PASS Information

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™)
Version identifier of the study report	1.0
Date of last version of study report	29 March 2017
EU PAS register number	EUPAS13422
Active substance	Drugs Used in Diabetes, Insulin Lispro ATC code: A10AB04
Medicinal product(s):	Humalog® 200 units/ml KwikPen™ Liprolog® 200 units/ml KwikPen™ (in Germany only)
Product reference:	EU/1/96/007/039-042 EU/1/01/195/028-029
Procedure numbers:	EMEA/H/C/000088/MEA/025 EMEA/H/C/000393/MEA/018.2
Marketing authorisation holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research question and objectives	This study aims to evaluate the impact of additional risk minimisation measures on healthcare professional (HCP) 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	France, Germany, Sweden
Author	Dr. Ayad Ali Senior Pharmacoepidemiologist Eli Lilly and Company

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V. Utrecht, The Netherlands
MAH contact person	Dr. Ayad Ali Senior Pharmacoepidemiologist Eli Lilly and Company

Table of Contents

Section **Page**

List of Tables

1. Abstract

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™)

Name and affiliation of main author:

Ayad Ali, PhD
Eli Lilly and Company

Keywords: Humalog® 200 units/ml KwikPen™/Liprolog® 200 units/ml KwikPen™, hyperglycaemia, hypoglycaemia, insulin lispro

Rationale and background:

Eli Lilly and Company (Lilly) conducted surveys to evaluate the effectiveness of additional risk minimisation measures to minimise the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with the administration of Humalog® 200 units/ml KwikPen™. These surveys assessed healthcare professional (HCP) and patient understanding and behaviours relevant to the key safety messages that were communicated via Direct Healthcare Professional Communication (DHPC) and patient communication.

Research question and objectives:

The study aimed to evaluate the impact of the additional risk minimisation measures on HCP 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™. The additional risk minimisation measures will be considered effective if the majority of respondents demonstrate they are aware of the key risks communicated.

Study design:

This was a multi-national, observational, and cross-sectional study. Data were collected via multiple response and closed-end survey questions administered online and by telephone. Separate surveys were administered to HCPs and to patients. All statistical analyses were descriptive; no formal hypothesis was tested.

Setting:

The surveys were administered to HCPs and patients in France, Germany, and Sweden. Countries were selected based on product launch, market uptake, and ability to conduct patient surveys.

Subjects and study size, including dropouts:

HCPs involved in the treatment and management of patients with diabetes and aware of the insulin product Humalog® 200 units/ml KwikPen™ were eligible. Patients who were 18 years or older, had diabetes, and had been prescribed Humalog® 200 units/ml KwikPen™ were eligible to participate. The target sample size for the HCP and patient populations was 280 completed surveys for each population.

Variables and data sources:

The surveys collected information about participants' understanding of the key safety messages in the risk minimisation communication and information about potential behaviour as well as a variety of demographic characteristics.

In this survey, the data source for HCPs was a purchased IMS list of HCP specialists reflecting the distribution of the HCP communication by country. Random samples, stratified by country, were taken from this data source and the selected HCPs were invited to participate in the survey. Patients were only contacted through their HCP given the data protection regulations in the European Union (EU).

Results:

Healthcare Professionals

Invitation letters were sent to 6,129 HCPs and 180 responded. Of these respondents, 149 HCPs were eligible to participate and 146 completed the survey.

Of the 146 HCPs who completed the survey, 36.3% reported they were familiar with the DHPC on the correct use of Humalog® 200 units/ml KwikPen™ to minimise medication errors. Of these, 73.6% reported that they had read it.

Additionally, 41.8% reported that they were familiar with the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro*) and of these, 65.6% reported that they had read it. In addition, 30.8% reported they were aware of the website where patients can access the patient communication.

Of the 120 HCPs who reported that for their patients they prescribe or manage treatment with Humalog® 200 units/ml KwikPen, 28.3% reported that they or another HCP at their practice had provided the patient communication to their patients when patient received their first prescription of Humalog® 200 units/ml KwikPen, and 41.7% reported that they or another HCP at their

practice had discussed the patient communication with their patients at time of initial prescription of Humalog® 200 units/ml KwikPen™.

The correct response rates across the 3 HCP questions related to understanding the risks associated with and safe use of Humalog® 200 units/ml KwikPen™ ranged from 91.1% (95%CI=85.3%-95.2%) (awareness of the importance of clearly indicating the correct strength on prescriptions), to 59.6% (95%CI=51.2%-67.6%) (knowledge that it is not necessary to convert the dose of insulin when changing patient from one Humalog strength to the other), to 27.4% (95%CI=20.3%-35.4%) (understanding that Humalog® 200 units/ml KwikPen™ is not approved for transfer to different insulin delivery systems).

Patients

A total of 6,002 HCPs were asked to provide invitation letters to their patients for participation in the survey. A total of 79,620 invitation letters were provided to HCPs to be distributed to patients. The actual number of invitation letters issued to patients by the HCPs is unknown. A total of 11 patients responded to the survey, of which 7 were eligible and completed the survey. Due to the small sample size of completed patient surveys, no patient results are reported.

Discussion:

This study showed that 2 out of the 3 HCP key safety messages for Humalog® 200 units/ml KwikPen™ were effectively communicated to the majority of HCPs. Although no conclusions could be drawn from the patient survey due to very low recruitment, a similar study in the US demonstrated that the majority of patients did understand the key safety messages, including that Humalog® 200 units/ml should not be transferred from the prefilled KwikPen™ to another device. Medical research in the form of surveys is inherently difficult to conduct in the EU due to the data protection regulations which pose significant challenges in recruiting participants. Routine pharmacovigilance data provided complimentary information relevant for this assessment of the effectiveness of the key safety messages communicated. Safety surveillance data reflected that there was no increase in medication errors in EU for insulin lispro (Humalog®) after the launch of Humalog® 200 units/ml KwikPen™. As medication error rates will continue to be monitored via routine safety surveillance, it is concluded that no further additional risk minimisation activities or assessments are currently required.

Marketing Authorisation Holder:

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

Names and affiliations of principal investigators:

Ayad Ali, PhD
Senior Pharmacoepidemiologist
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

2. List of abbreviations

Term	Definition
AE	Adverse Event
BfArM	Federal Institute for Drugs and Medicinal Devices
CI	Confidence Interval
DHPC	Direct Healthcare Professional Communication
EASD	European Association for the Study of Diabetes
EDC	Electronic Data Capture
EMA	European Medicines Agency
ESC	European Society of Cardiology
EU	European Union
GP	General Practitioner
HCP	Healthcare Professional
ID	User Identification
Lilly	Eli Lilly and Company
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
NCA	National Competent Authorities
Pen	Multi-dose pen-injector device
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
T2DM	Type 2 Diabetes Mellitus

UBC	United BioSource Corporation
UK	United Kingdom
US	United States

3. Investigators

Principal Investigator(s) of the Protocol

Name, degree(s)	Role in Study	Affiliation
Ayad Ali, PhD	Principal Investigator	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA Email: ali_ayad@lilly.com Tel: +1 317 433 8868

4. Other responsible parties

All Main Responsible Parties

Name, degree(s)	Role in Study	Affiliation
Ayad Ali, PhD	Principal Investigator	Eli Lilly and Company

5. Milestones

Milestone	Planned date	Actual date	Comments
Date of PRAC approval of protocol		30 November 2015	
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	16 May 2016	
End of data collection	When the desired number of surveys have been completed	01 December 2016	
Registration in the EU PAS register	Prior to start of data collection	10 May 2016	ENCePP Registration
Report of study results	Within 12 months after the end of data collection	March 2017	

6. 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).

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 the multi-dosepen-injector devices (pen). These errors may result in hyper/hypoglycaemia.

Humalog® 200 units/ml KwikPen™ (and in Germany, also Liprolog® 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. For the purposes of this report, the data for Humalog and Liprolog survey results have been combined. 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 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. Because of these data and to further optimise the benefit-risk balance of the formulation, additional risk minimisation measures beyond routine risk minimisation measures have been implemented, including communications to Healthcare Professionals (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 between Humalog® 100 U/ml and Humalog® 200 units/ml KwikPen™.

The additional risk minimisation measures included a Direct Healthcare Professional Communication (DHPC) that was 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. A patient communication document was distributed to HCPs targeted for the DHPC. The DHPC asked 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 have been 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.

7. Research question and objectives

The primary objective of the survey was to evaluate the impact of additional 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 additional risk minimisation measures.

The secondary objective of the survey was 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 additional risk minimisation measures.

Specifically, this report refers to the results of surveys that were 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 additional risk minimisation measures. The additional risk minimisation measures included the following key safety 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 additional risk minimisation measures will be considered effective if the majority of respondents demonstrate they are aware of the key risks communicated.

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

HCPs:

- Extent of understanding of the key safety messages for Humalog® 200 units/ml KwikPen™, as communicated through the DHPC (i.e., Were the key safety messages communicated in the DHPC understood by the HCP?)
- Extent that the patient communication has been provided to patients (i.e., 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™ with reference to the key safety messages. (i.e., 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™?)

Patients:

- Extent of understanding of the key safety messages for Humalog® 200 units/ml KwikPen™, as communicated through the additional risk minimisation measures (i.e., 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™ (i.e., Did 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™ (i.e., Will the patient consider the key safety messages communicated when administering Humalog® 200 units/ml KwikPen™?)

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
None				

9. Research methods

9.1 Study design

This study was multi-national, observational, and cross-sectional in design. Separate surveys were administered to HCPs involved in the treatment and management of patients with diabetes and to patients with diabetes who had been prescribed Humalog® 200 units/ml KwikPen™. The study was designed, executed, and analysed in collaboration with United BioSource Corporation (UBC). The surveys were developed to enable the study objectives to be met.

User Testing was performed on each survey with a sample of 10 HCPs and 9 patients, respectively. 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 the User Testing were incorporated into the surveys. A copy of *User Testing/Qualitative Topline Report: Humalog 200 units/ml Risk Minimisation Programme Survey Questions for Healthcare Professionals and Patients in the EU* is located in Annex 1, Appendix 1.1 of this report.

Surveys about the additional risk minimisation measures were used to determine whether the target populations were aware of and adherent to the key safety message themes regarding the risk of hypoglycaemia and/or hyperglycaemia attributed to medication errors associated with the administration of Humalog® 200 units/ml KwikPen™. All statistical analyses were descriptive, that is, no formal hypothesis was tested.

9.2 Setting

The timing of the initiation of the survey depended on the product launch dates and the product uptake in each country. Data collection was to be initiated as soon as 12 months but no later than 18 months from launch of the product. The survey was conducted in France, Germany, and Sweden. Countries were selected based on product launch, market uptake, and ability to conduct patient surveys.

The target population in each selected country received a safety communication with similar key safety messages as approved by the National Competent Authority, provided in their official national language. Additionally, the same survey was used in all 3 countries in order to test the target population in the same way and on the same key safety messages. To ensure comprehension of the invitations and surveys, all outreach was conducted in the official national language. The survey and invitation as well as any reminder letters were translated by a certified translation vendor.

UBC administered the surveys to the study population who responded to the invitations to participate in the study. The Electronic Data Capture (EDC) system was programmed to ensure desired distribution by requiring a minimum number of eligible participants from each country.

Pan-European diabetes treatment guidelines issued by professional organisations such as European Association for the Study of Diabetes (EASD; Inzucchi et al, 2015) and the European Society of Cardiology (ESC) for the management of patients with diabetes, are in existence to standardise clinical management of diabetes. It was therefore expected that the difference in clinical practice in the 3 EU countries would be negligible (Ryden L et al, 2013).

Therefore, selection bias and variability of survey results based on geography were largely prevented due to common clinical practice, standardised messaging, and survey implementation. It is therefore anticipated that Germany, France and Sweden are representative of the EU.

HCPs:

Surveys targeting eligible HCPs were administered via the Internet, which allowed respondents to participate at a time and location that was convenient for them, and by telephone, to allow participation of respondents who did not have Internet access. Both modalities offered the same survey.

Eligible HCPs received an invitation letter (Annex 1, Appendix 1.2 of the protocol [Annex 1, Appendix 1.2 of this document]) in the postal mail inviting them to participate in the survey. The invitation letter included 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 was used only once.

