100.0) [54.1-100.0]	32 (100.0) [89.1-100.0]	30 (96.8) [83.3-99.9]	7 (100.0) [59.0-100.0]	29 (100.0) [88.1-100.0]	13 (100.0) [75.3-100.0]	117 (99.2) [95.4-100.0]

Table 10-5: Analysis of responses to questions linked to the primary objectives (Completed Survey Set; only correct responses shown)

Question	Austria (N=6) n (%) [95% CI] [a]	France (N=32) n (%) [95% CI] [a]	Germany (N=31) n (%) [95% CI] [a]	Italy (N=7) n (%) [95% CI] [a]	Spain (N=29) n (%) [95% CI] [a]	United Kingdom (N=13) n (%) [95% CI] [a]	Overall (N=118) n (%) [95% CI] [a]

CI=confidence interval; N=total number of respondents; n=number of respondents
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] For Germany and Austria, the correct response is A, B, and C and for all other countries the correct response is A and B.
Data source: Table 3.1

10.4.1.3 Subgroup analyses

10.4.1.3.1 By region

The survey questions supporting the primary objectives together with their correct responses by region are presented in Table 10-6 and Table 10-7.

- A total of 22/105 (21.0%) physicians (95% CI: 13.6 to 30.0) in EU countries and 2/13 (15.4%) physicians (95% CI: 1.9 to 45.4) in non-EU countries provided correct responses to all 9 questions linked to the primary objective.
- The mean percentage of correct responses to any questions supporting the primary objectives per survey participant in EU and non-EU countries were 85.2% (95% CI: 82.9 to 87.4) and 80.3% (95% CI: 73.5 to 87.1), respectively.

Awareness Questions (survey questions 4, 5, and 6)

- A total of 92/105 (87.6%) physicians (95% CI: 79.8 to 93.2) in EU countries and 9/13 (69.2) physicians (95% CI: 38.6 to 90.9) in non-EU countries confirmed to have received (Question 4) and 89/105 (84.8%) physicians (95% CI: 76.4 to 91.0) in EU countries and 11/13 (84.6) physicians (95% CI: 54.6 to 98.1) in non-EU countries read (Question 5) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine.
- A total of 89/105 (84.8%) physicians (95% CI: 76.4 to 91.0) in EU countries and 8/13 (61.5%) physicians (95% CI: 31.6 to 86.1) in non-EU countries correctly identified the available Fintepla educational materials for fenfluramine (Question 6).

Correct responses to all 3 Awareness Questions were provided by 79/105 (75.2%) physicians (95% CI: 65.9 to 83.1) in EU countries and 6/13 (46.2%) physicians (95% CI: 19.2 to 74.9) in non-EU countries.

Knowledge Questions (survey questions 8, 11, and 14)

- A total of 100/105 (95.2%) physicians (95% CI: 89.2 to 98.4) in EU countries and 13/13 (100.0%) physicians (95% CI: 75.3 to 100.0) in non-EU countries correctly identified the potential risks associated with higher than approved doses of fenfluramine (Question 8).
- A total of 53/105 (50.5%) physicians (95% CI: 40.5 to 60.4) in EU countries and 6/13 (46.2%) physicians (95% CI: 19.2 to 74.9) in non-EU countries correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11).
- A total of 83/105 (79.0%) physicians (95% CI: 70.0 to 86.4) in EU countries and 8/13 (61.5%) physicians (95% CI: 31.6 to 86.1) in non-EU countries correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine (Question 14, see Table 10-7 for the correct response and Table 3.1.1 for all response choices offered in the survey).

Correct responses to all 3 Knowledge Questions were provided by 39/105 (37.1%) physicians (95% CI: 27.9 to 47.1) in EU countries and 4/13 (30.8%) physicians (95% CI: 9.1 to 61.4) in non-EU countries.

Compliance Questions (survey questions 12, 15, and 16)

- A total of 97/105 (92.4%) physicians (95% CI: 85.5 to 96.7) in EU countries and 13/13 (100%) physicians (95% CI: 75.3 to 100.0) in non-EU countries identified performing the correct regular monitoring during treatment with fenfluramine (Question 12; echocardiogram).
- A total of 98/105 (93.3%) physicians (95% CI: 86.7 to 97.3) in EU countries and 13/13 (100.0%) physicians (95% CI: 75.3 to 100.0) in non-EU countries correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or suspicion of PAH (Question 15).
- A total of 104/105 (99.0%) physicians (95% CI: 94.8 to 100.0) in EU countries and 13/13 (100.0%) physicians (95% CI: 75.3 to 100.0) in non-EU countries correctly identified the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine (Question 16).

Correct responses to all 3 Compliance Questions were provided by 90/105 (85.7%) physicians (95% CI: 77.5 to 91.8) in EU countries and 13/13 (100.0%) physicians (95% CI: 75.3 to 100.0) in non-EU countries.

Table 10-6: Summary analysis of responses to questions linked to primary objectives by region (Completed Survey Set)

	EU countries (N=105) n (%)	Non-EU countries (N=13) n (%)
Number of correct responses, n (%) [95% CI] [a]		
4 correct responses	1 (1.0)	0
5 correct responses	3 (2.9)	0
6 correct responses	9 (8.6)	3 (23.1)
7 correct responses	26 (24.8)	6 (46.2)
8 correct responses	44 (41.9)	2 (15.4)
9 correct responses	22 (21.0) [13.6-30.0]	2 (15.4) [1.9-45.4]
Average number of correct responses, mean (SD) [95% CI] [b]	7.7 (1.05) [7.5-7.9]	7.2 (1.01) [6.6-7.8]
Percentage of correct responses, mean (SD) [95% CI] [b]	85.2 (11.70) [82.9-87.4]	80.3 (11.25) [73.5-87.1]
Correct response to all Awareness Questions (Questions 4, 5, and 6), n (%) [95% CI] [a]	79 (75.2) [65.9-83.1]	6 (46.2) [19.2-74.9]
Correct response to all Knowledge Questions (Questions 8, 11, and 14), n (%) [95% CI] [a]	39 (37.1) [27.9-47.1]	4 (30.8) [9.1-61.4]
Correct response to all Compliance Questions (Questions 12, 15, and 16), n (%) [95% CI] [a]	90 (85.7) [77.5-91.8]	13 (100.0) [75.3-100.0]
Percentage of correct responses overall, % [c]	85.2	80.3

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: Correct responses to the question associated with the primary objective: Question 4=Yes; Question 5=Yes; Question 6=A and B; Question 8=Valvular heart disease and pulmonary arterial hypertension; Question 11=A, B, and C (Austria/Germany) or A and B (except Austria/Germany); Question 12=Echocardiogram; Question 14=Every 6 months for the first 2 years and then annually thereafter; Question 15=True; Question 16=The need for echocardiogram monitoring.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentage of correct responses overall was calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 3.2.1

Table 10-7: Analysis of responses to questions linked to the primary objectives by region (Completed Survey Set; only correct responses shown)

	EU countries (N=105) n (%) [95% CI] [a]	Non-EU countries (N=13) n (%) [95% CI] [a]
Question 4: Have you received the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?		
Yes	92 (87.6) [79.8-93.2]	9 (69.2) [38.6-90.9]
Question 5: Have you read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?		
Yes	89 (84.8) [76.4-91.0]	11 (84.6) [54.6-98.1]
Question 6: Which Fintepla educational materials for fenfluramine are available?		
Risk management information for prescribers AND important information for patients and caregivers	89 (84.8) [76.4-91.0]	8 (61.5) [31.6-86.1]
Question 8: Do you know the potential risks associated with higher than approved doses of fenfluramine?		
Valvular heart disease and pulmonary arterial hypertension	100 (95.2) [89.2-98.4]	13 (100.0) [75.3-100.0]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (overall) [b]		
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension AND Should be considered for eligibility for the long-term patient safety registry OR Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension	53 (50.5) [40.5-60.4]	6 (46.2) [19.2-74.9]
Question 12: Which monitoring do you perform regularly during treatment with fenfluramine?		
Echocardiogram	97 (92.4) [85.5-96.7]	13 (100.0) [75.3-100.0]
Question 14: During fenfluramine treatment, echocardiogram monitoring should be conducted:		
Every 6 months for the first 2 years and then annually thereafter	83 (79.0) [70.0-86.4]	8 (61.5) [31.6-86.1]

Table 10-7: Analysis of responses to questions linked to the primary objectives by region (Completed Survey Set; only correct responses shown)

	EU countries (N=105) n (%) [95% CI] [a]	Non-EU countries (N=13) n (%) [95% CI] [a]
Question 15: If an echocardiogram indicates pathological valvular changes or suspicion of pulmonary arterial hypertension, then appropriate monitoring and follow-up should be provided in accordance with local guidelines:		
True	98 (93.3) [86.7-97.3]	13 (100.0) [75.3-100.0]
Question 16: You should inform the patients/caregivers about the following before and during fenfluramine treatment:		
The need for echocardiogram monitoring	104 (99.0) [94.8-100.0]	13 (100.0) [75.3-100.0]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Only the correct response for each question is shown. For all responses available for each question, see Table 3.1.1.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] For Germany and Austria, the correct response is A, B, and C and for all other countries the correct response is A and B.
Data source: Table 3.1.1

10.4.1.3.2 By physician specialty

The survey questions supporting the primary objectives together with their correct responses by physician specialty are presented in Table 10-8 and Table 10-9.

