PASS INFORMATIONENCEPP/SDPP/6083

Observational Study Protocol 31-13-300

Please note parts of the protocol including annexes have been currently redacted to avoid any bias to the study. The full protocol and annexes will be available when the study concludes.

Title	ABILIFY® for the Adolescent Bipolar I Mania Indication Tool Effectiveness Evaluation Survey
Protocol version identifier	Draft 5.0
Date of last version of protocol	15 October 2013
EU PAS register number	Study not registered
Active substance	Aripiprazole Antipsychotics ATC code: NO5AX12
Medicinal product	ABILIFY®
Product reference	PRD640634 PRD640635 PRD640636 PRD640637 PRD640638 PRD640639 PRD640640 PRD640641 PRD640642 PRD640643 PRD640644 PRD640645 PRD640646 PRD640647 PRD640665 PRD640648 PRD640649 PRD640650 PRD640651 PRD640652 PRD640653 PRD640654

	PRD640655 PRD640656 PRD640657 PRD640658 PRD28189 PRD640659 PRD640660 PRD640661 PRD640662 PRD640663 PRD640664
Procedure number	EMEA/H/C/000471
Marketing authorisation holder(s)	Otsuka Pharmaceutical Europe Ltd.
Joint PASS	No
Research question and objectives	The key research questions are: 1. What is the distribution of education material across the markets? 2. What is the usage of the RM tools by HCPs and patients / caregivers? 3. Do HCPs and patients / caregivers understand: a. the information presented in the RM tools, including b. the indicated age range, c. indicated dose, d. duration of treatment before prescribing ABILIFY e. the identified and potential risks of concern (extrapyramidal symptoms (EPS), weight gain, somnolence, fatigue) associated with ABILIFY for adolescent bipolar I mania indication 4. Do HCPs and patients / caregivers respond appropriately to hypothetical risk scenario based questions regarding the clinical use of ABILIFY for the adolescent bipolar I mania indication, the identified and potential risks, and the real-world usage, specifically the

	recommended starting dosage, and minimum recommended age of patients The primary objectives of the study are to: 1. To determine the proportion of HCPs, patients and caregivers that are aware of the RM tools and how the tools are accessed. 2. To determine when, how and by whom the tools are used. 3. To determine the level of knowledge and comprehension of the key risks associated with ABILIFY® when used for the treatment of paediatric bipolar I mania. 4. To evaluate HCP, patient and caregiver behaviours via behavioural questions and scenarios. 5. To assess the effect of the tools on the real-world risks that the educational tools have been designed to minimise, namely the maximum starting dose of ABILIFY® for the adolescent bipolar I mania indication is not exceeded, and the minimum age of patients receiving ABILIFY® for the adolescent bipolar I mania indication is not breached. This will be achieved by including in the HCP questionnaire the usual starting dose of ABILIFY® used in the adolescent indication, identifying the appropriate dose and the minimum age of the patient when the drug is prescribed, as well as the actual ages of patients doing the patient/carer questionnaire
Countries of study	UK, Germany, Spain, Italy, Sweden, Denmark, Norway, Ireland, Austria, Portugal, Slovenia, Greece/Cyprus
Author	Dr Andrew Makin, MD Acting VP Medical Affairs and Compliance - Europe Otsuka Pharmaceutical Europe Ltd.

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1 LIST OF ABBREVIATIONS

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
BMS	Bristol Myers Squibb
CI	Confidence Interval
EPS	Extrapyramidal Symptoms
EU PAS Register	European Union Post Authorisation Study Register
EU-RMP	European Risk Management Plan
HCP	Healthcare Provider
HCP FAQ	Healthcare Provider Frequently Asked Questions (one of the RM tools)
MAH	Market Authorisation Holder
PCIB	Patient Caregiver Information Brochure (one of the RM tools)
PW	Pope Woodhead – external consultants conducting the study
RM	Risk Minimisation
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
URL	Uniform Resource Locator

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3 ABSTRACT

3.1 Title

Title	ABILIFY® for the Adolescent Bipolar I Mania Indication Tool Effectiveness Evaluation Survey
Version	Draft 4.0
Date	14 October 2013
Main author / affiliation	Dr Andrew Makin MD, FFPM Acting Vice President Medical Affairs and Compliance Otsuka Pharmaceutical Europe Limited

3.2 Rationale and Background

ABILIFY® (aripiprazole) is a drug indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older. It was approved by the European Commission on January 24th 2013. For reasons of conciseness, the indication throughout this protocol is termed **adolescent bipolar I mania**.

As part of marketing authorisation approval, the ABILIFY® risk management plan (RMP) requires distribution of two Risk Minimisation (RM) communication tools, additional to the SmPC, to Healthcare Providers (HCPs) prescribing ABILIFY® for the adolescent bipolar I mania indication. This distribution is managed by BMS / Otsuka or Lundbeck depending on the timeline and status for local transfer of responsibility in each country.

These tools are a Healthcare Provider Frequently Asked Questions Brochure (HCP FAQ) and a Patient / Caregiver Information Brochure (PCIB). The purpose of the HCP FAQ is to clearly explain to prescribers or other HCPs involved in patient treatment the need to carefully consider the indicated age range, dose, and duration of treatment before prescribing ABILIFY® for the adolescent bipolar I mania indication. Furthermore, vigilance is urged in the on-going evaluation of weight gain, EPS, and ADRs related to somnolence and fatigue. A PCIB is available for physicians to give to their patients (and their caregivers) to help them better understand and recognise specific ADRs.

