Study title	**Drug Utilisation Study of Intuniv® (guanfacine extended release) in European Countries**
Document title	Study protocol I: Database study: use of Intuniv® in Denmark, Germany, Norway, Spain, Sweden, and UK
Drug	Intuniv® (guanfacine) Extended release tablets 1mg, 2 mg, 3mg and 4mg
Indication	Intuniv® is indicated for 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 programme, typically including psychological, educational and social measures.
Development phase	Post-commercialization
Start of study period	January 2016
End of study period	December 2021
Location of data sources	Europe (Belgium, Denmark, Finland, Germany, Ireland, The Netherlands, Norway, Spain, Sweden, UK)
Company / sponsor	Shire Pharmaceuticals
Subcontractor	IQVIA
Date of the document	2018-07-17 CONFIDENTIAL

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2 ABBREVIATIONS

ADHD:	Attention Deficit Hyperactivity Disorder
ATC:	Anatomical Therapeutic Chemical
CPRD:	Clinical Practice Research Datalink
DA:	Disease Analyzer
DUS:	Drug Utilisation Study
EC:	Ethics Committee
EMA:	European Medicines Agency
EMR:	Electronic Medical Record(s)
ENCePP:	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU:	European Union
GP:	General Practitioner
GVP:	Good Pharmacovigilance Practice
HCP:	Health Care Professional
HEOR:	Health Economics and Outcomes Research
HES:	Hospital Episode Statistics
HIPAA:	Health Insurance Portability and Accountability Act
ICD:	International Classification of Diseases
ISAC:	Independent Scientific Advisory Committee
ISPE:	International Society for Pharmacoepidemiology
ISPE GPP:	Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology
LPD:	Longitudinal Patient Database
PAS:	Post-Authorisation Study
PASS:	Post-Authorisation Safety Study
PhD:	Doctor of Philosophy
PRAC:	Pharmacovigilance and Risk Assessment Committee
OTC:	Over-The-Counter
QMS:	Quality Management System
QOF:	Quality and Outcomes Framework
QoL:	Quality of Life
RMP:	Risk Management Plan
RWES:	Real World Evidence Solutions
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SOPs:	Standard Operating Procedure(s)
THIN:	The Health Improvement Network
UK:	United Kingdom

Title of the document

Drug Utilisation Study of Intuniv® (guanfacine extended release) in European Countries

Marketing authorisation holder

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3 RESPONSIBLE PARTIES

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

Contractor: IQVIA

IQVIA is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IQVIA is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

Project team:
The project will be managed by the IQVIA Centre of Excellence (COE) in Retrospective Studies. As team members are likely to change over the project period of 5.5 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 SYNOPSIS

Title	Drug Utilisation Study of Intuniv® (guanfacine extended release) in European Countries
Rationale and background	Shire Pharmaceuticals plans to launch Intuniv® in Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Spain, Sweden and UK from January 2016 onwards. Shire Pharmaceuticals will conduct a drug utilization study for up to five years as part of the risk management plan for Intuniv® in Europe.
Indication	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 programme, typically including psychological, educational and social measures (1).
Objectives	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. 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 o Adults o Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv® o 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
Study design and data sources	This is a multi-country drug utilization study using retrospective database analysis. A single database for all target countries is not available. Therefore an approach was chosen which includes multiple data sources. In case longitudinal patient level data do not exist in a target country, a prescriber survey will be conducted. The prescriber survey will be described in a separate protocol. The following data sources will be used: • Longitudinal patient level databases o Electronic medical records database ▪ IMS Disease Analyzer (Germany) ▪ IMS LPD (Spain) ▪ THIN (UK) o National registries (Denmark , Norway, Sweden)

	• Prescriber survey
	  ○ Belgium
	  ○ Finland
	  ○ Ireland
	  ○ Netherlands

Population	Patients who have been prescribed Intuniv® at least once during the reporting period.
Sample size	The target sample size is at least 100 patients who have been prescribed Intuniv® at least once in each country. All prescriptions for Intuniv® available in the databases will be analyzed. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv® in the respective countries. In case the number of 100 patients is not reached in a country, data will be analysed to the extent possible.
Variables	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), prescriber specialty, frequency of monitoring and weight, blood pressure, heart rate if information is available in the data source.
Data Analysis	The analysis will be done descriptively for all parameters analyzed. 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, 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.
Reporting	Annual reports will be provided, including both annual and cumulative data. In total four reports will be prepared. The first report is planned for June 2019.