HCPs in the applicable countries who were involved in the treatment and management of patients with diabetes were invited to participate in the survey. The respondent population included a mix of prescribers who had and had not prescribed Humalog® 200 units/ml. The response rate was monitored throughout the data collection period. Reminder notices were sent via postal mail to HCPs who had been invited but not yet participated. One round of reminder letters was sent to HCPs in France and Sweden, and one round each for Humalog and Liprolog were sent to HCPs in Germany. New HCP replacement records were obtained for some returned mail. New HCP invitation letters were sent to the HCP replacements at same time as the reminder letters. HCPs who completed the survey were reimbursed for their time spent participating as governed by local laws and country regulations.

Patients:

Surveys targeting eligible patients were administered via the Internet which allowed respondents to participate at a time and location that was convenient for them, and by telephone, to allow participation of respondents who did not have Internet or were not computer literate. Both modalities offered the same survey.

Patients were recruited via study packets that were provided to HCPs. The original random sample of HCPs who received an invitation to participate in the HCP survey also received a study packet of patient invitations in the postal mail and a letter asking them to invite eligible patients to participate in the survey and instructing them how to request additional patient invitation packs if needed. The packet contained 10 invitation letters to be distributed. The patient invitation letter included 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 was used only once. The HCPs were not asked to select specific patients based on eligibility criteria; HCPs forwarded the patient invitations to their patients for whom they had prescribed Humalog® 200 units/ml.

HCPs and Patients:

In an effort to maximise the convenience to participate and minimise barriers to participation, Lilly provided pre-paid stamps and envelopes with the patient invitation packages sent to HCPs.

As the patient response rate was much lower than anticipated during the survey, the HCP reminder letters included information about how to request additional patient invitation packs. Although the intent of Lilly was well founded, no requests for additional patient invitations were received.

Lilly informed the European Medicines Agency (EMA) of the low number of HCP and patient respondents on 26 October 2016. After discussion with the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur, it was agreed to close the survey and submit a study report for PRAC review. The surveys were closed on 1 December 2016.

9.3 Subjects

HCPs:

HCPs involved in the treatment and management of patients with diabetes who were aware of the insulin product Humalog® 200 units/ml KwikPen™ were eligible. The respondent population included a mix of prescribers who had and had not prescribed Humalog® 200 units/ml KwikPen™. Those employed in research full-time or hospital administration and those who had ever worked for or had immediate family members who had ever worked for Lilly, UBC, the EMA, or any national medicines regulatory agencies were excluded.

Patients:

Patients who were 18 years or older, had diabetes, and had been prescribed Humalog® 200 units/ml KwikPen™ were eligible. Those who had ever worked for or had immediate family members who had ever worked for Lilly, UBC, or the EMA were excluded.

9.4 Variables

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

9.5 Data sources

A list of HCPs for each country was purchased from IMS Health based on specialties reflecting the National Competent Authorities (NCA) agreed distribution for the HCP communication per country. In each country, a random sample of approximately 2,000 HCPs from the list were invited to participate in the survey and to invite patients to participate in the survey. New HCP replacement records were obtained for returned mail, and new HCP invitation letters were sent to the HCP replacements.

Structured self-administered surveys (Annex 1, Appendices 1.1 and 1.3 of the protocol [Annex 1, Appendix 1.2 of this document]) with 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) were used to collect the survey data. The surveys collected data on respondent characteristics and their responses to the key safety message questions. The data collected from the surveys were used to inform the evaluation of the effectiveness of the additional risk minimisation measures.

The survey was designed to be completely voluntary and anonymous to prevent the collection of any personal identifying information from participants. Each participant was given a unique code to access the survey. Each code was deactivated upon its use to prevent the code from being used to complete the survey twice.

Unique codes were provided to HCPs who were invited to participate in the survey. Unique codes in the patient invitations were randomly assigned and not tracked; therefore, no identification of patients who had not responded could be performed. Because invited participants did not have to actively decline to complete the survey, there was no ability to track which participants were actively deciding to not complete the survey. This survey design

encouraged patient participation and answer honesty by ensuring that the responses were completely anonymous.

Each survey began with a screening module of questions to confirm eligibility. Depending on the answers to the screening questions, survey participation was either terminated or continued. If ineligible, the respondent was immediately notified with a "thank you" message that survey participation had ended. If eligible, the respondent was allowed to continue survey participation.

HCPs:

The survey included questions/statements that assessed the risk understanding and behaviour of the HCPs. The understanding level and behaviours were analysed using descriptive statistics and confidence intervals (CIs) and were used to determine the effectiveness of the additional risk minimisation measures:

- Awareness of the DHPC on the correct use of Humalog® 200 units/ml KwikPen
- Understanding of the key safety messages
- Self-reported practices with respect to communication of the key safety messages in clinical practice

Patients:

The survey included questions/statements that assessed the risk understanding and behaviour of patients. The understanding level and behaviours were analysed using descriptive statistics and CIs and were used to determine the effectiveness of the additional risk minimisation measures:

- Awareness of the *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro)*
- Receipt of or access to the *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro)*
- Understanding of the key safety messages
- Patient behaviour with respect to the key safety messages

9.6 Bias

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

- Lists of response options were randomised to minimise the potential for positional bias.
- The Internet and telephone surveys were programmed to ensure that questions were asked in the appropriate sequence and all questions were presented in a standard order to reduce exposure bias.

- Respondents could not skip ahead or go back to a question once the question had been answered. All questions presented had to be answered in order to complete a survey. Not all questions may have been presented due to skip logic within the survey.
- Respondents were provided with a unique code during the recruitment process and asked to provide the unique code in order to gain access to the Internet-based and telephone administration systems. The code was inactivated after use to minimise exposure bias and fraud.

9.7 Study size

The target sample size for the HCP and patient populations was 280 completed surveys for each population. This sample size was determined based on the width of confidence intervals it would provide. Table 9-1 shows 2-sided 95% CIs based on the normal approximation to the binomial distribution (Equation 9-1) for a single sample size of 280.

Equation 9-1:

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

In addition, the sample was divided by countries according to the distribution of eligible participants in each country. The EDC system was programmed with country-specific limits of 150 eligible participants per country for each survey, to ensure desired distribution.

Table 9-1: Sample size calculations

Sample Size	Observed Response Rate* (i.e., 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.

9.8 Data transformation

All data collected during the survey were held confidentially by UBC. The EDC system used for data collection encrypted all respondent-identifying information, and respondent identifiers were stored separately from the survey responses. The data from the surveys collected were stratified by country as well as combined for analysis in this final study report.

9.9 Statistical methods

9.9.1 Main summary measures

The Survey Analysis Plan (SAP) (approved 08 August 2016) for this study describes the planned analyses for the results of the HCP and patient surveys. For the HCP survey, all planned analyses were performed and from a statistical point of view, 146 completed surveys is an acceptable sample size to make meaningful conclusions. Details are provided in Section 9.9.5. Due to the low response rate for the patient survey with only 7 completed surveys, no patient results are reported.

Statistical analyses were primarily descriptive, that is, no formal hypothesis was tested. Counts and percentages were calculated for each question/item in the questionnaire. All CIs around the percentages are exact two-sided 95% CIs calculated according to the method of Clopper-Pearson (Clopper and Pearson, 1934). The surveys contained skip patterns, that is, some questions were to be skipped depending on the answer of a previous question. Percentages were based on the population to whom a specific question was presented.

The analysis populations included:

All Respondents – The All Respondents population consisted of respondents that had accessed the survey using a unique code (see Sections 9.2 and 9.5 for further details). These respondents were used as the denominator for percentages in survey administration statistics, unless otherwise specified, and in the survey eligibility results analysis.

Completed Surveys (Primary Population) – The population for all remaining analyses included only those with completed surveys. "Completed" was defined as an eligible respondent who had no missing data with the exception of data from skip patterns. An eligible respondent was defined as one who completed all eligibility questions and met all inclusion criteria and none of the exclusion criteria.

In Germany, HCPs and patients who were aware of or received, respectively, Humalog or Liprolog were surveyed. For the presentation of the questions in the tables, the term 'Humalog' was consistently used also for the Liprolog users/prescribers.

9.9.2 Main statistical methods

Analysis of the Primary Objectives:

All responses to questions around the primary objectives were summarised by counts and percentages. Exact binomial two-sided 95% CIs were calculated for the proportion of respondents who gave the correct or desired responses.

Analysis of Additional Survey Questions:

All other questions were also analysed, including demographics; inclusion/exclusion criteria; safety of Humalog® 200 units/ml KwikPen™; questions about familiarity with and reading of the DHPC; familiarity, reading, providing and discussing the patient communication; and awareness of the website. The number and percentage of respondents were summarised by their responses to each question.

Subgroup Analysis:

Some subgroups analyses were planned, but due to small sample size, the ones planned for the patient survey are not reported. In addition, for the purposes of this report the data for Humalog and Liprolog survey results are combined. Therefore, only the following subgroup analyses for the HCP survey are reported:

- **Subgroup analysis: Country of Practice:**
  - France
  - Germany
  - Sweden
- **Subgroup analysis: Medical Specialty (Question 4):**
  - General Internal Medicine

- Endocrinology/Diabetology
- Family Medicine
- Other

Adverse Events and Product Complaints:

Patients or HCPs may have reported adverse events (AEs) or product complaints while in conversation with a Survey Coordinating Center Associate. If either of these was reported, then the verbatim terms were to be provided in a separate listing and categorised as appropriate.

9.9.3 Missing values

In order to minimise bias, the survey was programmed to ensure respondents could not skip ahead and only allowed for missing data when caused by skip patterns. In instances where there was missing data not due to skip patterns (that is, respondent did not complete the survey), the respondent was not considered in the analysis.

9.9.4 Sensitivity analyses

No sensitivity analysis was performed for this study.

9.9.5 Amendments to the statistical analysis plan

Although a sample size of 280 HCPs was targeted, previous power calculations show that the response rate of a sample of 146 HCPs still has an acceptable precision. The statistical analyses for the patient survey deviated from the SAP. Due to small sample size of only 7 patient surveys, no patient results are reported.

9.10 Quality control

The survey was programmed to ensure Internet and telephone respondents could not skip ahead and would only allow for missing data when caused by skip patterns. In instances where there were missing data not due to skip patterns (that is, the respondents did not complete the survey), the respondent was not considered in the analysis.

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

Respondents were provided with a unique code during the recruitment process in order to gain access to the system online or to provide when calling the Survey Coordinating Center. The code was inactivated after use to minimise exposure bias and fraud. If it was discovered (during fulfillment reconciliation) that a respondent completed more than one survey, only the results from the first completed survey (based on time completed) were to be included in the analyses. There were no duplicate surveys.

10. Results

10.1 Participants

Due to the low recruitment rate, especially for the patient population, the targeted sample size of 280 completed surveys could not be met. Although the completed HCP surveys was less than the targeted sample size of 280, power calculations showed that a sample of 146 HCPs had limited impact on the precision of the response rate. The half-width of the CIs for a comprehension rate of 50% increased from 5.9% to 8.1%, which is still an acceptable precision (see Table 9-1 in Section 9.7, and Table 10-1 below). Therefore a sample of 146 HCPs is large enough to measure the effectiveness of the additional risk minimisation communications. At the time of survey closure, 146 HCPs and 7 patients completed the survey.

Table 10-1: Precision of demonstrated understanding with a sample size of 146 (2-sided 95% confidence intervals)

Estimated Rate of Understanding*	Estimated 2-Sided 95% Confidence Interval		
	Half-width	Lower Limit	Upper Limit
50%	8.1%	41.9%	58.1%
60%	7.9%	52.1%	67.9%
70%	7.4%	62.6%	77.4%
80%	6.5%	73.5%	86.5%
90%	4.9%	85.1%	94.9%

*Percentage of responders who correctly answered a question.

10.1.1 Healthcare professionals

Survey administration statistics for HCPs are presented in Table 10-2.

A total of 6,129 HCPs involved in the treatment and management of patients with diabetes were invited to participate in the survey. This includes an original random sample of 6,002 HCPs and an additional sample of 127 HCPs to replace a portion of original invitations that were returned as undeliverable. A sample of 1,960 German HCPs, who had not responded to the Humalog invitation or reminder, subsequently received a separate Liprolog invitation. A total of 6,129 Humalog and 1,960 Liprolog invitations were sent to HCPs, and a total of 5,703 Humalog

reminders and 1,930 Liprolog reminders were sent to HCPs. In Germany, HCPs may have received more than one reminder since 1,872 Humalog and 1,930 Liprolog reminders were sent to a total of 2,080 HCPs.