- A total of 14/82 (17.1%) pediatric neurologists (95% CI: 9.7 to 27.0) and 10/31 (32.3%) neurologist (95% CI: 16.7 to 51.4) provided correct responses to all 9 questions linked to the primary objective.
- The highest mean percentage of correct responses to any questions supporting the primary objectives per survey participant was 87.5% (95% CI: 82.8 to 92.1) and provided by neurologists.

Awareness Questions (survey questions 4, 5, and 6)

- Most of the physicians were pediatric neurologists (87.8% [72/82]; 95% CI: 78.7 to 94.0) who confirmed to have received (Question 4) and read (Question 5) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine.
- The majority of physicians were pediatric neurologists (84.1% [69/82]; 95% CI: 74.7 to 91.3) who correctly identified the available Fintepla educational materials for fenfluramine (Question 6).

Correct responses to all 3 Awareness Questions were provided by 2/3 (66.7%) pediatricians (95% CI: 9.4 to 99.2), 62/82 (75.6%) pediatric neurologists (95% CI: 64.9 to 84.4), 19/31 (61.3%) neurologists (95% CI: 42.2 to 78.2), and 2/2 (100.0%) physicians of other specialty (95% CI: 15.8 to 100.0).

Knowledge Questions (survey questions 8, 11, and 14)

- All of the neurologists (100.0% [31/31]; 95% CI: 88.8 to 100.0) and physicians of other specialty (100.0% [2/2]; 95% CI: 15.8 to 100.0) correctly identified the potential risks associated with higher than approved doses of fenfluramine (Question 8). Of the remaining physicians, 78/82 (95.1%; 95% CI: 88.0 to 98.7) pediatric neurologists and 2/3 (66.7%; 95% CI: 9.4 to 99.2) pediatricians correctly identified the potential risks associated with higher than approved doses of fenfluramine.
- Most of the neurologists (77.4% [24/31]; 95% CI: 58.9 to 90.4) correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11).
- The majority of physicians were neurologists (83.9% [26/31]; 95% CI: 66.3 to 94.5) who correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine (Question 14, see Table 10-9 for the correct response and Table 3.1.2 for all response choices offered in the survey).

Correct responses to all 3 Knowledge Questions were provided by 24/82 (29.3%) pediatric neurologists (95% CI: 19.7 to 40.4) and 19/31 (61.3%) neurologists (95% CI: 42.2 to 78.2).

Compliance Questions (survey questions 12, 15, and 16)

- The majority of physicians who identified performing the correct regular monitoring during treatment with fenfluramine were pediatric neurologists (95.1% [78/82]; 95% CI: 88.0 to

98.7) and neurologists (93.5% [29/31]; 95% CI: 78.6 to 99.2) (Question 12; echocardiogram).

- All of the pediatricians (100.0% [3/3]; 95% CI: 29.2 to 100.0) and physicians of other specialty (100.0% [2/2]; 95% CI: 15.8 to 100.0) correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or suspicion of PAH (Question 15). Of the remaining physicians, 76/82 (92.7%; 95% CI: 84.8 to 97.3) pediatric neurologists and 30/31 (96.8%; 95% CI: 83.3 to 99.9) neurologists correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or PAH.
- All physicians (in all specialties) except 1 physician of other specialty correctly identified the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine (Question 16).

Correct responses to all 3 Compliance Questions were provided by 2/3 (66.7%) pediatricians (95% CI: 9.4 to 99.2), 72/82 (87.8%) pediatric neurologists (95% CI: 78.7 to 94.0), 28/31 (90.3%) neurologists (95% CI: 74.2 to 98.0), and 1/2 (50.0%) physicians of other specialty (95% CI: 1.3 to 98.7).

Table 10-8: Summary analysis of responses to questions linked to primary objectives by physician specialty (Completed Survey Set)

	Pediatrician (N=3) n (%)	Pediatric neurologist (N=82) n (%)	Neurologist (N=31) n (%)	Other (N=2) n (%)
Number of correct responses, n (%) [95% CI] [a]				
4 correct responses	1 (33.3)	0	0	0
5 correct responses	0	1 (1.2)	2 (6.5)	0
6 correct responses	0	9 (11.0)	2 (6.5)	1 (50.0)
7 correct responses	2 (66.7)	26 (31.7)	4 (12.9)	0
8 correct responses	0	32 (39.0)	13 (41.9)	1 (50.0)
9 correct responses	0 [0.0-70.8]	14 (17.1) [9.7-27.0]	10 (32.3) [16.7-51.4]	0 [0.0-84.2]
Average number of correct responses, mean (SD) [95% CI] [b]	6.0 (1.73) [1.7-10.3]	7.6 (0.94) [7.4-7.8]	7.9 (1.15) [7.5-8.3]	7.0 (1.41) [-5.7-19.7]
Percentage of correct responses, mean (SD) [95% CI] [b]	66.7 (19.25) [18.9-114.5]	84.4 (10.46) [82.1-86.7]	87.5 (12.75) [82.8-92.1]	77.8 (15.71) [-63.4-219.0]
Correct response to all Awareness Questions (Questions 4, 5, and 6), n (%) [95% CI] [a]	2 (66.7) [9.4-99.2]	62 (75.6) [64.9-84.4]	19 (61.3) [42.2-78.2]	2 (100.0) [15.8-100.0]
Correct response to all Knowledge Questions (Questions 8, 11, and 14), n (%) [95% CI] [a]	0 [0.0-70.8]	24 (29.3) [19.7-40.4]	19 (61.3) [42.2-78.2]	0 [0.0-84.2]
Correct response to all Compliance Questions (Questions 12, 15, and 16), n (%) [95% CI] [a]	2 (66.7) [9.4-99.2]	72 (87.8) [78.7-94.0]	28 (90.3) [74.2-98.0]	1 (50.0) [1.3-98.7]
Percentage of correct responses overall, % [c]	66.7	84.4	87.5	77.8

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: Correct responses to the question associated with the primary objective: Question 4=Yes; Question 5=Yes; Question 6=A and B; Question 8=Valvular heart disease and pulmonary arterial hypertension; Question 11=A, B, and C (Austria/Germany) or A and B (except Austria/Germany); Question 12=Echocardiogram; Question 14=Every 6 months for the first 2 years and then annually thereafter; Question 15=True; Question 16=The need for echocardiogram monitoring.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentage of correct responses overall was calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 3.2.2

Table 10-9: Analysis of responses to questions linked to the primary objectives by physician specialty (Completed Survey Set; only correct responses shown)

	Pediatrician (N=3) n (%) [95% CI] [a]	Pediatric neurologist (N=82) n (%) [95% CI] [a]	Neurologist (N=31) n (%) [95% CI] [a]	Other (N=2) n (%) [95% CI] [a]
Question 4: Have you received the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?				
Yes	2 (66.7) [9.4-99.2]	72 (87.8) [78.7-94.0]	25 (80.6) [62.5-92.5]	2 (100.0) [15.8-100.0]
Question 5: Have you read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?				
Yes	2 (66.7) [9.4-99.2]	72 (87.8) [78.7-94.0]	24 (77.4) [58.9-90.4]	2 (100.0) [15.8-100.0]
Question 6: Which Fintepla educational materials for fenfluramine are available?				
Risk management information for prescribers AND important information for patients and caregivers	2 (66.7) [9.4-99.2]	69 (84.1) [74.4-91.3]	24 (77.4) [58.9-90.4]	2 (100.0) [15.8-100.0]
Question 8: Do you know the potential risks associated with higher than approved doses of fenfluramine?				
Valvular heart disease and pulmonary arterial hypertension	2 (66.7) [9.4-99.2]	78 (95.1) [88.0-98.7]	31 (100.0) [88.8-100.0]	2 (100.0) [15.8-100.0]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (overall) [b]				
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension AND Should be considered for eligibility for the long-term patient safety registry OR Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension	1 (33.3) [0.8-90.6]	33 (40.2) [29.6-51.7]	24 (77.4) [58.9-90.4]	1 (50.0) [1.3-98.7]
Question 12: Which monitoring do you perform regularly during treatment with fenfluramine?				
Echocardiogram	2 (66.7) [9.4-99.2]	78 (95.1) [88.0-98.7]	29 (93.5) [78.6-99.2]	1 (50.0) [1.3-98.7]

Table 10-9: Analysis of responses to questions linked to the primary objectives by physician specialty (Completed Survey Set; only correct responses shown)

	Pediatrician (N=3) n (%) [95% CI] [a]	Pediatric neurologist (N=82) n (%) [95% CI] [a]	Neurologist (N=31) n (%) [95% CI] [a]	Other (N=2) n (%) [95% CI] [a]
Question 14: During fenfluramine treatment, echocardiogram monitoring should be conducted:				
Every 6 months for the first 2 years and then annually thereafter	1 (33.3) [0.8-90.6]	63 (76.8) [66.2-85.4]	26 (83.9) [66.3-94.5]	1 (50.0) [1.3-98.7]
Question 15: If an echocardiogram indicates pathological valvular changes or suspicion of pulmonary arterial hypertension, then appropriate monitoring and follow-up should be provided in accordance with local guidelines:				
True	3 (100.0) [29.2-100.0]	76 (92.7) [84.8-97.3]	30 (96.8) [83.3-99.9]	2 (100.0) [15.8-100.0]
Question 16: You should inform the patients/caregivers about the following before and during fenfluramine treatment:				
The need for echocardiogram monitoring	3 (100.0) [29.2-100.0]	82 (100.0) [95.6-100.0]	31 (100.0) [88.8-100.0]	1 (50.0) [1.3-98.7]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Only the correct response for each question is shown. For all responses available for each question, see Table 3.1.2.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] For Germany and Austria, the correct response is A, B, and C and for all other countries the correct response is A and B.
Data source: Table 3.1.2

10.4.1.3.3 By last fenfluramine prescription date

The survey questions supporting the primary objectives together with their correct responses by last fenfluramine prescription date are presented in Table 10-10 and Table 10-11.