5 AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
Original protocol Version 1.0	30 Sep 2013	New protocol	nap	nap
Amended protocol, Version 2.0	02 Dec 2014	Synopsis and Section 8: Objectives	Specification of 'use in adults' as off-label use	To give more specific information
Amended protocol, Version 3.0	17 Jul 2017	Title page Synopsis	Update of title	Addition of a non-EU country (Switzerland)
		Title page Section 6: Milestones	Update on timelines	Alignment with actual launch of Intuniv® and data availability in the respective countries
		Title page Synopsis Section 7: Background and rationale	Update of indication	To match the final summary of product characteristics
		Title page and throughout the document where applicable	Update on participating countries	Change in countries with planned launch of Intuniv®
		Synopsis Section 8: objectives	Addition of another objective to measure the effectiveness of the additional risk minimisation measure	Alignment with the current Shire risk management plan
		Synopsis and Section 9.1: Study design	Split of protocol into two separate protocols: 1.One protocol for a database study to be conducted in Denmark, France, Germany, Norway, Spain, Sweden, Switzerland and UK 2.A second protocol for a survey to be conducted in Belgium, Finland, Ireland,	Split of the protocol into a database and a survey protocol will allow independent review and conduct of the two study parts

			Netherlands and Switzerland	
		Synopsis and Section 9.1: Study design Section 9.4: Data sources	Update on data sources; inclusion of description of LPD databases for Spain and France and THIN database for UK; deletion of data sources that will not be used for this study	Availability of a better database in Spain and France; UK: more robust study anticipated due to higher patient counts for Intuniv® noted during feasibility assessment
		Synopsis and Section 9.3: Variables	The following variables were newly added: frequency of monitoring, weight, blood pressure and heart rate; Tables 2 and 3 were updated accordingly	Alignment with the current Shire risk management plan
		Section 2: Abbreviations	Update of list of abbreviations	List updated to match the current document
		Section 3: Responsible parties	Update on project management	Changes in staff
		Section 9.2: Setting	More detailed description on the setting	Alignment with current EMA-PASS template
		Section 9.7.2:	Potential for sampling bias	To align with the current data sources
		Section 9.8: Quality control	update	To align with current QuintilesIMS policies
		Section 9.9: Limitations	update	To align with the current data sources
		Section 13: References	Addition of two references.	To add information regarding representativeness of THIN data
		Throughout the document	Update the name of the subcontractor IMS Health to QuintilesIMS	Name change due to a merger of IMS Health and Quintiles
		Appendix:	Tables regarding methylphenidate use were replaced	To give more current information which

			by expected sales figures of Intuniv®	will allow a better sample size estimation
Amended protocol, Version 4.0	19 Dec 2017	Throughout the document	Update the name of the subcontractor QuintilesIMS to IQVIA	Name change of company
		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 that analysis will be conducted even if less than 100 patients were included in a country	For clarification of the setting
		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	Information regarding lag times of the databases was given	To allow an estimation as to when data will be available for analysis.
		Section 9.5: Study size and feasibility	Additional information given	Clarification regarding target size of study
		Appendices	Addition of Table regarding estimated sample size	For clarification on the number of patients expected using the given data sources

Amended protocol, Version 5.0	18 May 2018	Throughout document	Removal of France and Switzerland	Intuniv® not likely to launch in France and Switzerland in sufficient time for this study.
		Section 3: Responsible parties	Update of the MAH contact information	New MAH project manager.
		Section 9.3.4: Coverage of databases	Table added	Table with coverage of databases added
		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.
		Annex 3: List of stand-alone documents	Update of table	New versions of stand-alone documents available.
Amended protocol, Version 7.0	17 July 2018	Section 7: Rationale and background	Sentence added	Clarification that Intuniv® is indicated as second line treatment
		14: Appendix	Update of table	New versions of stand-alone documents available.

