PASS INFORMATION

Study title	**Drug utilisation study of Intuniv® (guanfacine extended release) in European Countries – A prescriber survey**
Protocol Version identifier	Version 5.0 17 July 2018
Date of last version of protocol	Version 4.0 12 June 2018
EU PAS Register number	EUPAS18739
Active substance	Guanfacine (ATC code: C02AC02)
Medicinal product	Intuniv®
Product reference	Marketing authorisation numbers: • 1mg: EU/1/15/1040/001-002 • 2mg: EU/1/15/1040/003-005 • 3mg: EU/1/15/1040/006-007 • 4mg: EU/1/15/1040/008-009
Procedure number	EMEA/H/C/03759
Marketing authorization holder (MAH) or sponsor company	Shire Pharmaceuticals
Joint PASS	No
Research question and objectives	**Research question:** Implementation of a multi-country drug utilization study for up to 5 years with Intuniv® and provision of data on an annual basis in up to 10 European countries. In Belgium, Finland, Ireland and Netherlands data on the use of Intuniv® will be collected within a prescriber survey which is described in this protocol. In other countries a database analysis will be performed which is described in a separate protocol. **Study objectives:** **Primary objectives:** • To characterize patients who are prescribed Intuniv® with a specific focus on o Indications other than ADHD o Children less than 6 years of age

	○ Adults ○ Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv® ○ Prescribed overdose of >7 mg/day or of >4 mg/day for patients ≤12 years of age • To describe prescribing patterns of Intuniv® among physicians **Secondary objective:** • To describe the effectiveness of the additional risk minimisation measure (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment
Countries of study	Belgium, Finland, Ireland, Netherlands
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1. TABLE OF CONTENTS

LIST OF TABLES

2. ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AR	Adverse reaction
ASOCS	Association of Opinion and Behaviour in health field research companies
CHMP	Committee for Medicinal Products for Human Use
CI EC	Confidence interval Ethics committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
GVP	Good pharmacovigilance practices
GP	General practitioner
HCP	Health care professional
IR	Immediate release
MAH	Marketing authorization holder
MR	Modified release
PASS	Post-authorization safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
RMP	Risk minimization plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOP	Standard operating procedures
SmPC	Summary of product characteristics
STROBE	Strengthening the reporting of observational studies in epidemiology

3. RESPONSIBLE PARTIES

Sponsor: Shire Pharmaceuticals

Project team:

Project Manager: [redacted], PhD, [redacted] Pharacoepidemiology; Shire (e-mail: [redacted]);

Global Drug Safety: [redacted], PhD; Shire (e-mail: [redacted])

Global Drug Safety: [redacted], PhD; Shire (e-mail: [redacted])

Contractor: IQVIA

Real world Insights and Medical Radar divisions

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The project will be managed by the IQVIA Centre of Excellence (COE) in Retrospective Studies in collaboration with the IQVIA Medical Radar Team for fieldwork. As team members are likely to change over the project period of 5 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 experts. These teams have many years combined experience of analyzing and drawing statistically robust findings from longitudinal and cross-sectional patient data.

4. ABSTRACT

4.1 Title

Drug utilisation study of Intuniv® (guanfacine extended release) in European Countries – A prescriber survey

Version 5.0, 17 July 2018
Main author: [redacted], PhD, [redacted], IQVIA RWI Germany

4.2 Rationale and background

Shire Pharmaceuticals has launched or plans to launch Intuniv® in Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Portugal, Spain, Sweden and UK from January 2016 onwards. Intuniv® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective (1). Shire Pharmaceuticals will conduct a drug utilization study as part of the risk management plan for Intuniv® in Europe.

In Belgium, Finland, Ireland, and the Netherlands, data on the use of Intuniv® will be collected within a prescriber survey which is described in this protocol. In other countries a database analysis will be performed which is described in a separate protocol (Annex 1).

4.3 Research question and objectives

Research question:

The study's overall research question and objective is to characterize patients who are prescribed Intuniv®, to describe prescribing patterns among physicians and to evaluate if additional risk minimisation measures that had been provided to physicians were successfully implemented and effective. Data on use of Intuniv® will be provided on an annual basis for up to 5 years in up to 12 European countries. In Belgium, Finland, Ireland, and Netherlands, data on the use of Intuniv® will be collected within a prescriber survey which is described in this protocol. In other countries a database analysis will be performed which is described in a separate protocol.

