Title	**Drug utilization study with VYVANSE® in Australia for Binge Eating Disorder**
Protocol version identifier	Version 2.0
Date of last version of protocol	Version 1.0 of 05 February 2018
Active substance	Pharmacotherapeutic group: centrally acting sympathomimetic ATC code(s): N06BA12 Active substance: Lisdexamfetamine
Medicinal product	VYVANSE ® Capsules: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg
Product reference	ARTG ID: 284019, 199227, 284020, 199226, 284021, 199228
Marketing authorisation holder(s)	Shire Australia Pty Limited (Shire is now part of Takeda) Level 39 Grosvenor Place 225 George Street Sydney, NSW 2000 Australia
Research question and objectives	Research question: Design and implementation of a drug utilization study (DUS) for on an annual basis 3 years in Australia to evaluate drug utilization of VYVANSE® with a special interest in BED, and to monitor its off-label use. Primary objective: • To characterize patients who are prescribed VYVANSE®, with a specific focus on compliance with o The indication o Patients' age relative to the product information o Visits and measurements performed during the first year of treatment Secondary objectives: • To describe prescribing patterns of VYVANSE® for BED • To monitor the effectiveness of the risk minimization measures described in the risk management plan (RMP) based on the outcomes measured in the DUS

Country of study	Australia
Author	IQVIA, Germany
Marketing authorisation holder(s)	Shire Australia Pty Limited (Shire is now part of Takeda) Level 39 Grosvenor Place 225 George Street Sydney, NSW 2000 Australia
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1 TABLE OF CONTENTS

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Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AMPCo	Australasian Medical Publishing Company
AMSRS	Australian Market Research Society
ATC	Anatomical therapeutic chemical
BE(D)	Binge eating (disorder)
CNS	Central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUS	Drug utilisation study
EPR	Electronic patient record
ESOMAR	European Society for Opinion and Market Research
FDA	Food and Drug Administration
GDS	Global Drug Safety
ICD	International Classification of Diseases
MAOI	Monoamine oxidase inhibitors
RMP	Risk management plan
SAP	Statistical analysis plan
SAS	Statistical analysis system
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SD	Standard deviation
SOP	Standard operating procedure(s)
TBD	To be determined
TGA	Therapeutic Goods Administration
US	United States
WHO	World Health Organization

3 RESPONSIBLE PARTIES

Sponsor: Shire Pharmaceuticals (now part of Takeda)

Project team:
Global Outcomes Research & Epidemiology

Takeda Pharmaceutical Company Limited

[redacted], MD, PhD (e-mail: [redacted])

[redacted], PhD; Takeda (e-mail: [redacted])

[redacted], PhD; Takeda (e-mail: [redacted])

Contractor: IQVIA

IQVIA is a member of Medicines Australia and adheres to their Code of Conduct. IQVIA Market Research personnel are members of the Australian Market & Social Research Society (AMSRS) and follow the Code of Professional Behaviour.

Project team:
The project will be managed by the IQVIA Centre of Excellence in Retrospective Studies. As team members are likely to change over the project period of 3 years, no individual names are listed here. All project tasks will be performed by adequately qualified staff, including experienced senior project coordinators, epidemiologists, and medical experts.

Statistical analysis will be conducted by IQVIA in-house global and local experts.

4 ABSTRACT

Title	Drug utilization study with VYVANSE® in Australia for Binge Eating Disorder
Rationale and background	Shire Pharmaceuticals received marketing approval for VYVANSE® for treatment of binge eating disorder (BED) in Australia on 22 January 2018. Shire Pharmaceuticals plans to conduct a drug utilization study (DUS) for three years as part of the risk management plan for VYVANSE® in Australia.
Research question and objectives	Research question: Design and implementation of a drug utilization study (DUS) on an annual basis for 3 years in Australia to evaluate drug utilization of VYVANSE® with a special interest in BED, and to monitor its off-label use. Primary objective: • To characterize patients who are prescribed VYVANSE®, with a specific focus on compliance with o The indication o Patients' age relative to the product information o Visits and measurements performed during the first year of treatment Secondary objectives: • To describe prescribing patterns of VYVANSE® for BED • To monitor the effectiveness of the risk minimization measures described in the risk management plan (RMP) based on the outcomes measured in the DUS
Study design and data sources	This is a drug utilization study using longitudinal secondary patient level data of a dispensing database and primary data obtained from repeated cross-sectional surveys among physicians. A single database with all relevant information does not exist. Therefore, data from the NostraData dispensing database, a longitudinal patient-level prescription database, are supplemented with data from a physician survey.
Population	Patients who have been prescribed VYVANSE® at least once during the reporting period without evidence of use of VYVANSE® for ADHD treatment.
Variables	Both data sources: • Data on patterns of drug use o Prescribed or calculated average daily dose o First time/repeat use o Treatment duration o Discontinuation of VYVANSE® therapy o Switches from/to VYVANSE® o Co-prescriptions of medications of interest