The EU-RMP committed Otsuka Pharmaceutical Europe Ltd., as the marketing authorisation holder (MAH), to evaluate the effectiveness of these additional RM activities (i.e. the RM tools and their distribution) for the adolescent bipolar I mania indication. This protocol describes the method for the HCP and Patient / Caregiver surveys that will be used to evaluate the

effectiveness of these RM tools, defined as a combination of effective distribution, usage, knowledge and adoption of appropriate stakeholder behaviours.
It should be noted that, for the duration of the surveys described in this protocol, Bristol-Myers Squibb (BMS) will retain responsibility for pharmacovigilance until Otsuka takes over responsibility for pharmacovigilance for ABILIFY® (mid 2016). Otsuka (the MAH) and Lundbeck affiliates (alliance partners in some markets participating in the survey) will be responsible for the operational aspects of implementing the surveys.
The results of the surveys are intended to assess the value of the current RM tools and to establish baseline levels of usage, knowledge and behaviours. The results will be reported to the EMA, and, if appropriate, lead to the modification of the ABILIFY® EU-RMP for the adolescent bipolar I mania indication. In addition, the results of the evaluation will inform the need for, and timing of, any subsequent tool evaluations.

3.3 Research Question and Objectives

3.3.1 Research Question

The key research questions are as follows:

1. What is the distribution of educational material across the markets?
2. What is the usage of the RM tools by HCPs and patients / caregivers?
3. Do HCPs and patients / caregivers understand:
    a. The information presented in the RM tools, including:
        i. the indicated age range,
        ii. indicated dose,
    b. Duration of treatment before prescribing ABILIFY®, and
    c. The identified and potential risks of concern (extrapyramidal symptoms (EPS), weight gain, somnolence, fatigue) associated with ABILIFY® for adolescent bipolar I mania indication?
4. Do HCPs and patients / caregivers respond appropriately to hypothetical risk scenario-based questions regarding the clinical use of ABILIFY® for the adolescent bipolar I mania indication, the identified and potential risks, and the real-world usage - specifically the recommended starting dosage, and minimum recommended age of patients?

3.3.2 Objectives

The objectives of the study are to evaluate the effectiveness of educational RM tools for ABILIFY® used in the adolescent bipolar I mania indication, in markets where this indication has been approved and ABILIFY® subsequently prescribed for at least six months.
The primary objectives of the study are:

1. To determine the proportion of HCPs, patients and caregivers that are aware of the RM tools and how these tools are accessed

2. To determine when, how and by whom the tools are used
3. To determine the level of knowledge and comprehension of the key risks associated with ABILIFY®, when used for the treatment of paediatric bipolar I mania
4. To evaluate HCP, patient and caregiver behaviours using behavioural questions and scenarios and minimisation of inappropriate starting dose and patient age

The evaluation is planned to be performed 12 months after implementation of the educational measures in up to 13 EU member states (where use of aripiprazole in paediatric patients is possible due to the availability of the oral solution, used at treatment initiation) to allow sufficient time for use and experience of the RM materials to conduct a meaningful assessment.

3.4 Study Design

This is a non-interventional, observational, cross-sectional study using HCP, Patient and Caregiver surveys. The surveys are intended to evaluate participants' awareness and use of tools, their knowledge of ADRs of interest, and their behaviours when presented with hypothetical risk scenarios. The surveys themselves are not intended as a mechanism for collecting ADR reports.

3.5 Population

The study population will comprise the target audiences for the RM tools (HCPs, and Patients and Caregivers) in markets where ABILIFY® has been used for the adolescent bipolar I mania indication for more than six months.

3.6 Variables

Variables of particular interest include:

- Patient age
- ABILIFY® dose
- Treatment duration
- Number of previous treatments
- HCPs' experience using ABILIFY® for the adolescent bipolar I mania indication
- Tool usage
- Medical speciality
- Geographical location (country)

3.7 Data Sources

The survey will include web-based structured questionnaires mainly comprising multiple choice questions, in addition to scenarios and some descriptive comments sections.

3.8 Study Size

Sample size is based upon an acceptable margin of error defined as less than 20% in the population of interest, with a significance level of < 0.05, and a correct response distribution to a knowledge-based question of 85%. This is anticipated to yield between 148 and 158 HCPs, and 148 to 158 patients participating, once the final evaluation has been completed.

3.9 Data Analysis

Descriptive statistics for discontinuous data will be used to examine the key research questions of interest. The data for the overall population will be examined by users and non-users, general psychiatrists, child / adolescent psychiatrists, nurses, pharmacists, patients and caregivers, and individual countries. The data will be presented with responses' frequency distributions and 95% confidence intervals.

3.10 Milestones

The study is planned to start 12 months following the launch of ABILIFY® for the adolescent bipolar I mania indication in each market. It is assumed that CHMP approval of the protocol will have been obtained by this time.

The protocol will, thereafter, be registered on the EU PAS Register (currently the E-Register of Studies) within one month of CHMP / PRAC approval (Q1 2014).

The content of the surveys will be finalised in Q1 2014, around a month later.

Study recruitment will start in Q2 2014, with data collection commencing around 2 months later, in Q2/3 2014.

Data collection is expected to take around 6 months to complete. The end of data collection, therefore, is expected to be in Q4 2014.

Analysis and reporting of results will be complete within four months of the end of data collection, between Q4 2014 and Q1 2015.

4 AMENDMENTS AND UPDATES

This is the second draft of the protocol, which addresses the feedback from the CHMP conclusion on 19 September 2013.

5 MILESTONES

The key milestones for this study are shown in Table 6-1:

Table 6-1: Study Milestones

Milestone	Planned Date
Registration in the EU PAS register	Q1 2014
Survey content finalisation	Q1 2014
Recruitment starts	Q2 2014
Start of data collection	Q2/3 2014
End of data collection	Q4 2014
Study progress report	Not planned
Interim report	Not planned
Final report of study results	Q4 2014 to Q1 2015

6 RATIONALE AND BACKGROUND

Bipolar I disorder (formerly called manic depression) in paediatrics is characterised by the occurrence of one or more manic or mixed (manic-depressive) episodes. It can significantly impact the wellbeing of the paediatric patient, and can negatively impact relationships with friends and family or success at school.

ABILIFY® (aripiprazole) is a drug indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older. It was approved by the European Commission on 24 January 2013. For reasons of conciseness the indication throughout this protocol is termed **adolescent bipolar I mania**.

