NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

PASS information

ENCEPP/SDPP/13422

Title	Healthcare Professional and Patient Surveys to Assess the Effectiveness of Additional Risk Minimisation Measures for Concentrated Insulin Lispro (Humalog 200 units/ml KwikPen; Liprolog 200 units/ml KwikPen)
Protocol version identifier	Version 1.0
Date of last version of protocol	30 November 2015
EU Post Authorisation Study (PAS) register number	
Active substance	Drugs Used in Diabetes, Insulin Lispro ATC code: A10AB04
Medicinal product	Humalog 200 units/ml KwikPen Liprolog 200 units/ml KwikPen (in Germany only) (For purposes of this protocol, the term Humalog 200 units/ml KwikPen will refer to both trade names Humalog and Liprolog)
Product reference	EU/1/96/007/039-042 EU/1/01/195/028-29
Procedure number	EMEA/H/C/000088/MEA/025
Marketing Authorisation Holder (MAH)	Eli Lilly Nederland B.V.
Joint PASS	No

Research question and objectives	This study aims to evaluate the impact of the additional risk minimisation measures on healthcare professional and patient understanding and behaviour regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 units/ml KwikPen.
Country(-ies) of study	Germany, United Kingdom (UK, if product uptake does not allow for participation, another comparable EU country will be selected), and a 3rd country to be determined based on launch and product uptake.
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Marketing Authorisation Holder(s)

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2. List of abbreviations

Abbreviation	Definition
AE	Adverse Event
aRMM	Additional Risk Minimisation Measures
BfArM	Federal Institute for Drugs and Medicinal Devices (Germany)
CIOMS	Council for International Organisations of Medical Sciences
CIs	Confidence Intervals
DHPC	Direct Healthcare Professional Communication
EC	Ethics Committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	(US) Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practices
HCPs	Healthcare Professionals
ID	Identification
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Definition
IT	Information Technology
Lilly	Eli Lilly Nederland B.V.
MHRA	Medicines and Healthcare products Regulatory Agency
NIS	Non-interventional Study
PASS	Post-Authorisation Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
RM	Risk Minimisation
RMM	Risk Minimisation Measures
SAP	Statistical Analysis Plan
SDLC	System Development Life Cycle
SOPs	Standard Operating Procedures
T2DM	Type 2 Diabetes Mellitus
UAT	User Acceptance Testing
UBC	United BioSource Corporation
UK	United Kingdom
US	United States

3. Responsible parties

Principal Investigator(s) of the Protocol

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4. Abstract

Protocol Version 1.0–Healthcare Professional (HCP) and Patient Surveys to Assess the Effectiveness of Risk Minimisation Measures for Concentrated Insulin Lispro (Humalog 200 units/ml KwikPen; Liprolog 200 units/ml KwikPen)

4.1. Rationale and Background

Diabetes, especially type 2 diabetes mellitus (T2DM), is increasing in global prevalence and associated economic and humanistic burdens. Despite tangible improvement in disease management, poor glycaemic control remains a problem in individuals with diabetes (Inzucchi et al, 2012). Diabetes management guidelines recommend early initiation of insulin therapy in individuals with poor T2DM control or those with poor response to other anti-diabetes medications (Petznick A, 2011; ADA, 2014). In addition, insulin resistance and progressive loss of pancreatic beta-cell function are prodromal features of T2DM, which partially contribute to the need for high-dose insulin therapy—worldwide, about 30% of patients using basal insulin require more than 60 units daily (Gough et al, 2013), and approximately half of patients with T2DM will eventually require insulin to manage their diabetes (Jabbour, 2008).

Insulin formulations are listed among the high-alert medications that have potential to cause significant patient harm due to medication errors—errors that occur across the continuum of medication-use processes; however, insulin prescribing and administration related medication errors are most common (Cobaugh et al, 2013). Medication errors involving insulin may include inadvertent interchange between insulin strengths or formulations, incorrect dosage, or incorrect use of pen-injector devices. These errors may result in hyper/hypoglycaemia.

Humalog 200 units/ml KwikPen is a prefilled and disposable pen-injector device (pen) that delivers subcutaneous injection of 200 units/ml insulin lispro for the maintenance of normal glucose homeostasis in adults with diabetes mellitus. Despite warning messages on the pen and in the instructions for use, results from Human Factors studies performed in the United States (US) showed that a small percentage of patients may choose to withdraw insulin from the pen cartridge with a syringe if faced with device malfunction. Anecdotal information also indicates that patients in the European Union (EU) may transfer insulin lispro from the pen cartridge into an insulin pump. Because of these data and to further optimise the benefit-risk balance of the formulation, additional risk minimisation measures beyond routine risk minimisation measures are being conducted.

The additional risk minimisation measures will include a Direct Healthcare Professional Communication (DHPC) that will be distributed to all healthcare professionals (HCPs) who are expected to be involved in the treatment and management of patients with diabetes; physicians, nurses, and where applicable, pharmacists who are expected to dispense medications for diabetes management. A patient communication document will be distributed to prescribing HCPs targeted for the DHPC. The DHPC will ask HCPs to provide the patient communication to patients receiving their initial prescription of Humalog 200 units/ml KwikPen. Where approved,

a web address link to the patient communication may be provided in the DHPC to allow either printing of the communication during the patient visit or provision of the link to the patient to enable the patient to directly access the communication.

4.2. Research Questions and Objectives

This primary study objective is to evaluate the effectiveness of the additional risk minimisation activities on HCP and patient understanding regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors/ misuse associated with administration of Humalog 200 units/ml KwikPen

The secondary objective is to evaluate behaviour of HCPs and patients regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 units/ml KwikPen as communicated through the risk minimisation measures.

Specifically, this protocol refers to the surveys that are designed to assess the effectiveness of communications to HCPs and patients by assessing their understanding of the risks and safe use of Humalog 200 units/ml KwikPen which were communicated through the risk minimisation measures.

4.3. Study Design

This study will be multi-national, observational, and cross-sectional in design. Separate surveys have been developed for HCPs and patients to enable the study objectives to be met. User Testing has been performed on each survey with samples of HCPs and patients and the feedback and recommended modifications have been incorporated into the surveys.

HCPs:

Surveys targeting eligible HCPs will be administered via the Internet, which will allow respondents to participate at a time and location that is convenient for them and by telephone to allow participation by respondents who may not have Internet access. Each invitation will include information on how to access the online survey and provide the toll-free number for accessing the telephone survey. Respondent-identifying information will be collected for the purposes of providing payment as allowed by local laws.

Patients:

Surveys targeting eligible patients will be administered via the Internet, which will allow respondents to participate at a time and location that is convenient for them and by telephone, which will allow participation of respondents who do not have Internet access or who are not computer literate. Each invitation will include information on how to access the online survey and will provide the toll-free number for accessing the telephone survey. Alternate modalities such as paper versions of the survey with a postage paid envelope for returning the completed survey, will be provided if the Internet and telephone modalities are found to be barriers to participation, or if disability proves to be a limiting factor (for example, a deaf patient who is not

computer literate). Respondent-identifying information will be collected for the purposes of providing payment as allowed by local laws.

4.4. Populations

The survey will be administered to HCPs and patients in the United Kingdom (UK, if product uptake does not allow for participation, another comparable EU country will be selected), Germany, and one additional EU country, to be determined based on product launch and market uptake. The timing of survey implementation will vary according to the individual country launch plans and the extent of Humalog 200 units/ml KwikPen uptake after launch. Screening questions will be used to determine respondent eligibility.

HCPs:

HCPs involved in the treatment and management of patients with diabetes who are aware of the insulin product Humalog 200 units/ml KwikPen will be eligible. The respondent population will include a mix of prescribers who have and have not prescribed Humalog 200 units/ml. Those employed in research full-time or hospital administration and those who have ever worked for or have immediate family members who have ever worked for Eli Lilly and Company (Lilly), United BioSource (UBC), or any national regulatory agency, such as but not limited to European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) and Federal Institute for Drugs and Medicinal Devices (BfArM) will be excluded.

Patients:

Patients who are 18 years or older, have diabetes and have been prescribed Humalog 200 units/ml KwikPen will be eligible. Those who have ever worked for or have immediate family members who have ever worked for Lilly, UBC, or any national regulatory agency, such as but not limited to EMA, MHRA, and BfArM will be excluded.

4.5. Study Endpoints

The additional risk minimisation measures will be considered effective if the majority of respondents demonstrate they are aware of the key risks communicated.

HCPs:

- Demonstrating that they understand the key safety messages communicated in the DHPC
- Reporting that they provide patients with a copy of or means to access the Humalog 200 units/ml KwikPen patient communication at the time of initial prescription
- Reporting they discuss the key safety messages in the patient communication to their patients who are receiving their first prescription of Humalog 200 units/ml KwikPen.