	• Prescriber specialty
	Additional in the physician survey:
	• Indication of use (diagnosis)
	• Presence/absence of contraindications
	• Patient characteristics
	  ○ Age
	  ○ Gender
	• Frequency of monitoring of cardiovascular status (blood pressure, heart rate)

Study size	Prescription database: All prescriptions for VYVANSE® without evidence of its use for ADHD treatment in the NostraData database in Australia will be analysed. Physician survey: It is planned to collect data for 150 patients, who have been prescribed VYVANSE® at least once during the study period for an indication other than ADHD. Data of 100 patients will be provided by psychiatrists expected to treat patients with BED. In addition, data for 50 patients will be provided by other physician specialties to allow a more comprehensive understanding of real-world prescribing.
Data analysis	All analyses conducted will be descriptive. The description of missing data for each outcome of interest will be provided. For continuous variables, the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be presented. Categorical variables will be displayed with frequencies and percentages. A detailed statistical analysis plan (SAP) will be agreed on prior to the start of the analysis.
Milestones	VYVANSE® approval for BED: 22 January 2018 Start of observation period: 17 February 2018 (launch date) Start of data collection: June 2019 End of data collection: August 2021 First study report: October 2019 Second study report: October 2020 Last (third) study report: October 2021

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5 AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
Original protocol Version 1.0	05 Feb 2018	New protocol	Not applicable	Not applicable
Amended protocol Version 2.0	11 Oct 2019			
		Title page	Addition to the name of the MAH: "Shire is now part of Takeda"	Change of business name as of January 2019
		Title page Section 3. Responsible parties	Change of MAH contact person, of project team and of e-mail addresses	Change in staff Administrative changes of contact information at Shire when it became part of Takeda
		Abstract Section 6 Milestones: Section 12 Reporting:	Specification of milestones	After approval and launch of VYVANSE® for BED it was possible to clearly define milestones
		Section 9.1: Study design Section 9.4.2 Physician survey:	Amendment of physician specialties who are eligible to provide data	As specialties other than psychiatrists (e.g., general practitioners) were also noted to be treating patients with VYVANSE® for BED, data of patients reported by other specialties will also be included in the study
		Section 9.2.1.2 Sensitivity analyses: Section 9.4.1 Data sources:	Amendment of a third sensitivity analysis of prescription data	Exclusion of patients who received their prescription of VYVANSE® at <18 years of age
		Section 9.2.2 Physician survey:	Amendment of inclusion and	Specification of inclusion and

			exclusion criteria for physician survey	exclusion criteria, as they had not been shown in the original protocol in detail
		Section 9.4.1Longitudinal prescription databases: Section 9.5: Study size and feasibility Throughout the document when applicable	Revision of the description of the pharmacy data source	Updates due to amendments of the pharmacy database: pharmacy coverage increased from 70% to 82% Age information available for some patients Unique ID allows tracking of patients across pharmacies
		Abstract: Section 9.4.2 Physician survey: Section 9.5: Study size and feasibility Throughout the document when applicable	Sample size for Physician survey was increased from 100 patients to 150 patients: 100 patients reported by psychiatrists, 50 patients reported by other specialties	Real world data showed evidence for treatment of BED with VYVANSE® by other specialties, which is also of interest of the survey
		Section 13: References	Update of date of product information to 24 January 2018	Release of product information by TGA

6 MILESTONES

Milestone	**Planned date**
VYVANSE® approval for BED:	22 January 2018
Start of observation period:	February 2018
Start of data collection:	June 2019
End of data collection:	August 2021
First study report:	October 2019
Second study report:	October 2020
Last (third) study report:	October 2021

7 RATIONALE AND BACKGROUND

7.1 Binge eating disorder

Binge eating disorder is gaining recognition as a serious public health problem. BED is characterised by recurrent episodes of excessive food consumption accompanied by a sense of loss of control and psychological distress but without the inappropriate compensatory weight-loss behaviours of bulimia nervosa. Since the publication of the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM–V), BED is an officially recognized diagnosis.[1] BED lacks approved pharmacotherapies and is associated with obesity and psychiatric comorbidities.