- Most of the physicians (25.0% [3/12]; (95% CI: 5.5 to 57.2) who provided correct responses to all 9 questions linked to the primary objective did not recall the last fenfluramine prescription date.
- The mean percentage of correct responses to any questions supporting the primary objectives per survey participant was comparable within this subgroup.

Awareness Questions (survey questions 4, 5, and 6)

- The majority of physicians (90.3% [28/31]; 95% CI: 74.2 to 98.0) who confirmed to have received (Question 4) and read (Question 5) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine had prescribed fenfluramine for the last time ≥6 months before completing the survey.
- The majority of physicians (95.5% [21/22]; 95% CI: 77.2 to 99.9) who correctly identified the available Fintepla educational materials for fenfluramine (Question 6) had prescribed fenfluramine for the last time 3 to 5 months before completing the survey.

The majority of correct responses to all 3 Awareness Questions were provided by physicians who had prescribed fenfluramine for the last time 3 to 5 months before completing the survey (81.8% [18/22]; 95% CI: 59.7 to 94.8).

Knowledge Questions (survey questions 8, 11, and 14)

- The proportion of physicians who correctly identified the potential risks associated with higher than approved doses of fenfluramine (Question 8) was comparable within this subgroup.
- Most of the physicians (58.3% [7/12]; 95% CI: 27.7 to 84.8) who correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11) did not recall the last fenfluramine prescription date.
- Of all the physicians who correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine, 12/12 (100%; 95% CI: 73.5 to 100.0) physicians did not recall the last fenfluramine prescription date (Question 14; see Table 10-11 for the correct response and Table 3.1.3 for all response choices offered in the survey).

The majority of correct responses to all 3 Knowledge Questions were provided by physicians who did not recall the last fenfluramine prescription date (58.3% [7/12]; 95% CI: 27.7 to 84.8).

Compliance Questions (survey questions 12, 15, and 16)

- The majority of physicians (96.8% [30/31]; 95% CI: 83.3 to 99.9) who identified performing the correct regular monitoring during treatment with fenfluramine had prescribed fenfluramine for the last time ≥6 months before completing the survey (Question 12; echocardiogram).

- The proportion of physicians who correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or suspicion of PAH was comparable within this subgroup (Question 15).
- The proportion of physicians who correctly identified the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine was comparable within this subgroup (Question 16).

The majority of correct responses to all 3 Compliance Questions were provided by physicians who had prescribed fenfluramine for the last time ≥6 months before completing the survey (93.5% [29/31]; 95% CI: 78.6 to 99.2).

Table 10-10: Summary analysis of responses to questions linked to primary objectives by last fenfluramine prescription date (Completed Survey Set)

	<3 months (N=52) n (%)	3 - 5 months (N=22) n (%)	≥6 months (N=31) n (%)	I do not recall (N=12) n (%)
Number of correct responses, n (%) [95% CI] [a]				
4 correct responses	0	1 (4.5)	0	0
5 correct responses	3 (5.8)	0	0	0
6 correct responses	5 (9.6)	1 (4.5)	4 (12.9)	2 (16.7)
7 correct responses	15 (28.8)	5 (22.7)	8 (25.8)	3 (25.0)
8 correct responses	19 (36.5)	11 (50.0)	12 (38.7)	4 (33.3)
9 correct responses	10 (19.2) [9.6-32.5]	4 (18.2) [5.2-40.3]	7 (22.6) [9.6-41.1]	3 (25.0) [5.5-57.2]
Average number of correct responses, mean (SD) [95% CI] [b]	7.5 (1.09) [7.2-7.8]	7.7 (1.13) [7.2-8.2]	7.7 (0.97) [7.4-8.1]	7.7 (1.07) [7.0-8.3]
Percentage of correct responses, mean (SD) [95% CI] [b]	83.8 (12.14) [80.4-87.1]	85.4 (12.55) [79.8-90.9]	85.7 (10.81) [81.7-89.6]	85.2 (11.92) [77.6-92.8]
Correct response to all Awareness Questions (Questions 4, 5, and 6), n (%) [95% CI] [a]	38 (73.1) [59.0-84.4]	18 (81.8) [59.7-94.8]	21 (67.7) [48.6-83.3]	7 (58.3) [27.7-84.8]
Correct response to all Knowledge Questions (Questions 8, 11, and 14), n (%) [95% CI] [a]	18 (34.6) [22.0-49.1]	7 (31.8) [13.9-54.9]	11 (35.5) [19.2-54.6]	7 (58.3) [27.7-84.8]
Correct response to all Compliance Questions (Questions 12, 15, and 16), n (%) [95% CI] [a]	45 (86.5) [74.2-94.4]	18 (81.8) [59.7-94.8]	29 (93.5) [78.6-99.2]	10 (83.3) [51.6-97.9]
Percentage of correct responses overall, % [c]	83.8	85.4	85.7	85.2

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: Correct responses to the question associated with the primary objective: Question 4=Yes; Question 5=Yes; Question 6=A and B; Question 8=Valvular heart disease and pulmonary arterial hypertension; Question 11=A, B, and C (Austria/Germany) or A and B (except Austria/Germany); Question 12=Echocardiogram; Question 14=Every 6 months for the first 2 years and then annually thereafter; Question 15=True; Question 16=The need for echocardiogram monitoring.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentage of correct responses overall was calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 3.2.3

Table 10-11: Analysis of responses to questions linked to the primary objectives by last fenfluramine prescription date (Completed Survey Set; only correct responses shown)

	<3 months (N=52) n (%) [95% CI][a]	3 - 5 months (N=22) n (%)[95% CI][a]	≥6 months (N=31) n (%) [95% CI][a]	I do not recall (N=12) n (%) [95% CI][a]
Question 4: Have you received the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?				
Yes	44 (84.6) [71.9-93.1]	19 (86.4) [65.1-97.1]	28 (90.3) [74.2-98.0]	9 (75.0) [42.8-94.5]
Question 5: Have you read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?				
Yes	44 (84.6) [71.9-93.1]	18 (81.8) [59.7-94.8]	28 (90.3) [74.2-98.0]	9 (75.0) [42.8-94.5]
Question 6: Which Fintepla educational materials for fenfluramine are available?				
Risk management information for prescribers AND important information for patients and caregivers	42 (80.8) [67.5-90.4]	21 (95.5) [77.2-99.9]	24 (77.4) [58.9-90.4]	9 (75.0) [42.8-94.5]
Question 8: Do you know the potential risks associated with higher than approved doses of fenfluramine?				
Valvular heart disease and pulmonary arterial hypertension	49 (94.2) [84.1-98.8]	21 (95.5) [77.2-99.9]	30 (96.8) [83.3-99.9]	12 (100.0) [73.5-100.0]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (overall) [b]				
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension AND Should be considered for eligibility for the long-term patient safety registry OR Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension	24 (46.2) [32.2-60.5]	11 (50.0) [28.2-71.8]	17 (54.8) [36.0-72.7]	7 (58.3) [27.7-84.8]
Question 12: Which monitoring do you perform regularly during treatment with fenfluramine?				
Echocardiogram	49 (94.2) [84.1-98.8]	19 (86.4) [65.1-97.1]	30 (96.8) [83.3-99.9]	11 (91.7) [61.5-99.8]

Table 10-11: Analysis of responses to questions linked to the primary objectives by last fenfluramine prescription date (Completed Survey Set; only correct responses shown)

	<3 months (N=52) n (%) [95% CI][a]	3 - 5 months (N=22) n (%)[95% CI][a]	≥6 months (N=31) n (%) [95% CI][a]	I do not recall (N=12) n (%) [95% CI][a]
Question 14: During fenfluramine treatment, echocardiogram monitoring should be conducted:				
Every 6 months for the first 2 years and then annually thereafter	40 (76.9) [63.2-87.5]	17 (77.3) [54.6-92.2]	22 (71.0) [52.0-85.8]	12 (100.0) [73.5-100.0]
Question 15: If an echocardiogram indicates pathological valvular changes or suspicion of pulmonary arterial hypertension, then appropriate monitoring and follow-up should be provided in accordance with local guidelines:				
True	48 (92.3) [81.5-97.9]	21 (95.5) [77.2-99.9]	30 (96.8) [83.3-99.9]	11 (91.7) [61.5-99.8]
Question 16: You should inform the patients/caregivers about the following before and during fenfluramine treatment:				
The need for echocardiogram monitoring	52 (100.0) [93.2-100.0]	22 (100.0) [84.6-100.0]	30 (96.8) [83.3-99.9]	12 (100.0) [73.5-100.0]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Only the correct response for each question is shown. For all responses available for each question, see Table 3.1.3.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] For Germany and Austria, the correct response is A, B, and C and for all other countries the correct response is A and B.
Data source: Table 3.1.3

10.4.1.4 Sensitivity analyses

10.4.1.4.1 By survey completion status

The survey questions supporting the primary objectives together with their correct responses by survey completion status are presented in Table 10-12.