Of those invited, 180 (3.1%) responded to the invitation using their unique ID. Of the 180 respondents, 149 (82.8%) were eligible for participation and of those, 146 respondents completed the survey.

Table 10-2: Survey Administration Statistics - HCPs

Parameter, n (%)	
Number of HCPs invited	6,129
Number of invitations returned as undeliverable	242
Number of reminder letters distributed	7,633
All Respondents[a]	180 (3.1)
Eligible Respondents[b]	149 (82.8)
Completed the survey[b]	146 (81.1)
Did not complete the survey[b]	3 (1.7)
Respondents not eligible[b,c]	31 (17.2)

[a] Number of respondents who accessed the survey. Percentage is based on the number of HCPs invited excluding the number of invitations returned as undeliverable.
[b] Percentages are based on the number of all respondents.
[c] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions. The responses to the eligibility criteria with the reason for ineligibility are presented in Table 10-4.

The 6,129 HCPs invited were evenly distributed among the 3 countries; 2,080 were from Germany, 2,049 were from Sweden, and 2,000 HCPs were from France. The largest proportion of eligible HCPs was from Sweden (49.0%), followed by Germany (32.9%), and France (18.1%). The country of practice and primary medical specialty of eligible HCPs compared to all invited HCPs are presented in Table 10-3.

Table 10-3: Eligible HCPs compared to all invited HCPs

Question	Eligible HCPs (N=149) n (%)	All invited HCPs (N=6129) n (%)
Country (Q12)		
Germany	49 (32.9)	2080 (33.9)
Sweden	73 (49.0)	2049 (33.4)
France	27 (18.1)	2000 (32.6)
Primary medical specialty? (Q5)[a]		
General Internal Medicine	55 (39.6)	5000 (82.9)
Endocrinology/Diabetology	23 (16.5)	1020 (16.9)
Family Medicine	48 (34.5)	0
Other	13 (9.4)	13 (0.2)
N/A (Not a Physician)	10	96

[a] Physicians only. Counts and percentages are calculated based on the number of Physicians.

Survey participant eligibility results for HCPs are shown in Table 10-4.

Of the 31 respondents who were ineligible to participate, 4 reported they were not involved in the management of patients with diabetes and 2 indicated they did not know if they were involved in the management of patients with diabetes. Eight respondents reported they were not aware of the insulin product Humalog® 200 units/ml KwikPen™, 1 did not know if they were aware of the insulin product Humalog® 200 units/ml KwikPen™, 3 indicated they did not know whether any immediate family members had ever worked for Lilly, UBC, the EMA, or any national medicines regulatory agencies, and 1 did not agree to take part in the survey. Fifteen respondents did not complete the screening questions (counted as “discontinued” in eligibility results) and were therefore considered as not eligible to participate.

In an effort to collect as much demographic data as possible on the invited population, HCPs were not terminated from participation until they had responded to all screening questions. Therefore, with the exception of those who discontinued participating or responded that they did not agree to take part in the survey, there may have been more than one reason for a respondent’s ineligibility, if ineligible. The data presented throughout this report includes both Humalog and Liprolog survey results, combined.

Table 10-4: Survey Participant Eligibility Results - All Respondents - HCPs

Question	HCPs (N=180) n (%)
I hereby expressly agree to participate in the study under all the aforementioned conditions.	
Yes	169 (93.9)
No[a]	0
Discontinued	11 (6.1)
Question 2: Do you agree to take part in this survey about Humalog® 200 units/ml KwikPen™?	
Yes	167 (92.8)
No[a]	1 (0.6)
Discontinued	12 (6.7)
Question 3: Are you involved in the management of patients with diabetes? This includes prescribing products to treat diabetes or providing education to help manage diabetes.	
Yes	161 (89.4)
No[a]	4 (2.2)
I don't know[a]	2 (1.1)
Question not asked[b]	1 (0.6)
Discontinued	12 (6.7)
Question 4: What is your role in the management of patients with diabetes?	
Physician	149 (82.8)
Registered Nurse	9 (5.0)
Other	2 (1.1)
I don't treat patients with diabetes[a]	0
Question not asked[b]	7 (3.9)
Discontinued	13 (7.2)
Question 8: *Are you aware of the insulin product Humalog 200® units/ml KwikPen™?*	
Yes	155 (86.1)
No[a]	8 (4.4)
I don’t know[a]	1 (0.6)
Question not asked[b]	1 (0.6)
Discontinued	15 (8.3)

Table 10-4: Survey Participant Eligibility Results - All Respondents - HCPs

Question	HCPs (N=180) n (%)
Question 13: 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[a]	0
No	161 (89.4)
I don't know[a]	3 (1.7)
Question not asked[b]	1 (0.6)
Discontinued	15 (8.3)

[a] Ineligible to participate in the survey.
[b] Question not asked due to the skip pattern in the survey or previous question termination.
Note: Respondents are counted as discontinued if they did not answer all eligibility questions without being identified as ineligible in a previous question. Once respondents are counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

10.1.2 Patients

Survey administration statistics for patients are presented in Table 10-5.

Recruitment of patients was particularly challenging due to the inability to contact patients directly given the stringent data protection regulations in the EU. The original random sample of 6,002 HCPs who received an invitation to participate in the HCP survey also received a packet of patient invitations by mail and a letter asking them to invite potentially eligible patients to participate in the survey.

Each packet contained 10 invitation letters to be distributed. These HCPs were provided 6,002 Humalog and 1,960 Liprolog patient invitation packets containing a total of 79,620 invitation letters to be distributed to their patients. The actual number of invitation letters issued to patients by the HCPs is unknown. A total of 11 patients responded to the invitation, of which 7 were eligible and completed the survey.

Table 10-5: Survey Administration Statistics - Patients

Parameter, n (%)	
Number of HCPs asked to invite patients to participate	6,002
Number of patient invitations provided to HCPs (including both Humalog and Liprolog)	79,620
All Respondents[a]	11 (0.0)
Eligible Respondents[b]	7 (63.6)
Completed the survey[b]	7 (63.6)
Did not complete the survey[b]	0
Respondents not eligible[b,c]	4 (36.4)

[a] Number of respondents who accessed the survey. Percentage is based on the number of invitations provided to HCPs.
[b] Percentages are based on the number of all respondents.
[c] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

10.2 Descriptive data

10.2.1 Healthcare professionals

The description of HCP survey participants (eligible HCPs) is presented in Table 10-6.

Of the 146 HCP participants, most (93.2%) reported their role as physician. Of the 136 physicians, 39.7% reported primarily practicing general internal medicine, 35.3% reported family medicine, and 15.4% reported endocrinology/diabetology. Of the 146 HCP participants, the majority (56.8%) reported working in general practice. Among all HCP participants, 30.1% reported prescribing or managing treatment with Humalog® 200 units/ml KwikPen™ for 1 to 5 patients and 21.2% reported prescribing or managing treatment with Humalog® 200 units/ml KwikPen™ for more than 20 patients. The majority (63.7%) of HCP participants reported being 30 to 49 years of age and 66.4% reported being male. Almost half (49.3%) of all HCP participants reported working in Sweden; 32.9% reported working in Germany and 17.8% reported working in France.

Of the 144 physicians and registered nurses, 34.0% reported that they had been in practice for 5 to 10 years, 27.8% reported practicing more than 15 years, 25.7% reported less than 5 years, and 12.5% reported that they had been practicing 11 to 15 years.

Table 10-6: Description of Eligible HCPs - Completed Surveys

Question	HCPs (N=146) n (%)
Question 4: What is your role in the management of patients with diabetes?	
Physician	136 (93.2)
Registered Nurse	8 (5.5)
Other	2 (1.4)
Question 5: What is your primary medical specialty?[a]	
General Internal Medicine	54 (39.7)
Endocrinology/Diabetology	21 (15.4)
Family Medicine	48 (35.3)
Other	13 (9.6)
N/A (Answered "Registered Nurse" or "Other" to Question 4)	10
Question 6: How many years have you been in practice as a physician or nurse since completing your medical/nursing education?[a]	
Less than 5 years	37 (25.7)
5 – 10 years	49 (34.0)
11 – 15 years	18 (12.5)
More than 15 years	40 (27.8)
N/A (Answered "Other" to Question 4)	2
Question 7: In what type of facility do you work?	
General Practice	83 (56.8)
Hospital	52 (35.6)
Other	11 (7.5)
Question 9: For how many patients have you prescribed, or managed their treatment with, Humalog 200® units/ml KwikPen™?	
0[b]	26 (17.8)
1 – 5	44 (30.1)
6 – 10	27 (18.5)
11 – 20	18 (12.3)
More than 20	31 (21.2)

Table 10-6: Description of Eligible HCPs - Completed Surveys

Question	HCPs (N=146) n (%)
Question 10: Which of the following groups best describes your age?	
Less than 30	11 (7.5)
30 – 39	57 (39.0)
40 – 49	36 (24.7)
50 – 59	27 (18.5)
60 – 69	11 (7.5)
70 or older	4 (2.7)
Question 11: What is your sex?	
Male	97 (66.4)
Female	49 (33.6)
Question 12: In what country do you work?	
Germany	48 (32.9)
Sweden	72 (49.3)
France	26 (17.8)

[a] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[b] Survey would have been terminated if 140 or more respondents answered 0.

10.2.2 Patients

Only 7 patients participated; therefore, no patient results are reported.

10.3 Outcome data

Not applicable.

10.4 Main results

10.4.1 Healthcare professionals

Responses to all questions related to the primary study objectives and the understanding of the key safety messages in completed HCP surveys are shown in Table 10-7.

Of the 146 eligible HCP respondents who completed the survey, 91.1% (95%CI=85.3%-95.2%) knew that when prescribing Humalog® 200 units/ml KwikPen, it is important to clearly indicate the correct strength on the prescription.

The majority (59.6%, 95%CI=51.2%-67.6%) of HCPs knew that the dose of insulin does not need to be converted when changing patients from one Humalog strength to the other.

Only 27.4% (95%CI=20.3%-35.4%) understood that Humalog® 200 units/ml is not approved for transfer to different insulin delivery systems. The high rate of incorrect responses to this question included 40.4% of HCP respondents who answered "I don't know" to this question.

Subgroup analysis tables showing stratification of responses by HCP respondents' country of practice and medical specialty are located in Section 10.5.

Table 10-7: Responses to all Questions Related to the Primary Study Objectives - Completed Surveys - HCPs

Question	HCPs (N=146) n (%)[95% CI][a]
Question 14: Please answer True, False, or I don't know for each of the following statements regarding Humalog 200® units/ml KwikPen™.	
14A: Humalog 200® units/ml is approved for transfer to different insulin delivery systems.	
True	47 (32.2)
False[b]	40 (27.4) [20.3-35.4]
I don't know	59 (40.4)
14B: 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™).	
True[b]	87 (59.6) [51.2-67.6]
False	45 (30.8)
I don't know	14 (9.6)
14C: When prescribing Humalog® 200 units/ml KwikPen™ it is important to clearly indicate the correct strength on the prescription.	
True[b]	133 (91.1) [85.3-95.2]
False	8 (5.5)
I don't know	5 (3.4)

[a] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[b] Correct response.

Responses to questions related to the secondary objectives in the completed HCP surveys are presented in Table 10-8.

Of the 146 HCPs who completed the survey:

- Fifty-three (36.3%) reported that they were familiar with the DHPC provided to them by Lilly on the correct use of Humalog® 200 units/ml KwikPen™ to minimise medication errors. Of these, 39 (73.6%) reported that they had read the DHPC.
- Sixty-one (41.8%) reported that they were familiar with the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro)* provided by Lilly. Of these, 40 (65.6%) reported that they had read the patient communication.
- Forty-five (30.8%) reported that they were aware of the website at which patients can access the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro).*

Of the 120 HCPs who completed the survey and reported that for their patients they prescribe or manage treatment with Humalog® 200 units/ml KwikPen™, 34 (28.3%) reported that they or another HCP at their practice had provided the patient communication: *IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro)* to their patients when patient received their first prescription of Humalog® 200 units/ml KwikPen™ and 50 (41.7%) reported that they or another HCP at their practice had discussed the patient communication with their patients.