6 MILESTONES

Start of data collection:	February 1, 2019
End of data collection:	March 31, 2022
Study period:	January 2016 – December 2021
Report of study results:	Four reports will be written: First report June 30, 2019, annual reports thereafter Last report June 30, 2022

All prescription information for Intuniv® dispensed from January 2016 up to December 2021, if available, will be extracted from the described databases. Extractions will take place annually for each of the four reports. The last annual extraction will include data covering the period from approximately January 2021 up to December 2021, and cumulative data from January 2016 up to December 2021. The exact data period covered each year will depend on the launch date in each country and the lag time for data availability in the databases. The four reports provided will include five years of data.

Table 1: 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	

7 BACKGROUND AND RATIONALE

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 years 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. 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 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 1.

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

In this drug utilization study, retrospective data from different sources covering the time period from January 2016 to December 2021 (up to 5 years post product launch) will be analyzed. Both annual and cumulative study reports will be generated by IQVIA and sent to Shire.

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

8 RESEARCH QUESTION AND OBJECTIVES

Overall research question and objective:

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. The planned study is part of the risk management plan for Intuniv® which had been proposed by Shire Pharmaceuticals.

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

9 RESEARCH METHODS

This is a multi-country drug utilization study using retrospective database analysis for countries with a suitable database. A single database for all target countries is not available. Therefore, a study approach was chosen which includes multiple data sources to gather drug utilization data for Intuniv® in European target countries.
If available, databases with longitudinal patient level data collected continuously over time will be used. Electronic medical records (EMR) databases are preferred, as they contain the most comprehensive information. Longitudinal prescription databases are the next best choice.

Patients with at least one prescription for Intuniv® during the reported period will be included. In addition, subgroup analyses for off-label use and for relevant co-morbidities will be performed for patients with a history of at least 12 months in the database prior to their first prescription of Intuniv® within the reported period. For analysis of first time/repeat use and duration of exposure to Intuniv®, a subgroup analysis will be conducted for patients who were observable in the database within the reported calendar year as well as within the entire time period since the country-specific launch date. Furthermore, in order to assess compliance with visits and measurements needed during the first year of treatment with Intuniv®, a subgroup analysis will be conducted for patients who were observable in the database at least 12 months after index date (date of the first prescription of Intuniv® since country-specific launch date). Please also refer to the statistical analysis plan (SAP) for further information regarding the definitions of specific variables. In Belgium, Finland, Ireland, and Netherlands where sufficient suitable longitudinal patient level data are not available or difficult to access, a prescriber survey will be conducted which will allow the evaluation of health care professionals (HCPs) real-life practice. The survey will also allow to more specifically assess knowledge and implementation of the additional risk minimization measures, which is not always available in the databases. The survey will be described in a separate protocol.

Information on the selected databases is summarized in section 9.4.

9.1 Setting

All patients available in the databases who have been prescribed Intuniv at least once in the reported period will be considered for the analysis. The database study described in this protocol will include data from Germany, Spain, UK, Denmark, Norway and Sweden.

All prescriptions for Intuniv® available in the databases will be analyzed. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv® in the respective countries. Analysis will be performed at the patient level. All available prescriptions for a given patient will be considered. More details on the specifics of the analysis are provided in the SAP.

The overall study period will cover the time period from January 2016 to December 2021 (up to 5 years post product launch). The study time per country will depend on the respective launch date.

9.2 Variables

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

The following information will be obtained if available in the databases used for the specific country:

- specialty of prescriber

- 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 (history of prior use of Intuniv®)
    - 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 greater than 7 mg or of 4mg in patients below 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 (if available in the databases)

A detailed description of all variables and definitions is provided in Table 4 of the SAP for the database protocol. Codes to comorbidities are also listed in the SAP (Appendix 2).

9.3 Data sources

The following longitudinal patient level databases will be used:

- Electronic medical records database
    - IMS Disease Analyzer (Germany)
    - IMS LPD (Spain)
    - THIN (UK)
- National registries (Denmark, Norway, Sweden)

Information on data availability of the requested variables in the country specific databases is summarized in Tables 2 and 3.

The specific databases are described in Section 9.4.1 – 9.4.3.