Study objectives:

Primary objectives:

- To characterize patients who are prescribed Intuniv® with a specific focus on
  - Indications other than ADHD
  - Children less than 6 years of age
  - Adults
  - Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv®
  - Prescribed overdose of >7 mg/day or of >4 mg/day for patients ≤12 years of age

- To describe prescribing patterns of Intuniv® among physicians

Secondary objective:

- To measure the effectiveness of the additional risk minimisation measure (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment

4.4 Study design

This is a multinational, cross-sectional, non-interventional and anonymous survey carried out among physicians who will be asked to provide de-identified patient data. The survey will be conducted through a web-questionnaire among prescribers of Intuniv® in four European countries (Belgium, Finland, Ireland, and Netherlands).

4.5 Population

Patients who have been prescribed Intuniv ® at least once during the study period.

The survey will be conducted annually from 2019 to 2022 among prescribers, or potential prescribers, of Intuniv® representative for the selected countries (Belgium, Finland, Ireland, and Netherlands). The physicians will be instructed to select the most recent patient records, for patients for who at any time in the last 12 months (or, for the first report, since country specific launch) they have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit).

1 to 10 patients per physician may be reported, with the most recent patients being reported first.

4.6 Variables

The collected information includes:

- Physician related data (demographics, setting, prescriber's specialty)
- Drug utilization data: indication of use/diagnosis, patient characteristics (age, gender, comorbidities), data on patterns of drug use (dosing, first time user, repeat user, duration, discontinuation of ADHD therapy and switches), frequency of monitoring and weight, blood pressure, heart rate if information is available.

4.7 Data sources

The survey will collect data from the following data sources:

- Physicians files (OneKey lists) for gender, specialty and region
- Data collected through a web questionnaire, including de-identified patient data provided by a representative sample of physicians known to treat patients with ADHD – predominantly paediatricians, psychiatrists, neurologists and GPs (representatively selected throughout the participating countries)

4.8 Study size

Per country and year, the target is to collect anonymous data of 50 to 100 patients, who have been prescribed Intuniv® at least once during the study period. Data will be provided by representative physicians qualified to treat patients with ADHD.

4.9 Data analysis

All analysis will be descriptive in nature and no statistical comparison will be done in this study. Results will be presented by country.

4.10 Milestones

Milestone	Planned date
Start of data collection (fieldwork) for first survey report, expected duration two months	01 February 2019
End of data collection (fieldwork) for last survey report	31 March 2022
Registration in the EU PAS register	26 April 2017
First survey report	30 June 2019
Second survey report	30 June 2020
Third survey report	30 June 2021
Last survey report	30 June 2022

5. AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
Original protocol Version 1.0	16 Dec 2016	New protocol	nap	nap
Amended protocol, Version 2.0	19 Dec 2017	Throughout the document	Update the name of the subcontractor QuintilesIMS to IQVIA	Name change of company
		Page 1 of document	Update of address of the subcontractor	Office was moved
		Section 6: Milestones	Added launch date of Intuniv® in Spain	Launch date is available now and Intuniv® was

				launched in Spain
		Section 7: Rational and background	Expanded rationale of the study	Recommended to justify the need for the study and the assessment of the risk minimisation measures
		Synopsis and Section 8	Reworded research question	Rewording was done to align more with the objectives of the study
		Section 9.1: study design	More detailed description of the study design and reference to the statistical analysis plan	To allow a better understanding of the study design
		Synopsis and Section 9.2: Setting	Specified how recruitment for the survey will be done	For clarification of the setting and describe how representativeness is planned to be achieved
		Section 9.3: variables	A reference to the SAP was made	For clarification that a detailed description and definitions of all variables are given there
		Section 9.4: Data sources	Addition of questions was described	to assess knowledge of physicians regarding the risk minimisation measures were added to the questionnaire
		Section 9.7.3 Questionnaire analysis	Hypothesis was added and description on how successful implementation of the risk minimisation	To include a process indicator that allows to measure if knowledge of the physicians with respect to the

			measures would be assessed.	educational material is adequate.
		Appendices	List of stand alone document was amended	For completeness
Amended protocol, Version 3.0	18 May 2018	Title page	Update of MAH contact	New MAH contact
		Throughout the document	Removal of France and Switzerland	Intuniv® not likely to launch in France and Switzerland in sufficient time for this study.
		Section 4.3: Research question and objectives	Update of study objectives	Harmonization of study objectives and criteria for off-label use.
		Section 6: Milestones and throughout the document	Update of milestones and reporting dates	Data collection period and reporting dates adapted according to expected protocol endorsement by the PRAC.
		Section 7: Rationale and background	Rewording of criteria for off-label use	Harmonization of study objectives and criteria for off-label use
		Section 8.2: Objectives	Update of study objectives	Harmonization of study objectives and criteria for off-label use.
		Section 9.2.1.	Clarification of inclusion criterion	Clarification that for the first report, patients who have received Intuniv® since the country specific launch date may be included
		Section 9.7.1:	Update of tables	Fieldwork and