7.2 Causes of BED

Genetic, pharmacologic findings and animal models suggest that pathologic overeating may be related to dysfunction of the dopamine and norepinephrine systems, resulting in a hyper-responsiveness to reward caused by highly palatable and calorically dense foods.[1] In individuals with BED, food stimulation may generate abnormal dopamine responses, and inhibition of dopamine transport by methylphenidate leads to greater increases of dopamine levels within the caudate of patients with BED compared to those without BED.[2]

7.3 Treatment of BED

Cognitive behavioural therapy and/or interpersonal psychotherapy reduce BE behaviour, but not all patients respond adequately. Antidepressants are effective in reducing the frequency of BE behaviour but fail to have substantial weight-loss effects[2] and are not licenced for treatment of BED. Since 2015, lisdexamfetamine dimesilate (VYVANSE®) has been indicated in the treatment of BED[1] in the US, where it was the first approved medication for this disorder.

7.4 Lisdexamfetamine dimesilate (VYVANSE®)

Lisdexamfetamine dimesilate (VYVANSE®) has been authorized and marketed in the United States (US), Canada, Australia (brand name: VYVANSE®), Brazil (brand name: Venvanse®) and European countries (brand name Elvanse®) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). VYVANSE® is classified as a centrally acting sympathomimetic (ATC code N06BA12), is sold as capsule for once-a-day oral administration and is available in various strengths (20 mg to 70 mg VYVANSE®)[1]. In the US, VYVANSE® was also approved for moderate to severe binge eating disorder (BED) in 2015. At that time, VYVANSE® was the only medication approved for the treatment of BED[1]. Approval of VYVANSE® for treatment of BED was also given in Canada in 2016 and received in Australia in January 2018.

The efficacy of VYVANSE® in the treatment of ADHD was established on the basis of three short-term controlled trials in children ages 6 to 12 years, one short-term controlled trial in adolescents ages 13 to 17 years, two short-term controlled trials in adults, one maintenance trial in adults and two randomized withdrawal trials in children and adolescents (6 to 17 years) and adults (18 to 55 years). Efficacy of VYVANSE® in the treatment of BED has been established in two 12-week randomised, double-blind, multicentre, parallel-group, placebo-controlled trials in adults (18 to 55 years) with moderate to severe BED[3].

The indication for VYVANSE® for treatment of BED given in the Product Information is as follows[3]:

VYVANSE is indicated for the treatment of moderate to severe BED in adults when non-pharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a psychiatrist.

Need for comprehensive treatment programme: VYVANSE is indicated as part of a total treatment program for BED that optimally includes other measures (nutritional, psychological, and medical) for patients with this disorder. When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Limitation of Use: VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established. Prescribers should consider that serious cardiovascular events have been reported with this class of sympathomimetic drugs. The BED clinical trials were not designed to assess cardiovascular safety. While there is an accumulation of safety data with VYVANSE use in the ADHD population, this is of limited relevance regarding cardiovascular risk in the BED population. Given the higher cardiovascular risk associated with obesity, the BED population may be at a higher risk. See Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Cardiovascular disease and 4.2 DOSE AND METHOD OF ADMINISTRATION.

Long term use: for BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with VYVANSE is required. Periodic re-evaluation of the usefulness of VYVANSE for the individual patient should be undertaken. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

Based on this label, inappropriate use of VYVANSE® may include:

- Use for patients with a diagnosis other than ADHD or BED
- Use for age groups other than
    - ADHD: 6-55 years
    - BED: 18-55 years
- Prescribed dose of greater than 70 mg/day

7.5 Background and rationale of the current study

VYVANSE® for treatment of BED in adults in Australia was received on 22 January 2018. The full indication is presented in Section 7.4. In order to evaluate drug utilization and to monitor off-label use of VYVANSE® in Australia, Shire has proposed to conduct a drug utilization study (DUS) as part of the risk management plan (RMP) for VYVANSE®.

