NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

TITLE: SURVEY TO EVALUATE THE KNOWLEDGE AND UNDERSTANDING OF THE KEY SAFETY MESSAGES IN THE HEALTHCARE PROFESSIONAL GUIDE AND THE PATIENT GUIDE FOR SULIQUA

COMPOUND: SULIQUA

STUDY NUMBER: INSLIC08571

The study is conducted by the Sanofi-Aventis Group/IQVIA hereinafter referred also as the "MAH/MAH representative".

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Version Number:	6
Date:	24 February 2020
Total number of pages:	83

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PASS Information

Title	Survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide for SULIQUA
Protocol version identifier	V6
Date of last version of protocol	22nd November 2018
EU PAS register number	EUPAS23920
Active substance	Insulin glargine/lixisenatide, ATC code: A10AE54
Medicinal product	SULIQUA (Fixed ratio combination of Insulin glargine ([100 Units/ml]/lixisenatide)
Product reference	Not applicable
Procedure number	EMEA/H/C/4243
Marketing authorization holder(s)	Sanofi-Aventis groupe 54 Rue La Boetie, 75008 Paris, France
Joint PASS	No
Research question and objectives	Research question: Were the key safety messages in the healthcare professional guide and the patient guide, implemented as risk minimisation measures (RMM) beyond routine, effective in: o Providing good knowledge and understanding to health care professionals (HCPs) who prescribed or dispensed SULIQUA and to patients treated with SULIQUA o Reducing the risk of medication errors when prescribing/delivering or using SULIQUA Objective: To assess the knowledge and understanding of the key safety messages in the health care professional guide and patient guide among HCPs who prescribed or dispensed SULIQUA and patients treated with SULIQUA, respectively
Country(-ies) of study	Candidate countries: Wave 1 - Czech Republic, Hungary, Slovenia Wave 2 - Belgium, Croatia, Romania, United Kingdom Wave 3 - Countries will be selected based on the product launch and market uptake and the possibility for conducting Wave 3 will be revisited in November 2020 and communicated to PRAC (Pharmacovigilance Risk Assessment Committee) during Wave 2 interim report submission
Author	[redacted]

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Marketing authorization holder(s)

Marketing authorization holder(s)	Sanofi-Aventis groupe 54 Rue La Boetie, 75008 Paris, France
MAH/MAH REPRESENTATIVE contact person	[redacted]

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ASOCS	Association of Opinion and Behaviour in Health Field Research Companies
CI	Confidence interval
CSR	Clinical study report
DHPC	Direct Healthcare Professional Communication
EC	Ethics Committee
EM	Educational Materials
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
GDPR	General Data Protection Regulation
GLP-1	Glucagon-like peptide 1
GP	General Practitioner
GVP	Good pharmacovigilance practices
HCP	Healthcare professional
HMR	Healthcare Market Research
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
LOC	[Sanofi] Local Operating Company
PASS	Post-authorization safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk minimization measures
RMP	Risk management plan
SAE	Serious adverse event
SAS	Statistical analysis software
SAP	Statistical Analysis Plan
SDLC	System Development Life Cycle
SmPC	Summary of product characteristics
SOP	Standard operating procedures
STROBE	Strengthening the reporting of observational studies in epidemiology

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3 RESPONSIBLE PARTIES

Sponsor:

Sanofi-Aventis group is the Marketing Authorisation Holder (MAH)

Subcontractor acting as contracted principal investigator:

IQVIA

Contact person: [redacted]

Project team:

[redacted]

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4 ABSTRACT

Title

Survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide for SULIQUA

Rationale and background

In the risk management plan (RMP) assessment report by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA-PRAC), dated 7 July 2016, the Marketing Authorization Holder (MAH) was requested to submit key safety messages for inclusion in a healthcare professional guide and a patient guide to address the potential risk of medication errors occurring at the prescribing, dispensing and patient level. The MAH was further asked to propose a study to assess the effectiveness of these additional risk minimisation measures (RMMs [i.e. the healthcare professional guide and patient guide). Therefore, this study will evaluate the knowledge and understanding of the educational materials (EM)/guides provided to the health care professionals (HCPs) who prescribed or dispensed SULIQUA and to the patient population treated with SULIQUA after its approval and launch.