Patients:

- Demonstrating that they understand the key safety messages communicated about Humalog 200 units/ml KwikPen

- Reporting that they were provided with a copy of or means to access the Humalog 200 units/ml KwikPen patient communication from their HCP at the time of initial prescription
- Reporting that they take into account the key messages during administration of Humalog 200 units/ml KwikPen.

All statistical analyses will be descriptive, that is, no formal hypothesis will be tested.

4.6. Variables

The survey will collect each eligible participant's understanding of the key safety messages in the risk minimisation communication and potential behaviour regarding their treatment with Humalog 200 units/ml KwikPen. The survey will also collect demographic characteristics for all respondents. For HCPs, demographics include age, sex, geographical location, specialty and practice information, and experience with Humalog 200 units/ml KwikPen. For patients, demographics include age, sex, geographical location, length of time with diabetes and length of time of using any insulin therapy and Humalog 200 units/ml KwikPen.

4.7. Data Sources

Structured, self-administered surveys comprised of closed-ended questions or statements with multiple response choices (that is, questions or statements asking the respondent to choose from a defined list of responses) will be used to collect the survey data from random samples of HCPs (Appendix 1.1) and patients (Appendix 1.3).

4.8. Study Size

The target sample sizes for the HCP and patient populations are 280 completed surveys each. With a sample size of 280 completed surveys, the true value of the correctly answered questions lies within the 95% confidence interval (CI) of the observed response. This yields the largest sample size required to achieve response rates with CIs of a half-width of 5%.

The HCP and patient samples will be divided according to the distribution of eligible participants in each country. The electronic data capture (EDC) system will be programmed to ensure desired distribution by requiring a minimum number of eligible participants from each country. Both unweighted and weighted results will be presented in the final report.

4.9. Data Analysis

Data collected from the surveys will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for respondent responses to all questions that address the survey objectives. Depending on the sample size, survey data will be stratified by country and, for HCPs, medical speciality.

4.10. Milestones

The study will be implemented within 12 to18 months of product launch in the UK (if product uptake does not allow for participation, another comparable EU country will be selected),

Germany, and one additional EU country. The timing and countries chosen is dependent on launch dates and the uptake of the product in each country. Findings from the surveys will be reported to regulatory authorities as required.

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	**Planned Timeline***
Start of data collection	*Within 12-18 months from product launch in the applicable country, depending on launch dates and the uptake of the product in each country.*
End of data collection	*When the desired number of surveys have been completed.*
Registration in the EU Post-Authorisation Safety Studies (PASS) register	*Prior to start of data collection*
Final study report	*Within 12 months after the end of data collection*

*The study will be initiated after the distribution of the additional risk minimisation measures) across the 3 study countries and protocol review by PRAC. Therefore, the planned timeline is contingent upon the date of the approval of the RM tools by the local Health Authorities.

7. Rationale and background

Diabetes, especially T2DM is increasing in global prevalence and associated economic and humanistic burdens. Despite tangible improvement in disease management, poor glycaemic control remains a problem in individuals with diabetes (Inzucchi et al, 2012). Diabetes management guidelines recommend early initiation of insulin therapy in individuals with poor T2DM control or those with poor response to other anti-diabetes medications (Petznick A, 2011; ADA, 2014). In addition, insulin resistance and progressive loss of pancreatic beta-cell function are prodromal features of T2DM, which partially contribute to the need for high-dose insulin therapy—worldwide, about 30% of patients using basal insulin require more than 60 units daily (Gough et al, 2013), and approximately half of patients with T2DM will eventually require insulin to manage their diabetes (Jabbour, 2008).

Hypoglycaemia is an identified risk of insulin therapy, and compared to other anti-diabetes medications, hypoglycaemia risk is the highest with insulin (Maria Rotella et al, 2013). Hypoglycaemia may occur due to low carbohydrate intake, alcohol consumption, exercise, or stress. On the other hand, failure to receive an adequate amount of insulin can result in hyperglycaemia and poor diabetes control (Cornish, 2014). Hyperglycaemia may occur due to excessive carbohydrate intake, less than planned exercise, or stress. Additionally, medication errors may contribute to these two conditions.

Insulin formulations are listed among the high-alert medications that have the potential to cause significant patient harm due to medication errors—in hospital setting, about 24% of insulin errors contributed to patient harm and 33% of deaths due to medication errors were attributed to insulin therapy (Cobaugh et al, 2013). Insulin medication errors occur across the continuum of medication-use process; however, prescribing and administration related medication errors are most common (Cobaugh et al, 2013). Medication errors involving insulin may include inadvertent interchange between insulin strengths or formulations, incorrect dosage, or incorrect use of pen-injector devices. These errors may result in hyper/hypoglycaemia.

Humalog 200 units/ml KwikPen is a prefilled and multi-dose pen-injector device (pen) that delivers by subcutaneous injection insulin lispro for the maintenance of normal glucose homeostasis in adults with diabetes mellitus. Compared to Humalog 100 U/ml, it contains the same number of units of insulin lispro in half the volume. Despite warning messages on the pen and in the instructions for use, results from Human Factors studies performed in the US showed that a small percentage of patients may choose to withdraw insulin from the pen cartridge with a syringe if faced with device malfunction. Anecdotal information also indicates that patients in the EU may transfer insulin lispro from the pen cartridge into an insulin pump. Because of these data and to further optimise the benefit-risk balance of the formulation, additional Risk Minimisation Measures beyond routine risk minimisation measures (are being implemented, including communications to HCPs and patients to minimise the risk of hypoglycaemia and/or hyperglycaemia associated with insulin transfer from the pen cartridge to an alternative administration device without concentration adjustment and dose adjustment when transferring from Humalog 100 U/ml to Humalog 200 units/ml KwikPen.

The additional risk minimisation measures include a DHPC that will be distributed to all physicians and nurses who are expected to be involved in the treatment and management of patients with diabetes and, where required, all pharmacists who are expected to dispense Humalog 200 units/ml KwikPen (HCPs). A patient communication document will be distributed to HCPs targeted for the DHPC. The DHPC will ask the HCPs to provide the patient communication to patients receiving their initial prescription of Humalog 200 units/ml KwikPen. Where approved, a web address link to the patient communication may also be provided in the DHPC to allow either printing of the communication during the patient visit or provision of the link to the patient to enable the patient to directly access the communication.

8. Research question and objectives

This primary study objective is to evaluate the impact of the risk minimisation measures on HCP and patient understanding regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 units/ml KwikPen as communicated through the risk minimisation measures.

The secondary objective is to evaluate behaviour of HCPs and patients regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 units/ml KwikPen as communicated through the risk minimisation measures.

Specifically, this protocol refers to the surveys that are designed to assess the effectiveness of communications to HCPs and patients by assessing their understanding of the risks and safe use of Humalog 200 units/ml KwikPen which were communicated through risk minimisation measures including the following key messages:

HCPs:

- It is not necessary to adjust the insulin dose when switching from one strength of Humalog to the other
- Humalog 200 units/ml should not be transferred from the KwikPen to alternative administration devices
- It is necessary to specify the Humalog strength on prescriptions

Patients:

- It is not necessary to adjust the insulin dose when switching from one strength of Humalog to the other
- Humalog 200 units/ml should not be transferred from the KwikPen to alternative administration devices

The surveys are also designed to answer the following process research questions to assess the effectiveness of communications to HCPs and patients through the risk minimisation measures. By testing a representative population about their knowledge and understanding of key message themes, we can generalise the:

HCPs:

- Extent of understanding of the key safety messages for Humalog 200 units/ml KwikPen, as communicated through the DHPC (Were the key safety messages communicated in the HCP communication understood by the HCP?)
- Extent that the patient communication has been provided to patients (Was the patient communication or the means to access the patient communication provided to each patient upon first prescription of Humalog 200 units/ml KwikPen?)

- Extent of discussion between HCPs and patients when initially prescribing or dispensing Humalog 200 units/ml KwikPen (Did the HCP convey the key safety messages in the patient communication to patients when they received their initial prescription of Humalog 200 units/ml KwikPen?) with reference to the following safety messages.

Patients:

- Extent of understanding of the key safety messages for Humalog 200 units/ml KwikPen, as communicated through risk minimisation measures (Were the key safety messages in the patient communication understood by the patient?)
- Extent of recall/receipt of the patient communication or the means to access the patient communication from prescribers upon first prescription of Humalog 200 units/ml KwikPen (Does the patient recall receiving the patient communication document or the means to access from their HCP?)
- Extent of key safety message consideration by patients during administration of Humalog 200 units/ml KwikPen (Will the patient consider the safety messages communicated during administration of Humalog 200 units/ml KwikPen?)