		General statistical observations	and text	observation period adapted to new reporting dates.
		Section 9.8: Quality control	Update of SOPs in accordance with the IQVIA system	Due to the restructuring of the company to IQVIA the numbering system of SOPs and policies had been changed.
		14: Appendix	Update of table	New versions of stand-alone documents available.
Amended protocol, Version 5.0	17 July 2018	Section 7: Rationale and background	Text added	Clarification that Intuniv® is indicated as second line treatment
		Section 9.7.3: Questionnaire analysis	The predefined percentage to conclude effectiveness of aRMM was increased.	To into account the risks intended to be managed.
		14: Appendix	Update of table	New versions of stand-alone documents available.

6. MILESTONES

Table 1: Milestones

Milestone	Planned date
Start of data collection (fieldwork) for first survey report, expected duration two months per year	01 February 2019
End of data collection (fieldwork) for last survey report	31 March 2022
Registration in the EU PAS register	26 April 2017
First survey report	30 June 2019
Second survey report	30 June 2020
Third survey report	30 June 2021
Last survey report	30 June 2022

A survey report including the results for each of the four target countries will be provided annually. In total four reports will be prepared in frame of current study. The first report is planned for June 2019. The last report is planned for June 2022. The first survey will ask physicians to provide data on patients from the launch of Intuniv until the conduct of the survey, a period which could be longer than 1 year depending on the country. As such, the four reports provided will provide approximately five years of data. For country specific reporting schedule please refer to Table 2.

Table 2: Planned launch and reporting date by country (as of September 2016)

Country	**Launch date of Intuniv®**	Report 30 Jun 2019	Report 30 Jun 2020	Report 30 Jun 2021	Report 30 Jun 2022
Belgium**	1 Nov 2016	x	x	x	x
Denmark+	18 Jan 2016	x	x	x	x
Finland**	15 May 2016	x	x	x	x
Germany+	15 Jan 2016	x	x	x	x
Ireland**	02 May 2016	x	x	x	x
Netherlands**	01 Nov 2016	x	x	x	x
Norway+	15 May 2016	x	x	x	x
Spain+	Jan 2017	x	x	x	x
Sweden+	15 Feb 2016	x	x	x	x
UK+	01 Feb 2016	x	x	x	x

**country where survey is planned; +country where database study is planned

7. RATIONALE AND BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a developmental disorder (2). It is primarily characterized by the co-existence of attentional problems and hyperactivity, with each behaviour occurring infrequently alone and several inattentive or hyperactive-impulsive symptoms present prior to age 12 (2, 3). ADHD is the most commonly studied and diagnosed psychiatric disorder in children, affecting about 3 to 5 percent of children globally (4-6) and diagnosed in about 2 to 16 percent of school aged children (5). ADHD is a lifetime disorder (7) with 30 to 50 percent of those individuals diagnosed in childhood continuing to have symptoms into adulthood (7, 8). These symptoms include significant social, emotional and academic problems, low self-esteem, poor peer relationships, delinquency and substance abuse (5).

Causes of ADHD

The exact causes of ADHD are not known, although many studies suggest that there is a large genetic influence (9). Like many other psychiatric illnesses, ADHD results from a combination of factors. In addition to genetics, scientists are investigating possible effects of environmental factors, brain injuries, nutrition and the social environment on the development of ADHD (10).

Treatment of ADHD

Currently available treatments focus on reducing the symptoms of ADHD and improving functioning. Treatments include medication, various types of psychotherapy, education or training, or a combination of treatments.

Most commonly, ADHD is treated with stimulant medications, which are designed to have a calming effect on children with ADHD. Different types of stimulant medications are available, such as methylphenidate (e.g. Ritalin®, Concerta®), dexamphetamine (e.g. Attentin®) and lisdexamfetamine (e.g. Elvanse®). In general, their mechanism of action is on catecholaminergic neurons in the brain and ultimately leads to an increase of extracellular dopamine and norepinephrine levels in the prefrontal cortex (11).