In this DUS, electronic patient-level dispensing data and patient medical record data, covering a period of 3 years post-product launch will be analysed. Annual study reports will be generated by IQVIA, sent to Shire, and then submitted to the Therapeutic Goods Administration (TGA) by Shire.

This protocol specifies the objectives of the study, describes the methodology and data sources, outlines the plans for statistical analysis, and details the tasks and timelines for the project.

8 RESEARCH QUESTION AND OBJECTIVES

Research question:

Design and implementation of a drug utilization study (DUS) on an annual basis for 3 years in Australia to evaluate drug utilization of VYVANSE® with a special interest in BED, and to monitor its off-label use.

Primary objective:

- To characterize patients who are prescribed VYVANSE®, with a specific focus on compliance with
    - The indication
    - Patients' age relative to the product information
    - Visits and measurements performed during the first year of treatment

Secondary objectives:

- To describe prescribing patterns of VYVANSE® for BED
- To monitor the effectiveness of the risk minimization measures described in the RMP based on the outcomes measured in the DUS

9 RESEARCH METHODS

9.1 Study design

This is a DUS using longitudinal secondary patient level data of a dispensing database and primary data obtained from repeated cross-sectional surveys among physicians.

A single longitudinal data source that would represent the Australian BED population adequately and contain variables needed to monitor off-label use does not exist. Therefore, this study will combine data from two sources of patient-level drug utilization data for VYVANSE®:

- NostraData database:
    - Longitudinal patient level prescription dispensing database
- Physician survey:
    - De-identified patient data provided by representative psychiatrists and other physicians expected to treat patients with BED in Australia.

In the NostraData database, actual drug dispensing data are collected, which allows for the generation of information on actual drug usage. However, these data do not contain certain patient variables, such as age and indication, needed to monitor potential off-label use. Therefore, these data must be supplemented with another data source. The physician survey will provide the data not included in the NostraData database. More detailed information on the database and physician survey is given in Section 9.4.

9.2 Setting

Prior to conducting the survey and the first analyses of prescription data, IQVIA recommends a feasibility assessment to verify that enough prescribers of VYVANSE® who treat patients with BED will be available to ensure that the required sample size will be reached. If, based on the feasibility assessment, sample size is too low (e.g., due to delay in launch or slow uptake), data collection, analysis and report (Section 6) may need to be postponed.

The overall observational period will cover 36 months after the launch date.

9.2.1 Dispensing database (NostraData)

9.2.1.1 Main prescription data analysis:

Patients must fulfil the following criteria to be eligible for the main prescription data analysis:

- Inclusion criterion:
    - At least one prescription for VYVANSE® recorded in the NostraData database in Australia.

9.2.1.2 Sensitivity analysis of prescription data

In order to exclude patients likely to have received VYVANSE® for treatment of ADHD, three sensitivity analyses will be conducted.

Patients must fulfil the following criteria:

<u>For all sensitivity analyses (sensitivity analysis I, II and III):</u>

- Inclusion criterion:
    - At least one prescription for VYVANSE® recorded in the NostraData database in Australia during the defined observation period of the study.
- Exclusion criteria:
    - Evidence of use for VYVANSE® for treatment of ADHD, as shown by prescription records for ADHD medication other than VYVANSE® at any time;
    - Record of at least one VYVANSE® prescription prior to launch of VYVANSE® for BED (17 Feb 2018).

<u>Additional exclusion criteria for the specific sensitivity analyses:</u>

- For sensitivity analysis I:
    - Prescriptions for VYVANSE® issued by pediatricians or child psychiatrists.
- For sensitivity analysis II:
    - Prescriptions for VYVANSE® issued by all prescribers other than psychiatrists (e.g., pediatricians, GPs).
- For sensitivity analysis III:
    - Prescriptions for VYVANSE® issued by pediatricians or child psychiatrists;
    - For patients with age available, patients with evidence for age at first prescription below 18 years.

9.2.2 Physician survey

It is planned to collect data for 150 patients, who have been prescribed VYVANSE® at least once during the study period for an indication other than ADHD. Data of 100 patients will be provided by psychiatrists expected to treat patients with BED as described in Section 9.4.2. In addition, data for 50 patients will be provided by other physician specialties.