Awareness Questions (survey questions 4, 5, and 6)

- Of the 118 physicians who completed the whole survey (also referred to as completers), 101 (85.6%) physicians (95% CI: 77.9 to 91.4) confirmed to have received (Question 4) and 100/118 (84.7) physicians (95% CI: 77.0 to 90.7) read (Question 5) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine.
- A total of 97/118 (82.2%) completers (95% CI: 74.1 to 88.6) correctly identified the available Fintepla educational materials for fenfluramine (Question 6).
- One physician who was eligible but did not complete the survey (also referred to as noncompleter) confirmed to have received and read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine, however did not correctly identify the available Fintepla educational materials for fenfluramine (Question 6).

Knowledge Questions (survey questions 8, 11, and 14)

- A total of 113/118 (95.8%) completers (95% CI: 90.4 to 98.6) and the noncompleter correctly identified the potential risks associated with higher than approved doses of fenfluramine (Question 8).
- A total of 59/118 (50.0%) completers (95% CI: 40.7 to 59.3) correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11).
- A total of 91/118 (77.1%) completers (95% CI: 68.5 to 84.3) correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine (Question 14, see Table 3.1.4 for all response choices offered in the survey). The noncompleter did not correctly identify Questions 11 and 14.

Compliance Questions (survey questions 12, 15, and 16)

- A total of 110/118 (93.2%) completers (95% CI: 87.1 to 97.0) and the noncompleter identified performing the correct regular monitoring during treatment with fenfluramine (Question 12; echocardiogram).
- A total of 111/118 (94.1%) completers (95% CI: 88.2 to 97.6) correctly identified the need for appropriate monitoring and follow up (in accordance with local guidelines) if an echocardiogram indicates pathological valvular changes or suspicion of PAH (Question 15).
- A total of 117/118 (99.2%) completers (95% CI: 95.4 to 100.0) correctly identified the requirement to inform patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine (Question 16). The noncompleter did not correctly identify Questions 15 and 16.

Table 10-12: Analysis of responses to questions linked to the primary objectives by survey completion status (Eligible Survey Set; only correct responses shown)

	Completer (N=118) n (%) [95% CI] [a]	Noncompleter (N=1) n (%) [95% CI] [a]
Question 4: Have you received the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?		
Yes	101 (85.6) [77.9-91.4]	1 (100.0) [2.5-100.0]
Question 5: Have you read the Fintepla educational materials regarding the minimization of risks associated with fenfluramine?		
Yes	100 (84.7) [77.0-90.7]	1 (100.0) [2.5-100.0]
Question 6: Which Fintepla educational materials for fenfluramine are available?		
Risk management information for prescribers AND important information for patients and caregivers	97 (82.2) [74.1-88.6]	0 [0.0-97.5]
Question 8: Do you know the potential risks associated with higher than approved doses of fenfluramine?		
Valvular heart disease and pulmonary arterial hypertension	113 (95.8) [90.4-98.6]	1 (100.0) [2.5-100.0]
Question 11: Prior to initiating treatment with fenfluramine, all patients: (overall) [b]		
Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension AND Should be considered for eligibility for the long-term patient safety registry OR Should undergo an echocardiogram AND Should be checked to establish a baseline to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension	59 (50.0) [40.7-59.3]	0 [0.0-97.5]
Question 12: Which monitoring do you perform regularly during treatment with fenfluramine?		
Echocardiogram	110 (93.2) [87.1-97.0]	1 (100.0) [2.5-100.0]
Question 14: During fenfluramine treatment, echocardiogram monitoring should be conducted:		
Every 6 months for the first 2 years and then annually thereafter	91 (77.1) [68.5-84.3]	0 [0.0-97.5]
Question 15: If an echocardiogram indicates pathological valvular changes or suspicion of pulmonary arterial hypertension, then appropriate monitoring and follow-up should be provided in accordance with local guidelines:		
True	111 (94.1) [88.2-97.6]	0
Question 16: You should inform the patients/caregivers about the following before and during fenfluramine treatment:		
The need for echocardiogram monitoring	117 (99.2) [95.4-100.0]	0

Table 10-12: Analysis of responses to questions linked to the primary objectives by survey completion status (Eligible Survey Set; only correct responses shown)

	Completer (N=118) n (%) [95% CI] [a]	Noncompleter (N=1) n (%) [95% CI] [a]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Only the correct response for each question is shown. For all responses available for each question, see Table 3.1.4.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] For Germany and Austria, the correct response is A, B, and C and for all other countries the correct response is A and B.
Data source: Table 3.1.4

10.4.2 Results supporting the secondary objectives

The survey questions supporting the secondary objectives are presented in Table 10-14 together with their correct responses.

- A total of 27/118 (22.9%) physicians (95% CI: 15.7 to 31.5) provided correct responses to all 4 questions linked to the secondary objectives. Additionally, 36/118 (30.5%), 34/118 (28.8%), and 19/118 (16.1%) physicians provided correct responses to any 3, 2, or 1 questions each, respectively (Table 10-13).
- The mean percentage of correct responses to any questions supporting the secondary objectives per survey participant was 64.2% (95% CI: 59.3 to 69.1).

Physician-reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine was one of the secondary objectives of the study. Survey question number 7 (self-reported compliance variable domain) supports this objective (see Table 9-3).

The number of physicians providing the correct response was as follows (Table 10-14):

- A total of 60/118 (50.8%) physicians (95% CI: 41.5 to 60.2) reported that they had provided the dedicated educational materials and the latest version of the package leaflet (Question 7) to patients/caregivers who may initiate fenfluramine.

Awareness, knowledge, and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management was one of the secondary objectives of the study. Survey questions 9 (knowledge variable domain), 10 (self-reported compliance variable domain), and 13 (knowledge variable domain) support this objective (see Table 9-4).

The number of physicians providing the correct response was as follows (Table 10-14):

- A total of 113/118 (95.8%) physicians (95% CI: 90.4 to 98.6) confirmed they would not prescribe fenfluramine for weight management (Question 9).
- A total of 71/118 (60.2%) physicians (95% CI: 50.7 to 69.1) were aware that they should have informed patients/caregivers about the negative benefit-risk of fenfluramine off-label use for weight management (Question 10). However, it is noteworthy to mention that

19/118 (16.1%) and 15/118 (12.7%) physicians confirmed they should inform patients/caregivers that the benefit-risk of fenfluramine off-label use for weight management was neutral and positive, respectively (Table 4.1).

- A total of 59/118 (50.0%) physicians (95% CI: 40.7 to 59.3) correctly identified the content included in the Fintepla educational materials (Question 13, "Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND if there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed"). A total of 38/118 (32.2%) physicians inadvertently identified importance of electrocardiogram monitoring as the content included in the Fintepla educational materials (see Table 4.1 for all response choices offered in the survey).

Correct responses to all questions regarding prevention of off-label use were provided by 40 (33.9%) physicians (95% CI: 25.4 to 43.2) (Table 10-13).

Table 10-13: Summary analysis of responses to questions linked to the secondary objectives (Completed Survey Set)

	Austria (N=6)	France (N=32)	Germany (N=31)	Italy (N=7)	Spain (N=29)	United Kingdom (N=13)	Overall (N=118)
Number of correct responses, n (%) [95% CI] [a]							
0 correct response	0	0	0	1 (14.3)	1 (3.4)	0	2 (1.7)
1 correct response	1 (16.7)	3 (9.4)	1 (3.2)	2 (28.6)	9 (31.0)	3 (23.1)	19 (16.1)
2 correct responses	1 (16.7)	11 (34.4)	4 (12.9)	3 (42.9)	12 (41.4)	3 (23.1)	34 (28.8)
3 correct responses	3 (50.0)	10 (31.3)	12 (38.7)	1 (14.3)	6 (20.7)	4 (30.8)	36 (30.5)
4 correct responses	1 (16.7) [0.4-64.1]	8 (25.0) [11.5-43.4]	14 (45.2) [27.3-64.0]	0 [0.0-41.0]	1 (3.4) [0.1-17.8]	3 (23.1) [5.0-53.8]	27 (22.9) [15.7-31.5]
Average number of correct responses, mean (SD) [95% CI] [b]	2.7 (1.03) [1.6-3.8]	2.7 (0.96) [2.4-3.1]	3.3 (0.82) [3.0-3.6]	1.8 (0.75) [1.0-2.6]	2.0 (0.84) [1.6-2.3]	2.5 (1.13) [1.9-3.2]	2.6 (1.02) [2.4-2.8]
Percentage of correct responses, mean (SD) [95% CI] [b]	66.7 (25.82) [39.6-93.8]	68.0 (23.96) [59.3-76.6]	81.5 (20.38) [74.0-88.9]	39.3 (24.40) [16.7-61.8]	47.4 (22.50) [38.9-56.0]	63.5 (28.17) [46.4-80.5]	64.2 (26.65) [59.3-69.1]
Correct response to all Knowledge Questions (Questions 9 and 13), n (%) [95% CI] [a]	4 (66.7) [22.3-95.7]	11 (34.4) [18.6-53.2]	23 (74.2) [55.4-88.1]	3 (42.9) [9.9-81.6]	9 (31.0) [15.3-50.8]	7 (53.8) [25.1-80.8]	57 (48.3) [39.0-57.7]
Correct response to all Compliance Questions (Questions 7 and 10), n (%) [95% CI] [a]	2 (33.3) [4.3-77.7]	15 (46.9) [29.1-65.3]	20 (64.5) [45.4-80.8]	0 [0.0-41.0]	3 (10.3) [2.2-27.4]	4 (30.8) [9.1-61.4]	44 (37.3) [28.6-46.7]
Correct response to all questions regarding prevention of off-label use (Questions 9, 10, and 13), n (%) [95% CI] [a]	2 (33.3) [4.3-77.7]	11 (34.4) [18.6-53.2]	17 (54.8) [36.0-72.7]	1 (14.3) [0.4-57.9]	4 (13.8) [3.9-31.7]	5 (38.5) [13.9-68.4]	40 (33.9) [25.4-43.2]
Percentage of correct responses overall, % [c]	66.7	68.0	81.5	39.3	47.4	63.5	64.2