The early diagnosis and prompt management of Adverse Drug Reactions (ADRs), according to recommended guidelines, is important for minimising the potential of severe outcomes. As part of marketing authorisation approval, Otsuka has implemented a risk management plan (RMP) that distributes two RM communication tools, additional to the SmPC, to HCPs prescribing ABILIFY® for the adolescent bipolar I mania indication.

Specifically, the two RM tools, additional to the SmPC, from the EU-RMP are:

1. **Healthcare Professional Frequently Asked Questions (FAQs) Brochure**
   A reference document in a Q&A format which informs HCPs about administering ABILIFY® for the adolescent bipolar I mania indication, and appropriately identifying and managing ADRs. The brochure also guides HCPs on distributing the Patient / Caregiver information brochure, educating patients / caregivers about ADRs and the need to contact the treating physician if signs of ADRs are suspected.
   The purpose of the FAQs Brochure is to clearly explain to prescribers the need to carefully consider the indicated age range, dose, and duration of treatment before prescribing ABILIFY® for the indication of adolescent bipolar I mania.
   Furthermore, vigilance is urged in the on-going evaluation of weight gain, EPS, and ADRs related to somnolence and fatigue.
   Overall, the HCP Brochure is designed to inform HCPs about ABILIFY® treatment in this indication, highlight ADRs of concern, remind them to discuss potential ADRs, and to distribute tools to patients / carers. This education is aimed at raising awareness and vigilance in the HCP and patient populations.
2. **Patient / Caregiver Information Brochure (PCIB)**
   A reference document provided to HCPs for distribution to their patients / caregivers outlining the treatment of adolescent bipolar I mania with ABILIFY, including advice on being vigilant for adverse drug reactions (ADRs) and contacting their treating physician immediately if signs of ADRs are suspected. Overall, the Patient brochure is designed to educate patients and carers on how to take ABILIFY®, to be vigilant for ADRs and report

immediately.

The key risks minimised by these RM tools are:

- Weight gain
- Extrapyramidal symptoms (EPS)
- Fatigue, and
- Somnolence

Another critical aspect of the risk minimisation education is to ensure that that maximum recommended dose is not exceeded and the minimum age of patients is not breached and the effectiveness evaluation survey will collect specific data to evaluate knowledge and prescribing behaviours for age and dose.

The tools clearly state the importance of being vigilant for the ADRs of concern and reporting them immediately, should they arise.

The RM tools also cover the contraindications and other common side-effects that are described in the product labelling. Further to this, the tools discuss how treatment should be initiated and titrated, that the treatment regimen should only be altered, or discontinued, by the prescriber.

The EU-RMP committed Otsuka Pharmaceutical Europe Ltd., as the marketing authorisation holder (MAH), to evaluate the effectiveness of these additional RM activities for the adolescent bipolar I mania indication. This protocol describes the method for the HCP and Patient / Caregiver surveys that will be used to evaluate the effectiveness of these RM tools defined as a combination of effective distribution, usage, knowledge and adoption of appropriate stakeholder behaviours.

It should be noted that, for the duration of the surveys described in this protocol, Bristol-Myers Squibb (BMS) will retain responsibility for pharmacovigilance until Otsuka takes over responsibility for pharmacovigilance for ABILIFY® (mid 2016). Otsuka (the MAH) and Lundbeck affiliates (alliance partners in some markets participating in the survey) will be responsible for the operational aspects of implementing the surveys.

The results of the surveys are intended to assess the value of the current RM tools (additional to the SmPC) and to establish baseline levels of usage, knowledge and behaviours. The results will be reported to the EMA and, if appropriate, lead to the modification of the ABILIFY® EU-RMP for the adolescent bipolar I mania indication. In addition, the results of the evaluation will inform the need for, and timing of, any subsequent tool evaluations.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

The key research questions are as follows:

1. What is the distribution of educational material across the markets?
2. What is the usage of the RM tools by HCPs and patients / caregivers?
3. Do HCPs and patients / caregivers understand:
    a. The information presented in the RM tools, including:
        i. the indicated age range,
        ii. indicated dose,
    b. The appropriate duration of treatment before prescribing ABILIFY, and
    c. The identified and potential risks of concern (extrapyramidal symptoms (EPS), weight gain, somnolence, fatigue) associated with ABILIFY® for adolescent bipolar I mania indication?
4. Do HCPs and patients / caregivers respond appropriately to hypothetical risk scenario-based questions regarding the clinical use of ABILIFY® for the adolescent bipolar I mania indication, the identified and potential risks, and the real-world usage – specifically, the recommended starting dosage and minimum recommended age of patients?

7.2 Objectives

The concept of evaluation of the effectiveness of RM plans is defined by EU guidance: Module XVI[(1)] and Module XVI B.B11.4[(1)].

Effectiveness, for the purposes of this study, is defined as a combination of effective distribution, usage, knowledge, and adoption of appropriate stakeholder behaviours by HCPs, patients and caregivers.

The objectives of the survey are to evaluate the effectiveness of ABILIFY® RM tools in markets where the adolescent bipolar I mania indication has been approved, and where ABILIFY® has subsequently been prescribed in this indication for at least 6 months.

The surveys will provide information from HCPs (see Annex 1), and patients (see Annex 2) and caregivers (see Annex 3) on:

1. Distribution of the RM tools
2. Awareness and usage of the RM tools
3. Knowledge and comprehension of the key important identified risks
4. Behavioural responses to hypothetical risk scenarios
5. Minimisation of inappropriate starting dose and patient age

The evaluation is planned to be performed 12 months after implementation of the educational measures, in up to 13 EU member states (where usage of aripiprazole in paediatric patients is highest), to allow sufficient time for use and experience of the materials to conduct a meaningful assessment.

7.2.1 Primary Objectives

The five-level RM evaluation model, shown in Figure 1, developed by Pope Woodhead, describes how effectiveness can be measured at different levels. This has been used to determine the primary objectives for the study; which will investigate the first four of these (distribution, awareness and utilisation, risk knowledge and comprehension and behaviours).