Table 10-8: Responses to Questions about Humalog® 200units/ml KwikPen™ Communication Materials - Completed Surveys - HCPs

Question	HCPs (N=146) n (%)
Question 15: 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	53 (36.3)
No	75 (51.4)
I don't know	18 (12.3)
Question 16: 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?[a]	
Yes	39 (73.6)
No	11 (20.8)
I don't know	3 (5.7)
N/A (Answered "No" or "I don't know" to Question 15)	93

Table 10-8: Responses to Questions about Humalog® 200units/ml KwikPen™ Communication Materials - Completed Surveys - HCPs

Question	HCPs (N=146) n (%)
Question 17: 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	61 (41.8)
No	72 (49.3)
I don't know	13 (8.9)
Question 18: Did you read the patient communication: *Important Safety Information For Humalog 200® units/ml KwikPen™ (insulin lispro)* provided by Eli Lilly and Company?[a]	
Yes	40 (65.6)
No	16 (26.2)
I don't know	5 (8.2)
N/A (Answered "No" or "I don't know" to Question 17)	85
Question 19: Are you aware of the website, at which patients can access the patient communication: *Important Safety Information For Humalog® 200 units/ml KwikPen™ (insulin lispro)*?	
Yes	45 (30.8)
No	99 (67.8)
I don't know	2 (1.4)
Question 20: 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?[a]	
Yes	34 (28.3)
No	49 (40.8)
I don't know	37 (30.8)
N/A (Answered "0" to Question 9)	26
Question 21: 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™?[a]	
Yes	50 (41.7)
No	47 (39.2)
I don't know	23 (19.2)
N/A (Answered "0" to Question 9)	26

[a] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

10.4.2 Patients

Only 7 patients participated; therefore, no patient results are reported.

10.5 Other analyses

10.5.1 Subgroup analyses

Subgroup analyses based on HCP respondents' country of practice are shown in Table 10-9.

The analysis stratified by country of practice (Sweden: N=72; Germany: N=48; France N=26) showed that HCP respondents who reported Germany as their country of practice achieved a correct response rate of 47.9% (95%CI=33.3%-62.8%), those practicing in France demonstrated a correct response rate of 19.2% (95%CI=6.6%-39.4%), and those in who practiced in Sweden obtained a correct response rate of 16.7% (95%CI=8.9%-27.3%) regarding knowledge that Humalog® 200 units/ml should not be transferred from the KwikPen™ to alternative administration devices.

In addition, the analysis stratified by country of practice showed that HCP respondents who reported Sweden as their country of practice achieved a correct response rate of 61.1% (95%CI=48.9%-72.4%), those practicing in Germany demonstrated a correct response rate of 60.4% (95%CI=45.3%-74.2%), and those in France achieved a correct response rate of 53.8% (95%CI=33.4%-73.4%) regarding understanding that that the dose of insulin does not need to be converted when changing patients from one Humalog strength to the other.

The analysis stratified by country of practice showed that, regarding understanding that it is important to clearly indicate the correct strength on the prescription when prescribing Humalog® 200 units/ml KwikPen™, HCP respondents who reported France as their country of practice achieved a correct response rate of 100.0% (95%CI=86.8%-100.0%), HCP respondents who reported practicing in Germany demonstrated a correct response rate of 93.8% (95%CI=82.8%-98.7%), and HCPs who reported practicing in Sweden achieved a correct response rate of 86.1% (95%CI=75.9%-93.1%).

Table 10-9: Responses to all Questions Related to the Primary Study Objectives by Country of Practice - Completed Surveys

Question	Country of Practice		
	France (N=26) n (%) [95% CI][a]	**Sweden (N=72) n (%) [95% CI][a]**	**Germany (N=48) n (%) [95% CI][a]**
Question 14: Please answer True, False, or I don't know for each of the following statements regarding Humalog 200® units/ml KwikPen™.			
14A: Humalog 200® units/ml is approved for transfer to different insulin delivery systems.			
True	10 (38.5)	27 (37.5)	10 (20.8)
False[b]	5 (19.2) [6.6-39.4]	12 (16.7) [8.9-27.3]	23 (47.9) [33.3-62.8]
I don't know	11 (42.3)	33 (45.8)	15 (31.3)
14B: 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™).			
True[b]	14 (53.8) [33.4-73.4]	44 (61.1) [48.9-72.4]	29 (60.4) [45.3-74.2]
False	5 (19.2)	22 (30.6)	18 (37.5)
I don't know	7 (26.9)	6 (8.3)	1 (2.1)
14C: When prescribing Humalog® 200 units/ml KwikPen™ it is important to clearly indicate the correct strength on the prescription.			
True[b]	26 (100.0) [86.8-100.0]	62 (86.1) [75.9-93.1]	45 (93.8) [82.8-98.7]
False	0	5 (6.9)	3 (6.3)
I don't know	0	5 (6.9)	0

[a] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[b] Correct response.

Subgroup analyses based on HCP respondents' medical specialty are shown in Table 10-10.

The analysis stratified by primary medical specialty (General Internal Medicine: N=54; Family Medicine: N=48; Endocrinology/Diabetology: N=21) showed that Endocrinology/Diabetology specialists achieved a correct response rate of 52.4% (95%CI=29.8%-74.3%), General Internal Medicine HCPs demonstrated a correct response rate of 38.9% (95%CI=25.9%-53.1%), and Family Medicine HCPs obtained a correct response rate of 6.3% (95%CI=1.3%-17.2%) regarding knowledge that Humalog® 200 units/ml should not be transferred from the KwikPen™ to different insulin delivery systems.

The analysis stratified by primary medical specialty showed that Endocrinology/Diabetology specialists achieved a correct response rate of 85.7% (95%CI=63.7%-97.0%), General Internal

Medicine HCPs demonstrated a correct response rate of 59.3% (95%CI=45.0%-72.4%), and Family Medicine HCPs obtained a correct response rate of 50.0% (95%CI=35.2%-64.8%) regarding understanding that the dose of insulin does not need to be converted when changing patients from one Humalog strength to the other.

The analysis stratified by primary medical specialty showed that, regarding understanding that it is important to clearly indicate the correct strength on the prescription when prescribing Humalog® 200 units/ml KwikPen™, Endocrinology/Diabetology specialists achieved a correct response rate of 100.0% (95%CI=83.9%-100.0%), General Internal Medicine HCPs demonstrated a correct response rate of 90.7% (95%CI=79.7%-96.9%), and Family Medicine HCPs achieved a correct response rate of 87.5% (95%CI=74.8%-95.3%).

Results for the population of HCPs respondents who reported their primary medical specialty as "Other" (N=13) are shown in the table below.

Table 10-10: Responses to all Questions Related to the Primary Study Objectives by Medical Specialty - Completed Surveys - HCPs

Question	Medical Specialty			
	General Internal Medicine (N=54) n (%) [95% CI][a]	**Endocrinology/ Diabetology (N=21) n (%) [95% CI][a]**	**Family Medicine (N=48) n (%) [95% CI][a]**	**Other (N=13) n (%) [95% CI][a]**
Question 14: Please answer True, False, or I don't know for each of the following statements regarding Humalog 200® units/ml KwikPen™.				
14A: Humalog 200® units/ml is approved for transfer to different insulin delivery systems.				
True	16 (29.6)	6 (28.6)	20 (41.7)	4 (30.8)
False[b]	21 (38.9) [25.9-53.1]	11 (52.4) [29.8-74.3]	3 (6.3) [1.3-17.2]	1 (7.7) [0.2-36.0]
I don't know	17 (31.5)	4 (19.0)	25 (52.1)	8 (61.5)
14B: 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™).				
True[b]	32 (59.3) [45.0-72.4]	18 (85.7) [63.7-97.0]	24 (50.0) [35.2-64.8]	3 (23.1) [5.0-53.8]
False	20 (37.0)	3 (14.3)	18 (37.5)	4 (30.8)
I don't know	2 (3.7)	0	6 (12.5)	6 (46.2)

Table 10-10: Responses to all Questions Related to the Primary Study Objectives by Medical Specialty - Completed Surveys - HCPs

Question	Medical Specialty			
	General Internal Medicine (N=54) n (%) [95% CI][a]	**Endocrinology/ Diabetology (N=21) n (%) [95% CI][a]**	**Family Medicine (N=48) n (%) [95% CI][a]**	**Other (N=13) n (%) [95% CI][a]**
14C: When prescribing Humalog® 200 units/ml KwikPen™ it is important to clearly indicate the correct strength on the prescription.				
True[b]	49 (90.7) [79.7-96.9]	21 (100.0) [83.9-100.0]	42 (87.5) [74.8-95.3]	12 (92.3) [64.0-99.8]
False	4 (7.4)	0	3 (6.3)	0
I don't know	1 (1.9)	0	3 (6.3)	1 (7.7)

[a] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[b] Correct response.

10.5.2 Routine safety surveillance data

Routine safety surveillance data for Humalog® 200 units/ml KwikPen™ in the EU are presented below:

10.5.2.1 Humalog® 200 units/ml KwikPen™ exposure

Humalog® 200 units/ml KwikPen™ was introduced into the EU market on 16 February 2015. From 01 February 2015 through 31 December 2016, the number of units of Humalog® 200 units/ml KwikPen™ sold in the EU was 2,531,871,000. During the same period, there was an estimated 277,000 patient-years of exposure for patients in the EU.

10.5.2.2 Post-authorisation medication error reports for Humalog® 200 units/ml KwikPen™

Post-authorisation cases of medication errors for Humalog® 200 units/ml KwikPen™ have been reported to the MAH since introduction to the European market. In an effort to provide a practical analysis of the safety of the Humalog® 200 units/ml KwikPen™ and correlate measurable data with the survey results, a query of the Lilly Safety System database was conducted using the Medication Error Standardised MedDRA Query (SMQ) version 19.1.

The query provided data for a cumulative review of medication errors associated with Humalog® 200 units/ml KwikPen™ in the EU between 01 February 2015 through 31 December 2016. Overall, there were 39 cases of medication errors spontaneously reported in the EU. Of these 39 cases, there were 17 cases with 18 medication errors that were directly related to the key

safety messages in the DHPC and patient communications. Of these 17 cases related to safety messages, 5 cases described transferring or withdrawing from the KwikPen, 9 cases were due to dose conversion errors, and 3 cases described *intercepted* dispensing or prescribing errors of the 200 units/ml KwikPen™ for pump use. In these 17 cases, 6 were related to hyperglycaemia, 4 to hypoglycaemia, and 7 with no AEs. There were 4 serious adverse events (SAEs).

The 5 cases of withdrawal errors involved 4 instances of withdrawal to an insulin pump, 1 of which resulted in an SAE of severe hypoglycaemia from which the patient recovered. The other 3 cases reported 1 AE of decreased blood glucose, 1 AE of increased blood glucose, and 1 case with no AE. The outcomes for these 3 AEs were unknown. The remaining 1 case of withdrawal error involved the withdrawal into a syringe. This case involved a nurse withdrawing from the KwikPen™ of a hospitalised patient. The patient's blood glucose of 400 mg/dl reportedly normalised and patient recovered.

The 9 cases of dose conversion error involved 7 underdose errors and 2 overdose errors. Regarding the underdose errors, there were 5 cases of increased blood glucose and 2 of the cases reported no associated AE. There was 1 SAE with an unknown outcome, 1 AE where the patient recovered, and 1 AE where the patient reportedly had not recovered at time of followup. Both cases of overdose error resulted in SAEs. In 1 case the patient doubled the dose per the pharmacist instructions, was subsequently hospitalised, and outcome was unknown. In the second case, the patient doubled the dose per pharmacist and physician instructions and experienced severe hypoglycaemia with an unknown outcome.

The remaining 3 prescribing/dispensing errors were all intercepted and there were no associated AEs. Of the remaining 22 cases not related to the safety messages, the majority (14; 64%) were device-related issues such as pen malfunction.

