

|                          |  |
|--------------------------|--|
| Study title              | <b>Drug Utilisation Study of Intuniv<sup>®</sup><br/>(guanfacine extended release) in<br/>European Countries</b>   |
| Document title           | Study protocol I: Database study: use of Intuniv <sup>®</sup><br>in Denmark, Germany, Norway, Spain, Sweden, and UK  |
| Drug                     | Intuniv <sup>®</sup> (guanfacine)<br>Extended-release tablets 1mg, 2 mg, 3mg and 4mg   |
| Indication               | Intuniv <sup>®</sup> is indicated for treatment of attention deficit<br>hyperactivity disorder (ADHD) in children and adolescents<br>6 to 17 years old for whom stimulants are not suitable, not<br>tolerated or have been shown to be ineffective. Intuniv must<br>be used as a part of a comprehensive ADHD treatment<br>programme, typically including psychological, educational<br>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,<br>The Netherlands, Norway, Spain, Sweden, UK)  |
| Company / sponsor        | Takeda Pharmaceuticals   |
| Subcontractor            | IQVIA  |
| Date of the document     | 2022-07-26<br>CONFIDENTIAL   |

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**Signature page**

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


**Study number: SHP503-802**

**Version number: 7.2, (26 JUL 2022)**

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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<sup>®</sup> (guanfacine extended release) in European Countries

## **Marketing authorisation holder**

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## **3 RESPONSIBLE PARTIES**

### **Sponsor: Takeda Pharmaceuticals**

#### *Project team:*

Center for Post Approval Safety Studies: [REDACTED], PhD; Takeda (e-mail: [REDACTED])

Center for Post Approval Safety Studies: [REDACTED], MPH; Takeda (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 <sup>®</sup> (guanfacine extended release) in European Countries   |
| Rationale and background      | Shire Pharmaceuticals (now part of Takeda) plans to launch Intuniv <sup>®</sup> in Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Spain, Sweden and UK from January 2016 onwards. Shire Pharmaceuticals (now part of Takeda) will conduct a drug utilization study for up to five years as part of the risk management plan for Intuniv <sup>®</sup> in Europe.   |
| Indication                    | Intuniv <sup>®</sup> 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 <sup>®</sup> must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures (1).  |
| Objectives                    | <p>The study's overall research question and objective is to characterize patients who are prescribed Intuniv<sup>®</sup>, 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.</p> <p>Primary objectives:</p> <ul style="list-style-type: none"> <li>• To characterize patients who are prescribed Intuniv<sup>®</sup> with a specific focus on: <ul style="list-style-type: none"> <li>○ Indications other than ADHD</li> <li>○ Children less than 6 years of age</li> <li>○ Adults</li> <li>○ Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv<sup>®</sup></li> <li>○ Prescribed overdose of &gt;7 mg/day or of &gt;4 mg/day for patients ≤12 years of age</li> </ul> </li> <li>• To describe prescribing patterns of Intuniv<sup>®</sup> among physicians</li> </ul> <p>Secondary objective:</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> |
| Study design and data sources | <p>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.</p> <p>The following data sources will be used:</p> <ul style="list-style-type: none"> <li>• Longitudinal patient level databases <ul style="list-style-type: none"> <li>○ Electronic medical records database <ul style="list-style-type: none"> <li>▪ IMS Disease Analyzer (Germany)</li> <li>▪ IMS LPD (Spain)</li> </ul> </li> </ul> </li> </ul>   |

|               |  |
|---------------|--|
|               | <ul style="list-style-type: none"> <li>▪ THIN (UK) <ul style="list-style-type: none"> <li>○ National registries (Denmark , Norway, Sweden)</li> </ul> </li> <li>• Prescriber survey <ul style="list-style-type: none"> <li>○ Belgium</li> <li>○ Finland</li> <li>○ Ireland</li> <li>○ Netherlands</li> </ul> </li> </ul>   |
| Population    | Patients who have been prescribed Intuniv <sup>®</sup> at least once during the reporting period.  |
| Sample size   | The target sample size is at least 100 patients who have been prescribed Intuniv <sup>®</sup> at least once in each country. All prescriptions for Intuniv <sup>®</sup> available in the databases will be analyzed. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv <sup>®</sup> 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<br>Version 1.0 | 30 Sep 2013 | New protocol   | nap  | nap  |
| Amended protocol,<br>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,<br>Version 3.0 | 17 Jul 2017 | Title page<br>Synopsis   | Update of title  | Addition of a non-EU country (Switzerland)   |
|                                  |             | Title page<br>Section 6:<br>Milestones                           | Update on timelines  | Alignment with actual launch of Intuniv <sup>®</sup> and data availability in the respective countries                       |
|                                  |             | Title page<br>Synopsis<br>Section 7:<br>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 <sup>®</sup>  |
|                                  |             | Synopsis<br>Section 8:<br>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:<br>Study design                        | Split of protocol into two separate protocols:<br>1. One protocol for a database study to be conducted in Denmark, France, Germany, Norway, Spain, Sweden, Switzerland and UK<br>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 |