Table 2: Availability of study relevant parameters per data source and country

Target country	Type of data source	Parameters available: demographic and clinical characteristics							
		Age, gender	Prescriber specialty	Number of physicians visit within 1 year after initiation	Indication of use (diagnosis)	Co-morbidities	Weight	Blood pressure	Heart rate
Denmark	National Registry	yes	yes	no	yes[1,3]	yes[1]	no	no	no
Germany	EMR	yes	yes	yes	yes[2]	yes	(yes)	(yes)	no
Norway	National Registry	yes	yes	no	free text[3,4]	yes	no	no	no
Spain	EMR	yes	yes	yes	yes	yes	no	no	no
Sweden	National Registry	yes	yes	no	yes[1,3]	yes[1]	no	no	no
UK	EMR	yes	GP panel	yes	yes	yes	(yes)	(yes)	(yes)

[1] link of registers required
[2]Physician is requested to provide information on diagnosis for the drug prescribed. If direct link between diagnosis and medication is missing, inference is made based on co-occurring diagnosis
[3] Inference between drug and diagnosis is made based on co-occurring diagnosis
[4]Dosage and indication as written by the doctor, ICD-10 codes or ICPC codes for reimbursed drugs
(yes): not available for all patients

Table 3: Databases and prescription information per country

Target country	Database	Parameters available: prescription information				
		First time user / repeat user	Disconti-nuation	Switch	Dosing	Duration of treatment / exposure
Denmark	National Registry	yes	yes[1]	yes[1]	yes[1]	yes
Germany	DA	yes	yes	yes	yes	yes
Norway	National Registry	yes	yes[1]	yes[1]	free text	yes
Spain	LPD	yes	yes	yes	no	yes
Sweden	National Registry	yes	yes[1]	yes[1]	free text	yes[1]
UK	THIN	yes	yes	yes	yes	yes

[1] with assumptions (inferred/calculated)

9.3.1 Longitudinal EMR databases

Longitudinal patient-level electronic medical records databases providing information from continuing physician and patient interaction on consultations, diagnoses and treatment:

Germany – IMS Disease Analyzer (DA)

The German Disease Analyzer database is based on patient records continuously collected from 2,400 computerized practices (including specialists) throughout Germany. The practices are assigned to panels of specialists, which include diabetologists, cardiologists, gynecologists, psychiatrists/ neurologists, orthopedics, pediatricians and urologists, as well as a GP panel. The sampling method for the Disease Analyzer database is based on summary statistics of all doctors in Germany published yearly by the German Medical Association (Bundesärztekammer) [http://www.baek.de].

The statistical unit of IQVIA uses these statistics to determine the panel design according to the following strata: specialist group, German federal state, community size category, and age of physician. For further details please refer to Becher et al. 2009 (13). Comparisons with external data sources (e.g. data from statutory health insurances) underline the validity and representativeness of the German IMS DA in pharmacoepidemiological and pharmacoeconomic studies (13).

DA Germany includes a GP/Internal medicine panel and, separately, panels of office-based pediatricians and psychiatrists/neurologists. Amongst the unique physicians included, as of 2016, the database covers approximately 2.9% of the ~51,998 GPs (n = 1,486 physicians), approximately 5.2% of the ~5,850 office-based pediatricians (n = 306 physicians) and approximately 3.6% of the~ 6,621 office-based neurologist (n=239 physicians) in Germany. It is not possible to track an individual between different panels, but IQVIA can analyze records

on ADHD in the GP panel and in the pediatrician panel separately. As children in Germany are usually seen by pediatricians and not GPs, whereas adults are seen by GPs, overlap of patients and patient switching between these two types of primary care physicians, which could lead to duplicate counts, is unlikely.

The lag time for data availability for Disease Analyzer Germany is 6 to 8 weeks.

UK – THIN

THIN is a large UK primary care database containing EMR information. As of May 2017, THIN contained pseudonymised primary care medical records from over 15 million patients, of which approximately 2.9 million are currently active, representing almost 5% of the UK population. Data are available from 1990 onwards for many patients, with summarized medical information detailed prior to that. The database holds all prescribed medication, signs, diagnoses, lab tests and additional information such as lifestyle factors, BMI and vaccinations.