Research question and objectives

Research question: Were the key safety messages in the healthcare professional guide and the patient guide, implemented as RMM beyond routine, effective in:

- Providing good knowledge and understanding to HCPs who prescribed or dispensed SULIQUA and to patients treated with SULIQUA
- Reducing the risk of medication errors when prescribing/delivering or using SULIQUA

Objective: To assess the knowledge and understanding of the key safety messages in the health care professional guide and patient guide among HCPs who prescribed or dispensed SULIQUA and patients treated with SULIQUA, respectively.

Study design

The study will be a cross-sectional survey conducted in 3 distinct waves in selected European countries where SULIQUA is marketed (Wave 1: Hungary, Czech Republic, Slovenia, Wave 2: Belgium, Croatia, Romania, United Kingdom, and Wave 3: countries will be selected based on the product launch and market uptake). Croatia is at risk and Italy has been dropped from this study due to challenges related to the ethics committee (EC) approvals. Latvia was planned as a candidate country for Wave 1 but was dropped from the survey due to difficulties to setup the study.

Each wave of the study will correspond to the sequential inclusion of the targeted countries according to the timing of SULIQUA launch and implementation of RMM in these countries. The possibility for conducting Wave 3 will be revisited in November 2020 and communicated to Pharmacovigilance Risk Assessment Committee (PRAC) during Wave 2 interim report submission.

The surveys will be hosted online. In addition, phone (for HCPs) or paper-based questionnaires (for patients) will also be offered as an option for those who have challenges in accessing the internet. The survey questionnaires will comprise multiple-choice and true/false questions. The survey questionnaires were developed jointly by the Sanofi-Aventis Group and IQVIA based on the final approved healthcare professional guide and patient guide and are included as Annex 2 and Annex 3 of

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this study protocol. The HCP questionnaire was developed and tested among 6 HCPs for its comprehensibility, consistency and the appropriateness of medical terms. HCPs' comments were implemented in the final version. In addition, a patient/caregiver questionnaire was also tested among 6 non-HCPs for optimal readability by patients.

Population

HCP enrolment

A random sample of at least 150 HCPs prescribing/delivering SULIQUA (general practitioner [GP], endocrinologist/diabetologist, internist, gastroenterologist, nurse, geriatrist and pharmacist) will be recruited per wave, . To minimize selection bias, a database of registered HCPs will be used to randomly enrol HCPs (OneKey, IQVIA). An HCP will only participate in one wave of the survey. All HCPs will provide consent for participation in the survey and data will be anonymous when presented to the MAH.

Patient enrolment:

The target patient population per wave will consist of 150 patients treated with SULIQUA. An invitation letter to participate in the study will be randomly given to patients treated with SULIQUA by the HCP. A patient will only participate in one wave of the survey. There will be no limit on the number of patients recruited per HCP. Patients will provide informed consent and data will be anonymous to IQVIA and to the MAH.

Variables

1. Collected/estimated through HCP questionnaire:
    - Information related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate
    - Variables related to HCPs practice information:
        - Duration of practice (years working with diabetic patients)
        - Specialty (GP, endocrinologist/diabetologist, pharmacist, internist, gastroenterologist, nurse, geriatrist)
        - Type of setting (office based, hospital based, both, outpatient pharmacy, hospital pharmacy, diabetes care clinic)
        - Past experience with SULIQUA (number of patients treated with SULIQUA pre-filled pen)
    - Variables related to the HCPs knowledge about the prescribing conditions and safety information/warnings of SULIQUA:
        - HCP knowledge about SULIQUA pre-filled pen guide for HCPs
        - Awareness of the responsibility to provide each patient with the guide for patient treated with SULIQUA
        - Knowledge of the instructions for appropriate utilization of SULIQUA pre-filled pen (dose titration, pen choice, storage, adverse reactions)
        - Appropriate labelling of dose range and strength of SULIQUA pre-filled pen and dose steps to be administered in prescription (yes/no)
        - Education/Advice of the patient with regard to dose steps required, design features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information)
        - Number of recorded medication errors since EM distribution
    - Receipt of SULIQUA pre-filled pen Guide for HCPs (yes/no)
    - Distribution to patients/caregivers of the guide for patient treated with SULIQUA (yes/no)