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|  |  |   | Netherlands and Switzerland  |   |
|  |  | Synopsis and Section 9.1:<br>Study design<br>Section 9.4:<br>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;<br>UK: more robust study anticipated due to higher patient counts for Intuniv® noted during feasibility assessment |
|  |  | Synopsis and Section 9.3:<br>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:<br>Abbreviations   | Update of list of abbreviations  | List updated to match the current document  |
|  |  | Section 3:<br>Responsible parties   | Update on project management   | Changes in staff  |
|  |  | Section 9.2:<br>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:<br>Quality control   | update   | To align with current QuintilesIMS policies   |
|  |  | Section 9.9:<br>Limitations   | update   | To align with the current data sources  |
|  |  | Section 13:<br>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 by expected sales   | To give more current information which will allow a better sample size estimation   |

|                               |             |   |   |  |
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|                               |             |   | figures of Intuniv <sup>®</sup>   |  |
| 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 <sup>®</sup> in Spain  | Launch date is available now and Intuniv <sup>®</sup> 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                  |

|                               |              |   |  |  |
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| Amended protocol, Version 5.0 | 18 May 2018  | Throughout document   | Removal of France and Switzerland                      | Intuniv <sup>®</sup> 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                                   | Text added   | Clarification that Intuniv <sup>®</sup> is indicated as second line treatment  |
|                               |              | 14: Appendix  | Update of table  | New versions of stand-alone documents available.   |
| Amended protocol, Version 7.1 | 22 June 2022 | Title page  | Update date of document                                | To reflect date of changes.  |
|                               |              | Responsible parties   | Update project team information                        | Update project team information.   |
|                               |              | Milestones  | Update last report date from June 2022 to June 2023    | Delivery of data from Danish Registry is delayed – an amendment report, which will include Danish Registry data until 2020 will be submitted in June 2023. |
|                               |              | Section 11 Managing and reporting of adverse events/adverse reactions | Update language related to reporting of adverse events | To reflect updated language re: reporting of safety events from studies based on the secondary use of existing health information.                         |
|                               |              | Throughout document   | Changed 'Shire' to 'Takeda' or 'Shire (now part of     | To reflect acquisition of Shire by Takeda in the time since protocol   |

|                               |              |                       |  |  |
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|                               |              |                       | Takeda)' where appropriate   | version 7.0 was submitted                    |
|                               |              | Throughout document   | Formatting changes   | Remove spacing, and other formatting changes |
| Amended protocol, Version 7.2 | 26 July 2022 | Throughout document   | Removal of any reference to the fourth interim report and the interim final report | Update in response to PRAC request.          |
|                               |              | Throughout document   | Administrative changes   | Minor wording and grammar changes            |
|                               |              | Beginning of document | Administrative changes   | Insert signature page                        |

## 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:<br>First report June 30, 2019, annual reports thereafter<br>Last report June 30, 2023 |

All prescription information for Intuniv<sup>®</sup> 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 <sup>®</sup> | Report 30 Jun 2019 | Report 30 Jun 2020 | Report 30 Jun 2021 | Report 30 Jun 2023 |
|-------------|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| 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                  |

\*The delivery of data from Danish Registry is delayed. Therefore, the annual Danish data for 2019 and 2020 will be included in the final report in June 2023.

## 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 behavior 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<sup>®</sup>, Concerta<sup>®</sup>), dexamphetamine (e.g., Attentin<sup>®</sup>) and lisdexamfetamine (e.g., Elvanse<sup>®</sup>). 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<sup>®</sup>) 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 (now part of Takeda) has launched a novel non-stimulant drug in USA and Canada: extended-release guanfacine (Intuniv<sup>®</sup>). Intuniv<sup>®</sup> 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. 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<sup>®</sup> can be prescribed as monotherapy and as adjunctive therapy to stimulant medications. Intuniv<sup>®</sup> 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<sup>®</sup> is not a controlled substance, which sets it apart from most other ADHD drugs.