9. Research methods

9.1. Study design

This study is a multi-national, observational, cross-sectional survey design. Separate surveys will be administered to HCPs involved in the treatment and management of patients with diabetes and to patients with diabetes who have been prescribed Humalog 200 units/ml KwikPen. The study has been designed and will be executed and analysed in collaboration with UBC. The surveys have been developed to enable the study objectives to be met (Section 8).

User Testing was performed on each survey with a sample of 10 HCPs and 9 patients. The User Testing procedure was designed to assess comprehension among patients regarding the words and phrases used in select survey questions and response options. User Testing also assessed the clarity of the survey questions as presented to HCPs and the interest and acceptance of the surveys among all prospective respondents, flow and ease of completing the surveys, and preferred modes of administration. Findings and recommendations from User Testing have been incorporated into the surveys.

Assessment of the additional risk minimisation measures in the participating samples will be used to determine whether the target populations are aware of and adherent to the key message themes regarding the risk of hypoglycaemia and/or hyperglycaemia attributed to medication errors or misuse associated with the administration of Humalog 200 units/ml KwikPen. All statistical analyses will be descriptive, that is, no formal hypothesis will be tested. Study endpoints are as follows:

The tools will be considered effective if the majority of respondents demonstrate they are aware of the key risks communicated.

HCPs:

- Demonstrating that they understand the key safety messages communicated in the DHPC
- Reporting that they provided the patient communication or means to access the communication to patients at the time of first Humalog 200 units/ml KwikPen prescription
- Reporting they discussed the key safety messages in the patient communication with their patients who are receiving their first prescription of Humalog 200 units/ml KwikPen

Patients:

- Demonstrating that they understand the key safety messages communicated
- Reporting that they were provided with a copy of or means to access the Humalog 200 units/ml KwikPen patient communication from their HCP at the time of initial prescription
- Reporting that they consider the key messages during administration of Humalog 200 units/ml KwikPen

9.2. Setting

The assessment surveys will be executed as soon as 12 months but no later than 18 months from launch of the product in Germany, the UK (if product uptake does not allow for participation, another comparable EU country will be selected), and a third EU country to be determined. Countries will be selected based on a sufficient number of prescribers and volume of presecriptions to allow for a successful enrolment of HCPs and patients. Pan-European diabetes treatment guidelines issued by professional organizations such as European Association for the Study of Diabetes (EASD; Inzucchi et al. 2015) and the European Society of Cardiology for the management of patients with diabetes, such that the difference in clinical practices in different EU countries should be negligible (ESC Task Force 2013). Therefore, selection bias will be largely prevented due to common clinical practice, standardized messaging, and survey implementation. The timing of the initiation of the survey depends on the product launch dates and the product uptake in each country.

The target population in each selected county will receive the same risk communication, to be provided in their official national language. Additionally, the same survey will be used in all 3 countries in order to test the target population on the same key safety messages. As such, variability of survey results based on geography is not anticipated and therefore 3 countries will be representative of the EU.

The UBC will administer the surveys to the study populations who respond to the invitations to participate in the study. Every effort will be made to ensure the samples participating from each country in the survey will be proportional to the expected eligible population among participating countries. The EDC system will be programmed to ensure desired distribution by requiring a minimum number of eligible participants from each country.

HCPs:

Surveys targeting eligible HCPs will be administered via the Internet, which will allow respondents to participate at a time and location that is convenient for them, and by telephone, to allow participation of respondents who do not have Internet access. Both modalities will offer the same survey.

Eligible HCPs will receive an invitation letter via email if an email address is available, or a letter in the postal mail inviting them to participate in the survey. The invitation letter (Appendix I.2) will include: an overview of the rationale for the survey, information on how to access the survey online and by telephone, and a unique User Identification (ID) to ensure that the invitation is used only once.

HCPs in the applicable countries who are involved in the treatment and management of patients with diabetes will be invited to participate in the survey. The respondent population will include a mix of prescribers who have and have not prescribed Humalog 200 units/ml. The response rate will be monitored throughout the data collection period. Reminder notices will be sent via email and postal mail, and telephone calls will be made periodically to HCPs who have been invited

but not yet participated. The HCPs that complete the survey will be reimbursed for their time spent participating as governed by local laws and country regulations.

Patients:

Surveys targeting eligible patients will be administered via the Internet, which will allow respondents to participate at a time and location that is convenient for them, and by telephone, to allow participation of respondents who do not have Internet access or are not computer literate. Both modalities will offer the same survey.

Patients will be recruited via study packets that will be provided to HCPs due to privacy concerns in the EU. All HCPs who receive an invitation to participate in the HCP survey will also receive a study packet of patient invitiations in the postal mail and a letter asking them to invite eligible patients to participate in the survey. The packet will contain 10 invitation letters to be distributed. The patient invitation letter (Appendix I.4) will include an overview of the rationale for the survey, information on how to access the survey online, the toll-free number for accessing the telephone survey, and a unique User ID to ensure that the invitation is used only once. The HCPs will not be asked to select specific patients based on eligibility criteria. HCPs will forward the patient invitations to their patients for whom they have prescribed Humalog 200 units/ml. In the event an HCP has prescribed Humalog 200 units/ml to more than 10 patients, the HCP will arbitrarily select 10 patients regardless of any additional eligibility criteria.

Notices will be sent and telephone calls will be made periodically to HCPs reminding them to invite patients to participate in the survey. During reminder telephone calls, feedback will be elicited regarding barriers to patient participation. If feedback is received showing that Internet and telephone modalities are barriers to survey completion, HCPs will be provided with paper versions of the survey. Each paper survey will include a postage paid envelope for returning the completed patient survey.

Patients who complete the survey will be offered reimbursement for their time spent participating as governed by local laws and country regulations.

If the rate of response is not sufficient to reach the goal population within the planned survey period, Lilly may employ additional measures in an effort to complete the sample, such as but not limited to, extend the survey period, increase the payment amount provided to stakeholders as allowed by local laws and country regulations, increase the frequency of or change the method of outreach to HCPs, and allow for respondents to schedule an appointment to take the survey over the phone or provide the means to participate by paper survey.

To ensure comprehension of the invitations and surveys, all of the outreach will be conducted in the official national language. The survey and invitation as well as any reminder letters will be translated by a certified translation vendor.

9.2.1. Inclusion criteria

The HCPs must meet the following criteria to be eligible for inclusion in the survey:

- HCPs are aware of the insulin product Humalog 200 units/ml KwikPen; and
- HCPs are involved in the treatment and management of patients with diabetes.

Patients must meet all of the following criteria to be eligible for inclusion in the survey:

- Patients are 18 years or older;
- Patients have diabetes; and
- Patients have been prescribed Humalog 200 units/ml KwikPen.

9.2.2. Exclusion criteria

The HCPs meeting any of the following criteria will not be included in the survey:

- Employed in full time research or hospital administration (i.e., non-practising physicians)
- Current or past employment by Lilly, UBC, or any national regulatory agency, such as but not limited to EMA, Medicines and MHRA and BfArM

Patients meeting any of the following criteria will not be included in the survey:

- Patients with diabetes who are not prescribed Humalog 200 units/ml KwikPen
- Current or past employment by Lilly, UBC, or any national regulatory agency, such as but not limited to EMA, MHRA, and BfArM

9.3. Variables

The surveys will collect participants' understanding of the key safety messages in the risk minimisation communication and information about potential behaviour. Additionally, the HCP survey will collect information on demographic characteristics that include age, sex, geographical location, HCP specialty, and practice information. The HCP-identifying information will be collected for the purposes of providing HCP honorarium as allowed by local laws and country regulations. The patient survey will collect a variety of respondent demographic characteristics that include age, sex, geographical location, and their length of experience with any insulin therapy and Humalog 200 units/ml KwikPen. Patient-identifying information will be collected for the purposes of providing payment for participation where applicable.

9.4. Data sources

In this survey, data sources for HCPs may be Lilly's lists of HCPs who received the DHPC (in countries where local privacy regulations or standard practices allow this list to be provided to UBC) and/or UBC's HCP reference files or panels. From these data sources, random samples of HCPs will be invited to participate in the survey and to invite patients to participate in the survey.

Structured, self-administered surveys (Appendix I.1 and Appendix I.3) comprised of closed-ended questions or statements with multiple response choices (that is, questions or statements asking the respondents to choose from a defined list of responses) will be used to collect the survey data. The surveys will collect data on respondent characteristics and their responses to

the risk understanding questions. The data collected from the surveys will be used to inform the evaluation of the effectiveness of the risk minimisation measures.