The primary objectives are:

1. *Evaluation of RM tool awareness and effective distribution (see Figure 1; levels 1 and 2):*
   To determine the proportion of HCPs that are aware of the existence of the RM tools and how the tools were accessed (i.e. paper or electronic versions).
2. *Evaluation of RM tool utilisation (see Figure 1; level 2):*
   To determine who uses the RM communication tools, how, when they are used and how often they are used.
3. *Evaluation of risk knowledge and comprehension (see Figure 1; level 3):*
   To determine the level of knowledge and comprehension of the key risks associated with ABILIFY® when used for the treatment of adolescent bipolar I mania. The responses of HCPs and patients / caregivers will be evaluated according to their:
   a. Knowledge of indicated age range, indicated dosage (HCPs only), and duration of treatment
   b. Knowledge / understanding of important safety and tolerability information
   c. Knowledge / understanding of those symptoms that require immediate contact with the treating HCP (patients / caregivers only)
   d. Knowledge to respond appropriately to hypothetical risk scenarios (HCPs) and more simple information about identified risks (patients / caregivers)

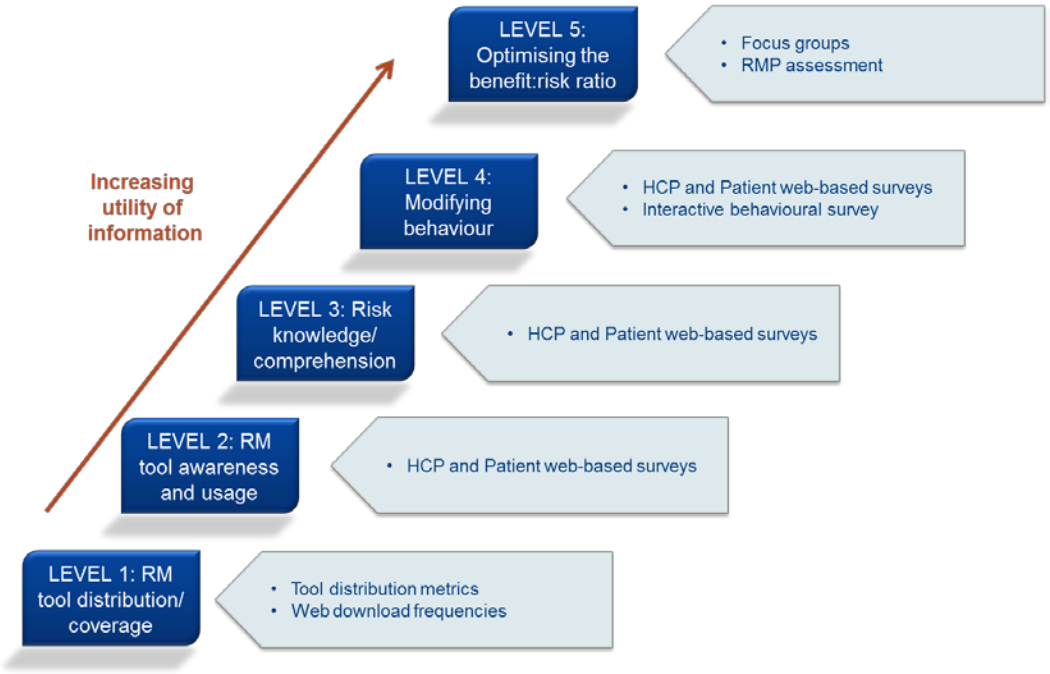

Figure 1: Five-Level Model for Risk Minimisation Evaluation

4. *Evaluation of behaviour (see Figure 1; level 4):*
   To evaluate HCP and patient behaviours using behavioural questions and scenarios, certain desired behaviours of HCPs and patients / caregivers will be evaluated through responses to behavioural questions as follows:
   a. Do HCPs review safety information with their patients / caregivers?
   b. Do HCPs distribute the patient information brochure to their patients / caregivers?
   c. Do HCPs educate patients / caregivers about symptoms of ADRs of concern (i.e. extrapyramidal symptoms, weight gain, somnolence, and fatigue), and about the need to report these ADRs immediately to the treating physician?
   d. Would patients / caregivers immediately notify their treating physician of the potential ADRs of concern (i.e. extrapyramidal symptoms, weight gain, somnolence, and fatigue)?

The results of this study will also be used to assess if the RM tools on the real-world risks that the tools have been designed to minimise especially that the maximum starting dose of ABILIFY® for the adolescent bipolar I mania indication is not exceeded, and that the minimum age of patients receiving ABILIFY® for the bipolar I mania indication is not breached. This will be achieved by including in the HCP questionnaire the usual starting dose of ABILIFY® used in the adolescent indication, identifying the appropriate dose and the minimum age of the patient when the drug is prescribed, as well as the actual ages of patients doing the patient/carer questionnaire.

8 RESEARCH METHODS

8.1 Study Design

This study is a non-interventional, observational, cross-sectional study comprising three sets of web-based surveys to examine the effectiveness of the RM materials used to educate HCPs, patients and caregivers on the appropriate use of ABILIFY® for the adolescent bipolar I mania indication.

Each survey (for HCPs or Patients / Caregivers) will have two parts:

1. A structured questionnaire (predominantly multiple-choice answers) to test participants' awareness of tools and to gather evaluation metrics related to the utility, use and understanding of tool content and messages designed to educate HCPs and educate patients / caregivers either via their HCP(s) or from the PCIB.
2. Hypothetical scenarios are presented to ascertain whether the education provided by the tools influences the user's behaviour in an appropriate way.