THIN data have been shown to be generally representative of the UK population in terms of age and gender comparisons, and "quality and outcomes framework" (QOF) chronic disease prevalence (17, 18). In addition, a study has been performed which compares THIN data with practices using a different general practice software system (EMIS), and it was shown to match closely with these data, with the main exception that THIN data patients are slightly more representative of the most affluent social classes. As this socioeconomic information is available in THIN data, researchers are able to adjust for it in analyses. Studies using THIN require review by the Scientific Review Committee (SRC) with no requirement for publication.

Data files in THIN are arranged in standardised tables. Diagnoses are coded in hierarchical Read codes which are grouped in themed "chapters" and include terms relating to symptoms, diagnoses, procedures, and laboratory tests. Prescription items are coded using Gemscript codes, based on NHS dictionary of medicines and devices and linked to BNF chapters. Hospital Episode Statistics (HES) data have been linked and pseudonymised at the patient level and combined with THIN to form THIN-HES.

It is possible to examine diagnostic Read codes and an associated hospital admission / discharge letter within THIN (without the linkage to HES discharge data). An advantage of using THIN is that the loss of sample size is prevented (up to 50% loss of patients) resulting from mismatch in linking which significantly enhances the statistical power of the study.

The lag time for data availability for THIN data from UK is 2 to 3 months.

Spain - LPD

The LPD Database for Spain is based on patient records collected from 2,873 prescribers (including specialists) throughout Spain. The practices are assigned to a longitudinal panel based on 21 specialties, including cardiologists, gynecologists, psychiatrists / neurologists, orthopedics, pediatricians, urologists, cardiologist, oncologist as well as a general practitioners' (GP) panel.

The database covers approximately 2.1% of the ~47,526 GPs (n= 1,018 physicians), approximately 3.0% of the ~13,120 paediatricians (n= 397 physicians) and approximately 2.2% of the ~6,085 psychiatrists (n= 131 physicians) in Spain.

The data in LPD database are generated directly from the electronic medical records of the panel physicians' practice via standardized interfaces and provide monthly routine information on patients' diseases and therapies. The lag time of data availability is 5 to 6 weeks.

It is possible to track an individual patient recorded across different specialties, so the history of the patient's treatment at different specialists can be analysed.

The lag time for data availability for LPD data from Spain is approximately 2 months.

9.3.2 National disease and prescription registries (Nordic countries)

The Nordic countries have a long tradition of registry-based epidemiological research. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. In recent years, each country has established a national database to track drug prescription data to individuals in ambulatory care.

Five Nordic countries collect drug exposure data based on drugs dispensed at pharmacies and have the potential to link these data to health outcomes. The databases together cover 25 million inhabitants (Denmark: 5.5 million; Finland: 5.3 million; Iceland: 0.3 million; Norway: 4.8 million; and Sweden: 9.2 million).

The population-based data of three Northern-European countries (Denmark, Norway and Sweden) will be used in the current study. The prescription registries contain nationwide information since 1994 (Denmark), 2004 (Norway), and 2005 (Sweden). For Finland, due to limited access to Finnish registry data and for more comprehensive information, data will be collected within a prescriber survey.

In order to retrieve patient level information on drug use and diagnoses, the research undertaken needs to be approved by relevant ethics review boards. The national prescription registries will be linked to the hospital discharge/patient registries in the individual countries, and this linking will also need to be approved and performed according to local regulations.

The update of information collected in Swedish National registries takes place yearly in June and the data is approximately available for analysis in quarter 3 of the respective year. For Norway the prescription register and patient register are updated monthly and annually, respectively.

Several steps are required to get access to the national prescription and diagnosis information from the Danish, Norwegian, and Swedish registries. Most important, the research question needs to be of a scientific nature that would require linkage of patient level data. The research project will have to comply with the regulations and policies of each country and registry, including acts on data privacy and public information.

There are some differences between the country specific registries. No information on indication is available in the Swedish prescription registry, therefore it requires linkage with the patient registry where inpatient and outpatient diagnoses are registered. For the Norwegian prescription database, the indication is specified for reimbursed drugs (refusjonskod for blåresept). No information on over-the-counter (OTC) drugs is captured in the Norwegian or Swedish prescription registry.