Based on patient exposure of 277,000 patient-years since launch of Humalog® 200 units/ml KwikPen™ in the EU, the overall reporting rate of medication errors for Humalog® 200 units/ml KwikPen™ is 0.01% (39 cases). The reporting rate of medication errors related to the safety messages is 0.006% (17 cases). This is lower than the medication error reporting rate typically seen with all insulin lispro (Humalog®) products. Based on data provided in the past several Periodic Safety Update Reports (PSURs), the medication error reporting rate for all insulin lispro formulations ranges from 0.02% to 0.04%.

These data indicate that there is no increase in the medication error rate for insulin lispro (Humalog®) since the launch of Humalog® 200 units/ml KwikPen™ in EU countries, and these events are rarely reported.

10.6 Adverse events/adverse reactions

10.6.1 Healthcare professionals

There were no reports of potential AEs or product complaints by HCP respondents during the surveys (Annex 1, Appendix 1.5, Listing 1).

10.6.2 Patients

There were no reports of potential AEs or product complaints by patient respondents during the surveys (Annex 1, Appendix 1.6, Listing 1).

11. Discussion

This study assessed HCP and patient awareness regarding the risk of hypoglycaemia and hyperglycaemia due to medication errors for Humalog® 200 units/ml KwikPen™.

The following 3 key safety messages were assessed for HCP awareness:

- Humalog® 200 units/ml KwikPen™ is not approved for transfer to different insulin delivery systems (*i.e., transfer to other device message*);
- The dose of insulin does not need to be converted when changing patients from one Humalog® strength to the other (*i.e., dose conversion message*); and
- When prescribing Humalog® 200 units/ml KwikPen™ it is important to clearly indicate the correct strength on the prescription (*i.e., prescribing correct strength message*).

The study showed that the majority of HCPs surveyed were aware of 2 out of the 3 key safety messages. The vast majority of HCPs were aware of the importance to clearly indicate the correct strength when prescribing Humalog® 200 units/ml KwikPen™ (91.1%, 95%CI=85.3%-95.2%), and the majority of HCPs understood that it is not necessary to convert the insulin dose when changing patients from one strength of Humalog® to the other (59.6%, 95%CI=51.2%-67.6%). However, HCPs' awareness of the transfer to other device message was low and below the protocol threshold (27.4%, 95%CI=20.3%-35.4%). Although a sample size of 280 HCPs was targeted, 146 HCPs completed the survey. However, power calculations show that a sample of 146 HCPs has limited impact on the precision of the estimation of HCPs' knowledge rate and therefore, was large enough to measure the effectiveness of the HCP communication for Humalog® 200 units/ml KwikPen™.

Of the 146 HCPs who completed the survey, 36.3% reported that they were familiar with the HCP communication and of these, 73.6% reported that they had read it. On the other hand, 41.8% of HCPs surveyed reported they were familiar with the patient communication and of these, 65.6% reported that they had read it. Across the 3 countries, more than 150,000 communications were distributed to HCPs involved in the management and treatment of patients with diabetes. The communication was distributed at product launch and again 12 months post-launch. The relatively low awareness rate of 36.3% may in part be due to the fact that Humalog® is not a new and innovative product and HCPs are overburdened with healthcare and safety communications. Additionally, each DHCP had the patient communication attached or referenced, and therefore, the fact that more HCPs were aware of the patient communication than the DHCP (41.8% vs. 36.3%) may again reflect that HCPs are overburdened by this type of communication.

For the patient survey, a total of 11 patients responded to the survey (a response rate of 0.014%), of which only 7 were eligible and completed the survey (4 in Germany, and 3 in Sweden). The sample size for patients in the EU was too small to report any meaningful results or to draw any conclusion.

A total of 6,002 HCPs were asked to provide invitation letters to their patients for participation in the survey. Although 79,620 invitations were provided for distribution to patients, the actual number of invitation letters issued to patients by the HCPs is unknown. For this study it may have been that the HCP did not forward the invitation to the patient as it was perceived as too burdensome; however, the administrative burden related to sending out these patient invitations was minimised as much as possible, including prepaid postage. It may also have been the case that for those patients who did actually receive the invitation from their HCP, they did not want to participate in such a survey, especially as it had no impact on their treatment. However, a second patient survey with similar assessment questions based on similar key safety messages in the patient communication was conducted in the US. The US survey showed that patient knowledge met the protocol threshold for all safety messages tested and that the vast majority of the 300 patients who were treated with Humalog® 200 units/ml in the product's KwikPen™ and completed the survey were aware of the key safety message that Humalog® 200 units/ml in the product's KwikPen™ should only be injected using the prefilled KwikPen™ device in which it is supplied (97%, 95%CI=94.4%-98.6%). Given the similarity in communication materials and assessment surveys between the US and the EU patient surveys, there is no reason to believe that patient's awareness level in the EU is significantly different than that in the US with regard to the transfer to other device safety message.

This study has several limitations. The HCP communication was distributed to HCPs involved in the management and treatment of patients with diabetes. As the number of HCP receiving the communication was large, not all recipients were invited to participate in the survey. A random sample of approximately 2,000 HCPs per country was created and utilised in attempts to ensure the survey goal was met. It is unknown if the enrolled HCPs reflect the targeted HCPs who received the risk minimisation communication for Humalog® 200 units/ml KwikPen™ as privacy and data protection regulations in the EU prevent the identification and transfer of this information. Recruitment of patients was particularly challenging due to stringent data protection regulations in the EU. The sponsor was reliant on the HCP to invite their patients to participate in the survey, as the sponsor and vendor were unable to contact the patient directly. Therefore, self-selection bias may have been introduced, in both populations, HCPs due to the survey selection process and patients due to selection for survey completion by HCPs.

Although the choice of EU countries to participate in the survey was limited by product launch timings, access challenges, and market uptake, it is believed that the results are generalisable. In the EU, due to common clinical practice in diabetes care and the standardised safety communication, it is believed that France, Germany, and Sweden are representative of the EU. At the country level, HCPs were randomly sampled from a wide HCP population within each country and across specialty, and therefore, the findings at a country level should be generalisable to HCPs involved in the treatment and management of patients with diabetes and who had knowledge of Humalog® 200 units/ml KwikPen™.

In the EU, insulin products are generally prescribed and used in prefilled pens and cartridge dosage forms (Perfetti, 2010). Therefore, HCPs in the EU may be unfamiliar with prescribing and using insulins from a vial and syringe. Although Humalog® 100 units/ml is available in the EU in vial dosage forms for injection using a 100-units insulin syringe, this transfer of insulin from a vial is uncommon and may have contributed to the low knowledge rate for the question on transferring Humalog® 200 units/ml from the KwikPen™ to another device. In addition, the 27.4% HCPs knowledge rate about the transfer to other device safety message may be due to the fact that 74% of the HCPs who responded to this survey were general internal medicine and family medicine practitioners and had a knowledge rate for this transfer question of 38.9% and 6.3%, respectively. For both of these groups, transfer to another device such as an insulin pump may be outside their scope of practice, hence the lack of awareness for the safety message of transfer to another device. Endocrinologists did show a better knowledge rate (52.4%), as they are more familiar with the transfer of insulin to pump devices. HCPs may not have understood the reason for the safety message that Humalog® 200 units/ml in the product's KwikPen™ is not approved for transfer to different insulin delivery systems. This may have contributed to the "don't know" responses to this key safety message.

Medical research in the form of surveys is inherently difficult to conduct in the EU, primarily due to the data protection regulations in the region which pose significant challenges in recruiting participants. This was highlighted in a White Paper by the International Society for Pharmacoepidemiology and presented at the European Medicines Agency's Workshop on Measuring the Impact of Pharmacovigilance Activities (Sobel and Madison, 2016). There are difficulties in targeting the specific HCP audience required to be studied which could lead to selection bias, as there are constraints on the sharing of personal information between sponsor and vendors who administer the surveys. Additionally, experience from other surveys suggests that participation rates among recruited HCPs and patients are generally poor (Bester et al, 2016). This could reflect a low interest in participating in such studies, perhaps because survey participation is not mandated by regulatory bodies, nor is it a requirement for patients to gain access to treatment. There may be a perception that these surveys are too burdensome and of little scientific interest (Banerjee et al, 2014).

The effectiveness of additional risk minimisation measures is better evaluated holistically via a dual evidence approach, which involves process indicators such as HCPs' knowledge rates of communicated risks, as well as outcome indicators such as the reporting rates of communicated risks (Prieto et al, 2012; Zomerdijk et al, 2013); and in some situations, outcome-based approaches provide more valuable information on the effectiveness of additional risk minimisation measures than process-based approaches (Banerjee et al, 2014).

Routine pharmacovigilance data provide complimentary information relevant for the assessment of the effectiveness of the key safety messages communicated. Safety surveillance data showed that reporting rate of medication errors for Humalog® 200 units/ml KwikPen™ is less than typically observed in all Humalog® products (0.01% vs. 0.02%-0.04%). Based on estimated

Humalog® 200 units/ml exposure of 277,000 patient-years in Europe, the overall number of medication errors is low and the reported rate of errors is considered rare (n=39, 0.01%). The reporting rate is lower when considering only the medication errors directly related to the key safety messages (n=17, 0.006%). Forty-one percent of the cases (n=7) were not related to any AE, 35% (n=6) were related to hyperglycaemia, and 24% (n=4) were related to hypoglycaemia. The majority of these medication errors related to the key safety messages were non-serious (n=13, 76%). By comparing the reporting rates of medication errors related to the key safety messages for Humalog® 200 units/ml KwikPen™ with corresponding reporting rates for all Humalog® products, conclusions about correlating the additional risk minimisation measures with safety outcomes can be made. Since the overall goal of the additional risk minimisation measures is to minimise the risk of medication errors associated with Humalog® 200 units/ml KwikPen™ administration, successful implementation of the measure is indicated by no increase in medication errors reported for Humalog®, reflecting HCP and patient knowledge of the risks communicated as well as appropriate HCP prescribing behaviour.

Furthermore, knowledge about key safety messages can be gained from other sources in addition to the communication materials for the additional risk minimisation measure, such as the product packaging and user guide. Ultimately, it is the patient's understanding of the transfer key safety message that is important. For each administration of Humalog® 200 units/ml in the product's KwikPen™ the patient is reminded of the message as a warning label on the cartridge holder states "**USE ONLY IN THIS PEN, OR SEVERE OVERDOSE CAN RESULT**" (Figure 11-1); this warning statement is also on the carton and the user guide.

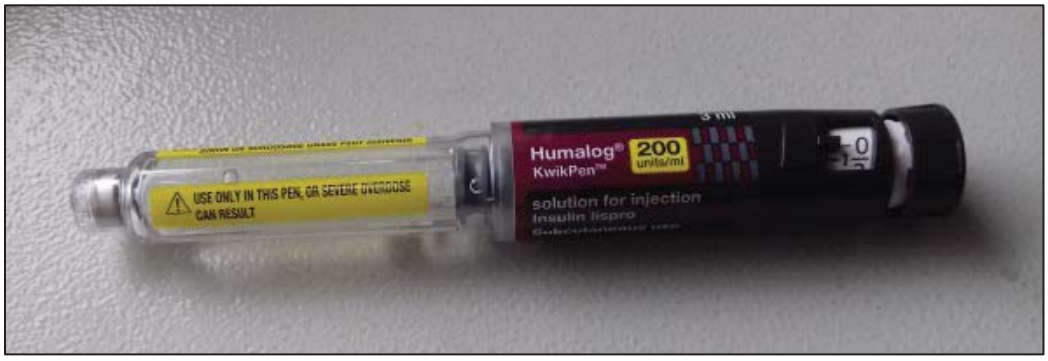


Figure 11-1: The warning label on the cartridge holder of the Humalog® 200 units/ml KwikPen™

12. Other information

Not applicable.

13. Conclusion

This study shows that 2 out of the 3 HCP key safety messages for Humalog® 200 units/ml KwikPen™ were effectively communicated to the majority of HCPs. Although no conclusions can be drawn from the patient survey due to very low recruitment, a similar study in the US demonstrated that the majority of patients did understand the key safety messages. In addition, routine safety surveillance data indicate that there was no increase in medication errors for insulin lispro in EU after the launch of Humalog® 200 units/ml KwikPen™. As medication error rates will continue to be monitored via routine safety surveillance, it is concluded that no further additional risk minimisation activities or assessments are currently required.