Table 10-13: Summary analysis of responses to questions linked to the secondary objectives (Completed Survey Set)

	Austria (N=6)	France (N=32)	Germany (N=31)	Italy (N=7)	Spain (N=29)	United Kingdom (N=13)	Overall (N=118)

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: For all summary analyses, missing responses were counted as an incorrect response.
Note: Correct responses to the questions associated with the secondary endpoint: Question 7=Yes; Question 9=No; Question 10=Negative; Question 13=A and B.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentages of correct responses overall were calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 4.2

Table 10-14: Analysis of responses to questions linked to the secondary objectives (Completed Survey Set; only correct responses shown)

	Austria (N=6) n (%) [95% CI] [a]	France (N=32) n (%) [95% CI] [a]	Germany (N=31) n (%) [95% CI] [a]	Italy (N=7) n (%) [95% CI] [a]	Spain (N=29) n (%) [95% CI] [a]	United Kingdom (N=13) n (%) [95% CI] [a]	Overall (N=118) n (%) [95% CI] [a]
Question 7: Have you provided patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet?							
Yes	3 (50.0) [11.8-88.2]	18 (56.3) [37.7-73.6]	24 (77.4) [58.9-90.4]	1 (14.3) [0.4-57.9]	8 (27.6) [12.7-47.2]	6 (46.2) [19.2-74.9]	60 (50.8) [41.5-60.2]
Question 9: Would you prescribe fenfluramine for weight management?							
No	6 (100.0) [54.1-100.0]	32 (100.0) [89.1-100.0]	31 (100.0) [88.8-100.0]	6 (85.7) [42.1-99.6]	25 (86.2) [68.3-96.1]	13 (100.0) [75.3-100.0]	113 (95.8) [90.4-98.6]
Question 10: You should inform patients/caregivers about the benefit-risk of using fenfluramine off-label for weight management as being:							
Negative	3 (50.0) [11.8-88.2]	26 (81.3) [63.6-92.8]	23 (74.2) [55.4-88.1]	1 (14.3) [0.4-57.9]	11 (37.9) [20.7-57.7]	7 (53.8) [25.1-80.8]	71 (60.2) [50.7-69.1]
Question 13: What content is included in the Fintepla educational materials?							
Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND If there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed.	4 (66.7) [22.3-95.7]	11 (34.4) [18.6-53.2]	23 (74.2) [55.4-88.1]	3 (42.9) [9.9-81.6]	11 (37.9) [20.7-57.7]	7 (53.8) [25.1-80.8]	59 (50.0) [40.7-59.3]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Denominator was the number of responses not missing.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
Data source: Table 4.1

10.4.2.1 Domain analysis

Survey questions 7 and 10 cover the self-reported compliance variable domain (see Section 9.4.3). For each of these questions, the number of physicians providing the correct response was as follows (Table 10-14):

- A total of 60 (50.8%) physicians (95% CI: 41.5 to 60.2) correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet (Question 7).
- A total of 71 (60.2%) physicians (95% CI: 50.7 to 69.1) were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine off-label use for weight management (Question 10).

Correct responses to both questions in the self-reported compliance variable domain were provided by 44 (37.3%) physicians (95% CI: 28.6 to 46.7) (Table 10-13).

Survey questions 9 and 13 cover the knowledge variable domain (see Section 9.4.3). For each of these questions, the number of physicians providing the correct response was as follows (Table 10-14):

- A total of 113 (95.8%) physicians (95% CI: 90.4 to 98.6) confirmed they would not prescribe fenfluramine for weight management (Question 9).
- A total of 59 (50.0%) physicians (95% CI: 40.7 to 59.3) correctly identified the content included in the Fintepla educational materials (Question 13, see Table 10-14 for the correct response and Table 4.1 for all response choices offered in the survey).

Correct responses to both questions in the knowledge variable domain were provided by 57 (48.3%) physicians (95% CI: 39.0 to 57.7) (Table 10-13).

10.4.2.2 Subgroup analyses

10.4.2.2.1 By region

The survey questions supporting the secondary objectives together with their correct responses by region are presented in Table 10-15 and Table 10-16.

- A total of 24/105 (22.9%) physicians (95% CI: 15.2 to 32.1) in EU countries and 3/13 (23.1%) physicians (95% CI: 5.0 to 53.8) in non-EU countries provided correct responses to all 4 questions linked to the secondary objectives.
- The mean percentage of correct responses to any questions supporting the secondary objectives per survey participant in EU and non-EU countries were 64.3% (95% CI: 59.1 to 69.4) and 63.5% (95% CI: 46.4 to 80.5), respectively.

Self-reported compliance (Question 7)

- A total of 54/105 (51.4%) physicians (95% CI: 41.5 to 61.3) in EU countries and 6/13 (46.2%) physicians (95% CI: 19.2 to 74.9) in non-EU countries correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet (Question 7).

Awareness, knowledge, and self-reported compliance (Questions 9, 10, and 13)

- A total of 100/105 (95.2%) physicians (95% CI: 89.2 to 98.4) in EU countries and 13/13 (100%) physicians (95% CI: 75.3 to 100.0) in non-EU countries confirmed they would not prescribe fenfluramine for weight management (Question 9).
- A total of 64/105 (61.0%) physicians (95% CI: 50.9 to 70.3) in EU countries and 7/13 (53.8%) physicians (95% CI: 25.1 to 80.8) in non-EU countries were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine off-label use for weight management (Question 10).
- A total of 52/105 (49.5%) physicians (95% CI: 39.6 to 59.5) in EU countries and 7/13 (53.8%) physicians (95% CI: 25.1 to 80.8) in non-EU countries correctly identified the content included in the Fintepla educational materials (Question 13, see Table 10-16 for the correct response and Table 4.1.1 for all response choices offered in the survey).

Correct responses to all questions regarding prevention of off-label use were provided by 35/105 (33.3%) physicians (95% CI: 24.4 to 43.2) in EU countries and 5/13 (38.5%) physicians (95% CI: 13.9 to 68.4) in non-EU countries.

Table 10-15: Summary analysis of responses to questions linked to secondary objectives by region (Completed Survey Set)

	EU countries (N=105) n (%)	Non-EU countries (N=13) n (%)
Number of correct responses, n (%) [95% CI] [a]		
0 correct response	2 (1.9)	0
1 correct response	16 (15.2)	3 (23.1)
2 correct responses	31 (29.5)	3 (23.1)
3 correct responses	32 (30.5)	4 (30.8)
4 correct responses	24 (22.9) [15.2-32.1]	3 (23.1) [5.0-53.8]
Average number of correct responses, mean (SD) [95% CI] [b]	2.6 (1.01) [2.4-2.8]	2.5 (1.13) [1.9-3.2]
Percentage of correct responses, mean (SD) [95% CI] [b]	64.3 (26.60) [59.1-69.4]	63.5 (28.17) [46.4-80.5]
Correct response to all Knowledge Questions (Questions 9 and 13), n (%) [95% CI] [a]	50 (47.6) [37.8-57.6]	7 (53.8) [25.1-80.8]
Correct response to all Compliance Questions (Questions 7 and 10), n (%) [95% CI] [a]	40 (38.1) [28.8-48.1]	4 (30.8) [9.1-61.4]
Correct response to all questions regarding prevention of off-label use (Questions 9, 10, and 13), n (%) [95% CI] [a]	35 (33.3) [24.4-43.2]	5 (38.5) [13.9-68.4]
Percentage of correct responses overall, % [c]	64.3	63.5

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: For all summary analyses, missing responses were counted as an incorrect response.
Note: Correct responses to the questions associated with the secondary endpoint: Question 7=Yes; Question 9=No; Question 10=Negative; Question 13=A and B.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentages of correct responses overall were calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 4.2.1

Table 10-16: Analysis of responses to questions linked to the secondary objectives by region (Completed Survey Set; only correct responses shown)

	EU countries (N=105) n (%) [95% CI] [a]	Non-EU countries (N=13) n (%) [95% CI] [a]
Question 7: Have you provided patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet?		
Yes	54 (51.4) [41.5-61.3]	6 (46.2) [19.2-74.9]
Question 9: Would you prescribe fenfluramine for weight management?		
No	100 (95.2) [89.2-98.4]	13 (100.0) [75.3-100.0]
Question 10: You should inform patients/caregivers about the benefit-risk of using fenfluramine off-label for weight management as being:		
Negative	64 (61.0) [50.9-70.3]	7 (53.8) [25.1-80.8]
Question 13: What content is included in the Fintepla educational materials?		
Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND If there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed.	52 (49.5) [39.6-59.5]	7 (53.8) [25.1-80.8]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Denominator was the number of responses not missing.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
Data source: Table 4.1.1

10.4.2.2.2 By physician specialty

The survey questions supporting the secondary objectives together with their correct responses by physician specialty are presented in Table 10-17 and Table 10-18.