9.3.2.1 Danish prescription database

Danish Intuniv® prescription data will be collected from the Danish Medicines Agency (DMA) database (http://dkma.medstat.dk). The DMA administers legations on medicinal products, reimbursement, pharmacies, medical devices and euphoriants.

The DMA prepares statistics and analyses on the sales of medicinal products. The data are collected in the Register of Medicinal Products Statistics, which is a database covering total sales of medicinal products in Denmark. The information is collected from Danish community pharmacies, hospital pharmacies, the National Central Laboratory of the Danish Health System (Statens Serum Institut) and the Danish Veterinary Laboratory (Statens Veterinaere Serumlaboratorium), which registers every dispatch or delivery of medicinal products in Denmark.

Data available for public consultation are limited and not all variables required for the planned DUS are covered. The information is restricted to patients' age, gender and daily dose, and is reported by age groups on 5 year intervals. Information about diagnosis (perceived as the indication for the prescription) is not available in the public database. For parameter availability for planned analyses please refer to overview in Table 2 and Table 3.

9.3.2.2 Norwegian prescription database

The NorPD (Norwegian title: Reseptregisteret, http://www.norpd.no) was established on January 1st, 2004 at the Norwegian Institute of Public Health. The NorPD collects and processes data on drug consumption by humans and animals in Norway. The Database only monitors drugs that are dispensed by prescription in Norway, and therefore, drugs that are purchased without prescription (OTC drugs) are not included.

The NorPD prescription database contains information from all prescriptions and requisitions that are dispensed at Norwegian pharmacies. NorPD includes the following information: assigned pseudonym for the patient and the prescriber, patient information (gender, date of birth and of death, municipality of residence), prescriber information (gender, year of birth, profession and specialty), drug information including product and package size (part number for both the requested product and dispensed prescribing by generic substitution), the number of packages, ATC category, and defined daily dose (DDD), reimbursement and refund amounts, price, dosage, diagnosis code according ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision), the pharmacy's license number and the municipality, deliveries to the institution, the health unit registry number (HERE) and the delivery date.

For parameter availability for the current study please refer to overview in Table 2 and Table 3.

9.3.2.3 Swedish prescription database

The Swedish Prescribed Drug Register (SPDR) contains information about unique patient identifiers for all prescriptions dispensed to the whole population of Sweden (9 million inhabitants) (14). For prescribed drugs, the register includes data on dispensed item, substance, brand name, formulation, package size, dispensed amount, dosage, expenditure, and reimbursement. There is also information on date of prescribing and dispensing, as well as, prescriber's profession and practice. All drugs are classified according to the ATC. There is no information on OTC medications and for drugs used or administered in hospitals.

In order to evaluate the indication, the SPDR data will be linked to the Swedish patient register (15), which includes ICD-10 diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, also with national coverage. The data on parameter availability is displayed in overview in Table 2 and Table 3.

9.3.3 Coverage of databases

In Table 4 the coverage of the used databases is summarized.

Table 4: Coverage of databases

Country	Database	% approx.coverage	Number of potential prescribers per specialty in the database
Denmark	National Registry	100% of population	• 530 Neurologists • 430 Paediatricians • 948 Psychiatrists • 4,912 GP's • 456 Int. Medicine • 200 Child and Adolescent Psychiatrists
Germany	EMR	• 2.9% of the ~51,998 GPs • 5.2% of the ~5,850 office-based paediatricians • 3.6% of the~ 6,621 office-based neurologist	• 1,486 GPs • 306 paediatricians • 239 neurologists
Norway	National Registry	100% of population	• 553 Neurologists • 703 Paediatricians • 1,611 Psychiatrists • 6,123 GP's • 1,466 Int. Medicine • 451 Child and Adolescent Psychiatrists
Spain	EMR	• 2.1% of the ~47,526 GPs • 3.0% of the ~13,120 paediatricians • 2.2% of the ~6,085 psychiatrists	• 1,018 GPs • 397 paediatricians • 131 psychiatrists
Sweden	National Registry	100% of population	• 562 Neurologists • 1,364 Paediatricians • 1,794 Psychiatrists • 7,569 GP's • 1,514 Int. Medicine • 401 Child and Adolescent Psychiatrists
UK	EMR	5% of UK population	GPs

9.4 Study size and feasibility

This is a descriptive study that describes and quantifies Intuniv® use in the target countries; therefore, no formal sample size calculations were conducted.