The survey is designed to be completely voluntary and anonymous to prevent the collection of any personal identifying information from participants. Each participant will be given a unique code to access the survey. Each code is deactivated upon its use to prevent the code from being used to complete the survey twice. Each code is randomly assigned and not tracked; therefore, no identification of patients who have or have not responded can be performed. The participants do not have to actively 'decline to complete the survey'. Therefore, there is no ability to track which participants are actively deciding to not complete the survey. This survey design encourages patient participation and answer honesty by ensuring that the responses are completely anonymous.

Each survey will begin with a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation will either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

HCPs:

Screening questions:

- Agreement to participate
- Involved in the management of patients with diabetes
- Prior or current employment by Lilly, UBC, or any national medical governing body, such as but not limited to EMA, MHRA, and BfArM
- Awareness of Humalog 200 units/ml KwikPen

Data on demographic characteristics:

- Age
- Sex
- Role at facility
- Facility type
- Country
- HCP medical specialty (for example, endocrinology, primary care)
- Number of years practicing medicine/nursing
- Number of Humalog 200 units/ml KwikPen-treated patients the HCP managed in the 12 month period preceding the survey (self-reported)

Data pertaining to evaluation of the effectiveness of the risk minimisation measures:
The survey includes questions/statements that will assess the risk understanding and behaviour of the HCPs. The understanding level and behaviours will be analysed using descriptive statistics and CIs and will be used to determine the effectiveness of the risk minimisation measures:

- Awareness of the DHPC on the correct use of Humalog 200 units/ml KwikPen
- Understanding of the key risk messages

- Self-reported practices with respect to communication of the key risk messages in clinical practice

Patients:

Screening questions:

- Agreement to participate
- Diagnosis of diabetes
- Prescribed Humalog 200 units/ml KwikPen
- 18 years or older
- Prior or current employment by Lilly, UBC, or any national medical governing body, such as but not limited to EMA, MHRA, and BfArM

Data on demographic characteristics:

- Age
- Sex
- Country
- Education status
- Length of time with diabetes
- Length of time on any insulin therapy
- Length of time on Humalog 200 units/ml KwikPen
- Length of time on Insulin used prior to Humalog 200 units/ml

Data pertaining to evaluation of the effectiveness of the risk minimisation measures:
The survey includes questions/statements that will assess the risk understanding and behaviour of patients. The understanding level and behaviours will be analysed using descriptive statistics and CIs and will be used to determine the effectiveness of the risk minimisation measures:

- Awareness of the Important Safety Information for Humalog 200 units/ml KwikPen
- Receipt of or access to the Important Safety Information
- Understanding of the key risk messages
- Patient behaviour with respect to the key risk messages

9.4.1. Data collection process

The survey start date will be within 18 months from product launch in the individual countries. This date will vary by country based on market uptake. Survey data collection will be closed when the desired number of surveys have been completed.

The Internet survey will be self-administered. For the telephone survey, a trained interviewer from the Survey Coordinating Centre will conduct the telephone interviews using a Computer-Assisted Telephone Interviewing (CATI) programme and enter participant responses directly into the EDC while in conversation with the respondent. Questions are programmed to ensure that they are asked in the appropriate sequence and skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot

skip ahead. Statements requiring response and response options presented in a list are randomised to minimise positional bias. Paper surveys, if employed, will have instructions to guide respondents through the survey correctly and a Call Centre Associate (CCA) will enter the responses into the EDC verbatim from the paper survey received.

Follow-up reminder process

HCPs:

The database of invited HCPs will be routinely updated with responders and after each mailing, the database will be cross-checked with any correspondence that had an invalid address, bounced back or had incorrect contact details. The target sample for survey reminders is HCPs who received the invitation (that is, no reason for not receiving, such as invalid address) but did not respond within 2 weeks from initial mailing. Using the updated database, at least one reminder will be sent to the sample defined above. The total number of reminders will be based on the response rate at predefined recruitment milestones identified by Lilly. The interval between the reminders will be approximately 2 to 3 weeks.

Patients:

The response rate will be closely monitored and reminders will be sent to HCPs periodically. After each mailing, the database will be cross-checked with any correspondence that had an invalid HCP address, were returned as undeliverable or had incorrect contact details. The target sample for survey reminders is HCPs who received the request to invite eligible patients to participate in the survey (that is, no reason for not receiving, such as invalid address) in the initial mailing. Using the updated database, at least one reminder will be sent to the sample defined above. The total number of reminders will be based on the response rate at predefined recruitment milestones identified by Lilly. The interval between the reminders will be approximately 2 to 3 weeks.

9.5. Study size

The target sample sizes for the HCP and patient populations are 280 completed surveys for each population. This sample size was determined based on the width of confidence intervals it will provide. Table 1 shows 2-sided 95% confidence intervals based on the normal approximation to the binomial distribution (Equation 1) for a single sample of size of 280.

The samples will be divided by countries according to the distribution of eligible participants in each country. The EDC system will be programmed with country-specific limits to ensure desired distribution. Both unweighted and weighted results will be presented in the final report.

Equation 1.

$$95\%CI = Response\ Rate \pm 1.96 \left\{\sqrt{\left[\frac{Response\ Rate(1-Response\ Rate)}{Sample\ Size}\right]}\right\}$$

Table 1. Sample size calculations

Sample Size	Observed Response Rate* (e.g. Knowledge)	2-Sided 95% Confidence Interval		
		Half-width	Lower Limit	Upper Limit
280	50%	5.9%	44.1%	55.9%
	60%	5.7%	54.3%	65.7%
	70%	5.4%	64.6%	75.4%
	80%	4.7%	75.3%	84.7%
	90%	3.5%	86.5%	93.5%

*Percentage of responders who correctly answered a question.

9.6. Data management

All data collected during the survey will be held confidentially by UBC. The EDC system used for data collection encrypts all respondent-identifying information, and respondent identifiers are stored separately from the survey responses. No identifiable information will be required from patients, but will be collected if they are eligible to and wish to receive payment, if offered based on local laws and regulations. The data from the surveys collected will be stratified by country as well as combined for analysis in a final study report for each stakeholder population.

The survey is programmed to ensure Internet and telephone respondents cannot skip ahead and will only allow for missing data when caused by skip patterns. Paper surveys, if used, will have instructions to guide respondents through the survey correctly in an effort to avoid missing data. In instances where there is missing data not due to skip patterns (that is, respondent did not complete the survey), the respondent will not be considered in the analysis.

Skip logic as well as the ability to mark only one response or multiple responses are part of the programming for the survey administration and minimise the occurrence of data entry errors. There will be no queries to respondents for this project.

9.7. Data analysis

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for respondent responses to all questions that address the survey objectives. Responses to each question relating to the key risk messages will be categorised as "Correct response" and "Incorrect response". "I don't know" is generally categorised as an incorrect response unless otherwise specified.

In addition to the overall analysis, survey data will be analysed to determine if there are any differences by country and, for HCPs, medical speciality. Sub-group analyses will include all requested subgroups including patients switched from other 100 units/ml insulins, Humalog 100 U/ml, how long patients were on insulin, and which other insulins have been used as captured in the questionnaire. Additionally, a subgroup analysis will be performed to identify possible differences in the responses based on length of Humalog 200 units/ml use.

The following will be reported as part of the analysis:

HCPs:

- *Survey administration*
  - The number of survey invitations issued by strata (i.e., by country and specialty)
  - The number of survey invitations returned due to incorrect mailing address of HCPs invited to participate in the survey
  - The number of HCPs who responded to the invitation to participate in the survey
  - The number of HCPs eligible for participation in the survey
  - The number of ineligible HCPs along with the reasons for ineligibility
  - The number of eligible HCPs who completed the survey
- *Demographic characteristics of participants*
  - Distribution of participants by age groups
  - Distribution of participants by sex
  - Distribution of participants by practice setting
  - Distribution of participants by country
  - Distribution of participants by medical specialty
  - Distribution of participants by years in medical practice
  - Distribution of participants by number of patients treated with Humalog 200 units/ml KwikPen
- *Responses to questions pertaining to the survey objectives:*
  - Awareness of the DHPC on the correct use of Humalog (insulin lispro) 200 units/ml KwikPen
  - Understanding of the risk messages
  - Self-reported practices with respect to communication of the key risk messages in clinical practice

Patients:

- *Survey administration*
  - The number of HCPs asked to invite patients to participate
  - The number of invitations provided to HCPs
  - The number of patients who responded to the invitation to participate in the survey
  - The number of patients eligible for participation in the survey
  - The number of ineligible patients along with the reasons for ineligibility
  - The number of eligible patients who completed the survey

- *Demographic characteristics of participants*
    - Distribution of participants by age groups
    - Distribution of participants by sex
    - Distribution of participants by country
    - Distribution of participants by years with diabetes
    - Distribution of participants by length of time treated with any injectable insulin therapy
    - Distribution of participants by length of time treated with Humalog 200 units/ml KwikPen
    - Distribution of participants by insulin used prior to Humalog 200 units/ml KwikPen
- *Patient responses to questions pertaining to the survey objectives:*
    - Awareness of the Important Safety Information for Humalog 200 units/ml KwikPen
    - Receipt of or access to Important Safety Information including the source of this information
    - Understanding of the risk messages
    - Self-reported practices with respect to the risk messages

9.8. Quality control

Data will be collected using a secure online EDC system that has been developed and fully validated. A rigorous System Development Life Cycle (SDLC) is used for validation that complies with 23 internal IT Standard Operating Procedures (SOPs) of UBC. Unit testing and formal validation occur on all appropriate systems and components during the build stage. The SDLC is fortified with SOPs addressing validation for all clinical and risk minimisation-related applications. The Internet-based repository will be used to store survey data and other relevant programme information. The system is EudraLex Annex 11 (and 21 CFR Part11 in the US) compliant for the entry, storage, manipulation, analysis and transmission of electronic information. This platform ensures compliance with all relevant regulatory guidelines. Respondent-identifying information is stored separately from survey data.