Nonetheless, a subset of ADHD patients will either fail to respond to stimulants or have side effects that preclude their use (tics, severe loss of appetite, marked insomnia). For such patients, non-stimulant agents (like atomoxetine, trade name Strattera®) serve as second-line treatment.

Stimulants have been available for decades in Europe. The first non-stimulant medication was approved in the United Kingdom in 2004, and in Germany in 2005. In 2009, Shire Pharmaceuticals has launched a novel non-stimulant drug in USA and Canada: extended-release guanfacine (Intuniv®). Intuniv® is a long-acting, once-daily formulation of guanfacine (a selective alpha-2A-adrenergic receptor agonist) indicated for treatment of ADHD in 6 to 17 year old children and adolescents. It is indicated as a second-line treatment for patients for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. As listed in the SmPC, Intuniv is indicated for the treatment of ADHD in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

Intuniv® can be prescribed as monotherapy and as adjunctive therapy to stimulant medications. Intuniv® has demonstrated improvement of a range of ADHD symptoms that can

be disruptive, such as inattention, hyperactivity, impulsivity, and extensive loss of temper (12). Intuniv® is not a controlled substance, which sets it apart from most other ADHD drugs. The active compound of Intuniv®, guanfacine, is also used for treatment of hypertension, but the marketing authorization does of Intuniv® does not include that indication. Therefore, use of Intuniv for treatment of hypertension would be considered off-label use. The effects of Intuniv® for treatment of ADHD have been demonstrated in controlled trials in children and adolescents and in adult healthy volunteers (1).

Background and rationale of the current study

Intuniv® has not been studied in children under age 6 years, adults and the elderly. Therefore, in order to avoid any potential or unknown risks, it is currently not indicated for use in these populations.

Furthermore, there are identified risks of bradycardia, syncope, hypotension/decreased blood pressure, withdrawal blood pressure increase, sedative events, and weight increase. In order to minimize these identified risks, careful assessment of patients' blood pressure, weight and heart rate is required before initiation and during treatment of a patient with Intuniv®.

To increase awareness and knowledge on these requirements, Shire Pharmaceuticals has developed and distributed educational materials to potential prescribers of Intuniv®.

Shire Pharmaceuticals also proposed to conduct a drug utilization study as part of their risk management plan to assess effectiveness of these measures: The study described in this protocol has been designed to evaluate drug utilization and to monitor inappropriate use of Intuniv® in Europe, Shire Pharmaceuticals considers this study an important activity to evaluate whether Intuniv® is being prescribed within the approved SmPC and whether current risk minimisation measures are adequate.

Shire Pharmaceuticals has launched/ plans to launch Intuniv® from January 2016 onwards in Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Spain, Sweden, and UK for treatment of ADHD. Expected launch dates are given in Table 2. In order to evaluate drug utilization and to monitor appropriate and potential inappropriate use of Intuniv® in Europe, Shire Pharmaceuticals proposed to conduct a drug utilization study as part of their risk management plan.

The indication for Intuniv® given in the Summary of Product Characteristics is as follows (1):

Intuniv® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Intuniv® must be used as a part of a comprehensive ADHD treatment program, typically including psychological, educational and social measures.

Based on this label, inappropriate use of Intuniv® may include use in

- Patients with indications other than ADHD
- Children less than 6 years of age
- Adults
- Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv®

- Patients with prescribed overdose of >7 mg/day, or of >4 mg/day for patients ≤12 years of age

In this drug utilization study, patient medical record data will be collected within a prescriber survey. Annual study reports will be generated by IQVIA and sent to Shire in 2019, 2020, 2021 and 2022.

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

8.1 RESEARCH QUESTION

Research question:

The study's overall research question and objective is to characterize patients who are prescribed Intuniv®, to describe prescribing patterns among physicians and to evaluate if additional risk minimisation measures that had been provided to physicians were successfully implemented and effective. Data on use of Intuniv® will be provided on an annual basis for up to 5 years in up to 10 European countries. In Belgium, Finland, Ireland, and Netherlands, data on the use of Intuniv® will be collected within a prescriber survey which is described in this protocol. In other countries a database analysis will be performed which is described in a separate protocol (Protocol data base study).

8.2 OBJECTIVES

Primary objectives:

- To characterize patients who are prescribed Intuniv® with a specific focus on
  - Indications other than ADHD
  - Children less than 6 years of age
  - Adults
  - Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv®
  - Prescribed overdose of >7 mg/day, or of >4 mg/day for patients ≤12 years of age
- To describe prescribing patterns of Intuniv® among physicians

Secondary objective:

- To measure the effectiveness of the additional risk minimisation measure (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a multi-national, cross-sectional, non-interventional and anonymous web-based survey carried out among physicians. This approach was chosen as it will allow to collect all variables required, including data to assess compliance with the indication and with visits and measurements needed during the first year of treatment.