All patients available in the databases meeting the inclusion criteria will be included in the analysis. The target sample size is to include at least 100 patients per country who have been prescribed Intuniv® at least once during the observational period. However, in case the number of 100 patients is not reached in a country, data will be analysed to the extent possible. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv® in the respective countries. All prescriptions for Intuniv® available in the databases will be analyzed.

The targeted 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).

Table 5 in the Appendix provides expected sales figures as number of patients per target country for one year.

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

9.5 Data management

The study will be conducted according to the standard operating procedures of IQVIA. The datasets extracted from the databases will be stored at IQVIA files to allow analysis in the future.

9.6 Data analysis

9.6.1 General statistical considerations

Descriptive analyses will be performed based on the prescriptions contained in the databases from each reporting period. The use of Intuniv® will be analysed using the prescriptions collected during the 5-year assessment period.

All prescription information for Intuniv® dispensed from January 2016 up to December 2021, if available, will be extracted from the described databases. Extractions will take place once per year for each of the four reports. The last annual extraction will include data covering the period from approximately January 2021 up to December 2021, and cumulative data from

January 2016 up to December 2021. The exact data period covered each year will depend on the launch date in each country and the lag time for data availability in the databases.

Data from different sources will not be directly combined. Study tables will reference the data source used for each set of results.

9.6.2 Potential for sampling bias

Overall, some imprecision of estimates may result if the total uptake of Intuniv® prescriptions in single countries is low. This might be the case especially in the time period immediately after launch and if projected figures are used.

Longitudinal EMR databases (IMS Disease Analyzer, LPD and THIN):
As the German Disease Analyzer is representative for Germany (13) no major selection bias is expected. Similarly, for the LPD-database used in Spain, the panel of contributing physicians is maintained as a representative sample of the respective physician population in each country according to age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile.

THIN data have been shown to be generally representative of the UK in terms of age and gender comparisons, and QOF chronic disease prevalence (17, 18). In addition, a study has been performed which compares THIN data with practices using a different general practice software system (EMIS), and it was shown to match closely with these data, with the main exception that THIN data patients are slightly more representative of the most affluent social classes... No major selection bias is expected here either. However, the THIN database covers GPs only. GPs are expected to take care of the follow-up prescriptions for Intuniv®, whereas the first prescription would most likely be done by a specialist not covered by the THIN database. Therefore, there could be a bias concerning people who only get one prescription from a specialist, but no follow-up prescriptions from the GP. These patients will not be captured. For patients who do get a prescription from a specialist followed by prescriptions from GPs, the start date will not be captured appropriately.

National Registries:
No major selection bias is expected for the data obtained from national prescription registries in Nordic countries, because dispatches made at pharmacies nationwide are available.

9.6.3 Descriptive 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.

Indication of use, patient characteristics, patterns of drug use and drug dosage will be described.

For continuous variables the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented. Categorical variables will be displayed with frequencies and percentages. Analyses will be performed using appropriate statistics software (like SAS 9.2).

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 and example of figures that will be produced will be included in the SAP.

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.

9.7 Quality control

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 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".

9.8 Limitations of the research methods

Panel composition and representativeness

It may be argued that the physicians who participate in panels may have different practice behavior than other physicians who do not take part in such activity. The panel of contributing physicians is maintained as a representative sample of the primary care physician population in each country according to age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile.

Data collection

The IMS® Disease Analyzer, LPD- and THIN databases have limitations consistent with a provider-sourced EMR database. Patients who seek care outside the EMR practice setting will not have that utilization recorded in the database. However, in UK, GPs function as gate keepers, therefore the majority of information is expected to be available in THIN. In Germany, children tend to go to the same pediatrician; therefore information is also expected to be relatively complete for children in DA. Nevertheless, it needs to be taken into consideration that databases contain prescriptions written by the participating physician, but not actual prescription fills.