The active compound of Intuniv<sup>®</sup>, guanfacine, is also used for treatment of hypertension, but the marketing authorization of Intuniv<sup>®</sup> does not include that indication. Therefore, use of Intuniv for treatment of hypertension would be considered off-label use.

The effects of Intuniv<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>.

To increase awareness and knowledge on these requirements, Shire Pharmaceuticals (now part of Takeda) has developed and distributed educational materials to potential prescribers of Intuniv<sup>®</sup>.

Shire Pharmaceuticals (now part of Takeda) 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<sup>®</sup> in Europe, (now part of Takeda) considers this study an important activity to evaluate whether Intuniv<sup>®</sup> is being prescribed within the approved SmPC and whether current risk minimization measures are adequate.

Shire Pharmaceuticals (now part of Takeda) has launched/ plans to launch Intuniv<sup>®</sup> 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<sup>®</sup> given in the Summary of Product Characteristics is as follows (1):

Intuniv<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 (now part of Takeda).



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

### Overall research question and objective:

The study's overall research question and objective is to characterize patients who are prescribed Intuniv<sup>®</sup>, to describe prescribing patterns among physicians and to evaluate if additional risk minimization measures that had been provided to physicians were successfully implemented and effective. Data on use of Intuniv<sup>®</sup> 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<sup>®</sup> which had been proposed by Shire Pharmaceuticals (now part of Takeda).

### Study Objectives:

#### Primary objectives:

- To characterize patients who are prescribed Intuniv<sup>®</sup> 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<sup>®</sup>
  - Prescribed overdose of >7 mg/day, or of >4 mg/day for patients ≤12 years of age
- To describe prescribing patterns of Intuniv<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> within the reported period. For analysis of first time/repeat use and duration of exposure to Intuniv<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup> 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 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<sup>®</sup> available in the databases will be analyzed. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv<sup>®</sup> 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<sup>®</sup> and describe prescribing patterns of Intuniv<sup>®</sup> 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<sup>®</sup>)

- duration of treatment
- discontinuation of ADHD therapy
- switches (both from Intuniv<sup>®</sup> to other ADHD medications and other ADHD medications to Intuniv<sup>®</sup>)
- dosing/ overdose (defined as daily dose of greater than 7 mg or of 4mg in patients below 12 years of age)
- use of Intuniv<sup>®</sup> as second-line treatment after psychostimulant prescription at any time prior to the patient's first prescription of Intuniv<sup>®</sup>
- frequency of monitoring (physician) visits during the first year of therapy
- weight, blood pressure and heart rate during Intuniv<sup>®</sup> 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, and 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 <sup>1,3</sup>            | yes <sup>1</sup> | no     | no             | no         |
| Germany        | EMR                 | yes  | yes                  | yes   | yes <sup>2</sup>              | yes              | (yes)  | (yes)          | no         |
| Norway         | National Registry   | yes  | yes                  | no  | free text <sup>3,4</sup>      | yes              | no     | no             | no         |
| Spain          | EMR                 | yes  | yes                  | yes   | yes                           | yes              | no     | no             | no         |
| Sweden         | National Registry   | yes  | yes                  | no  | yes <sup>1,3</sup>            | yes <sup>1</sup> | no     | no             | no         |
| UK             | EMR                 | yes  | GP panel             | yes   | yes                           | yes              | (yes)  | (yes)          | (yes)      |

<sup>1</sup>Link of registers required

<sup>2</sup>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

<sup>3</sup> Inference between drug and diagnosis is made based on co-occurring diagnosis

<sup>4</sup>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                  | Discontinuation  | Switch           | Dosing           | Duration of treatment / exposure |
| Denmark        | National Registry | yes  | yes <sup>1</sup> | yes <sup>1</sup> | yes <sup>1</sup> | yes                              |
| Germany        | DA                | yes  | yes              | yes              | yes              | yes                              |
| Norway         | National Registry | yes  | yes <sup>1</sup> | yes <sup>1</sup> | free text        | yes                              |
| Spain          | LPD               | yes  | yes              | yes              | no               | yes                              |
| Sweden         | National Registry | yes  | yes <sup>1</sup> | yes <sup>1</sup> | free text        | yes <sup>1</sup>                 |
| UK             | THIN              | yes  | yes              | yes              | yes              | yes                              |

<sup>1</sup>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 pharmacoepidemiologic and pharmaco-economic 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 patients 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 pseudonymized 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 standardized 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 pseudonymized 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<sup>®</sup> 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 euphoriant.