- A total of 1/3 (33.3%) pediatricians (95% CI: 0.8 to 90.6), 21/82 (25.6%) pediatric neurologists (95% CI: 16.6 to36.4) and 5/31 (16.1%) neurologists (95% CI: 5.5 to 33.7) provided correct responses to all 4 questions linked to the secondary objectives.
- The highest mean percentage of correct responses to any questions supporting the secondary objectives per survey participant was 83.3% (95% CI: 47.5 to 119.2) and provided by pediatricians.

Self-reported compliance (Question 7)

- Most of the physicians (66.7% [2/3]; (95% CI: 9.4 to 99.2) were pediatricians who correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet (Question 7).

Awareness, knowledge, and self-reported compliance (Questions 9, 10, and 13)

- The proportion of physicians who confirmed they would not prescribe fenfluramine for weight management (Question 9) was comparable within the subgroup except for physician of other specialty.
- All the pediatricians were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine off-label use for weight management (Question 10). A total of 54/82 (65.9%) pediatric neurologists (95% CI: 54.6 to 76.0) and 14/31 (45.2%) neurologists (95% CI: 27.3 to 64.0) were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine off-label use for weight management.
- The majority of physicians (66.7% [2/3]; 95% CI: 9.4 to 99.2) who correctly identified the content included in the Fintepla educational materials (Question 13) were pediatricians (see Table 10-18 for the correct response and Table 4.1.2 for all response choices offered in the survey).

The majority of correct responses to all questions regarding prevention of off-label use was provided by 2/3 (66.7%) pediatricians (95% CI: 9.4 to 99.2).

Table 10-17: Summary analysis of responses to questions linked to secondary objectives by physician specialty (Completed Survey Set)

	Pediatrician (N=3) n (%)	Pediatric neurologist (N=82) n (%)	Neurologist (N=31) n (%)	Other (N=2) n (%)
Number of correct responses, n (%) [95% CI] [a]				
0 correct response	0	0	1 (3.2)	1 (50.0)
1 correct response	0	14 (17.1)	5 (16.1)	0
2 correct responses	0	21 (25.6)	12 (38.7)	1 (50.0)
3 correct responses	2 (66.7)	26 (31.7)	8 (25.8)	0
4 correct responses	1 (33.3) [0.8-90.6]	21 (25.6) [16.6-36.4]	5 (16.1) [5.5-33.7]	0 [0.0-84.2]
Average number of correct responses, mean (SD) [95% CI] [b]	3.3 (0.58) [1.9-4.8]	2.7 (1.04) [2.4-2.9]	2.4 (0.97) [2.1-2.8]	2.0 (-)
Percentage of correct responses, mean (SD) [95% CI] [b]	83.3 (14.43) [47.5-119.2]	66.5 (26.12) [60.7-72.2]	58.9 (26.26) [49.2-68.5]	25.0 (35.36) [-292.7-342.7]
Correct response to all Knowledge Questions (Questions 9 and 13), n (%) [95% CI] [a]	2 (66.7) [9.4-99.2]	37 (45.1) [34.1-56.5]	17 (54.8) [36.0-72.7]	1 (50.0) [1.3-98.7]
Correct response to all Compliance Questions (Questions 7 and 10), n (%) [95% CI] [a]	2 (66.7) [9.4-99.2]	34 (41.5) [30.7-52.9]	8 (25.8) [11.9-44.6]	0 [0.0-84.2]

Table 10-17: Summary analysis of responses to questions linked to secondary objectives by physician specialty (Completed Survey Set)

	Pediatrician (N=3) n (%)	Pediatric neurologist (N=82) n (%)	Neurologist (N=31) n (%)	Other (N=2) n (%)
Correct response to all questions regarding prevention of off-label use (Questions 9, 10, and 13), n (%) [95% CI] [a]	2 (66.7) [9.4-99.2]	30 (36.6) [26.2-48.0]	8 (25.8) [11.9-44.6]	0 [0.0-84.2]
Percentage of correct responses overall, % [c]	83.3	66.5	58.9	25.0

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: For all summary analyses, missing responses were counted as an incorrect response.
Note: Correct responses to the questions associated with the secondary endpoint: Question 7=Yes; Question 9=No; Question 10=Negative; Question 13=A and B.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentages of correct responses overall were calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 4.2.2

Table 10-18: Analysis of responses to questions linked to the secondary objectives by physician specialty (Completed Survey Set; only correct responses shown)

	Pediatrician (N=3) n (%) [95% CI] [a]	Pediatric neurologist (N=82) n (%) [95% CI] [a]	Neurologist (N=31) n (%) [95% CI] [a]	Other (N=2) n (%) [95% CI] [a]
Question 7: Have you provided patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet?				
Yes	2 (66.7) [9.4-99.2]	46 (56.1) [44.7-67.0]	12 (38.7) [21.8-57.8]	0 [0.0-84.2]
Question 9: Would you prescribe fenfluramine for weight management?				
No	3 (100.0) [29.2-100.0]	80 (97.6) [91.5-99.7]	29 (93.5) [78.6-99.2]	1 (50.0) [1.3-98.7]
Question 10: You should inform patients/caregivers about the benefit-risk of using fenfluramine off-label for weight management as being:				
Negative	3 (100.0) [29.2-100.0]	54 (65.9) [54.6-76.0]	14 (45.2) [27.3-64.0]	0 [0.0-84.2]
Question 13: What content is included in the Fintepla educational materials?				

Table 10-18: Analysis of responses to questions linked to the secondary objectives by physician specialty (Completed Survey Set; only correct responses shown)

	Pediatrician (N=3) n (%) [95% CI] [a]	Pediatric neurologist (N=82) n (%) [95% CI] [a]	Neurologist (N=31) n (%) [95% CI] [a]	Other (N=2) n (%) [95% CI] [a]
Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND If there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed.	2 (66.7) [9.4-99.2]	38 (46.3) [35.3-57.7]	18 (58.1) [39.1-75.5]	1 (50.0) [1.3-98.7]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Denominator was the number of responses not missing.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
Data source: Table 4.1.2

10.4.2.2.3 By last fenfluramine prescription date

The survey questions supporting the secondary objectives together with their correct responses by last fenfluramine prescription date are presented in Table 10-19 and Table 10-20.

- The majority of physicians (30.8% [16/52]; 95% CI: 18.7 to 45.1) who provided correct responses to all 4 questions linked to the secondary objectives had prescribed fenfluramine for the last time <3 months before completing the survey.
- The highest mean percentage of correct responses to any questions supporting the secondary objectives per survey participant was 70.2% (95% CI: 62.9 to 77.5) and was provided by physicians who had prescribed fenfluramine for the last time <3 months before completing the survey.

Self-reported compliance (Question 7)

- The majority of physicians (63.5% [33/52]; (95% CI: 49.0 to 76.4) who correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet (Question 7) had prescribed fenfluramine for the last time <3 months before completing the survey.

Awareness, knowledge, and self-reported compliance (Questions 9, 10, and 13)

- The proportion of physicians who confirmed they would not prescribe fenfluramine for weight management (Question 9) was comparable with the subgroup.
- The majority of physicians (72.7% [16/22]; 95% CI: 49.8 to 89.3) who were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine

off-label use for weight management (Question 10) had prescribed fenfluramine for the last time 3 to 5 months before completing the survey.

- The proportion of physicians who correctly identified the content included in the Fintepla educational materials (Question 13) was comparable with this subgroup (see Table 10-20 for the correct response and Table 4.1.3 for all response choices offered in the survey).

The majority of correct responses to all questions regarding prevention of off-label use was provided by physicians who had prescribed fenfluramine for the last time <3 months before completing the survey (42.3% [22/52]; 95% CI: 28.7 to 56.8).