Programming will be reviewed by Quality Control and simulated users [User Acceptance Testing (UAT)] prior to implementation.

At the completion of data collection, data will be extracted from the EDC and mapped to SAS datasets (SAS V9.1.3 or higher). The mapping of raw data will be validated, as will the programming of the analysis tables created from the raw EDC data. The raw EDC data is used to populate analysis tables that are programmed by SSRS according to the statistical analysis plan (SAP). Additionally, the EDC data will also be mapped to SAS datasets by a SSRS programmer as defined in the aDCTs and validated by the QC team.

The UBC has an IT Quality Assurance Group that is responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

9.9. Limitations of the research methods

The survey recruitment strategies are intended to recruit heterogeneous samples of HCPs prescribing or managing diabetic patients, and patients being treated with Humalog 200 units/ml KwikPen. The participants will be self-selected since they will voluntarily respond to the invitation to participate; however, those who read the invitation to participate are more likely to be attentive to all Humalog 200 units/ml KwikPen information, and therefore more compliant. Additionally, there is the potential to introduce bias in the patient results if only highly compliant HCPs recruit their patients for survey participation.

Additionally, inherent in survey research is the reliance on the respondent's recall for whether or not the risk minimisation communication was received in order to evaluate the scope of risk minimisation measures. If the respondent says she/he did not receive the communication, the risk minimisation programme is evaluated as not optimally disseminating material. It is possible, however, that respondents may simply not recall receiving the tools that were, in fact, received. It is also possible that they have acceptable understanding of the risks and appropriate behaviours despite not receiving or recalling receipt of the risk minimisation measure-specific communication. All data from the survey are self-reported and therefore susceptible to possible reporting bias. This is also applicable to the patients' self-reporting of their practice behaviours to minimise the risks. There may be discrepancies between what respondents report about their practices and their actual behaviours.

9.9.1. Controls to minimise bias

A number of controls will be in place to ensure the survey is conducted in a professional manner and to minimise bias, including the following:

- Lists of response options will be randomised to minimise the potential for positional bias.
- The Internet and telephone surveys will be programmed to ensure that questions are asked in the appropriate sequence and all questions will be presented in a standard order to reduce exposure bias. Respondents cannot skip ahead or go back to a question once the question has been answered. All questions presented must be answered in order to complete a survey. Not all questions may be presented due to skip logic within the survey.
- Respondents will be provided with a unique code during the recruitment process and will then be asked to provide the unique code in order to gain access to the Internet-based and telephone administration systems. The code will be inactivated after use to minimise exposure bias and fraud.
- Each HCP will only be provided 10 patient packets to mimimise potential over-representation bias by highly compliant HCPs (Section 9.2).

9.10. Other aspects

Not applicable.

10. Protection of human subjects

10.1. Personal Information and Consent

All data collected during the survey will be held confidential by the survey administrator and used only for the purposes stated in the survey instructions. Respondent names and addresses are collected for the purposes of mailing a thank you letter and payment, if applicable, after the survey is completed. The EDC system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

By answering the first question of the survey ("Do you agree to participate in this survey?") after reading the introductory message ("Preamble 1"), respondents are acknowledging informed consent for participation in the research study.

If, during survey completion, UBC personnel are made aware of a safety event (SE), the UBC project personnel will follow the reporting structure described in Section 11. The respondent will be asked for consent to allow their contact information to be provided to Lilly, so that Lilly may contact them for additional information. If the consent is not granted, UBC personnel will report the SE with the information provided by the respondent.

10.2. Respondent withdrawal

Respondents can decline to participate or stop taking the survey at any time. Only complete surveys will be included in the analysis.

10.3. Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, survey, other relevant documents (for example, recruitment advertisements), and any protocol amendments, if applicable, from the individual country's Ethics Committee (EC). All correspondence with the EC will be maintained in the Investigator File by Lilly.

Approval of this protocol by the respective local ECs will be sought prior to initiating the survey in each country.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the *Guideline on Good Pharmacovigilance Practices* (GVP) Module XVI- Risk Minimisation Measures: Selection of Tools and EMA, *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), *Good Epidemiological Practice* (GEP) guidelines issued by the International Epidemiological Association (IEA), *Good Outcomes Research Practices* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organisations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards*

in Pharmacoepidemiology, and FDA Guidance for Industry: *Good Pharmacovigilance and Pharmacoepidemiologic Assessment*.

11. Management and reporting of adverse events/adverse reactions

This study does not involve data collection on clinical endpoints on individual patients.

The Internet survey does not include questions that could potentially identify a safety event, nor does it provide a free text field where study participants could specify information that may constitute a safety event (defined as an adverse event, product complaint, or other reports; e.g. overdose, abuse, misuse, off label use, pregnancy exposures, breast feeding exposures, lack of drug effect, medication error and suspected transmission of infectious disease).

However, it is possible that while in conversation with a CCA, a telephone respondent may provide information that could constitute a SE. Additionally, a participant responding by paper survey may provide information that could constitute a SE in a handwritten response on their paper survey. An AE is any undesirable medical occurrence in a patient administered a Lilly product (drug or device) and which does not necessarily have to have a causal relationship with the treatment. Trained CCAs will record any reference to a SE in temporal association with Humalog 200 units/ml as stated (verbatim) in the UBC Humalog 200 units/ml SE Form, along with the respondent's contact information, if consent to provide contact information is given. The respondent will also be informed that someone from Lilly may contact them to obtain additional information about the event. If consent is not granted, UBC personnel will report the SE with the information provided by the respondent. Information on all reports (telephone or paper) that may constitute a SE will be forwarded to Lilly as described in the Safety Event Project Specific Procedure (SE/PSP). Lilly will report all safety event information to ECs and applicable regulatory agencies as required.

Study personnel are requested to report suspected adverse reactions with Lilly drugs not under evaluation and with any non-Lilly drugs to one appropriate party to avoid duplication, (for example, regulators or Lilly) as they would in normal practice as required by applicable laws, regulations and practices.

12. Plans for disseminating and communicating study results

A final report for each stakeholder group describing the survey objectives, detailed methods, results, discussion, and conclusions will be developed at the end of the survey for submission to EMA and applicable local regulatory agencies within the timeframe specified in 'Section 6. Milestones.' In addition, the study results will be published on the EU PASS register.

13. References

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Annex 1. List of Standalone Documents

Number	Document reference number	Date	Title
1	Appendix I.1		Draft HCP Survey
2	Appendix I.2		Draft Survey Invitation letter for HCPs
3	Appendix I.3		Draft Patient Survey
4	Appendix I.4		Draft Survey Invitation letter for Patients
5	Appendix I.5		Direct Healthcare Professional Communication on the correct use of *Humalog 200 units/ml KwikPen*
6	Appendix I.6		Important Safety Information for *Humalog 200 units/ml KwikPen*

APPENDIX I.1 HEALTHCARE PROFESSIONAL SURVEY

SURVEY LEGEND

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone only (for example, spontaneous AE reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online.

- **[BEGIN SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMISE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomised. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomised responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

SURVEY LEGEND

- **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]** indicates to the programmer that the response should be a drop-down list containing the countries in the table below.

United Kingdom (or other comparable EU country based on product uptake)	Germany	TBD

[WELCOME PAGE]

This survey should take approximately 15 minutes to complete. If you cannot complete the survey at this time, please return when you can. Once you begin the survey you will need to answer all questions; you will not be able to access the survey again if you exit.

Thank you in advance for your participation. Please note the application will time out after 30 minutes of inactivity.

If you are ready to begin the survey at this time, please click continue. If not, click Return Later.