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 1<sup>st</sup>, 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  |
|----------------|-------------------|--|--|
| <b>Denmark</b> | National Registry | 100% of population   | <ul style="list-style-type: none"> <li>• 530 Neurologists</li> <li>• 430 Paediatricians</li> <li>• 948 Psychiatrists</li> <li>• 4,912 GP's</li> <li>• 456 Int. Medicine</li> <li>• 200 Child and Adolescent Psychiatrists</li> </ul>       |
| <b>Germany</b> | EMR               | <ul style="list-style-type: none"> <li>• 2.9% of the ~51,998 GPs</li> <li>• 5.2% of the ~5,850 office-based paediatricians</li> <li>• 3.6% of the ~6,621 office-based neurologist</li> </ul> | <ul style="list-style-type: none"> <li>• 1,486 GPs</li> <li>• 306 paediatricians</li> <li>• 239 neurologists</li> </ul>  |
| <b>Norway</b>  | National Registry | 100% of population   | <ul style="list-style-type: none"> <li>• 553 Neurologists</li> <li>• 703 Paediatricians</li> <li>• 1,611 Psychiatrists</li> <li>• 6,123 GP's</li> <li>• 1,466 Int. Medicine</li> <li>• 451 Child and Adolescent Psychiatrists</li> </ul>   |
| <b>Spain</b>   | EMR               | <ul style="list-style-type: none"> <li>• 2.1% of the ~47,526 GPs</li> <li>• 3.0% of the ~13,120 paediatricians</li> <li>• 2.2% of the ~6,085 psychiatrists</li> </ul>                        | <ul style="list-style-type: none"> <li>• 1,018 GPs</li> <li>• 397 paediatricians</li> <li>• 131 psychiatrists</li> </ul>   |
| <b>Sweden</b>  | National Registry | 100% of population   | <ul style="list-style-type: none"> <li>• 562 Neurologists</li> <li>• 1,364 Paediatricians</li> <li>• 1,794 Psychiatrists</li> <li>• 7,569 GP's</li> <li>• 1,514 Int. Medicine</li> <li>• 401 Child and Adolescent Psychiatrists</li> </ul> |
| <b>UK</b>      | EMR               | 5% of UK population  | GPs  |

## 9.4 Study size and feasibility

This is a descriptive study that describes and quantifies Intuniv<sup>®</sup> 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<sup>®</sup> at least once during the observational period. However, in case the number of 100 patients is not reached in a country, data will be analyzed to the extent possible. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv<sup>®</sup> in the respective countries. All prescriptions for Intuniv<sup>®</sup> 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  $\alpha$  first-type error is the following:

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

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  $\pm 5\%$ , 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  $\pm 10\%$  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 (now part of Takeda) 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<sup>®</sup> will be analyzed using the prescriptions collected during the 5-year assessment period.

All prescription information for Intuniv<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup> 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).

## 11.1 Definitions

### 11.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject/patient to receive specific corrective therapy.
- A laboratory abnormality that leads to discontinuation of therapy.
- A laboratory abnormality that the health care provider considers to be clinically significant.

### 11.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

### 11.1.3 Adverse Drug Reactions

An Adverse Drug Reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

### 11.1.4 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

### 11.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:



- **Pregnancy:** Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- **Breastfeeding:** Infant exposure from breast milk.
- **Overdose:** All information of any accidental or intentional overdose.
- **Drug abuse, misuse, or medication error:** All information on medicinal product abuse, misuse, or medication error (potential or actual).
- **Suspected transmission of an infectious agent:** Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- **Lack of efficacy of Takeda Product.**
- **Accidental/Occupational exposure.**
- **Use outside the terms of the marketing authorization, also known as "off-label".**
- **Use of falsified medicinal product.**
- **Use of counterfeit medicinal product.**
- **Drug-drug interactions and drug-food interactions.**
- **Inadvertent or accidental exposure with or without an AE.**
- **Unintended benefit.**

An SSR should be reported even if there is no associated AE.