9.2 SETTING

The survey will be conducted among prescribers of Intuniv® in the selected countries (Belgium, Finland, Ireland, and Netherlands) and conducted annually from 2019 to 2022. In order to minimize selection bias, physicians will be randomly recruited using nationally representative external lists (OneKey lists). The prescriber sample selected will be described by specialty, graduation year, gender, and type of location (e.g. urban/rural). It is planned to collect data for 50 to 100 patients per country who have been prescribed Intuniv® at least once during the study period. Recruitment will occur from the total population of healthcare practitioner groups who are most likely to treat patients with ADHD. Physicians will be recruited as described in 9.5.1. The physicians who are eligible for participation will be instructed to select the patient record based on the last patient they have seen, for who at any time in the last 12 months (or, for the first report, since country specific launch) they have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit). Recruitment of physicians will be done at random for each annual survey, with the aim to avoid having the same physicians in each survey. However, overlaps within the groups of physicians are still possible. The number of physicians per specialty who provided data for the survey will be included in the report. Information regarding the total population of physicians will also be included. One to 10 patients per physician may be reported, with the most recent patients being reported first.

9.2.1 Inclusion criteria

The survey will be conducted among physicians meeting the following inclusion criteria:

- Prescribers of Intuniv®, i.e. physicians who know and have prescribed the drug at least once during the previous 12 months (or, for the first report, since country specific launch) (paediatricians, psychiatrists, neurologists and GPs)

9.2.2 Exclusion criteria

Inactive and retired physicians (when documented information is available to identify them) will be deleted from the contact lists before randomisation.

The following exclusion criteria will be checked at the beginning of the web-questionnaire:

- Physicians who do not treat patients or who may have a conflict of interest (i.e. physicians employed by regulatory bodies or pharmaceutical industries),

9.3 VARIABLES

The survey aims to characterize patients who are prescribed Intuniv® and describe prescribing patterns of Intuniv® among physicians in European countries.

The following information is planned to be collected in the survey:

- Physician related data
  - demographics
  - setting
  - prescriber's specialty
- patient characteristics
  - age
  - gender
  - co-morbidities
- indication of use (diagnosis) according to WHO ICD 10 classification
- data on patterns of drug use
  - first time user
  - repeat user
  - duration of treatment
  - discontinuation of ADHD therapy
  - switches (both from Intuniv® to other ADHD medications and other ADHD medications to Intuniv®)
  - dosing/ overdose (defined as daily dose of >7 mg or of >4mg in patients ≤12 years of age)
- use of Intuniv® as second line treatment after psychostimulant prescription at any time prior to the patient's first prescription of Intuniv®
- frequency of monitoring (physician) visits during the first year of therapy
- weight, blood pressure and heart rate during Intuniv® exposure

A detailed description of all variables and definitions is provided in Table 3 of the SAP for the survey protocol.

9.4 DATA SOURCES

Physician Survey

- de-identified patient data provided by a representative sample of physicians known to treat patients with ADHD – predominantly paediatricians, psychiatrists, neurologists and general practitioners (GPs), representatively selected throughout the respective countries. The physicians 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 (or, for the first report, since country specific launch) they have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit).

The survey will collect data from the following sources:

- physicians files (OneKey lists)
- information collected by a web questionnaire, including de-identified patient data

The questionnaire will be designed by experienced persons and will include both open and close-ended questions. Several questions directed to the physicians concerning their knowledge about the risk minimization measures and the educational material will be included. The web questionnaire completion is estimated to take 5 to 10 minutes for the general part and an additional 10 minutes per patient for the drug utilization data. Before being finalized, the questionnaire will be administered to/ tested by 5-6 physicians in order to make sure it is well understood and the wording appropriate to the survey topic. Physicians' comments will be implemented in the final version. Moreover, the questionnaire will be translated using the back and forth method (translation from English to local language, then again to English) to make sure the appropriate wording is used.

9.5 STUDY SIZE

9.5.1 Sampling plan

Per country and year, the target is to collect data from 50 to 100 patients, who have been prescribed Intuniv® at least once during the study period, provided by representative physicians qualified to treat patients with ADHD. It is planned to annually recruit 15 to 20 prescribers of Intuniv® per country who will be requested to complete, if possible, 1 to 10 medical record extracts.
A random sampling plan will be developed. Prescribers will be sampled among the lists of paediatricians, GPs, neurologists and psychiatrists.