Table 10-19: Summary analysis of responses to questions linked to secondary objectives by last fenfluramine prescription date (Completed Survey Set)

	<3 months (N=52) n (%)	3 - 5 months (N=22) n (%)	≥6 months (N=31) n (%)	I do not recall (N=12) n (%)
Number of correct responses, n (%) [95% CI] [a]				
0 correct response	0	0	1 (3.2)	1 (8.3)
1 correct response	8 (15.4)	0	7 (22.6)	4 (33.3)
2 correct responses	10 (19.2)	10 (45.5)	11 (35.5)	3 (25.0)
3 correct responses	18 (34.6)	10 (45.5)	6 (19.4)	1 (8.3)
4 correct responses	16 (30.8) [18.7-45.1]	2 (9.1) [1.1-29.2]	6 (19.4) [7.5-37.5]	3 (25.0) [5.5-57.2]
Average number of correct responses, mean (SD) [95% CI] [b]	2.8 (1.05) [2.5-3.1]	2.6 (0.66) [2.3-2.9]	2.4 (1.07) [2.0-2.8]	2.3 (1.27) [1.4-3.1]
Percentage of correct responses, mean (SD) [95% CI] [b]	70.2 (26.21) [62.9-77.5]	65.9 (16.45) [58.6-73.2]	57.3 (28.28) [46.9-67.6]	52.1 (34.47) [30.2-74.0]
Correct response to all Knowledge Questions (Questions 9 and 13), n (%) [95% CI] [a]	26 (50.0) [35.8-64.2]	10 (45.5) [24.4-67.8]	15 (48.4) [30.2-66.9]	6 (50.0) [21.1-78.9]
Correct response to all Compliance Questions (Questions 7 and 10), n (%) [95% CI] [a]	25 (48.1) [34.0-62.4]	7 (31.8) [13.9-54.9]	8 (25.8) [11.9-44.6]	3 (25.0) [5.5-57.2]
Correct response to all questions regarding prevention of off-label use (Questions 9, 10, and 13), n (%) [95% CI] [a]	22 (42.3) [28.7-56.8]	6 (27.3) [10.7-50.2]	8 (25.8) [11.9-44.6]	4 (33.3) [9.9-65.1]
Percentage of correct responses overall, % [c]	70.2	65.9	57.3	52.1

CI=confidence interval; N=total number of respondents; n=number of respondents; SD=standard deviation
Note: For all summary analyses, missing responses were counted as an incorrect response.
Note: Correct responses to the questions associated with the secondary endpoint: Question 7=Yes; Question 9=No; Question 10=Negative; Question 13=A and B.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
[b] CIs were based on normal distribution function.
[c] Percentages of correct responses overall were calculated as the number of correct responses from all respondents divided by the number of questions answered by all respondents.
Data source: Table 4.2.3

Table 10-20: Analysis of responses to questions linked to the secondary objectives by last fenfluramine prescription date (Completed Survey Set; only correct responses shown)

	<3 months (N=52) n (%) [95% CI] [a]	3 - 5 months (N=22) n (%) [95% CI] [a]	≥6 months (N=31) n (%) [95% CI] [a]	I do not recall (N=12) n (%) [95% CI] [a]
Question 7: Have you provided patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet?				
Yes	33 (63.5) [49.0-76.4]	10 (45.5) [24.4-67.8]	13 (41.9) [24.5-60.9]	3 (25.0) [5.5-57.2]
Question 9: Would you prescribe fenfluramine for weight management?				
No	50 (96.2) [86.8-99.5]	22 (100.0) [84.6-100.0]	30 (96.8) [83.3-99.9]	10 (83.3) [51.6-97.9]
Question 10: You should inform patients/caregivers about the benefit-risk of using fenfluramine off-label for weight management as being:				
Negative	36 (69.2) [54.9-81.3]	16 (72.7) [49.8-89.3]	13 (41.9) [24.5-60.9]	5 (41.7) [15.2-72.3]
Question 13: What content is included in the Fintepla educational materials?				
Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND If there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed.	27 (51.9) [37.6-66.0]	10 (45.5) [24.4-67.8]	15 (48.4) [30.2-66.9]	7 (58.3) [27.7-84.8]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Denominator was the number of responses not missing.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
Data source: Table 4.1.3

10.4.2.3 Sensitivity analyses

10.4.2.3.1 By survey completion status

The survey questions supporting the secondary objectives together with their correct responses by survey completion status are presented in Table 10-21.

Self-reported compliance (Question 7)

- Of the 118 physicians who completed the whole survey (also referred to as completers), 60 (50.8%) physicians (95% CI: 41.5 to 60.2) correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet (Question 7).

- One physician who was eligible but did not complete the survey (also referred to as noncompleter) also correctly identified providing patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet.

Awareness, knowledge, and self-reported compliance (Questions 9, 10, and 13)

- A total of 113/118 (95.8%) completers (95% CI: 90.4 to 98.6) and the noncompleter confirmed they would not prescribe fenfluramine for weight management (Question 9).
- A total of 71/118 (60.2%) completers (95% CI: 50.7 to 69.1) were aware of their responsibility to inform patients/caregivers of the negative benefit-risk of fenfluramine off-label use for weight management (Question 10).
- A total of 59/118 (50.0%) completers (95% CI: 40.7 to 59.3) correctly identified the content included in the Fintepla educational materials (Question 13, see Table 10-21 for the correct response and Table 4.1.4 for all response choices offered in the survey).

Table 10-21: Analysis of responses to questions linked to the secondary objectives by survey completion status (Eligible Survey Set; only correct responses shown)

	Completer (N=118) n (%) [95% CI] [a]	Noncompleter (N=1) n (%) [95% CI] [a]
Question 7: Have you provided patients/caregivers who may initiate fenfluramine the dedicated educational materials and the latest version of the package leaflet?		
Yes	60 (50.8) [41.5-60.2]	1 (100.0) [2.5-100.0]
Question 9: Would you prescribe fenfluramine for weight management?		
No	113 (95.8) [90.4-98.6]	1 (100.0) [2.5-100.0]
Question 10: You should inform patients/caregivers about the benefit-risk of using fenfluramine off-label for weight management as being:		
Negative	71 (60.2) [50.7-69.1]	0 [0.0-97.5]
Question 13: What content is included in the Fintepla educational materials?		
Patients/caregivers should be informed about the negative benefit-risk of fenfluramine in weight management AND If there is a suspicion that fenfluramine is used in weight management for other people, patients/caregivers should be reminded that fenfluramine may only be taken by the person for whom it was prescribed.	59 (50.0) [40.7-59.3]	0 [0.0-97.5]

CI=confidence interval; N=total number of respondents; n=number of respondents
Note: Denominator was the number of responses not missing.
[a] 95% exact 2-sided CIs were calculated using the Clopper-Pearson method.
Data source: Table 4.1.4

10.5 Other analyses

No other analyses were conducted for the final study report.

10.6 Adverse events/adverse reactions

This study was not designed to capture safety events associated with the use of fenfluramine. Therefore, the reporting of adverse events/adverse drug reactions was not applicable.

11 DISCUSSION

11.1 Key results

A total of 705 physicians were contacted from Austria, France, Germany, Italy, Spain, and UK. Final data were available on 119 survey respondents, 118 of whom completed the questions related to the primary objective.

Physician characteristics

All but 2/118 physicians had spent ≥5 years working in medical practice, and 21/118 (17.8%) of physicians had spent >25 years (Question 17). The most common specialty was pediatric neurologist (82/118 [69.5%]) (Question 18).

The physicians prescribed fenfluramine most commonly to patients aged 2 to 11 years (79/118 [66.9%]) (Question 20.1). The majority of the physicians (85/118 [72.0%]) had prescribed fenfluramine for the first time ≥6 months before completing the survey (Question 20.2) and 44.1% (52/118) for the last time <3 months before completing the survey (Question 20.3). Half of the physicians (59/118 [50.0%]) were familiar with the long-term Fintepla post-authorization safety registry (Question 21) study that collects data on the long-term safety of fenfluramine in routine practice and the risks of VHD and PAH. The majority of the physicians had not recruited any patients for the Fintepla post-authorization safety registry study (78/118 [66.1%]) (Question 22).

Primary objectives

In this final analysis, the percentage of physicians providing correct responses to all 9 questions supporting the primary objectives was 20.3% (24/118; 95% CI: 13.5 to 28.7).

Physicians were asked about their awareness and knowledge of the fenfluramine educational materials on the requirement of echocardiogram follow up. Most physicians confirmed having received (85.6% [101/118]) and read (84.7% [100/118]) the Fintepla educational materials regarding the minimization of risks associated with fenfluramine (Questions 4 and 5), and 82.2% (97/118) also correctly identified the type of available Fintepla educational materials for fenfluramine (Question 6). The majority of physicians (95.8% [113/118]) correctly indicated the potential risks associated with higher than approved doses of fenfluramine (Question 8). However, the proportions of physicians who correctly identified which actions should be taken for all patients before initiating treatment with fenfluramine (Question 11) was 50.0% (59/118; 56.8% [21/37] in Austria/Germany and 46.9% [38/81] in countries other than Austria/Germany). A total of 77.1% (91/118) correctly identified the frequency with which echocardiogram monitoring should be conducted during treatment with fenfluramine (Question 14).

The physicians were also asked questions to assess self-reported compliance to the recommendations provided in the educational material on echocardiogram follow up. Almost all physicians (93.2% [110/118]) identified echocardiogram as the correct regular monitoring that should be performed during treatment with fenfluramine (Question 12). Also, almost all physicians (94.1% [111/118]) correctly identified the need for appropriate monitoring and follow up if an echocardiogram indicates pathological valvular changes or suspicion of PAH (Question 15), and 99.2% (117/118) of physicians understood the requirement to inform

patients/caregivers about the need to perform echocardiogram monitoring before and during treatment with fenfluramine (Question 16).