Patient recruitment in surveys is extremely challenging which makes the collection of meaningful EU data for this important stakeholder very difficult. Guidance, along with a greater collaboration and discussion between industry and regulators would be welcomed to enable effective patient recruitment in this type of activity.

14. References

American Diabetes Association (ADA). Standards of medical care in diabetes—2014. *Diabetes Care*. 2014; 37 Suppl 1:S14-S80.

Banerjee AK, Zomerdijk IM, Wooder S, Ingate S, Mayall SJ. Post-approval evaluation of effectiveness of risk minimisation: methods, challenges and interpretation. *Drug Saf.* 2014;37:33-42.

Bester N, Di Vito-Smith M, McGarry T, Riffkin M, Kaehler S, Pilot R, Bwire R. The effectiveness of an educational brochure as a risk minimization activity to communicate important rare adverse events to health-care professionals. *Adv Ther*. 2016;33:167-177.

Clopper, C.J.; Pearson, E.S. (1934), "The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial", *Biometrika* 26(4): 404-413.

Cobaugh DJ, Maynard G, Cooper L, Kienle PC, Vigersky R, Childers D, Weber R, Carson SL, Mabrey ME, Roderman N, Blum F, Burkhoder R, Dortch M, Grunberger G, Hays D, Henderson R, Ketz J, Lemke T, Varma SK, Cohen M. Enhancing insulin-use safety in hospitals: practical recommendations from an ASHP Foundation expert consensus panel. *Am J Health Syst Pharm.* 2013;70(16):1404-1413.

Cornish W. Safe and appropriate use of insulin and other antihyperglycemic agents in hospital. *Can J Diabetes*. 2014; 38(2):94-100.

Food and Drug Administration. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. US Dept of Health and Human Services. Food and Drug Administration. Rockville, Maryland. March 2005.

Guideline on Good Pharmacovigilance Practices Module XVI (Risk minimisation measures: selection of tools and effectiveness indicators- April 2014)

Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidemiology (ISPE). *Pharmacoepidemiology and Drug Safety*. 2008;17:200-208.

Guidelines for Good Epidemiological Practice (GEP). International Epidemiological Association (IEA); April 2010.

Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); June 2013. (http://www.encepp.eu/standards_and_guidances)

Good Outcomes Research Practices. International Society for Pharmacoeconomic and Outcomes Research (ISPOR). http://www.ispor.org/research_initiatives/hs_initiatives.asp

Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care*. 2013; 36(9):2536-2542.

International Ethical Guidelines for Epidemiological Studies, issued by the Council for International Organisations of Medical Sciences (CIOMS), World Health Organisation (WHO) Press, Geneva Switzerland. April 2009.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379.

Jabbour S. Primary care physicians and insulin initiation: multiple barriers, lack of knowledge or both? *Int J Clin Pract*. 2008;62(6):845-47.

Maria Rotella C, Pala L, Mannucci E. Role of insulin in the type 2 diabetes therapy: past, present and future. *Int J Endocrinol Metab*. 2013;11(3):137-144.

Perfetti R. Reusable and disposable insulin pens for the treatment of diabetes: understanding the global differences in user preference and an evaluation of inpatient insulin pen use. *Diabetes Technol Ther*. 2010;12(S1):S79-85.

Petznick A. Insulin management of type 2 diabetes mellitus. *Am Fam Physician*. 2011;84(2):183-190.

Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. *Pharmacoepi Drug Saf*. 2012;21:896-899.

Ryden L, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2013;34:3035–3087.

Sobel R, Madison T. Evaluating the Effectiveness of Additional Risk Minimisation Measures via Surveys in Europe: Challenges and Recommendations. European Medicines Agency workshop on measuring the impact of pharmacovigilance activities, London, UK, December 6, 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500218531.pdf.

Zomerdijk IM, Trifiro G, Sayed-Tabatabaei FA, Sturkenboom MCJM, Straus SMJM. Additional risk minimisation measures in the EU—are they eligible for assessment? *Pharmacoepi Drug Saf*. 2013;22:1046-1053.

Annex 1. List of standalone documents

No.	Document Reference No	Date	Title
1.	Appendix 1.1	20 February 2015	User Testing/Qualitative Topline Report: Humalog 200 units/ml Risk Minimisation Programme Survey Questions for Healthcare Professionals and Patients in the EU
2.	Appendix 1.2	30 November 2015	Non-Interventional Study (NIS) HCP & Patient Protocol including Humalog HCP Survey & Patient Survey
3.	Appendix 1.3	*N/A*	HCP Communication
4.	Appendix 1.4	*N/A*	Patient Communication
5.	Appendix 1.5	16 February 2017	Potential AEs or product complaints by HCP respondents
6.	Appendix 1.6	23 December 2016	Potential AEs or product complaints by patient respondents

User Testing/Qualitative Topline Report: Humalog 200 units/ml Risk Minimisation Programme Survey Questions for Healthcare Professionals and Patients in the EU

UBC Contact: Rachel Sylvester-Bauman
+1-215-591-2880

Research Moderator: Megan Leone-Perkins, PhD

20 January 2015

Version 1.0

920 Harvest Drive
Suite 200
Blue Bell, PA 19422
United States
www.UBC.com

TABLE OF CONTENTS

1 Table of Contents

2 RESEARCH DESIGN

2.1 Goals and Objectives

This Qualitative Research (User Testing) was conducted to evaluate the comprehension levels and clarity of the proposed survey questions among patients and healthcare professionals (HCPs) as part of the Humalog 200 units/ml KwikPen risk minimisation assessment. The risk minimisation programme includes additional risk minimisation measures (aRMMs) of a Direct Healthcare Professional Communication (DHPC) and a Patient Communication document. Surveys will be performed to assess the impact of these communications. On behalf of Eli Lilly and Company (Lilly), United BioSource Corporation (UBC) conducted this User Testing of the risk minimisation assessment surveys with the target audiences for the Humalog aRMMs, namely patients and HCPs. The objectives of this User Testing were as follows:

PATIENTS:

1) Review the survey questions and response options from the patient perspective with respect to comprehension, ease of recall, relevance, and clarity.
2) Determine how participants understand specific questions and response options and why those questions are answered a particular way.
3) Probe “I don’t know” (IDK) response options, when “IDK” is selected.
4) Evaluate alternative language and phrasing based on any areas of confusion or misunderstanding.
5) Assess interest, acceptance, and implementation of the survey.

HCPs:

1) Evaluate overall clarity of the survey from the HCP perspective and identify areas of confusion or misinterpretation that may vary as a function of clinical role, practice setting, or other considerations.
2) Capture HCP reactions to the survey based on their level of understanding of the medication and its associated risks.
3) Determine how participants understand specific questions and response options and why those questions are answered a particular way.
4) Probe “I don’t know” (IDK) response options, when “IDK” is selected.
5) Elicit what information might be missing or not sufficiently addressed in the survey.
6) Assess interest, acceptance, and implementation of the survey.

2.2 Research Methodology

A total of nineteen (19) individual telephone depth interviews (TDIs) were conducted by the same experienced moderator to ensure comparability between participant interviews. The number of interviews, interview length and compensation by sample are summarized below.

Patient Interviews

1) A total of 9 patient TDIs, each lasted approximately 60-75 minutes
2) At the completion of interview, patients were compensated £30 based on fair market value.

HCP Interviews

1) A total of 10 HCP TDIs, each lasted approximately 45-60 minutes
2) At the completion of interview, HCPs were compensated based on fair market value:

Nurses/GPs	£80
Endocrinologists/ Diabetologists	£120

2.3 Eligibility Criteria

PATIENTS:

Patients who participated in this research met the following criteria:

1. Have a current diagnosis of diabetes.
2. Are using insulin to control their diabetes.
3. Represent a mix of literacy/education levels[1]
4. Represent a mix of ages - 18 and above.
5. Able to read and speak English.
6. Neither the participant nor his/her immediate family members has ever worked in the following industries: advertising or public relations, marketing, survey or market research, medicine (including physician, nurse, or other allied medical professional), the pharmaceutical/biotechnology industry (including Lilly), UBC, or a national regulatory agency, such as but not limited to European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA).
7. Must not have participated in a healthcare-related market research interview in the previous 3 months.

1 All efforts were made to recruit at least half of participants with less than or equal to a year 13 education (upper 6th form), however priority was be placed on the diagnosis criterion. Low literacy was also targeted by recruiting participants with a range of careers such as food service, retail sales, administrative support, manual labour (see Patient Screener for more detail).

The REALM® (Rapid Estimate of Adult Literacy in Medicine[2]) was administered by the research moderator as part of the research interview to assess health literacy for common medical terms.

HCPs:

HCPs who participated in this research met the following criteria:

1. Involved directly in the care and treatment of patients with diabetes, specifically with insulin products
2. Were from one of the following specialties:
    - Doctor (General Practitioner, diabetologist, endocrinologist)
    - Nurse
3. Saw/treated patients at least 75% of their professional time
4. Represented a mix of practice settings
5. Neither the participant nor his/her immediate family members had ever worked or consulted in the following industries or companies: advertising or public relations, marketing, survey or market research, the pharmaceutical/biotechnology industry, UBC, or a national regulatory agency, such as but not limited to EMA, MHRA.
6. Had not have participated in a healthcare-related market research interview in the previous 3 months.

In addition to the above eligibility criteria, all participants had to be willing to sign an Interview Release Form.

3 RECRUITMENT

Participants were identified using a database housed at a research facility. The database contains information about individuals who are interested in being included in research interviews or focus groups. These individuals have previously provided their information and permission to the facility to be contacted about research programmes.

Participants were screened based on the eligibility criteria in the Lilly-approved eligibility screener provided to the research facility by UBC.

2 Davis TC, Long SW, Jackson RH, Mayeaux EJ, George RB, Murphy PW, Crouch MA, Rapid estimate of adult literacy in medicine: a shortened screening instrument. Fam Med. 1993 Jun; 25(6):391-5.

4 INTERVIEW DESIGN

4.1 Prior to the Interview Session

Upon confirmation of participant eligibility and availability, the research facility emailed or faxed an interview confirmation to each participant. The participant was informed that they would receive a packet in the 1-5 days prior to their interview, instructed to open the packet as soon as he/she receives it, and to read the enclosed Introduction/Instruction letter.

The following materials were included in the participant's package:

1. Introduction/Instruction Letter, which included:
    a. Detailed instructions for dialling into the interview
    b. Instructions for returning materials via courier
2. **Sealed** envelope containing:
    a. A copy of the draft survey
    b. REALM Word List (PATIENTS ONLY)
3. Interview Release Form
4. Postage paid return envelope

The envelope containing the draft survey was sealed with a neon sticker instructing the participant not to open the envelope until instructed by the moderator.

4.2 During Interview Session

All interviews were guided by a scripted Moderator's Discussion Guide. When the participant joined the teleconference line, the moderator reviewed the following with the participant:

1. General introductions – The moderator thanked the participant for being part of the research and informed the participant that the interview will be audio-taped only to help prepare a written report for research purposes. The moderator then reconfirmed with the participant that audio-taping would begin and initiated recording upon participant's agreement.
2. Confidentiality – The moderator informed the participant that the information gathered was for research purposes only and that he/she would not be identified by name in any reports; that his/her input and opinions will be reported in aggregate and were important to assist in improving the materials.
3. Adverse Event (AE)/Product Complaint (PC)/Medical Information Request (MIR) reporting – The moderator informed the participant that should an AE, PC or MIR emerge for a Lilly product, the moderator was required to forward this information to the research sponsor.
4. Rapport building – The moderator learned a little bit about the participant, e.g., background, professional role and practice setting (HCPs), diagnosis (patients).

5. Survey review - Patients were administered the REALM test then reviewed the Patient RMP Survey content; HCPs proceeded directly to review of the HCP RMP Survey content.

At the close of the interview, the participant was instructed to send all materials back to the facility using a courier. Once the materials (including the Interview Release Form) were received, the research facility mailed the honorarium to the participant in compensation for his/her time and efforts.

5 INTERVIEW RELEASE PROCEDURES

All participants provided verbal consent to being audio recorded at the beginning of the research interview as well as a signed Interview Release Form with their materials following their interview. Participants were informed that the transcribed interviews may be shared with the sponsor and regulatory agencies; however, the moderator explained that neither participant's name nor other identifying information would be associated with the audio recording or the responses provided during the interview.