Web-based surveys have been selected as the appropriate research approach because:

1. The surveys include an assessment of behaviours using interactive scenarios that are difficult to implement by other means. Question navigation in scenarios, and the survey as a whole, also provides information about survey participants' behaviours (e.g. revising answers), which is not possible to collect through other means.
2. HCPs and patients are likely to be familiar with internet-based technologies; more than 40% of hospitals in Western Europe are now non-paper based – a proportion that is growing each year [(3)].
3. Web-based surveys can be answered at the participant's convenience and means that the participant does not have to arrange to be interviewed – this can increase participants' motivation to take part in the survey, thereby potentially improving response rates.
4. Web-based surveys ask standardised questions and will, therefore, elicit more consistent and reliable results [(4)] compared with telephone based interviews[(5)].
5. Web-based techniques allow for interactivity to be introduced into the survey; e.g. logic to ask follow-on or not ask irrelevant questions and ability for users to go back and change answers if they have reconsidered their answers which can strengthen behavioural surveys

The surveys are not intended as a mechanism for the collection of ADRs, they are designed to understand HCPs' and patients' awareness, utilisation, knowledge of ADRs of concern and behaviours (via scenarios).

Primary endpoints

The primary endpoints are:

1. To determine the proportion of HCPs, patients and caregivers that are aware of the existence of the RM communication tools and how these tools were accessed (i.e. paper or electronic versions).
2. To determine who uses the RM communication tools, and how, when and how often they are used.
3. To determine the level of knowledge and comprehension of the key elements of identified risks of concern associated with ABILIFY® for the adolescent bipolar I mania indication (i.e. EPS, weight gain, somnolence and fatigue).
4. To assess the effect of the tools on the real-world risks that the educational tools have been designed to minimise, namely the maximum starting dose of ABILIFY® for the adolescent bipolar I mania indication is not exceeded, and the minimum age of patients receiving ABILIFY® for the adolescent bipolar I mania indication is not breached.
5. To evaluate the HCP, patient and caregiver behaviours via behavioural questions and scenarios.

The following tables illustrate which components of the surveys will be used to carry out these evaluations:

Table 1: Demographic questions

Annex	**Questions examining participant demographics**
Annex 1: HCP survey	1 to 4
Annex 2: Patient survey	1 to 3
Annex 3: Caregiver survey	1 to 3

Table 2: Understanding RM tool awareness and distribution

Annex	**Questions designed to understand RM tool awareness and distribution**
Annex 1: HCP survey	7, 8, 15, 16
Annex 2: Patient survey	4, 5
Annex 3: Caregiver survey	4, 5

Table 3: Understanding RM tool use and utility

Annex	Questions designed to understand tool use and utility
Annex 1: HCP survey	9 to 14, and 17 to 23
Annex 2: Patient survey	6 to 11
Annex 3: Caregiver survey	6 to 13

For this survey, the intention is to primarily test knowledge indirectly, as meeting behavioural goals will require some degree of working-knowledge of ABILIFY® benefits and risk, when used for the adolescent bipolar I mania indication.
Tables 4 and 5 contain the questions that reflect understanding of how to take ABILIFY®, how to treat ADRs (HCPs), and awareness of risks and what to do if risks are identified (patients / caregivers).

Table 4: Understanding knowledge of RM tool content

Annex	Questions designed to understand knowledge of tool content
Annex 1: HCP survey	24 – 35
Annex 2: Patient survey	12 – 33
Annex 3: Caregiver survey	14 – 35

Table 5: Knowledge of potential or identified risks of concern

Identified or potential risk of concern	Question item in HCP survey	Question item in Patient / Caregiver survey
Age range	4	(Note that age of patients will be collected as a demographic (Q2). This may indirectly help to understand if ABILIFY® is prescribed to appropriate patients in this indication.)
Dose	5 Case Studies 1 (24) 2 (25) and 3 (28)	Indirectly 12 -17 (Patients), 14-19 (Caregivers)
Duration of treatment	Case studies 3 (29) and 4 (31-33)	Indirectly 3
Extrapyramidal symptoms (EPS)	30	24 – 26 / 26 – 28

Weight gain	26, 34, 35	19 – 23 / 21 – 25
Somnolence	32	30 – 32 / 32 – 34
Fatigue	31, 33	27 – 29 / 29 – 31

Table 6: Understanding behaviours

Appendix	Questions designed to understand behaviours
Appendix 1: HCP survey	Case studies
Appendix 2: Patient survey	23, 26, 29, 32
Appendix 3: Caregiver survey	25, 28, 31, 34

8.2 Setting

8.2.1 Study Population

The study population will comprise the target audiences for the RM tools (HCPs and patients / caregivers) in markets where ABILIFY® for use in the adolescent bipolar I mania indication has been marketed for at least six months.

The study population will go through a pre-screening process as a component of the recruitment process. This is further described in the following section. If Ethics approval is needed for any specific country, this will be done through an appropriate principal investigator from that country, who may also take part in the survey if randomised alongside all other participants.

8.2.2 Inclusion Criteria

HCPs (including nurses and pharmacists in appropriate European markets) will be considered for participation in the survey if they are involved in the care of patients with paediatric bipolar I mania who receive ABILIFY®.

Otsuka or Lundbeck (co-marketers of ABILIFY®) affiliates will provide lists of European HCPs involved in the care of patients with paediatric bipolar I mania being treated with ABILIFY®. For Ireland, this will be provided by BMS.

HCPs will be approached and asked to participate in the surveys through an email invitation from Pope Woodhead (PW). Prescribing physicians will be invited to refer non-prescribing colleagues (i.e. specialist nurses and pharmacists) to complete the survey where appropriate. These additional HCP types will be added to the original lists provided by the affiliates. Patients / Caregivers will be recruited by their HCPs.

PW will use the lists of HCPs to create quotas of target participants (Psychiatrists, Child / Adolescent psychiatrists, Nurses, and Pharmacists) who have expressed an interest in participating, who will be selected for participation using random number generator (RNG) software. Each of these lists will account for HCPs that are known to have been provided with the RM tools in each country. To ensure that sufficient HCPs are recruited (example given here is for larger countries), initial affiliate lists will be randomised to provide a target list of 50 participants. Of these 50 participants, it is intended to aim to recruit approximately 13 HCPs.

Recruitment will take place using invitation letters that will clearly identify the objectives of the study, the inclusion and exclusion criteria, and the expectations required of the HCP participants (e.g. an active role in patient recruitment).