Due to the low prescribing base, no quotas by physician types will be set. As many patient medical records (anticipated maximum: 100 records per country) from as many prescribing physicians who are willing to participate will be collected.

9.5.2 Study size calculation

As the expected number of patients receiving Intuniv® is expected to be very low, descriptive statistics will be applied. It is planned to collect, if possible, data for up to 100 patients per country, who have been prescribed Intuniv® at least once during the study period. Data will be provided by representative physicians qualified to treat patients with ADHD.

The exact number of prescriptions/ patient records to be analyzed will depend significantly on the market utilization of Intuniv® in the target countries.

The planned sample size of at least 100 patients 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 e with a two-sided α first-type error is the following:

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

Based on this sample, and considering a confidence interval of 95%, in order to be able to determine any percentage with a precision of at least ±5%, 384 subjects will be necessary. This corresponds to a hypothetical proportion of 50% which is generally considered as it yields to the largest sample size for each precision level. Respectively, a precision of at least ±10% would necessitate a sample size of 97 subjects.

In this study, assuming that we would like to be able to describe any proportion with a precision of at least 10% in each country, a minimum sample size of 100 cases per year is required for any of the countries. In the case this figure is not reached for the annual analyses of a target country IQVIA and Shire will discuss and mutually agree on alternative options (for example analyses of smaller sample sizes or postponement 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 survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA/ IQVIA Medical Radar. The datasets extracted from the databases will be stored at IQVIA files to allow analysis in the future.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country.

Data will be checked in terms of consistency before data analysis:

- removal of duplicates (if required),
- data labelling and data formatting,
- range and consistency checks for each variable to identify potential non admissible values,
- cross-check the consistency of data for related variables (if feasible).

9.6.1 Data collection

The data collection period will last about 4 to 8 weeks during the fieldwork period (expected in February and March) every year, starting in 2019 and taking place annually until 2022. It will be conducted in parallel in the five countries.

The survey will be conducted by IQVIA Medical Radar, a division of IQVIA specialized in the conduct of phone and web surveys for more than 20 years. IQVIA Medical Radar will create a web-based instance survey. The lists of physicians will be loaded into separate databases for the management of the survey.

Physicians will be randomly contacted, mainly by email and also by phone when needed, according to their stratum by the IQVIA Medical Radar team. Their recruitment will be done as follows:

- Physicians will be invited to participate in the survey (via phone calls or emails). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. If they

agree to participate in the survey, they will receive a link to access the survey and the instructions for the web-questionnaire completion.

- If the questionnaire is not completed and sent to IQVIA Medical Radar, the physicians will be sent a reminder by email one week after the start of the survey.
- If the target is not achieved in the stratum, a reminder by phone will be conducted 1.5 weeks after the start of the survey.
- If the questionnaire is still not completed and sent to IQVIA Medical Radar, the physicians will be sent a last reminder by email two weeks after the start of the survey.

If necessary, the recruitment will be performed by phone to achieve the target.

A physician will be considered as contacted if he/she has:

- completed the survey and sent it back to IQVIA Medical Radar,
- been reached out by phone or have opened their email (if the score is technically available in their country)
- refused to participate

Moreover, a physician will be considered as unreachable if he/she has been contacted at least 3 times without any answer.

For each physician of the sample file, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each country will be stopped when the target is reached.

9.6.2 Approaches for increasing the response rate

Physicians are increasingly contacted to participate in web or phone surveys. Their overall response rate of participation remains low according to international studies (13-15). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (15). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (16). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician response rates while non-monetary incentives were much less effective. These measures include the use of a short questionnaire, and questionnaires personalized, and approved by professional associations.

In order to increase the response rate, three actions will be applied to this survey:

- A compensation fee will be proposed to physicians for their participation in the survey.
- All physicians will be sent an email or contacted by experienced operators of IQVIA Medical Radar with extensive experience in conducting health related surveys.

- Each physician will be emailed or called up to 3-5 times before being considered as "not reachable", and reminders will be sent by email if IQVIA Medical Radar does not receive the web questionnaire.

9.7 DATA ANALYSIS

9.7.1 General statistical consideration

The statistical analysis will be conducted using the SAS® software (like SAS 9.3) on Windows™ (SAS Institute, North Carolina, USA).

A detailed statistical analysis plan (SAP), that could support independent replication of the study results, will be agreed on prior to the start of the analysis. Table shells, 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 be defined in the SAP.