Please note: Do not use the browser's back button during this survey.

[END WELCOME PAGE]

[BEGIN ONLINE PREAMBLE 1]

Disclaimer

Thank you for your interest in this voluntary research survey about Humalog 200 units/ml KwikPen, which is being conducted by United BioSource Corporation (UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly), the marketing authorisation holder of Humalog 200 units/ml KwikPen. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

How We Use Your Information

Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to Lilly, the European Medicines Agency (EMA), and any other locally applicable regulatory organisations. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive compensation based on your local rules and regulations. This compensation represents the fair value for your time in connection with completion of the survey. The amount of the compensation was not determined by the volume or value of any referrals or business

otherwise generated by you. Your name and address will only be used to send you the honorarium after you complete the survey.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Should a Safety Event in a specific patient be identified, we are required to report this even if it has already been reported to the manufacturer or the regulatory authority. Your choice to allow Lilly to use your answers to the survey questions is entirely voluntary but necessary to participate.

[BEGIN DISPLAY ONLY IN GERMANY SURVEY]

As per instructions of the Sponsor of this study, this study may be classified as a so-called non-interventional safety study.

In accordance with section § 63 subsection 4 Drug Law (AMG), the competent federal authority, National Association of Statutory Health Insurance Physicians (KBV), Central Federal Association of Health Insurance Funds and the Association of Private Health Insurance, must be notified about this study.

Pursuant to section § 63f subsection 4 AMG "he/she shall also provide information on the location, time, purpose and the protocol of study as well as the name and lifelong physician identification number of the participating doctors. In so far as participating doctors provide benefits that are reimbursed by the statutory health insurance, the type and amount of the compensation paid to them shall be communicated and a confirmation of the agreement with them submitted in the case of notifications pursuant to sentence 1." For details, please refer to the legal text of the AMG (esp. section § 63 subsection 4, AMG) and the published notification details by the competent authorities (e.g. GKV: http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/anwendungsbeobachtung/Arznei_AWB_Erlaeuterung_zum_Meldeformular_20130601.pdf).

I hereby expressly agree to participate in the study under all the aforementioned conditions.

- o Yes
- o No **[TERMINATE]**

[END DISPLAY ONLY IN GERMANY SURVEY]

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

humalogsurveysupport@ubc.com or [TELEPHONE NUMBER].

[END ONLINE PREAMBLE 1]

[BEGIN TELEPHONE PREAMBLE 1]

Disclaimer

Thank you for your interest in this voluntary research survey about Humalog 200 units/ml KwikPen, which is being conducted by United BioSource Corporation (UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly), the marketing authorisation holder of Humalog 200 units/ml KwikPen. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

This survey should take approximately 15 minutes to complete. If you cannot complete the survey at this time, please call back when you can. Once you begin the survey you will need to answer all questions during the same telephone call; you will not be able to access the survey again if you end this call.

How We Use Your Information

Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to Lilly, the European Medicines Agency (EMA), and any other locally applicable regulatory organisations. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive compensation based on your local rules and regulations. This compensation represents the fair value for your time in connection with completion of the survey. The amount of the compensation was not determined by the volume or value of any referrals or business otherwise generated by you. Your name and address will only be used to send you the honorarium after you complete the survey.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Should a Safety Event in a specific patient be identified, we are required to report this

even if it has already been reported to the manufacturer or the regulatory authority. Your choice to allow Lilly to use your answers to the survey questions is entirely voluntary but necessary to participate.

[BEGIN DISPLAY ONLY IN GERMANY SURVEY]

As per instructions of the Sponsor of this study, this study may be classified as a so-called non-interventional safety study.

In accordance with section § 63 subsection 4 Drug Law (AMG), the competent federal authority, National Association of Statutory Health Insurance Physicians (KBV), Central Federal Association of Health Insurance Funds and the Association of Private Health Insurance, must be notified about this study.

Pursuant to section § 63f subection 4 AMG "he/she shall also provide information on the location, time, purpose and the protocol of study as well as the name and lifelong physician identification number of the participating doctors. In so far as participating doctors provide benefits that are reimbursed by the statutory health insurance, the type and amount of the compensation paid to them shall be communicated and a confirmation of the agreement with them submitted in the case of notifications pursuant to sentence 1." For details, please refer to the legal text of the AMG (esp. section § 63 subsection 4 AMG) and the published notification details by the competent authorities (e.g. GKV: http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/anwendungsbeobachtung/Arznei_AWB_Erlaeuterung_zum_Meldeformular_20130601.pdf).

I hereby expressly agree to participate in the study under all the aforementioned conditions.

- o Yes
- o No **[TERMINATE]**

[END DISPLAY ONLY IN GERMANY SURVEY]

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

humalogsurveysupport@ubc.com or [TELEPHONE NUMBER].

[END TELEPHONE PREAMBLE 1]

[BEGIN SCREENING QUESTIONS]

Please provide a response to all questions and statements as they are presented.

1. Do you agree to take part in this survey about Humalog® 200 units/ml KwikPen™?

   - o Yes
   - o No **[TERMINATE]**

2. Are you involved in the management of patients with diabetes? This includes prescribing products to treat diabetes or providing education to help manage diabetes.

   - o Yes
   - o No **[GO TO Q6, TERMINATE AFTER Q12]**
   - o I don't know **[GO TO Q6, TERMINATE AFTER Q12]**

3. What is your role in the management of patients with diabetes?

   - o Physician
   - o Registered Nurse **[GO TO Q5]**
   - o Other **[GO TO Q6]**
   - o I don't treat patients with diabetes **[GO TO 6, TERMINATE AFTER Q12]**

4. What is your primary medical specialty?

   - o General Internal Medicine
   - o Endocrinology/Diabetology
   - o Family Medicine
   - o Other

5. How many years have you been in practice as a physician or nurse since completing your medical/nursing education?

- ○ Less than 5 years
- ○ 5 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years

6. In what type of facility do you work*?*

- ○ General Practice
- ○ Hospital
- ○ Other

7. *Are you aware of the insulin product Humalog 200 units/ml KwikPen?*

- ○ Yes
- ○ No **[GO TO Q9, TERMINATE AFTER Q12]**
- ○ I don't know **[GO TO Q9, TERMINATE AFTER Q12]**

8. For how many patients have you prescribed, or managed their treatment with, Humalog 200 units/ml KwikPen?

- ○ 0 **[TERMINATE IF 140 OR MORE COMPLETE RESPONDENTS HAVE ANSWERED 0, WHERE 140 IS A CONFIGURABLE NUMBER]**
- ○ 1 – 5
- ○ 6 – 10
- ○ 11 – 20
- ○ More than 20

9. Which of the following groups best describes your age?

   - ○ Less than 30
   - ○ 30 – 39
   - ○ 40 – 49
   - ○ 50 – 59
   - ○ 60 – 69
   - ○ 70 or older

10. What is your sex?

    - ○ Male
    - ○ Female

11. In what country do you work?

    [DROP-DOWN LIST OR SELECT BOX INPUT WITH COUNTRIES TABLE]

12. Have you or any of your immediate family members ever worked for Eli Lilly and Company (Lilly), United BioSource Corporation (UBC), the European Medicines Agency (EMA), or any national medicines regulatory agencies?

    - ○ Yes **[TERMINATE]**
    - ○ No
    - ○ I don't know **[TERMINATE]**

[END SCREENING QUESTIONS]

[BEGIN SURVEY CONTENT]

[PREAMBLE 2]

The following questions are about Humalog 200 units/ml KwikPen.

13. Please answer True, False, or I don't know for each of the following statements regarding Humalog 200 units/ml KwikPen.

	[RANDOMISE LIST]	True	False	I don't know
A	Humalog 200 units/ml is approved for transfer to different insulin delivery systems.	○	○	○
B	The dose of insulin does not need to be converted when changing patients from one Humalog strength to the other (for example, changing a patient from Humalog 100 U/ml to Humalog 200 units/ml KwikPen).	○	○	○
C	When prescribing Humalog 200 units/ml KwikPen, it is important to clearly indicate the correct strength on the prescription.	○	○	○

14. Are you familiar with the Direct Healthcare Professional Communication provided to you by Lilly on the correct use of Humalog (insulin lispro) 200 units/ml KwikPen to minimise medication errors?

- ○ Yes
- ○ No **[GO TO Q16]**
- ○ I don't know **[GO TO Q16]**

15. Did you read the Direct Healthcare Professional Communication provided to you by Eli Lilly and Company on the correct use of Humalog (insulin lispro) 200 units/ml KwikPen to minimise medication errors?