Physicians prescribing VYVANSE® will be instructed to select the patient record based on the last patient they have seen, for whom at any time in the last 12 months they have prescribed VYVANSE® for indications other than ADHD (whether VYVANSE® was prescribed at that last visit).

Physicians will be included in the analysis of the patient data if the following inclusion criteria are met and the exclusion criterion is not met:

- Inclusion criteria:
    - The physician completed the "Physician Demographics and Practice Information" section of the survey.
    - The physician prescribed VYVANSE® for indications other than ADHD in the last 12 months for at least one patient.
- Exclusion criterion:
    - The physician entered ADHD as the main indication for prescription of VYVANSE® (Q03) for all reported patients (if any patients were reported).

Patient population

Patients must meet the following inclusion criterion and not meet the follow exclusion criterion to be eligible for the analysis:

- Inclusion criterion:
    - Physician entered data for the patient until at least question 3 (Q03; main indication).
- Exclusion criterion:
    - Physician entered ADHD as main indication for prescription of VYVANSE® (Q03) for the patient.

9.3 Variables

The study aims to characterize patients who are prescribed VYVANSE® and describe prescribing patterns of VYVANSE® among physicians in Australia.

The following information will be obtained from the NostraData database:

- Direct prescription information
    - Patient information
        - First time user
        - Repeat user
        - Number of prescriptions per patient
    - Prescriber information
        - Physician specialty
    - Co-prescriptions of interest
        - MAOIs
        - SSRIs
        - SNRIs
        - Guanfacine hydrochloride
        - Other central nervous system (CNS) stimulants
    - Prescribed dose
- Information derived/ calculated from the NostraData database:
    - Duration of exposure
    - Discontinuation of therapy
    - Switch of therapy (from VYVANSE® / to VYVANSE®)
    - Average daily dose

The following information will be collected from the physician survey:

- Patient information
    - Age
    - Gender
    - First time user
    - Repeat user
- Prescriber information
    - Physician specialty
    - Location
    - Graduation year
- Treatment information
    - Duration of treatment

    - Prior treatment (other medication or psychotherapy)
    - Concomitant treatment
        - Co-prescriptions of interest (as above)
        - Psychotherapy
    - Discontinuation of therapy
    - Switch of therapy (from VYVANSE® / to VYVANSE®)
    - Prescribed daily dose
- Disease-related information
    - Date of initial diagnosis
    - Indication of use (diagnosis) according to WHO ICD-10 classification
- Presence / absence of contraindications
    - Advanced arteriosclerosis
    - Symptomatic cardiovascular disease including cardiac arrhythmia, ischaemic heart disease
    - Moderate to severe hypertension
    - Hyperthyroidism
    - Known hypersensitivity or idiosyncratic reaction to sympathomimetic amines or any of the excipients
    - Glaucoma
    - Agitated states such as severe anxiety, tension and agitation
    - Use during or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result)
    - Phaeochromatocytoma
    - Tourette's syndrome, other tic disorders
    - Patients who currently exhibit severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency
    - Patients with known drug dependence or alcohol abuse
- Frequency of monitoring of cardiovascular status (blood pressure, heart rate)

9.4 Data sources

9.4.1 Longitudinal prescription databases

The NostraData database is a longitudinal prescription database containing information on dispensed prescriptions at the patient level based on retail pharmacy data, including treatment initiation and renewals; however, no hospital-based pharmacies are included. NostraData Australia currently includes data from approximately 82% of all Australian pharmacies.

In the NostraData database, information is collected about medication dispensed, dose, form, strength, prescriber specialty and cost. Information about the age of the patient is partially available (if reported by the pharmacy). Patients can be tracked across pharmacies via a unique identifier (ID). This ID, coupled with the number of prescriptions being dispensed, enables classification of whether an individual is a new, switching, or repeat patient. Additional detail enables classifying which products the patient has switched between and the prescriber type driving these trends.

In this study, NostraData database data are used at the patient level. Thereby all patients and prescriptions without evidence of the use of VYVANSE® for ADHD will be tracked to determine the number of patients who have been initiated on VYVANSE® per 12-month period, the number of patients switching between products, number of repeats and the number of discontinuations. Information on VYVANSE® dose, treatment duration and specialty of treating physician will also be extracted. Suspected overdoses over the maximum recommended daily dose of 70 mg/day[3] can either be calculated based on the number of prescription renewals and dose thereon or directly assessed from physicians' dose instructions. Prescriptions, if any, by physicians outside the expected specialties could also be detected.