The statistical results of the five countries will be presented annually in the same report. Results will be presented by country. Due to the low sample size no stratification by specialty is planned.

All the analysis will be descriptive in nature and no statistical comparison will be done in this study.

The survey will be performed once per year for four years. Physicians will always be asked annually to provide information on the last patient they saw who they had prescribed Intuniv® to: for the first report patients for who they had prescribed Intuniv® since launch; for later reports the most recent patients who they had seen for who they had prescribed Intuniv® to within the previous 12 months period (patients' selection window), regardless whether the patient had received an Intuniv® prescription at his/ her last visit. The observation period for the first report will be the country-specific launch date to 31 March 2019; for consecutive reports – until 31 March of the respective study year. The last survey will cover the period until 31 March 2022.

9.7.2 Representativeness of participating physicians- Analysis of non-participation or refusal to participate rate

As often required by the Authorities, the following different cases of total non-response will be distinguished and analyzed:

- Targeted physicians: Physicians reached to whom an email or mail has been sent, or have been called.
- Contacted physicians: Physicians who have been reached out by phone or have opened their email (if the score is technically available in their country).
- Physicians who agreed to participate: Physicians willing to participate in the survey (e.g. by phone or by clicking on the link provided in the recruitment email).
- Physicians with complete questionnaire: Physicians who actually completed the questionnaire until its end**.**

The physicians' participation in the survey will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = Physicians who agreed to participate/ contacted physicians
- Cooperation rate = Physicians with complete questionnaire / Physicians who agreed to participate
- Refusal rate = contacted physicians minus physicians who agreed to participate / Physicians contacted

9.7.3 Questionnaire analysis

The reports will include descriptive statistics of all parameters analyzed. As part of this analysis, the description of missing data for each outcome of interest will be provided. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (17).

For continuous variables the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented.

Categorical data will be summarized using frequency and percentage. 95% confidence interval may be constructed around the percentage values for some variables. Some of the variables may also be summarized by country.

The educational materials will be considered to be effective if at least 80% of physicians will have responded correctly to at least 75% of the questions in the survey in which knowledge on the educational material is assessed.

This hypothesis is based on empirical numbers.

Evaluation of the success rate will be based on the percentage of correct answers to questions A2 to A5 in Section 4 (“Awareness and knowledge of risk minimisation measures”) of the survey questionnaire.

Two analyses to evaluate the effectiveness of the risk minimization measures will be performed:

In the main analysis all questionnaires will be evaluated. In the subgroup analysis, only questionnaires of the physicians who answered “Yes” to question A7 (“Did you receive educational material regarding Intuniv®?”) will be included. The subanalysis will allow to evaluate if awareness of the educational material may affect the number of correct answers.

More detailed information regarding the evaluation of the effectiveness is given in the survey SAP.

9.8 QUALITY CONTROL

9.8.1 General considerations

The quality control for validating the results will be conducted at five levels:

1.) At the study level, all aspects of the DUS Intuniv®, from scoping and protocol development to the reporting of the results will be conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance with the following policies and procedures:

- POL_QA_001 "Quality Management System" policy
- RWI_OP_PM0003 Post authorization safety studies (PASS)
- RWI_OP_PM0004 Quality control of project deliverables
- RWI_OP_PM0005 Quality control (QC) policy

According to the policies and procedures above, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.
- The Principal in charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study.

Also, the principal in charge of the study will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure SOP_QA_007 "Training of Quality and Operational Standards".

2.) At IQVIA Medical Radar management level, every effort will be undertaken to collect complete and valid data:

- Verification of the reliability and security of the web-questionnaire interface by a qualified web-master for each country,
- Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web-questionnaire, real-time checks of the answers provided by the respondents will be developed. Non admissible answers (i.e. incorrect or unusual values, outlying values) will be detected and queries sent to the physician.

3.) At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond data management process):

- Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage,
- Identification and count of non-analyzable questionnaires:

- Estimation of the percentage of physicians without complete analysable questionnaire.

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. After data have been validated and quality checked, the database will be locked.

4.) At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.

5.) At the results level, a data review will be done to ensure data integrity.

9.8.2 Approaches for validating the questionnaire

The questionnaire will be tested among 5-6 physicians for its comprehensibility, consistency and the appropriateness of medical terms. The questionnaire will be translated into local languages using the back and forth method (translation from English to local language, then again to English) to ensure correct translation and that appropriate wording is used.