6 SAFETY REPORTING

The UBC QR team followed the Lilly Humalog® Risk Minimisation Safety Event Reporting Procedure during the interview process although none were elicited during participants' review of the Humalog KAB Survey.

7 PARTICIPANT DEMOGRAPHICS

Patient Participants

The patients that participated in this research ranged in age from 31 to 80 years of age with a mean age of 55 years. All had been previously diagnosed with, and were currently taking medication for their diabetes. Further, most (6) of the participants were exclusively taking an injected medication to treat their diabetes whereas three (3) were taking an injected and an oral medication for their diabetes.

All participants scored at a "High School" level on the REALM medical literacy test.[3]

Patient Participants	
Total Sample	**(9)**
Gender	
Male	6
Female	3
Race/Ethnic Background	
White	8
Asian	1
Employment Status	
Employed, full-time	1
Employed, part-time	4
Not currently working	2
Retired	2
Highest Level of Education Completed	
A-level	2
A-level equivalent	1
GCSE or equivalent	5
NVQ (GCSE equivalent)	1

[3] The REALM is a U.S. validated instrument designed to measure patient literacy. Following administration of the test, raw scores are calculated that correspond to a U.S.-based "Grade Range Equivalent". For this research, the 9 patients that were interviewed all scored at a "High School" level which would correspond to the U.K. equivalent of "GCSE or equivalent".

HCP Participants

The HCPs that participated in these interviews represented a range of years in practice with half reporting that they had been in practice between 11-15 years (5) and 3 who reported 20+ years in practice. Further, one HCP reported being in practice 6-10 years and another reported being in practice 16-20 years.

Half (5) of the HCPs said that they spent 80% of their professional time with patients. Their demographic data is further displayed in the table below.

HCP Participants	
Total Sample	**(10)**
Gender	
Male	5
Female	5
Primary Specialty	
Family Practitioner/General Medicine	3
Endocrinology	2
Registered Nurse	5
Primary Practice Setting	
University Hospital	5
Office-based Practice	3
General Practice	1
Community Matron	1

8 HIGH-LEVEL FINDINGS

Overall Findings

Both patients and HCPs felt that most of the respective survey content was “straightforward” and relatively “clear”. As neither patients nor HCPs had been exposed to the risk minimisation materials or communications for the Humalog 200 units/ml KwikPen, some of the survey content was difficult to comprehend because they did not understand the “delivery system” or for patients in particular, information pertaining to medication “strength.”

Patient Survey Feedback

The nine patients interviewed were able to easily discuss and explain both the screening questions such as agreement to participate, age and confirmation of diabetes diagnosis.

Patients also reviewed and discussed the closing demographic questions such as years since their diabetes diagnosis as well as the country in which they currently reside.

Review of the survey questions that pertained to the patient communication material *Important Safety Information for Humalog 200 units/ml KwikPen* focused on receipt and use of these types of risk minimisation materials for their diabetes medications in general as none of the patients were currently being treated with the Humalog 200 unit/ml KwikPen nor had they been exposed to these materials prior to or as part of the research interviews. Instead, patients felt that the survey questions pertaining to these materials were clear and discussed in detail the role of their nurse or the nurse educator who tended to be the healthcare professional primarily responsible for providing them with detailed education about their diabetes medications.

Potential Areas for Patient Survey Clarification

There were some suggestions for clarification or revision from the patients interviewed. For example, a few patients (as well as HCPs) commented on the phrase *"My doctor or someone at my doctor's office"* which they felt did not clearly highlight the importance of the nurse educator. Instead, participants felt that the phrase "someone at my doctor's office" could instead be interpreted to mean someone at the front desk or an administrative staff member.

Based on these comments, some of the participants said that this phrase should reference "my doctor or nurse" or "my doctor or another healthcare professional" to clearly illustrate the importance of engaging in medication safety conversations with a healthcare professional.

Title of the Patient Hand-Out

In reviewing both the HCP and patient survey questions, there was some inconsistent formatting of the patient hand-out title: "IMPORTANT SAFETY INFORMATION FOR Humalog 200 units/ml KwikPen (insulin lispro)". For example, sometimes the title was written in initial capitals (e.g., "Important Safety Information…"), and, in other instances it was written in all capitals (e.g., "IMPORTANT SAFETY INFORMATION…"). Based on qualitative review of the both the patient and HCP surveys there was a perceived need for consistent formatting throughout the surveys.

Patient Survey: Statement 6B

"Your dose of insulin does not need to be converted when changing from one strength of Humalog to the other."

In reviewing this statement, multiple patients said that they would need to talk to their doctor about it (in part to have it explained) as they did not understand the information. Others tried to explain the statement by suggesting that perhaps the medicine was more concentrated and didn't need to be "converted".

"It doesn't actually make a lot of sense to me because in the UK, I'm not sure about the United States, but in the UK we have – it's simplified so that the insulin is 100 – I'll go and get a bottle of it if you want to, a pack of it. I'm not sure what it means to be converted." Male patient, diagnosed with diabetes 40+ years ago

"Maybe from using "strength" to "unit" makes it a bit clearer for me. Just maybe there's a sort of language barrier between the U.K. and America." Male patient, diagnosed with diabetes 14 years ago

As previously stated, none of the patients were either taking this medication or had been exposed to the safety communication materials. This lack of exposure may explain in part some of the confusion that emerged but may also suggest the need for further clarification such as providing examples of conversion.

Patient Survey: Statement 7C

"I think about the information in *Important Safety Information for Humalog 200 units/ml KwikPen* or refer to the paper or website to remind myself of risks when injecting my insulin."

During qualitative testing of survey statement 7C, patients felt that it was odd and somewhat confusing that they would think about a website or refer to a paper "when injecting my insulin". They tended to view the question quite literally and instead felt that it would be more appropriate to ask if patients "think about the information" rather than asking if they "refer to the paper or website to remind myself of risks when injecting my insulin."

The verbatim comments from two patients further illustrate their feedback to this survey statement.

It's an odd way to phrase it...To think about something implies that it's on your mind and it's playing with your mind but the last thing on my mind as a diabetic is a risk of injecting. It's the risks of diabetes that are most in my mind not the risk of injecting." Female patient, diagnosed 15+ years ago

"Will I think about the information and important safety information for Humalog 200 unit/ml Kwikpen or refer to the paper or website to remind myself of risks when injecting my insulin. That's a wee bit confusing that, when you get information twice so close together." Male patient, diagnosed with diabetes 3 years ago

Patient Survey: Demographics

Patients felt that the demographic questions included at the closing of the patient survey were straightforward and some said that they were familiar with answering these kinds of questions in surveys or health questionnaires.

Of the demographic questions that were evaluated, there were two that were discussed in somewhat more detail. Specifically, patients were asked to explain the phrase "any type of insulin" in the question: *"For how long have you been using any type of insulin to manage your diabetes?"* Patients said that it might include oral or injected insulin, or that maybe another question would ask for examples of the insulin type used. When presented with alternate wording of this demographic question, patients felt that it was easier to ask: *"For how long have you been using insulin to manage your diabetes?"*

Patients also felt that it might be more appropriate to ask: *"What is your gender?"* (rather than asking *"What is your sex?")* which some wondered whether or not the term "sex" was accurate or if they'd seen it previously worded in this manner. One participated said why not simply ask: *"Are you a male or female?"* Aside from these minor comments, patients felt that the demographic questions were quite clear.

HCP Survey Feedback

The HCPs that were interviewed felt that the survey content was "straightforward" and while none of them had been previously exposed to the Humalog 200 units/ml risk minimisation materials, HCPs were able to hypothesize about the survey questions in relation to other types of injectable medications to treat diabetes. Additionally, in a few instances, some of the HCPs said that they had "heard" about Humalog 200 units/ml KwikPen.

HCP Review of Risk Minimisation Materials

To review and discuss the survey questions that pertained exclusively to physician receipt and review of both the HCP and patient-directed Humalog 200 units/ml KwikPen safety materials, the HCPs were asked to discuss their receipt and review process for other comparable medications as they had not previously received or been exposed to these materials.

For example, HCPs said that they tend to review these types of materials when a medication becomes newly available. They also refer to their local or hospital guidelines regarding safe prescribing considerations for these medications. In addition, HCPs said that they also rely on their diabetes nurses or nurse educators to review patient-directed safety information.

Overall, HCPs felt that these survey questions were straightforward but based on the User Testing research, it was felt that clarification as to how they would receive, or alternatively, from whom they would receive the materials (e.g., sent to you from Eli Lilly and Company) would further enhance their recall and response to this survey subset.

HCP Survey: Use of the Phrase "Someone at your practice"

As reported earlier in regard to the patient comments, the HCPs interviewed also felt that it was more accurate to ask: *"do you or another healthcare professional"* or *"do you or a nurse"* rather than the current wording: *"do you or someone at your practice discuss"*. HCPs said that this type of clarification more clearly illustrated the important role of another healthcare professional such as a nurse or diabetes educator rather than say, an office administrator.

HCP Survey: Statement 5a

Q5a. "Humalog 200 units/ml is approved for transfer to different insulin delivery systems."

HCPs were somewhat confused by this statement in that it did not specify the "KwikPen" device and they had not yet seen the device. Some felt that it would be important to clarify this statement (e.g., specify "KwikPen") to enhance its overall comprehension.

HCP Survey: Statement 5b

Q5b. "The dose of insulin does not need to be converted when changing patients from one Humalog strength to the other."

Similar to the feedback received from patients, the HCPs interviewed felt that statement 5b could be further clarified by providing an example of changing from one dose to another. Their verbatim comments further illustrate their reactions to this survey statement.

> *"Well maybe they should specifically just say from Humalog 100 units per ml to Humalog 200 units per ml. They could just make it simpler really." Dermatologist, 16 years in practice*

> ***"**The dose of insulin does not need to be converted when changing patient from one human strength to the other." I'm not quite sure. I have to think about that. I would imagine maybe it's something to do with the profile of the insulin so that it maybe has got a flat profile. I don't know..."strength" is maybe not the right word, because it's more about the profile of the insulin to me, so I would want to know more about the profile, not about the strength because it's not about strength;" Community Nurse Matron, 12 years in practice*

> *"I don't really like Statement [5] B. A is very factual. A, C – it's very clear, but B – the dose didn't seem – that is a bit ambiguous. It's not very clear. A is very factual. C is very factual. B is a little bit wishy-washy." Nurse, 30 years in practice*

HCP Survey: Demographic Questions

Overall the demographic questions were felt to be clear and straightforward, although there were some discussions about the accuracy or relevance of the primary medical specialty and employment facility categories that comprised questions 17 and 18. For example, HCPs said

that the options “Diabetology” and “Endocrinology” were “one in the same” and that one of these two options should be deleted (“diabetology” proposed) or perhaps combine into one response option (e.g., “Endocrinology/Diabetology”).

HCPs also indicated that the “Office-based” option in question 18 was not relevant to the U.K. and instead they proposed “General practice” or “General practice surgery”.

Closing Comments

As previously mentioned, the patients and HCPs interviewed for this research felt that the survey content was overall clear and “straightforward”. They were also able to discuss the content in detail when asked to frame some of the questions (e.g., review and receipt of safety communications) in relation to their existing diabetes medications (patients) or diabetes medications for which they prescribe or educate patients (HCPs).

NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

PASS information

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

Approval Date: 08-Dec-2015 GMT

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.
Author	Dr. Ayad Ali, Pharmacoepidemiologist Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA Email: ali_ayad@lilly.com Tel: +1 317 433 8868

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V. Grootslag 1-5, NL-3991 RA Houten The Netherlands
MAH contact person	Dr. Ayad Ali, Pharmacoepidemiologist Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA Email: ali_ayad@lilly.com Tel: +1 317 433 8868

1. Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Annexes

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

Name, degree(s)	Title	Affiliation	Address
Ayad Ali, PhD	Pharmacoepidemiologist	Eli Lilly and Company	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA

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

American Diabetes Association (ADA). Standards of medical care in diabetes—2014. *Diabetes Care.* 2014; 37 Suppl 1:S14-S80.