A limitation of these prescription data is the lack of information on diagnoses and to some extent on age, which are important for monitoring potential off-label use. These data will be obtained from the physician survey described in Section 9.4.2.

As a result of missing information on the diagnosis, prescriptions for VYVANSE® intended to treat BED cannot be clearly distinguished from prescriptions intended to treat ADHD in the NostraData database. Therefore, three sensitivity analyses will be performed in addition to the main analysis. In all three sensitivity analyses, all prescriptions of patients who received any other type of ADHD medication will be excluded, as these patients are assumed to have received VYVANSE® for treatment of ADHD. Patients with prescriptions by paediatricians or child psychiatrists (sensitivity analysis I) will also be excluded for the same reason. In sensitivity analysis I, patients who have received prescriptions by other specialties (e.g., gastroenterologists) are not excluded, whereas in sensitivity analysis II, patients with prescriptions by physicians other than psychiatrists are excluded. In sensitivity analysis III, patients with prescriptions by paediatricians or child psychiatrists and all patients <18 years of age are excluded.

9.4.2 Physician survey

Representative psychiatrists and physicians of other specialties who may potentially treat BED will be randomly selected throughout Australia. De-identified patient data provided by them will be used to supplement information acquired from the prescription database. The information will be collected electronically using an online survey. For this survey, data relevant for the study objectives will be extracted from the patient records by physicians.

Physician sample

Recruitment will occur from psychiatrists and from other specialties who are most likely to treat patients with BED. Physicians will be screened as described below in more detail.

Suitable lists of physicians (e.g., OneKey lists) will be used for this study to ensure that an unbiased sample of psychiatrists is selected. Furthermore, physicians from other specialties who may treat patients with BED (e.g., general practitioners, paediatricians) will be contacted, based on suitable lists. The lists will be supplemented by the Australian Medical Publishing Company (AMPCo) list of relevant physicians, which is generated in part from the Australian Medical Association membership.

Patient sample

It is planned to collect data for 150 patients, who have been prescribed VYVANSE® at least once during the study period for an indication other than ADHD. Data of 100 patients will be provided by up to 100 psychiatrists expected to treat patients with BED. In addition, data for 50 patients will be provided by up to 50 physicians of other specialties.

Randomly selected physicians will be invited to participate in the survey. Participants that did not treat BED or did not prescribe VYVANSE® in the last 12 months will be excluded from the survey during the screening stage. Due to the low prescribing base for BED, no quotas for physicians of specialties other than psychiatrists will be set. Recruitment of participants will end if a maximum of a total of 150 records has been reached.

Recruitment

An experienced independent field team will start physician recruitment. A fax invitation will be sent at the end of the first year after the launch of VYVANSE® for treatment of BED to physicians who may be suitable for participation in the survey. The fax invitation will include questions regarding the following:

- The number of patients currently personally treated or managed for BED in the physician's primary practice location
- The number of patients with an indication other than ADHD whom they have prescribed/initiated VYVANSE® within the last 12 months

Physicians will also be asked to provide their e-mail address in case they might be interested in participating in a survey. The responses from this invitation will allow IQVIA to determine how many patient records will be requested from each physician. Only physicians who have prescribed VYVANSE® for indications other than ADHD will be included for the abstraction of patient records for this study.

Previous experience indicates a response rate of around 10% for specialists with this type of research (prior to any further screening criteria being applied). However, given that the prescribing of VYVANSE® for BED treatment will be quite rare, it is possible that the response rate will be substantially lower.

Logistical approach

An online physician survey is considered most appropriate for the data collection for this study.

Qualifying physicians will be sent a web link to the study by e-mail. They will be requested to complete the survey using information from patient records.

The physicians will be instructed to select the patient records of up to 10 patients, for whom at any time in the last 12 months they have prescribed VYVANSE® for indications other than ADHD (whether or not VYVANSE® was prescribed at that last visit), starting with the most recent patients they have seen.

Follow-up phone calls and emails will be conducted to physicians who have agreed to participate, but who do not complete the online form within a period of 1.5 to 2 weeks.

Questionnaire

The questionnaire reflects the objectives of this study and will be designed to cover the variables listed in Section 9.3 of this protocol. The questionnaire is a stand-alone document.