9.8.3 Safeguards, security and traceability of calls

The operators of the call centre specialized in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The phone calls will be traced using the call management software. All survey aspects from protocol development to the reporting of the results will be conducted according to the SOPs of IQVIA and IQVIA Medical Radar divisions.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Possible selection bias due to voluntary participation

The selection bias of physicians participating in a survey is an inherent bias to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of healthcare professional (country and specialty) will be compared between participants and non-participants.

9.9.2 Limits inherent to web-surveys

The questionnaire includes general questions followed by specific ones. As the physicians may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.

In such surveys, the generalisation and external validity of the results is restricted to physicians who have an active email address and willing (and able) to answer a

questionnaire online. These physicians may not be fully representative of the whole targeted population (18).

Among non-response bias, targeted physicians may also have activated filters in their mailbox in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address, or if the physicians do not check their email box frequently, they will not receive the invitation during the recruitment period. This is one of the reasons why the physicians will also be contacted by phone.

Moreover, web-surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior, e.g. physicians can copy-paste information collected online instead of giving their own opinions (18).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (19).

The access to the web-questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once and a traceability system. Thus stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfill the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

9.10 OTHER ASPECTS

None

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be analysed and communicated in a report.

10.1 REGULATORY AND ETHICS CONSIDERATIONS

10.1.1 Ethical principles, laws and regulations

The survey will follow the regulatory and ethical requirements of each country. IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) guidelines (20) for all participating countries, and specific local requirements will be applied. The study is not intended to influence the physicians' prescribing behavior by any means. Rather, it seeks to measure knowledge and prescribing behaviors of the physicians as closely as possible to real life practice.

10.2 PHYSICIANS INFORMATION

Physicians participating in the survey will be informed about targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and

their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data.

10.2.1 Physicians compensations

Physicians will be offered a compensation for the time spent participating in this survey (which they may refuse). The time to complete the survey is estimated to be between 5 to 10 minutes, plus an additional 10 minutes for each patient questionnaire.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, and which states:

“When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws”.

10.3 CONFIDENTIALITY

10.3.1 Patient confidentiality

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be communicated and analysed.

10.3.2 Data confidentiality / Data security

The answers provided by the physicians will be collected in an anonymous way. Only aggregated data and presented as a synthesis will be transmitted to the MAHs.

Participating physicians will access the website (https secured site) using a personalised login and their password.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time, and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. A copy of the data stored in the database will be transferred to MAHs at the end of the study.

Description of all elements of security and traceability will be available upon request.

10.4 RECORD RETENTION

The study documentation will be stored in the study master file.
The web questionnaires data will be stored on the survey database for 5 years.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines. This is a non-interventional study design which is based on retrospective data collection. This survey is designed to provide utilization data on Intuniv®, to allow an evaluation of off-label use, based on aggregate analyses. Adverse effects are not being measured directly in this survey. Therefore, Shire will only report aggregate findings as study reports, not individual spontaneous reports.

12. PLANS FOR DISSEMINATING AND COMMUNICATING SURVEY RESULTS

The survey has been registered in EU-PAS register (currently the ENCePP e-register of studies) by IQVIA. The EU-PAS register number is EUPAS18739.

The statistical results will be discussed with and approved by MAH.

Every year, a survey report including the results of the five countries will be written in English, using the IQVIA Health template (which is based on the template included in the GVP module VIII) and following STROBE recommendations in MS Word format (21).

Every year, the survey report validated by Shire will be communicated to EMA. The four reports will comprise approximately 5 years of data.

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14. APPENDICES

Annex 1

List of stand-alone documents

Number	Document reference number	Date	Title
1 Questionnaire	Version 5.0	17 July 2018	Drug Utilisation Study of Intuniv® (guanfacine extended release) in European Countries – A prescriber survey
2 Protocol data base study	Version 7.0	17 July 2018	Drug Utilisation Study of Intuniv® (guanfacine extended release) in European Countries Study protocol I: Database study: use of Intuniv® in Denmark, Germany, Norway, Spain, Sweden, and UK
3 Statistical Analysis Plan Survey	Version 4.0	17 July 2018	Statistical Analysis Plan II: Survey study: use of Intuniv® in Belgium, Finland, Ireland, and Netherlands
4 Statistical Analysis Plan Data Base Study	Version 4.0	17 July 2018	Statistical Analysis Plan I: Database study: use of Intuniv® in Denmark, Germany, Norway, Spain, Sweden, and UK
5 ENCePP checklist	Version 1.0	21 Dec 2017	Drug Utilization Study of Intuniv in European Countries