- ○ Yes
- ○ No
- ○ I don't know

16. Are you familiar with the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)* provided by Eli Lilly and Company?

- ○ Yes
- ○ No **[GO TO Q18]**
- ○ I don't know **[GO TO Q18]**

17. Did you read the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)* provided by Eli Lilly and Company?

- ○ Yes
- ○ No
- ○ I don't know

18. **[DISPLAY ONLY IN [ENTER COUNTRY THAT HAS WEBSITE]** Are you aware of the website [ENTER WEBSITE], at which patients can access the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)*?

- ○ Yes
- ○ No
- ○ I don't know

[DO NOT DISPLAY IF 0 IS SELECTED IN Q8]

19. **[DISPLAY ONLY IN [ENTER COUNTRY THAT DOES NOT HAVE WEBSITE]** Do you or another healthcare professional at your practice provide the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro,)* to patients receiving their first prescription of Humalog 200 units/ml KwikPen?

Do you or someone at your practice provide the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)* or the website at which the communication can be accessed, to patients receiving their first prescription?

- ○ Yes

- ○ No
- ○ I don't know

[DO NOT DISPLAY IF 0 IS SELECTED IN Q8]

20. Do you or another healthcare professional at your practice discuss the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)* with patients at the time of initial prescription of Humalog 200 units/ml KwikPen?

- ○ Yes
- ○ No
- ○ I don't know

[PHONE ONLY: BEGIN SAFETY EVENT]

(INTERVIEWER: Please record if respondent spontaneously reported a safety event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO END SAFETY EVENT SECTION]**

Enter Safety Event or Product Complaint Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Refer to Project Specific Procedure for next steps.)

[END SAFETY EVENT]

21. We would like to send you [AMOUNT/TYPE] as compensation for your time and effort, but need your name and address to do so. Do you agree to provide your contact information for this purpose?

- ○ Yes
- ○ No **[GO TO CLOSING]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

MIDDLE INITIAL: **[OPTIONAL; MUST BE 1-DIGIT ALPHA CHARACTER]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

COUNTRY: **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]**

POSTAL CODE: **[FREE TEXT]**

[CLOSING]

This completes the survey. Thank you again for your participation.

[END SURVEY CONTENT]

APPENDIX I.2 SAMPLE SURVEY INVITATION LETTER FOR HEALTHCARE PROFESSIONALS (HCPs)

DRAFT

[Date]

[Addressee's name]
[Title]
[Street address]
[City, State, Post code]
[Country]

Re: Invitation to Participate in Humalog® 200 units/ml KwikPen™ Survey

Dear Dr. [insert HCP LAST NAME],

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary research survey about insulin lispro in the strength of 200 units/ml, supplied as Humalog® 200 units/ml KwikPen™. The survey is part of a post-marketing commitment between Lilly and the European Medicines Agency (EMA) to assess the effectiveness of risk minimisation tools, and should take approximately 15 minutes to complete. If you complete the survey and provide your contact information, you have the opportunity to receive compensation based on your local rules and regulations to thank you for your time.

You may be eligible to participate if you have ever participated in the treatment and management of diabetic patients. For your convenience, the survey can be completed online at **[www.surveyURL.com]** or over the telephone at [TELEPHONE NUMBER].

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. All information that is collected during the course of the survey will be kept strictly confidential. Results will be reported in aggregate only. Your participation in the survey and your answers to the survey questions will not affect your ability to prescribe or manage patients prescribed Humalog 200 units/ml KwikPen. You will not be contacted for marketing purposes. Neither Lilly nor its contractors will sell, transfer, or rent your information.

Your assistance with this survey is greatly appreciated. Thank you for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customised accordingly}

APPENDIX I.3 PATIENT SURVEY

SURVEY LEGEND

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the phone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by phone only (for example, spontaneous safety event reporting).

- **[ONLINE]** indicates a question/section is worded specifically for administering the survey online.

- **[TELEPHONE]** indicates a question/section is worded specifically for administering the survey over the telephone.

- **[BEGIN SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMISE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomised. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomised responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

SURVEY LEGEND

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry.
- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.
- **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]** indicates to the programmer that the response should be a drop-down list containing the countries in the table below.

United Kingdom (or other comparable EU country based on product uptake)	Germany	TBD

The following is used to categorise survey populations into standard geographic regions but it is not displayed in the survey.

[WELCOME PAGE]

This survey should take approximately 15 minutes to complete. If you cannot complete the survey at this time, please return when you can. Once you begin the survey you will need to answer all questions; you will not be able to access the survey again if you exit.

Thank you in advance for your participation. Please note the application will time out after 30 minutes of inactivity.

If you are ready to begin the survey at this time, please click continue. If not, click Return Later.

Please note: Do not use the browser's back button during this survey.

[END WELCOME PAGE]

[BEGIN ONLINE PREAMBLE 1]

Disclaimer

Thank you for your interest in this research survey about Humalog 200 units/ml KwikPen, which is being conducted by United BioSource Corporation (UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly). The aim of this research is to learn more about patients' understanding of

key risks associated with Humalog 200 units/ml KwikPen. This survey is voluntary; you are not required to take part. You may refuse to take the survey or stop taking the survey at any time.

How We Use Your Information

Your answers to the survey questions will be combined with those from other patients taking the survey, and none of the responses you provide will be able to be traced back to you. All answers will be put together and reported to Lilly, the European Medicines Agency (EMA) (the organisation that regulates medicines in Europe), and possibly other regulatory agencies. Your name will not be used in any report.

[BEGIN SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]

You will be offered [PAYMENT TYPE/AMOUNT] for your time spent to take this survey. In order to receive payment, you will need to answer all questions and provide your name and mailing address. You may choose to take the survey and not receive payment. If you choose to not receive payment, your name and address are not required.

[END SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Your choice to allow Lilly to use your answers to the survey is entirely voluntary but necessary to take part in this research.

[BEGIN SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]Your choice to provide your name and address is also entirely voluntary but necessary to receive payment for taking the survey.

[END SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

humalogsurveysupport@ubc.com or [TELEPHONE NUMBER].

[END ONLINE PREAMBLE 1]

[BEGIN TELEPHONE PREAMBLE 1]

Disclaimer

Thank you for your interest in this research survey about Humalog 200 units/ml KwikPen, which is being conducted by United BioSource Corporation (UBC) on behalf of the sponsor, Eli Lilly and Company (Lilly). The aim of this research is to learn more about patients' understanding of

key risks associated with Humalog 200 units/ml KwikPen. This survey is voluntary; you are not required to take part. You may refuse to take the survey or stop taking the survey at any time.

This survey should take approximately 15 minutes to complete. If you cannot complete the survey at this time, please call back when you can. Once you begin the survey you will need to answer all questions during this telephone call; you will not be able to continue the survey again if you end this call.

How We Use Your Information

Your answers to the survey questions will be combined with those from other patients taking the survey, and none of the responses you provide will be able to be traced back to you. All answers will be put together and reported to Lilly, the European Medicines Agency (EMA) (the organisation that regulates medicines in Europe), and possibly other regulatory agencies. Your name will not be used in any report.

[BEGIN SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]You will be offered [PAYMENT TYPE/AMOUNT] for your time spent to take this survey. In order to receive payment, you will need to answer all questions and provide your name and mailing address. You may choose to take the survey and not receive payment. If you choose to not receive payment, your name and address are not required.

[END SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Your choice to allow Lilly to use your answers to the survey is entirely voluntary but necessary to take part in this research.

[BEGIN SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]Your choice to provide your name and address is also entirely voluntary but necessary to receive payment for taking the survey.

[END SHOW IN [ENTER COUNTRIES] ALLOWING PAYMENT]

How to Learn More about the Survey

If you have questions about or problems with the survey, please contact the Help Desk at:

humalogsurveysupport@ubc.com or [TELEPHONE NUMBER].

[END TELEPHONE PREAMBLE 1]

[BEGIN SCREENING QUESTIONS]

Please provide a response to all questions and statements.