If the recruitment target is not reached, the initial larger HCP lists (minus the 50 HCPs already approached) will be re-randomised to provide a further list of potential participants, who will then be approached in a similar fashion, and invited to participate accordingly. This process will continue and, if necessary, repeat until the required recruitment quotas are attained. A similar approach will be used to recruit in the medium and smaller sized markets.

HCPs will receive an honorarium (see below), which is payable only on survey completion, which compensates the HCPs for the time taken to participate in the survey and for providing PW with lists of patients / caregivers who will be randomised as part of the selection process.

PW will be responsible for providing HCPs with access to the web-based survey by providing a web-link and a unique HCP identifier.

If survey drop-outs rates are high, or recruitment rates are low, recruitment will continue until the required numbers of surveys have been completed. The sampling method will also ensure that, for selected markets, specialist nurses and pharmacists who are involved in the care of patients on ABILIFY® (used for the adolescent bipolar I mania indication) are included as potential survey participants.

This approach is designed to both select HCPs and account for low response rates (e.g. a response rate of approximately 30%).

It should be noted that, in all countries involved in the study, ABILIFY® for the adolescent bipolar I mania indication will not be actively promoted. Hence, the pool of HCPs involved in treating these patients is expected to be small.

This approach should cover at least 20 to 30% of those who actively prescribe ABILIFY® for the adolescent bipolar I mania indication, which is anticipated to result in margins of error of < 20%, with confidence intervals in all countries of 95%, assuming 85% correct responses to knowledge based questions[5].

The selection of the < 20% margin of error is driven by the small pool of HCPs treating patients within the adolescent bipolar I mania indication, and has been considered acceptable for similar evaluation of RM effectiveness surveys.

Bias will be avoided by random selection from a preliminary list, ensuring balance between the groups of Psychiatrists, Child / Adolescent Psychiatrists, Nurses and Pharmacists. To ensure that representatives from each target group are included in the study, the target lists will contain quotas of each subject type (e.g. 70 to 80% psychiatrists, 10 to 20% Nurses (if involved in treatment), and 5 to 10% pharmacists (if involved in treatment).

Random selection will then be carried out on each of the HCP types in order to generate lists containing appropriate proportions of each group. This approach will reduce the chances of significant selection bias (defined as particular HCP groups being favourably selected).

HCPs will be expected to complete the surveys within one month of being recruited.
Patient and caregiver recruitment will occur through the HCPs. To ensure an unbiased sample, up to three patients / caregivers can be recruited through a single HCP. It is, however, expected that most HCPs will recruit one or two patients / caregivers only. The prescribing physician will recruit consecutive patients / caregivers, and informed consent (via a letter provided as part of the recruitment process) will be taken once potential participants are randomly selected from the HCP lists submitted to PW. Assent will be taken from paediatric patients who are not old enough to give informed consent, and appropriate consent will be taken from parents / carers, as appropriate.
In order to minimise bias of selecting compliant patients, PW will randomly identify actual participants from lists of patients supplied by HCPs. A similar quota based methodology as used in HCP selection will be employed when recruiting patients and caregivers (e.g. recruitment continues until the target quota has been reached or exceeded). Patients and caregivers will be provided with an invitation letter (containing informed consent, and details of the survey and how to participate) through their HCP. The HCP will pass contact details of those patients and caregivers agreeing to take part to PW who will provide unique IDs and the web-link to a patient survey).
The Patient / Caregiver surveys will be answered either whilst the patient is still receiving ABILIFY® or within 2 months of receiving their last dose (this is to reduce risks of patients / carers not being able to recall aspects of treatment and use of the RM tools), and within 1 month of being recruited.
Question 3 in the Patient / carer survey asks how long the patient was treated for, and if they are still being treated. Question 2 asks how old the patient was at treatment initiation. PW will also administer the web questionnaires and collect results from the patients and caregivers.
A total sample size of 148 to 158 HCPs and 148 to 158 patients / caregivers, as discussed below, will be met.

8.2.3 Honorarium

HCPs will be contracted to complete the HCP survey and to encourage patients / caregivers to participate in surveys. For this work, and the time involved, HCPs will be offered a market rate and specific country specific honorarium. (confirmed honorarium will be added at a later date) Rates may be adapted if Otsuka standard honoraria fees or policies change during the execution of the surveys. Patients / caregivers will not receive honoraria.

8.2.4 Exclusion Criteria

HCPs will be excluded from the survey if they are not involved in the treatment of patients using ABILIFY for the adolescent bipolar I mania indication.

8.3 Variables

Variables of interest and their definition include:

- **Age of patient**
  Defined as the age of the patient at treatment initiation
- **Dose**
  Defined as the most recent dose taken before completing the survey
- **Treatment duration**
  Defined as the length of time since the first dose taken for this indication, irrespective of whether treatment is continuous or interrupted
- **HCPs' experience using** ABILIFY® **for the adolescent bipolar I mania indication**
  Defined as how many the HCP has treated with ABILIFY® for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older
- **Usage of tools**
  Defined as whether the respondent has used the RM tools on one or more occasions
- **Medical specialty**
  Defined as: psychiatrist, child / adolescent psychiatrist, nurse or prescriber

- **Country**
  Country where the HCP or patient / caregiver resides

The key survey effectiveness evaluation metrics are shown in Table 7. Questions designed to measure: demographics, awareness and distribution, use and utility, knowledge of tool content, knowledge of identified or potential risks of concern and behaviours are described in Section 9.1.1.

Table 7: Key effectiveness evaluation metrics

	Target Audience	
Metrics	**HCP**	**Patient / Caregiver**
Awareness of tools	X	X
Utilisation of tools	X	X
Knowledge and comprehension		
Symptoms requiring physician notification	X	X
Recommended age	X	N/A
Indicated dose	X	N/A
Indicated treatment duration	X	X
Risks of		
• EPS	X	X
• Weight gain	X	X
• Somnolence	X	X
• Fatigue	X	X
Ability to respond correctly to hypothetical risk scenarios	X	X
Behaviour		
Reviewing safety information with Patients / Caregivers	X	
Monitor for ARs and appropriate action if ADR is identified	X	
Distribution of Patient information brochure to Patients / Caregivers	X	X
Educating Patients / caregivers about symptoms of EPS, weight gain, somnolence and fatigue and need to report them to a physician	X	X

8.4 Data Sources

The survey will include web-based structured questionnaires comprised of mostly multiple choice questions with some descriptive comments sections.