It is anticipated that physicians spend around 15-20 minutes extracting the information from the medical records and record the responses for each patient questionnaire.

Physicians will be appropriately reimbursed for their time taken to complete the chart review and questionnaire.

All respondents will be de-identified and responses will remain confidential, in line with the European Society for Opinion and Market Research (ESOMAR) and the AMSRS Code of Professional Behaviour.

Furthermore, data collected on patients will be de-identified. Physicians will be asked to provide information on patient diagnoses and treatments, but not on identifiable details (as per the Privacy Act).

9.5 Study size and feasibility

Prescription database

Currently, about 82% of all Australians pharmacies provide data for NostraData.

For the main analysis, all prescriptions for VYVANSE® available in the NostraData database in Australia will be analysed.

In the three sensitivity analyses, all prescriptions for VYVANSE® without any evidence of its use in ADHD treatment available in the NostraData database in Australia will be analysed. In order to exclude prescriptions expected to be for ADHD, exclusion criteria will be applied as described in Section 9.2.1.2.

The exact number of prescriptions to be analysed will depend on the number of patients who were prescribed VYVANSE®.

Physician survey

It is planned to collect data for 150 patients per year, who have been prescribed VYVANSE® at least once during the study period, provided by representative physicians expected to treat patients with BED, as described in Section 9.4.2. As per product information, treatment of BED with VYVANSE® should be commenced and managed by a psychiatrist. Therefore, it is aimed to collect data of approximately 100 patients reported by psychiatrists. As real-world information shows that occasionally physicians of other specialties also prescribe VYVANSE® for BED, information on an additional 50 patients reported by other specialties will be also collected.

The sample size of approximately 100 patients per year reported by psychiatrists was determined as described here:

The sample size formula, based on the normal approximation to the binomial distribution, for calculation of the number of subjects (n) required to determine a proportion (p) with a precision € with a two-sided Type I error α is the following:

$$\boldsymbol{n = \frac{p \times (1-p) \times z_{1-\alpha/2}{}^2}{e^2}}$$

In order to be able to determine any percentage with a precision of at least ±10% and within a confidence interval of 95%, 97 subjects will be necessary. This corresponds to a hypothetical proportion (p) of 50%, which leads to the largest sample size for each precision level.

In the case this figure is not reached for the annual analyses, alternative options will be discussed (e.g., analyses of smaller sample sizes or postponement of the analysis to the subsequent year in order to reach a bigger sample size).

Prior to the analysis each year, actual numbers of available prescriptions will be checked to decide if the analysis will be feasible.

9.6 Data management

The study will be conducted according to the standard operating procedures (SOPs) of IQVIA. The datasets extracted from the Australian NostraData database will be stored at IQVIA Australia and IQVIA Bangalore. Data obtained from the physician survey will be checked in terms of consistency during data entry using automatic checks and before data analysis. Once validated and quality checked, the physician survey database will be locked. Survey data will be stored at IQVIA Australia.

9.7 Data analysis

9.7.1 General statistical considerations

Over the assessment period of three years, prescriptions recorded in the NostraData database from each 12-month reporting period as well as from the complete period at that time will be analysed using descriptive statistics.

Data from the NostraData database and the survey will not be combined directly. Study tables will reference the data source used for each set of results.

Analyses will be performed using appropriate statistical software (e.g., SAS 9.2 or higher).

All planned analyses including table shells will be described in a detailed statistical analysis plan (SAP) .

9.7.2 Potential for selection bias

Dispensing database

All prescriptions will be extracted from the NostraData database. Its high coverage of approximately 82% of all Australian pharmacies reduces the likelihood of substantial selection bias. Potential bias may nevertheless result if the total uptake of VYVANSE® prescriptions is very low and the number of remaining VYVANSE® prescriptions for ADHD superimpose prescriptions for BED. Exclusion criteria aiming to reduce the number of VYVANSE® prescriptions for ADHD (already studied in a separate report) might introduce sampling bias; however, their potential impact is considered minor.

Physician survey

In order to avoid any selection bias to the best possible extent, psychiatrists and physicians of other specialties will be randomly recruited using nationally representative external lists (e.g., One Key lists, as described in Section 9.4.2).

The prescriber sample selected will be described by specialty, graduation year, gender, and location. Presence or extent of selection bias will be assessed by comparing information on specialty and region of participating physicians with the national prescriber "universe". Nevertheless, the prescriber sample could deviate from the national prescriber universe because prescribers of VYVANSE® may be different from prescribers in general.