Cobaugh DJ, Maynard G, Cooper L, Kienle PC, Vigersky R, Childers D, Weber R, Carson SL, Mabrey ME, Roderman N, Blum F, Burkhoder R, Dortch M, Grunberger G, Hays D, Henderson R, Ketz J, Lemke T, Varma SK, Cohen M. Enhancing insulin-use safety in hospitals: practical recommendations from an ASHP Foundation expert consensus panel. *Am J Health Syst Pharm.* 2013; 70(16):1404-1413.

Cornish W. Safe and appropriate use of insulin and other antihyperglycemic agents in hospital. *Can J Diabetes.* 2014; 38(2):94-100.

Food and Drug Administration. Guidance for Industry. Good Pharmacovigilance Reporting and Pharmacoepidemiology Practices. US Dept of Health and Human Services. Food and Drug Administration. Rockville, Maryland. March 2005.

Guideline on Good Pharmacovigilance Practices Module XVI (Risk minimisation measure: selection of tools and effectiveness indicators- April 2014)

Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidemiology (ISPE). Pharmacoepidemiology and Drug Safety 2008; 17:200-208.

Guidelines for Good Epidemiological Practice (GEP). International Epidemiological Association (IEA); April 2010.

Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); June 2013. (http://www.encepp.eu/standards_and_guidances)

Good Outcomes Research Practices. International Society for Pharmacoeconomic and Outcomes Research (ISPOR). http://www.ispor.org/research_initiatives/hs_initiatives.asp

Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care.* 2013; 36(9):2536-2542.

International Ethical Guidelines for Epidemiological Studies, issued by the Council for International Organisations of Medical Sciences (CIOMS), World Health Organisation (WHO) Press, Geneva Switzerland. April 2009.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012; 35(6):1364-1379.

Jabbour S. Primary care physicians and insulin initiation: multiple barriers, lack of knowledge or both? *Int J Clin Pract.* 2008; 62(6):845-47.

Maria Rotella C, Pala L, Mannucci E. Role of insulin in the type 2 diabetes therapy: past, present and future. *Int J Endocrinol Metab.* 2013; 11(3):137-144.

Petznick A. Insulin management of type 2 diabetes mellitus. *Am Fam Physician.* 2011; 84(2):183-190.

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.

Leo Document ID = ebdf7781-cb59-4d8d-be3f-03cf4ece7e89

Approver: Ayad Ali (AM\C163552)
Approval Date & Time: 08-Dec-2015 18:53:19 GMT
Signature meaning: Approved

Approver: Jim Malone (AM\RM89606)
Approval Date & Time: 08-Dec-2015 20:27:02 GMT
Signature meaning: Approved

Month, 2014

Direct Healthcare Professional Communication on the correct use of Humalog (insulin lispro) 200 units/ml KwikPen to minimize medication errors

Dear Healthcare Professional,
This letter is to inform you of important safety information regarding insulin lispro, a mealtime insulin analogue now available in a strength of 200 units/ml (Humalog® 200 units/ml KwikPen™), for the treatment of diabetes mellitus in adults.

Summary

- **Insulin lispro 200 units/ml solution for injection should ONLY be administered using the Humalog 200 units/ml prefilled pen (KwikPen).**
- **Transfer of the higher strength insulin lispro 200 units/ml from the Humalog 200 units/ml KwikPen to a different insulin delivery system may lead to overdose and severe hypoglycaemia.**
- **It is important to make patients using the Humalog 200 units/ml KwikPen aware of this risk and instruct them NOT to transfer insulin from Humalog 200 units/ml KwikPen to a syringe or insulin pump for administration.**
- **When switching from one Humalog strength to another, the dose does not need to be converted – the dose-counter window on both pens displays the number of units of insulin lispro to be injected. Unnecessary dose conversion may lead to under/over dosing and resultant hyper/hypoglycaemia.**
- **When prescribing Humalog KwikPen please ensure that the correct strength is clearly written on the prescription.**
- **Please provide the attached patient communication for Humalog 200 units/ml KwikPen to all patients receiving their first prescription. [Website where patient communication is housed may be inserted].**

Further information on the safety concern and the recommendations

The European Commission has approved the Humalog 200 units/ml KwikPen for the treatment of adults with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

Humalog 200 units/ml KwikPen should be reserved for patients taking more than 20 units of rapid-acting insulin per day.

The Humalog 200 units/ml KwikPen contains 600 units of insulin lispro in 3 ml solution for injection, which is twice the concentration of standard 100 units/ml mealtime insulin. The maximum amount of insulin lispro which can be given in one injection from the Humalog 200 units/ml KwikPen is 60 units.

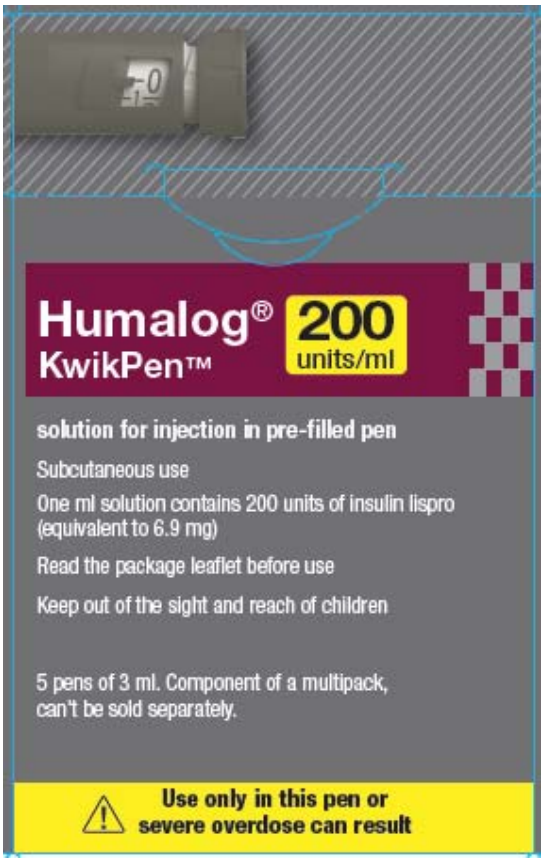
The carton containing the Humalog 200 units/ml KwikPen includes the following design features which will help to differentiate this carton from the carton of the Humalog 100 units/ml KwikPen:

- A yellow warning box containing the wording: Use only in this pen or severe overdose can result.

- The strength of “200 units/ml” is written in a yellow box.
- Background color is dark grey instead of white for the Humalog 100 units/ml KwikPen.

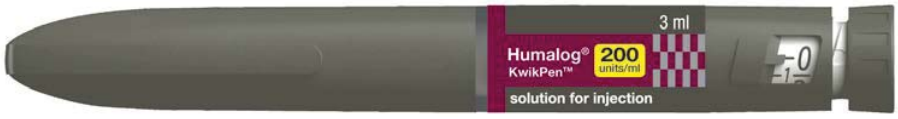
Images of the new Humalog 200 units/ml Kwikpen are below. Please advise new patients on the Humalog 200 units/ml design features using these images.

Humalog 200 units/ml KwikPen outer carton



The Humalog 200 units/ml prefilled pen contains the following design features which will help to differentiate this pen from the Humalog 100 units/ml KwikPen:

- The pen color is dark grey.
- The label of the pen is burgundy and contains a checkered box.
- The strength of 200 units/ml is written in a yellow box.



Humalog 200 units/ml KwikPen

Call for reporting

To report medication errors, adverse events or product complaints among patients taking Humalog 200 units/ml KwikPen, please contact Lilly at:

[local affiliate phone number].

Alternatively, medication errors, adverse event or product complaint information may be reported to the [local regulatory agency]:

Phone: [local regulatory agency phone number]
Facsimile: [local regulatory agency fax number]
Mail: [local regulatory agency mailing address/form]
Online: [local regulatory agency website]

Company contact point

This letter is not intended as a complete description of the risks associated with the use of Humalog 200 units/ml KwikPen. Please refer to the attached Summary of Product Characteristics (SPC) for a complete description of risks.

Please contact Lilly at: [local affiliate phone number] if you have any questions about the information in this letter or the safe and effective use of Humalog 200 units/ml KwikPen.

Sincerely,

Appropriate Lilly Signee, MD
Title, Department
Enclosure: Local Humalog 200 units/ml KwikPen Label

Patient Communication

IMPORTANT SAFETY INFORMATION FOR Humalog® 200 units/ml KwikPen™ (insulin lispro)

Dear Patient,
This letter is provided to give you important information about the safe and correct use of your new Humalog 200 units/ml KwikPen (insulin lispro). Before using this product, please make sure you read the provided Humalog 200 units/ml KwikPen Package Leaflet and User Manual for more information.

What is Humalog?

- Humalog is a rapid-acting (mealtime) insulin used to treat diabetes. It works by reducing your blood sugar level.
- Humalog solution for injection is available in 2 strengths. This is the amount of Humalog in units per milliliter (ml):
    - 100 units/ml and
    - 200 units/ml

What is Humalog 200 units/ml KwikPen?

- KwikPen is a disposable prefilled pen designed to deliver Humalog by subcutaneous injection (injection under the skin).
- Humalog 100 units/ml solution for injection is available in vials, cartridges and the KwikPen.
- Humalog 200 units/ml solution for injection is available ONLY in the pre-filled pen (the Humalog 200 units/ml KwikPen).
- Humalog 200 units/ml KwikPen has twice as many insulin units in each ml than Humalog 100 units/ml KwikPen.

What you need to know before you use Humalog 200 units/ml KwikPen

- Inject Humalog 200 units/ml solution for injection ONLY by the KwikPen in which it is supplied.
- DO NOT draw up Humalog 200 units/ml solution for injection from the KwikPen using an insulin syringe. The markings on insulin syringes will not measure your dose correctly.
- Using Humalog 200 units/ml solution for injection in any other type of delivery device, like an insulin syringe or an insulin infusion pump, may result in an overdose causing severe low blood sugar and MAY PUT YOUR LIFE IN DANGER.
- The dose indicator on the Humalog 200 units/ml KwikPen should always be used to select the dose. The Humalog 200 units/ml KwikPen will deliver the exact dose that is dialed.
- Do not convert your dose if you change from one Humalog strength to the other. This may lead to under or over dosing resulting in high or low blood sugar.
- Check how many units have been dialed on the Humalog 200 units/ml KwikPen before injecting the dose.
- When you receive your insulin, always check the package and the label of the pen for the name, type and strength of the insulin. Make sure you receive the Humalog 200 units/ml KwikPen that your healthcare professional has told you to use.

- The carton for the Humalog 200 units/ml KwikPen contains the following design features which will help you to be sure to have the correct medicine:
    - A yellow warning box containing the wording: “Use only in this pen or severe overdose can result.”
    - The strength of 200 units/ml is written in a yellow box.
    - Background color is dark grey instead of white for the Humalog 100 units/ml KwikPen.

- The prefilled pen itself contains the following design features which will help you to be sure to have the correct pen:
    - The pen color is dark grey.
    - The label of the pen is burgundy and contains a checkered box.
    - The strength of 200 units/ml is written in a yellow box.

Call for reporting
To report medication errors, adverse events or product complaints among patients taking Humalog 200 units/ml KwikPen, please contact Lilly at:
[local affiliate phone number].

Alternatively, medication errors, adverse event or product complaint information may be reported to the [local regulatory agency]:
Phone: [local regulatory agency phone number]
Facsimile: [local regulatory agency fax number]
Mail: [local regulatory agency mailing address/form]
Online: [local regulatory agency website]

This message is not meant to provide a complete description of the risks related to the use of the Humalog 200 units/ml KwikPen. Before using this product, please make sure you read the provided Humalog 200 units/ml KwikPen *Package Leaflet* and *User Manual* for more information. If you have any questions about your Humalog 200 units/ml KwikPen, contact your healthcare professional for help or Lilly at < *# to be completed by affiliate*>.

Listing 1: Listing of Potential Adverse Events and/or Potential Product Complaints Reported by Modality

Potential Adverse Event or Potential Product Complaint?	Modality of Report	Verbatim Text
No adverse events or product complaints reported.		

Listing 1: Listing of Potential Adverse Events and/or Potential Product Complaints Reported by Modality

Potential Adverse Event or Potential Product Complaint?	Modality of Report	Verbatim Text
No adverse events or product complaints reported.		

Annex 2. Additional information

Not applicable.