The surveys will determine:

1. General awareness of tools
2. When and how often the tools are used
3. If paper-based or web-based tools (downloads) are used

4. If HCPs use the tools themselves, if they give the PCIB to their patients / caregivers, and how and when they use the tools with Patients / Caregivers
5. If patients / caregivers received their PCIBs and if they use them
6. If the RM tools can be improved based upon feedback or proposals from HCPs, patients and caregivers
7. Knowledge and understanding of the specific ADRs associated with ABILIFY presented in the RM tools
8. If the tools promote appropriate behaviours (e.g. do physicians or other HCPs understand how to manage patients that may be experiencing ADRs and do Patients / Caregivers know what actions to take if they suspect they are suffering an ADR?)

For data protection, the identities of HCPs, Patients and Caregivers will be controlled by the use of unique identification codes provided to the participants by PW. The source ID numbers will be held securely on a separate system from that used to host the survey applications. This data will be used solely for the purpose of identifying whether the HCP, patient or caregiver has completed the survey.

Survey participants will be informed in the recruitment correspondence that the survey needs to be completed in a single sitting and that sufficient time (c.25 min for HCP s and c.15-20 min for the patients) needs to be set aside to complete the surveys. In the case of HCPs, the payment of the honoraria is contingent on completing the survey in this single sitting. This is to prevent users revising or studying for answers and using several sessions to answer a survey, thus reducing the possibility of biasing the survey by users answering the survey on multiple occasions.

The survey will be timed out after 20 minutes of continuous inactivity (e.g. user not interacting with the web-based survey for more than 20 minutes), which will also reduce the chances that participants consult reference sources. If users do not complete the surveys, their data will not be analysed and new participants will be sought.

8.5 Study Size

The sample size will be driven by the estimated size of the population receiving ABILIFY® for the adolescent bipolar I mania indication. The sample size is based on an acceptable margin of error of less than 20% in the population of interest. This will yield between 148 to 158 HCPs and 148 to 158 patients / caregivers once the final evaluation has been completed.

The calculation to determine sample size was performed using a sample size calculator available from Raosoft[(6)], and incorporated margins of error by country; hence, the range of 148 to 158 HCPs and 148 to 158 patients / caregivers. The calculation of sample sizes is described in Section 9.7.2.

To achieve a representative population of HCPs relevant to the local clinical practice of the country (e.g. nurses, ancillary HCPs and prescribers), and patients and caregivers, and to attain the ranges outlined above, approximately 20 to 30% of the actually prescribing / treating HCP

population would need to be invited as part of the recruiting process. For example, in the UK (estimated HCP population of 2188), a confidence level of 95% and 85% of correct responses to a knowledge based question, and a sample size of 13 HCPs, gives a margin of error of 19.36% (see Table 9).
It should be noted that ABILIFY® used in this indication is considered an area of specialised medicine. It is expected that some countries will have few prescribers, especially so since the product will not be actively promoted for use in the paediatric / adolescent population.
The actual numbers surveyed will depend on the specific numbers of centres and HCP users. These values may be adjusted accordingly if there are particularly high or low national usages of ABILIFY® for the adolescent bipolar I mania indication at the time of the survey.

The following numbers of HCPs, and Patients or carers will be included per country:

UK	13 HCPs and 13 Patients / caregivers
Germany	13 HCPs and 13 Patients / caregivers
Spain	13 HCPs and 13 Patients / caregivers
Italy	13 HCPs and 13 Patients / caregivers
Sweden	13 HCPs and 13 Patients / caregivers
Denmark	13 HCPs and 13 Patients / caregivers
Norway	12 HCPs and 12 Patients / caregivers
Ireland	12 HCPs and 12 Patients / caregivers
Austria	12 HCPs and 12 Patients / caregivers
Portugal	12 HCPs and 12 Patients / caregivers
Cyprus/Greece	12 HCPs and 12 Patients / caregivers
Slovenia	12 HCPs and 12 Patients / caregivers

These countries will be surveyed during Q1/2 2014 (assuming the protocol is approved before this).

The study will be registered on ENCEPP within one month of obtaining CHMP / PRAC approval of the study protocol.

8.6 Limitations of the Research Methods

Limitations include:

- Sampling bias of HCPs and patients (although measures are being put in place to minimise this).
- Participation bias (HCPs and patients or caregivers who volunteer to take part might be more likely to be interested in the product and RM), sampling will minimise bias owing to differential participation of different HCP types.

- Behaviour is being indirectly evaluated (as distinct from real-world behaviour).
- Survey is not relating use of tools to actual outcomes.
- It is not possible (for both ethical and practical reasons) to introduce a control (no exposure to RM tool) group, as RM tools must be universally offered in all countries as part of market authorisation.
- The level of education provided by different HCPs to patients / caregivers will affect how these answer survey questions – it will not be possible to stratify patient / carer responses by HCP type (e.g. some child psychiatrists may provide excellent education whilst others do not). The survey will not link the patient / carer to their HCP.
- Social desirability bias (SDB), although potentially present in sample questionnaire studies, will be limited by avoiding direct interviewer questionnaires, by wording the introduction to emphasise that there are no "correct" answers, the measurement of behavioural choice rather than simply thinking, and also wording pre-ambles and question stems appropriately, to avoid any risk of inference as to "desirable" response.

8.7 Other Aspects

Not applicable.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Ethics Committee Review and Informed Consent

9.1.1 Ethics Committee Review

This protocol will be submitted for review by ethics committees in each country wherein the study will be conducted, and the relevant national ethics committee will decide if any waiver applies.