9.7.3 Descriptive analysis

All analyses performed will be descriptive. Description of missing data for each outcome of interest will be provided.

Indication of use, patient characteristics, patterns of drug use, average and maximum daily dose, co-prescriptions and co-diagnoses will be described. Distribution of number of prescriptions and treatment duration will be evaluated.

For continuous variables the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be presented. Categorical variables will be displayed with frequencies and percentages.

Exact definitions of all variables (e.g., details on the calculation of average daily dose), the categories of variables to appear in the tables (e.g., age), and subgroup analyses of patients will also be defined in the SAP.

9.8 Quality control

Quality control will be conducted at several levels:

- To support nationally representative site selection for the physician survey, a robust, up-to-date, complete and representative list of Australian physicians will be used ("OneKey lists"). The list is generated by several thousand pharmaceutical company representatives visiting physicians and sending updates to this database on a daily basis. All updates are validated by telephone by a team of data integrity personnel. The database was established in the 1980s and is subscribed to by most of the major pharmaceutical companies. Recruitment of physicians will occur from the total population of psychiatrists and of other specialties in Australia.
- For site selection, all efforts will be undertaken to ensure that the sample is also representative by location – by state, metropolitan versus non-metropolitan areas and private versus public settings. In case the number of prescribers is too low so that a representative sample cannot be reached, this will be discussed in the report.
- At the site management level, significant effort will be expended to collect complete and valid data for the physician survey. Follow-up phone calls will be conducted to physicians who have agreed to participate but who do not complete the online questionnaire within 1.5 to 2 weeks. Logic checks will also be applied.
- NostraData Australia includes patient/ prescription information extracted directly from retail pharmacy computers to ensure completeness of the data. Each patient has an individual patient ID coupled with the number of prescriptions and the information given therein. For confidentiality reasons, de-identification of data is performed by a third party on behalf of IQVIA.

9.9 Limitations of the research methods

9.9.1 Panel composition and representativeness

It may be argued that the physicians who participate in the physician survey may have different practice behaviour than other physicians who do not take part in such activity. In the planned physician survey, participating physicians will be recruited using complete and representative lists of Australian psychiatrists.

9.9.2 Missing diagnoses

Dispensing database

In the dispensing database, information on age, gender and diagnosis is not provided. Therefore, prescriptions for VYVANSE® intended to treat BED cannot be clearly distinguished from prescriptions intended to treat ADHD. In order to ameliorate this limitation, exclusion criteria will be applied as described in Section 9.2.1, with the aim to exclude patients who are likely to have received VYVANSE® for treatment of ADHD.

Physician survey

Physician will be able to enter other indications for VYVANSE® than BED or ADHD. Thus, data on off-label use in other indications can be recorded. However, the recruiting of psychiatrists who are potentially treating BED excludes potential off-label use in indications that might be present in other specialties. As all specialties are present in the NostraData database, other relevant specialties can still be identified in the database part of the study and included in the survey in subsequent years if deemed appropriate. Data from the Electronic Patient Records (EPR) will be treated as confidential.

10 PROTECTION OF HUMAN SUBJECTS

This study is non-interventional study and the prescription data analysis will utilize secondary data. No identifying data are collected in any of the planned approaches. All databases (prescription database and database for the physician survey) will be set up following local law, including data privacy regulation.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In the event adverse reactions to VYVANSE® are identified during the course of the study, IQVIA will report them using the Shire AE Report Form within one business day of discovery to Shire Global Drug Safety (GDS) department at [redacted] as per company policy on safety reporting.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Three annual reports will be generated. All reports will be submitted to the TGA. Planned submission dates to TGA are October 2019, October 2020 and October 2021.

Publication of the results in a peer reviewed journal and/or an international conference is planned.

13 REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), American Psychiatric Society. 2013.
2. Guerdjikova AI, Mori N, Casuto LS, McElroy SL. Novel pharmacologic treatment in acute binge eating disorder – role of lisdexamfetamine. Neuropsychiatric Disease and Treatment. 2016;12:833-841.S80881.
3. Vyvanse®: Product Information Australia, Version 24 January 2018; https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02051-1&d=20180205161146224 83&d=201910251016933.