## **11.2 Collection and Notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance**

- SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints: Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.
- SAEs, AEs, SSRs and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints: Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.
- SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team: If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda Product (or unbranded generic), such information should be forwarded by CRO to the relevant Takeda Pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and events spontaneously notified which

are not study endpoints. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

- **SAE, AE, ADR, and SSR reports should be submitted to at GPSE@takeda.com.**
- **PQI reports should be submitted to pqc@takeda.com.**

## **12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS**

The first study report will be sent to Shire (now part of Takeda) in June 2019. Annual reports will be sent thereafter. The last report will be sent in June 2023.



### 13 REFERENCES

1. Intuniv<sup>®</sup>: EPAR-Product Information – European Medicines Agency (17.09.2015)
2. Diagnostic and Statistic Manual of Mental Disorders, Fifth Edition (DSM-V), American Psychiatric Society 2013.
3. Biederman J (1998). "Attention-deficit/hyperactivity disorder: a life-span perspective". *The Journal of Clinical Psychiatry* 59 Suppl 7: 4–16
4. Khan SA, Faraone SV. The genetics of attention-deficit/hyperactivity disorder: A literature review of 2005. *Current Psychiatry Reports*, 2006 Oct; 8:393-397.
5. Nair J, Ehimare U, Beitman BD, Nair SS, Lavin A (2006). "Clinical review: evidence-based diagnosis and treatment of ADHD in children". *Mo Med* 103 (6): 617–2
6. Polanczyk G. et al. 2007 The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *The American journal of psychiatry* 164 (6), S.942–948
7. Van Cleave J, Leslie LK (August 2008). "Approaching ADHD as a chronic condition: implications for long-term adherence". *Journal of Psychosocial Nursing and Mental Health Services* 46 (8): 28–37
8. Elia J, Ambrosini PJ, Rapoport JL (March 1999). "Treatment of attention-deficit-hyperactivity disorder". *The New England Journal of Medicine* 340 (10): 780–8.
9. Vorstman JA, Ophoff RA. Genetic causes of developmental disorders. *Curr Opin Neurol*. 2013 Apr;26(2):128-36.
10. Polańska K, Jurewicz J, Hanke W. Exposure to environmental and lifestyle factors and attention-deficit / hyperactivity disorder in children - a review of epidemiological studies. *Int J Occup Med Environ Health*. 2012 Sep;25(4):330-55.
11. Minzenberg MJ. "Pharmacotherapy for attention-deficit/hyperactivity disorder: from cells to circuits". *Neurotherapeutics*. 2012 Jul;9(3):610-21.
12. Biederman J, Melmed RD, Patel A, McBurnett K, Konow J, Lyne A, Scherer N; SPD503 Study Group. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics* 2008;121(1):e73-84
13. Becher et al. *International Journal of Clinical Pharmacology and Therapeutics*. 2009;47(10):617-26
14. Wettermark et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2008 May;17(5):533
15. Ludvigsson et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011, 11:450
16. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf*. Feb 27 2008;17(2):200-208.
17. Denburg MR, Haynes K, Shults J, Lewis JD, Leonard MB. Validation of The Health Improvement Network (THIN) Database for Epidemiologic Studies of Chronic Kidney Disease. *Pharmacoepidemiol Drug Saf*. Nov 2011;20(11):1138-1149.

18. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf.* Apr 2007;16(4):393-401.

## 14 APPENDICES

### Annex 1

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

|                | Month since country specific launch |       |       |       |       |       |       |       |       |       |       |       |
|----------------|-------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                | 1                                   | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     | 10    | 11    | 12    |
| <b>Germany</b> | 620                                 | 1,243 | 1,868 | 2,493 | 3,118 | 3,741 | 4,360 | 4,974 | 5,581 | 6,181 | 6,771 | 7,351 |
| <b>UK</b>      | 195                                 | 395   | 601   | 814   | 1,031 | 1,255 | 1,483 | 1,716 | 1,955 | 2,197 | 2,444 | 2,695 |
| <b>Denmark</b> | 80                                  | 161   | 244   | 326   | 410   | 493   | 577   | 660   | 743   | 825   | 907   | 988   |
| <b>Sweden</b>  | 174                                 | 351   | 530   | 711   | 893   | 1,077 | 1,262 | 1,447 | 1,631 | 1,816 | 1,999 | 2,181 |
| <b>Norway</b>  | 39                                  | 79    | 120   | 160   | 201   | 243   | 284   | 325   | 366   | 407   | 448   | 488   |
| <b>Spain</b>   | 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**

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

\*Depending on specialty.

<sup>1</sup>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   |

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**Timestamp**

**Certified Delivery Events**

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