9.1.2 Informed Consent

As part of the recruitment process, HCPs will be asked to encourage patients and carers to participate in the patient and carer surveys. HCPs will be given letters to give to the Patient / carer that contain an informed consent section. This section describes:

1. Why patients / carers are being invited,
2. What the survey aims to ascertain,
3. The duration of the survey,
4. How the data will be aggregated and anonymised, and
5. How personal data will be respected and protected (and how survey participants' identities will be protected through the use of unique identifiers).

Since the indicated patients are adolescents (aged between 13 and 17), parental / guardian consent will be required before patients are surveyed.

9.2 Confidentiality of Study Data

For the purposes of protecting a patient's identity, a unique code will be assigned to each patient, such as a series of numbers and/or letters (for example, OTXXXX-UK-00001). The survey data that is recorded with the patient's assigned code is called “key-coded data”. Key-coded study data will be managed by the sponsor and / or its delegate/s (PW) in a study-specific electronic database. Data that could potentially directly identify the patient will not be collected in the SafetyGauge survey database. Only the PW Project Lead and PW Project Administrator have access to the link between the patient’s assigned code and the patient’s identity – which is held in a different application and a different physical location. Access to the survey data database in the SafetyGauge application is password-protected and may only be accessed by 2 nominated members of the PW IT staff. In case of an audit or inspection, however, subject to local laws and regulations, government officials, IRB / EC representatives, and sponsor representatives may be provided this information.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is not intended to collect adverse events, but should AEs with the use of ABILIFY® be raised by the respondents of the survey, these will be reported to BMS and processed accordingly.

10.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (e.g. including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The causal relationship to the BMS product under study is determined by a physician and should be used to assess all AEs. The casual relationship can be one of the following:

- **Related**
  There is a reasonable causal relationship between the BMS product under study and the AE.
- **Not related**
  There is not a reasonable causal relationship between the BMS product under study and the AE.

The term "reasonable causal relationship" means that there is clinical evidence to suggest a causal relationship.

A ***non-serious adverse event*** is an AE not classified as serious.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
3. Requires inpatient hospitalisation or causes prolongation of existing hospitalisation (See Note below),
4. Results in persistent or significant disability / incapacity,

5. Is a congenital anomaly/birth defect, and / or
6. Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardise the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to: intensive treatment in an emergency room or at home for allergic bronchospasm; and blood dyscrasias or convulsions that do not result in hospitalisation.
7. Suspected transmission of an infectious agent, pathogenic or non-pathogenic, via the BMS product under study is an SAE.

An ***overdose*** is defined as the accidental or intentional administration of any dose of a product higher than the maximum recommended dose.

Although pregnancy, overdose and cancer are not always considered serious by regulatory definition, these events are dealt with as SAEs.

NOTE:

The following hospitalisations are <u>not</u> considered SAEs in BMS studies:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery, planned prior to signing consent.
- Routine health assessment requiring admission for baseline / trending of health status (e.g. routine colonoscopy).
- Medical / surgical admission other than to remedy ill health and planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical / surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, and administrative reasons).

10.2 Adverse Event Collection and Reporting

Non-serious AEs and serious AEs (SAEs) whether or not related to the BMS product under study, pregnancies, AEs associated with maternal exposure, and pregnancy outcomes ascertained in the study must be reported individually in the time frames noted below. All AEs collected will also be reported in aggregate in the final observational study report.

Any component of a study endpoint that is considered related to study therapy (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE.

10.2.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product under study, must be collected, including those thought to be associated with protocol-specified procedures.

SAEs must be recorded on the Solicited and Non-interventional Research AE / SAE Form and reported to BMS (or designee) within 24 hours / one business day to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Although overdose and cancer are not always considered serious by regulatory definition, these events should be recorded on a form and reported to BMS within 24 hours / one business day.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

- **SAE Email Address:** Worldwide.Safety@BMS.com
- **Facsimile Number:** 1-609-818- 3804 or local contact number

If only limited information is initially available, follow-up reports may be required.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within 24 hours / one business day by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

10.2.2 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study. Non-serious AE information should also be collected from the start of the observational period intended to establish a baseline status for the subjects.

Non-serious adverse events must be recorded on the Solicited and Non-interventional Research AE/SAE Form and individually reported to BMS (or designee) within 7 business days to comply with regulatory requirements.

All non-serious AEs must be reported by confirmed fax transmission or reported via electronic mail to:

- **Non-serious AE Email Address:** Worldwide.Safety@BMS.com
- **Non-serious AE Facsimile Number:** 1-609-818-3804 or local contact number

Non-serious AEs should be followed to resolution or stabilisation, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of the BMS product under study and for those present at the end of the study, as appropriate.

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Depending on survey results, if RM tools require modification of content or delivery, Otsuka will conduct Focus Groups (with patients / caregivers and HCPs) to gather detailed feedback about the tools with the aim of optimising:

1. How the tools reach the intended audiences.
2. How the tools promote appropriate use and behaviours with the aim of optimising the benefit : risk profile of ABILIFY® for the adolescent bipolar I mania indication.

The BMS Pharmacovigilance function will use the results of the surveys for PSUR / PBRER submission, and a summary of the results will be communicated to Health Authorities in PSUR section 8.4. The results will be included in a report in the next appropriate PBRER, which immediately follows the reporting period.

12 REFERENCES

1. Guideline on good pharmacovigilance practices (GVP) Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators
2. Guideline on good pharmacovigilance practices (GVP) Module V (Risk Management Systems) Section V.B.11.4 "RMP part V section *Evaluation of the effectiveness of risk minimisation activities"*
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9. 2002/58/EC of the European Parliament and of the Council of 12 July 2002 (Directive on privacy and electronic communications). EUR-Lex ref. 32002L0058
10. Directive 2009/136/EC of the European Parliament and of the Council of 25 November, 2009. EUR-Lex ref. L 337/1118, December, 2009

Please note parts of the protocol including annexes have been currently redacted to avoid any bias to the study. The full protocol and annexes will be available when the study concludes.