As with any other EMR databases, information will be available to the extent it is recorded by the physicians. Although the quality of data collection is monitored by database owners, the information provided by the physicians in health records can still be underreported.

Missing information

Not all information is available in all databases and all patients/ prescriptions. This applies especially for the monitoring parameters weight, blood pressure and heart rate which are not available in the registry data or in the LPD database.

For THIN, diagnosis information might be missing for some patients; this needs to be taken into account when off-label use is determined. The Swedish National Patient Register includes secondary care data only (hospital in- and outpatient setting). Information on indication can only be inferred from patients included in this database, resulting in missing information for patients who have received prescriptions in other settings.

Other

For Scandinavian registry data relatively long lag times has to be considered, for example the Swedish National patient Register annual uptake is completed approximately in September of the following year, with some variability and possible delays for providing the data. In Denmark, availability of data will depend on the local situation and the requirements of the Healthcare Data Protection Agency at the time when the analysis will be conducted.

10 PROTECTION OF HUMAN SUBJECTS

This study is non-interventional and analysis is based on secondary data use. No identifying data is collected in any of the planned approaches. All databases are set up following local law, including data privacy regulation.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines (16). This is a non-interventional study design which is based on retrospective data collection. This drug utilization study is designed to provide utilization data on Intuniv®, to allow an evaluation of inappropriate use, based on aggregate analyses. Adverse effects are not being measured directly in this study. Therefore, Shire will only report aggregate findings as study reports, not individual spontaneous reports.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The first study report will be sent to Shire in June 2019. Annual reports will be sent thereafter. The last report will be sent in June 2022.

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14 APPENDICES

Annex 1

Table 5: Expected sales figures in the first 12 months post launch, number of patients (estimate by Shire as of December 2015)

	Month since country specific launch											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Germany	620	1,243	1,868	2,493	3,118	3,741	4,360	4,974	5,581	6,181	6,771	7,351
UK	195	395	601	814	1,031	1,255	1,483	1,716	1,955	2,197	2.444	2,695
Denmark	80	161	244	326	410	493	577	660	743	825	907	988
Sweden	174	351	530	711	893	1,077	1,262	1,447	1,631	1,816	1,999	2,181
Norway	39	79	120	160	201	243	284	325	366	407	448	488
Spain	465	936	1,413	1,895	2,380	2,866	3,354	3,841	4,327	4,810	5,289	5,763

Annex 2

Table 6 : Sample size estimates based on sold tablets from 10/2016 - 09/2017

Country (launch date)	**Sales Units** (tablets) [10/2016 - 09/2017]	**Estimated number of patients**[1] [10/2016 - 09/2017]	**Data source for study** (Coverage of database)	**Expected number of patients in data source** [10/2016 - 09/2017]
Denmark (01/2016)	104,160	263	Registry (complete)	~250
Finland (*05/2016*)	*43,820*	*111*	*survey*	
Germany (01/2016)	1,874,684	4,719	IMS Disease Analyzer (2.9-5.2%* of physicians)	130 -250
Ireland (*05/2016*)	*34,972*	*89*	*survey*	
Norway (05/2016)	90,524	228	Registry (complete)	~220
UK (02/2016)	877,884	2,210	THIN (~5% of patients)	~100
Belgium (*10/2016*)	*21,070*	*54*	*survey*	
Netherlands (*09/2015*)	*31,976*	*81*	*survey*	
Spain (01/2017)	785,676	1,978	IMS LPD (2.1-3.0%* of physicians)	~40 - 60
Sweden (02/2016)	**1,007,244**	**2,536**	**Registry (complete)**	**~ 2500**

* depending on specialty;
[1]Approximated number of patients = based on a daily consumption of 1.0886 tablets/day and 365 days of treatment per year
Source daily consumption: IMS National Prescription Audit (NPA), Monthly; Source sales units: IMS MIDAS

Annex 3: 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 survey	Version 5.0	17 July 2018	Drug utilisation study of Intuniv® (guanfacine extended release) in European Countries – A prescriber survey
3 Statistical Analysis Plan Survey	Version 4.0	17 July 2018	Statistical Analysis Plan II: Survey study: use of Intuniv® in Belgium, Finland, Ireland, 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