Secondary objectives

In this final analysis, the mean percentage of correct responses to any questions supporting the secondary objectives per survey participant was 64.2% (95% CI: 59.3 to 69.1), whereas the total percentage of physicians providing correct responses to all 4 questions supporting the secondary objectives was 22.9% (27/118; 95% CI: 15.7 to 31.5).

Physicians were asked questions about their knowledge on prevention of off-label use of fenfluramine for weight management. A total of 113/118 (95.8%) physicians confirmed that they would not prescribe fenfluramine for weight management (Question 9), and 59/118 (50.0%) physicians correctly identified the content related to weight management included in the educational materials (Question 13).

Physicians were also asked to assess self-reported compliance. A total of 60/118 (50.8%) physicians reported that they had provided patients/caregivers the dedicated educational materials and the latest version of the package leaflet (Question 7), and 60.2% (71/118) of physicians were aware that they should have informed patients/caregivers about the negative benefit-risk of fenfluramine off-label use for weight management (Question 10).

11.2 Limitations

This noninterventional, cross-sectional, survey design is associated with some methodological limitations.

All data supplied were self-reported by the physician without the possibility to objectively verify the information. The quality of the data was dependent on the completeness and accuracy of the data entered. However, the survey contained validated questions with standardized response formats, and the EDC contained automated quality checks to improve data quality for analysis. Additionally, to reduce information bias, questions were close-ended to avoid errors in interpreting free text during analysis. Physicians did not have the possibility to come back and change their responses once submitted and were not contacted to clarify or revise their survey responses.

The study uses descriptive statistics and, although deemed sufficient for the objectives, it was not possible to determine whether findings were statistically significant or due to chance. Also, no baseline data (ie, no pre-effectiveness of Risk Minimization Measure data) were available to compare results between before and after the educational material was introduced to see what difference the education materials made.

11.3 Interpretation

It was estimated that approximately 1780 physicians could potentially prescribe fenfluramine within the target EU countries (SAP Section 3), with a 20% to 25% response rate for the survey expected. This final analysis included data from 119 survey respondents (705 Invitation Letters distributed in Austria, France, Germany, Italy, Spain, and UK).

During the analysis of the questions covering the description of the 119 eligible respondents, off-label use of fenfluramine in patients <2 years of age was identified: 22.0% (26/118) of the physicians reported prescribing fenfluramine in patients <2 years of age (Question 20.1).

In addition, in the questions covering the description of the respondents, it was noted that half of the physicians (50.0% [59/118]) were not familiar with the long-term Fintepla patient registry (Question 21), although it is mentioned in the educational materials. This registry of patients treated with Fintepla (Study EP0218) was a requirement from the PRAC to assess the long-term cardiac safety of fenfluramine as prescribed in routine clinical practice with a focus on the incidence of VHD and PAH. The Fintepla registry was launched at the time of survey data collection in all the countries except for Spain and Italy.

The Protocol-defined success criterion for effectiveness of the additional risk minimization measures was that ≥80% of physicians should provide correct answers to the survey questions related to the primary objectives' variables. In this final analysis, 20.3% (24/118; 95% CI: 13.5 to 28.7) of physicians provided correct responses to all 9 questions supporting the primary objectives, which did not reach the Protocol-defined criterion.

From the 9 questions supporting the primary objectives, 7 were answered correctly by over 80% of the physicians (4 of them over 90%). However, Questions 11 and 14 were answered correctly by 50.0% (59/118) and 77.1% (91/118), respectively, which greatly influenced the overall result:

- The correct answer for Question 11 ("Prior to initiating treatment with fenfluramine, all patients:") was "should undergo an echocardiogram", "should be checked to establish a baseline to exclude any pre-existing VHD or PAH", and "should be considered for eligibility for the long-term patient safety registry" for Austria/Germany and "should undergo an echocardiogram" and "should be checked to establish a baseline to exclude any pre-existing VHD or PAH" for countries other than Austria/Germany. Overall, 50.0% [59/118] of the physicians selected the correct response (56.8% [21/37] in Austria/Germany and 46.9% [38/81] in countries other than Austria/Germany). These data show that the educational materials were partially successful at raising awareness about the need to conduct the mandatory tests before starting treatment. In this study, data were collected 12 to 18 months after the implementation of educational materials in each country. In countries other than Austria/Germany, respondents inadvertently considered electrocardiography as a requirement prior to initiating treatment with fenfluramine, in addition to echocardiogram and baseline establishment of any pre-existing VHD or PAH (49.4% [40/81]; Table 3.1).
- The correct answer for Question 14 ("During fenfluramine treatment, echocardiogram monitoring should be conducted:") was selected by 91/118 (77.1%) physicians ("every 6 months for the first 2 years and then annually thereafter"). However, all but 3/118 of the remaining physicians selected a higher frequency of monitoring ("every 3 months for the first 2 years and then every 6 months thereafter" was selected by 14/118 (11.9%) physicians and "every 6 months" by 10/118 (8.5%) physicians. Hence, the results show that the educational materials were successful at raising awareness about the requirement for regular monitoring and that the minimum frequency is likely to be met. Two of the physicians selected the answers "annually" and 1 physician selected "none of the above."

The majority of physicians (95.8% [113/118]) correctly indicated the potential risks associated with higher than approved doses of fenfluramine (Question 8). It should be noted that, following the completion of the pivotal clinical studies in Dravet Syndrome and Lennox-Gastaut Syndrome (in the post-marketing period) cases of VHD and PAH were identified as occurring with

approved doses of fenfluramine as well (EMA, Fintepla SmPC, 2024). Question 8 was, however, consistent with the benefit/risk data available at that time.

A total of 27/118 (22.9%) physicians (95% CI: 15.7 to 31.5) provided correct responses to all 4 questions linked to the secondary objectives. Correct responses to all questions regarding prevention of off-label use were provided by 40/118 (33.9%). Many physicians (95.8% [113/118]) confirmed they would not prescribe fenfluramine for weight management. A total of 59/118 (50.0%) physicians (95% CI: 40.7 to 59.3) correctly identified the content included in the Fintepla educational materials, however, 38/118 (32.2%) physicians inadvertently identified importance of electrocardiogram monitoring as the content included in the Fintepla educational materials. The data indicates that the educational materials were effective in raising awareness about the off-label use for weight management.

Overall, although the Protocol-defined success criterion for effectiveness of the additional risk minimization measures was not met in the final analysis, the data confirm that the physicians had access to and read the educational materials and that the implementation of the CAP was being successful.

11.4 Generalizability

The survey recruitment strategies intended to recruit a heterogeneous sample of prescribers for participation. Although the sample of physicians invited to participate was a random sample of all Fintepla prescribers in the countries selected for participation, the sample was self-selected since they voluntarily responded to the invitation to participate. The results may likely have a positive bias, ie, they will appear more educated than the population of all potential prescribers of Fintepla (Madison et al, 2016).

12 OTHER INFORMATION

No other information was available for this final analysis.

13 CONCLUSION

- The study had a good response rate, with 118 responses (completed response to the primary endpoint questions) obtained (minimum sample size of 80 physicians targeted).
- The respondent characteristics were consistent with the target population (neuropediatricians or physicians specialized in pediatrics or neurology with experience in the treatment of epilepsy).
- The additional risk minimization measures for Fintepla were below what was deemed effective based on the Protocol-defined success criteria (ie, ≥80% of physicians should provide correct answers to the survey questions related to the primary objectives' variables). A contributor to missing this target could be the potential lack of knowledge about the long-term Fintepla patient registry study, which had not started at the time of the survey in Spain and Italy. Additionally, prescribers selecting a higher than recommended frequency than for echocardiogram monitoring during fenfluramine treatment could have also contributed to missing this target.
- Based on final analysis, the physicians were well aware of the risks of VHD and PAH as a high level of compliance with echocardiogram monitoring after initiating fenfluramine treatment was reported. Physicians also understand their role to inform patients/caregivers

about these risks. However, the educational materials seem partially successful in educating physicians about echocardiograms to exclude any pre-existing VHD/PAH prior to and during fenfluramine treatment.

- It is noteworthy to state that the physicians were aware of not prescribing fenfluramine for weight management. Thus, the risk of off-label use of fenfluramine for weight management is minimized. However, about 60% of the physicians were aware that they should have informed patients/caregivers about the negative benefit-risk of fenfluramine off-label use for weight management. Additionally, 50% of the physicians identified the content included in the educational materials and provided patients/caregivers the dedicated educational materials and the latest version of the package leaflet. However, since fenfluramine is available only on prescription, the high level of awareness about the benefit-risk of prescribing fenfluramine for weight management among the physicians is a key element to prevent the risk.
- In conclusion, some risk minimization measures were partially effective. The ongoing distribution of the updated educational material is an opportunity to re-emphasize the risk minimization measures, the role of physicians, and the importance of these activities. The benefit-risk balance for the use of Fintepla in patients with Dravet syndrome and Lennox-Gastaut Syndrome remains unchanged. UCB will continue to implement new measures to achieve its goal of educating both prescribers and patients/caregivers on identified VHD/PAH risks.

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APPENDICES

Not Applicable.