1. Do you agree to take part in this survey about Humalog® 200 units/ml KwikPen™?

   - o Yes
   - o No **[TERMINATE]**

2. Have you been diagnosed with diabetes?

   - o Yes
   - o No **[GO TO Q9; TERMINATE AFTER Q12]**
   - o I don't know **[GO TO Q9; TERMINATE AFTER Q12]**

3. How long have you had diabetes?

   - o Less than 1 year
   - o 1 – 5 years
   - o 6 – 10 years
   - o 11 – 15 years
   - o More than 15 years
   - o I don't know
   - o I don't have diabetes**[GO TO Q9; TERMINATE AFTER Q12]**

4. Do you use injectable insulin to treat your diabetes?

   - o Yes
   - o No **[GO TO Q6; TERMINATE AFTER Q12]**
   - o I don't know **[TERMINATE AFTER Q12]**
   - o I don't have diabetes **[TERMINATE AFTER Q12]**

5. For how long have you been using injectable insulin to manage your diabetes?

   - o Less than 1 year
   - o 1 – 5 years
   - o 6 – 10 years
   - o 11 – 15 years
   - o More than 15 years
   - o I don't know
   - o I don't have diabetes/I don't use insulin **[GO TO Q9; TERMINATE AFTER Q12]**

6. Have you been prescribed Humalog 200 units/ml KwikPen at least once?

   - o Yes
   - o No **[GO TO Q8; TERMINATE AFTER Q12]**
   - o I don't know **[GO TO Q8; TERMINATE AFTER Q12]**
   - o I don't have diabetes/I don't use insulin **[GO TO Q8; TERMINATE AFTER Q12]**

7. For how long have you been using Humalog 200 units/ml KwikPen?

   - o I have not used it yet
   - o Less than 3 months
   - o 3 – 6 months
   - o 7 – 12 months
   - o More than 1 year
   - o I don't know

- o I don't have diabetes/I don't use Humalog 200 units/ml KwikPen **[GO TO Q9; TERMINATE AFTER Q12]**

8. What type of insulin did you use prior to using Humalog 200 units/ml KwikPen?

   - o Humalog 100U/ml
   - o Other 100U/ml insulin
   - o I don't know/I don't remember
   - o I don't have diabetes/I don't use Humalog 200 units/ml KwikPen **[TERMINATE AFTER Q12]**

9. What is your gender?

   - o Male
   - o Female

10. What is the highest level of education you have completed?

    - o Some secondary school (or EU equivalent) or less
    - o Finished secondary school
    - o Some university or completed technical/trade school
    - o Graduated university
    - o Post graduate studies
    - o Prefer not to answer

11. In what country do you live?

    [DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]

12. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE AFTER Q12]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE AFTER Q12]**

13. Have you or any of your immediate family members ever worked for Eli Lilly and Company (Lilly), United BioSource Corporation (UBC), or the European Medicines Agency (EMA)?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

[END SCREENING QUESTIONS]

[BEGIN SURVEY CONTENT]

[PREAMBLE 2]

The following questions are about Humalog 200 units/ml KwikPen.

14. Please answer True, False, or I don't know for each of the following statements about Humalog 200 units/ml KwikPen.

	[RANDOMISE LIST]	**True**	**False**	**I don't know**
A	Humalog 200 units/ml should only be injected using the	○	○	○

prefilled KwikPen device in which it is supplied.

B	Your dose of insulin does not need to be converted when changing from one strength of Humalog to the other (for example, changing from Humalog 100 U/ml to Humalog 200 units/ml KwikPen).	○	○	○

15. Please answer Yes, No, or I don't know for each of the following statements about the patient communication titled *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)*.

	[RANDOMISE LIST]	**Yes**	**No**	**I don't know**
A	**[DISPLAY ONLY IN [ENTER COUNTRIES THAT DO NOT HAVE WEBSITE]]**The first time I was prescribed Humalog 200 units/ml KwikPen, my doctor or nurse provided me with a paper copy of *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)*. **[DISPLAY ONLY IN [ENTER COUNTRIES THAT HAVE WEBSITE]]**The first time I was prescribed Humalog 200 units/ml KwikPen, my doctor or nurse provided me with a paper copy or told me to access the website to view *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)*.	○	○	○
B	My doctor or nurse offered to explain the information in *IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro).*	○	○	○
C	I think about the important safety information for Humalog 200 units/ml KwikPen to remind myself of the risks when injecting my insulin.	○	○	○

16. Other than the information you received from your doctor or nurse, from what sources have you received and/or accessed information on the safe use and understanding of the *Humalog 200 units/ml KwikPen*. Please select all that apply

Pharmacist

Other Medical Professional

Diabetes Support Group

Internet

Other

[PHONE ONLY: BEGIN SAFETY EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported a safety event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1a]**

Enter Safety Event or Product Complaint Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Refer to Project Specific Procedure for next steps.)

[END SAFETY EVENT/PRODUCT COMPLAINT]

[CLOSING 1 DISPLAY ONLY IN [ENTER COUNTRIES OFFERING PAYMENT]]

We would like to send you [AMOUNT/TYPE] as compensation for your time and effort, but need your name and address to do so. Do you agree to provide your contact information for this purpose?

- ○ Yes
- ○ No **[GO TO CLOSING]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

MIDDLE INITIAL: **[OPTIONAL; MUST BE 1-DIGIT ALPHA CHARACTER]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

COUNTRY: **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]**

POSTAL CODE: **[FREE TEXT]**

[CLOSING 2]

This completes the survey. Thank you again for your participation.

[END SURVEY CONTENT]

APPENDIX I.4 SAMPLE SURVEY INVITATION LETTER FOR PATIENTS

DRAFT

[Date]

Re: Invitation to Participate in Humalog® 200 units/ml KwikPen™ Survey

Dear Patient:

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary research survey about insulin lispro, supplied as Humalog® 200 units/ml KwikPen™. The survey is part of an agreement between Lilly and the European Medicines Agency (EMA), the organisation that regulates medicines in Europe. It should take approximately 15 minutes to complete.

You may be eligible to participate if you have ever been prescribed used Humalog 200 units/ml KwikPen. For your convenience, the survey can be completed online at **[www.surveyURL.com]** or over the telephone at [TELEPHONE NUMBER].

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. You will be offered [PAYMENT TYPE/AMOUNT] for your time spent to take this survey. In order to receive payment, you will need to provide your name and mailing address. You may choose to take the survey and not receive payment. If you choose to not receive payment, your name and address are not required.

All information that is collected during the course of the survey will be kept strictly confidential. Results from your survey will be combined with other patients and all results will be reported anonymously. None of your responses will be able to be traced back to you. Your participation in the survey and your answers to the survey questions will not affect your ability to use Humalog 200 units/ml KwikPen or the care you receive from your doctor. You will not be contacted for marketing purposes. Neither Lilly nor its contractors will sell, transfer, or rent your information.

Your assistance with this survey is greatly appreciated. Thank you for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customised accordingly}

DRAFT (PAYMENT INELIGIBLE)

[Date]

Re: Invitation to Participate in Humalog® 200 units/ml KwikPen™ Survey

Dear Patient:

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary research survey about insulin lispro, supplied as Humalog® 200 units/ml KwikPen™. The survey is part of an agreement between Lilly and the European Medicines Agency (EMA), the organisation that regulates medicines in Europe. It should take approximately 15 minutes to complete.

You may be eligible to participate if you have ever been prescribed Humalog 200 units/ml KwikPen. For your convenience, the survey can be completed online at **[www.surveyURL.com]** or over the telephone at [TELEPHONE NUMBER].

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. All information that is collected during the course of the survey will be kept strictly confidential. Results from your survey will be combined with other patients and all results will be reported anonymously. None of your responses will be able to be traced back to you. Your participation in the survey and your answers to the survey questions will not affect your ability to use Humalog 200 units/ml KwikPen or the care you receive from your doctor. You will not be contacted for marketing purposes. Neither Lilly nor its contractors will sell, transfer, or rent your information.

Your assistance with this survey is greatly appreciated. Thank you for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customised accordingly}

APPENDIX I.5 DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION ON THE CORRECT USE OF *HUMALOG 200 UNITS/ML KWIKPEN*

APPENDIX I.6 PATIENT COMMUNICATION: IMPORTANT SAFETY INFORMATION FOR HUMALOG® 200 UNITS/ML KWIKPEN™ (INSULIN LISPRO)

Annex 2. ENCePP Checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evaluation of the effectiveness of additional risk minimisation measures (risk minimisation measures) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the EU.
Study reference number:
Protocol # A1501102

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒☐	☐	☐	13
1.1.3 Study progress report(s)	☐	☐	☒☒	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐		13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk	☒	☐	☐	14

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?	☒	☐	☐	14-15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12-13
4.2.2 Age and sex?	☒	☐	☐	
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This protocol describes HCP and patient surveys to evaluate the effectiveness of additional risk minimisation measures without medical intervention.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	16, 21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	21

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	23-24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	18
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	19-20
8.1.3 Covariates?	☒	☐	☐	21-22
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	19-20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19-20
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19-20
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	17

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☐	☐	☒	
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	26

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.3 Are methods of quality assurance described?	☒	☐	☐	26
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	26-27
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

For point 11.1, the design of the EDC system is such that respondents must complete each answer before advancing so there will not be missing data.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	23-24
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	23-24
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20-21
12.3 Does the protocol address other limitations?	☒	☐	☐	23-24

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	25

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	26
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	26

Comments:

Name of the main author of the protocol: Ayad Ali, PhD

Date:

Signature:

Annex 3. Additional Information

Not applicable.