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2. Variables collected through the patient questionnaire: patients related variables
    - Patients characteristics (age, gender, length of SULIQUA treatment)
    - Treating physician (GP, endocrinologist/diabetologist, internist, gastroenterologist, geriatrist)
    - Patient knowledge about SULIQUA pre-filled pen guide for patient (yes/no)
    - Patient knowledge about SULIQUA pre-filled pen conditions of use (features and appropriate utilisation of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information)

Data sources

The survey is a primary data collection conducted through 2 questionnaires administered by web, phone or paper:

- An HCP questionnaire (administered by web or phone)
- A patient questionnaire (administered by web or paper)

Study size

The sample survey will include HCPs from the IQVIA OneKey reference lists.

The sample size calculation is based on the survey objective, i.e. to assess the knowledge and understanding of the key safety messages in the health care professional guide and patient guide among HCPs who prescribed or dispensed SULIQUA and patients treated with SULIQUA, respectively.

Since the expected proportion of HCPs who received and understood the EM related to SULIQUA is not known and there is no evidence supporting it, the worst-case hypothesis will assume a proportion of 50%. The required sample size for the study would be 384 for a precision level of 5%. This sample will be divided into 3 waves, each comprising 128 HCPs and providing a precision of 8.66% for each wave based on the same formula. It is estimated that at least 85% of the questionnaires completed by HCPs will be analysable. Therefore, approximately 450 HCPs shall be surveyed in total. An overall sample of 150 HCPs will be needed for each wave.

Applying the same rule to patients to be recruited, the required sample size would be 150 per wave for a precision level of 8%.

Data analysis

The statistical analysis will be conducted using the statistical analysis software® (SAS) V9.4 on Windows™ (SAS Institute, North Carolina, US).

Results will be presented, overall and at country level per specialty.

Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, Q1, Q3, minimum, and maximum. No missing data will be replaced. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals (CI) of 95% will be calculated when relevant.

Calculations will first be performed on raw data per specialty and weighted according to the real proportion of targeted HCPs in each country to accurately reflect the population the survey seeks to measure.

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Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, age, gender, type of practice and specialty) between respondent and non-respondent HCPs.

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5 AMENDMENTS AND UPDATES

DOCUMENT HISTORY

Number	Date	Section of study protocol	Amendment or update	Reason
02	24 February 2020	Refer to protocol amendment summary of changes	Amendment	Refer to protocol amendment summary of changes

AMENDED PROTOCOL 02 (24 FEBRUARY 2019)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. This is because the actual launch schedules and the utilization of SULIQUA in the European Union (EU) are different from the previous projections utilized for the clinical conduct and timelines of the previous version of the submitted study protocol.

OVERALL RATIONALE FOR THE AMENDMENT

The SULIQUA launches in EU have started in the second quarter of 2018, and only in a few countries (list provided in Table 2 of protocol). In some countries, e.g. Sweden and Finland, only one of the two available pre-filled pens have been launched. Therefore, in these countries there is no need to distribute the healthcare professional guide or the patient guide, which addresses the potential risk of medication errors due availability of two pens. SULIQUA has not yet been launched in some of the major EU countries such as France, Germany and Spain. In summary, in EU, the utilization of SULIQUA has been much lower than projected.

Considering the actual launch and utilization of SULIQUA, the MAH plans to amend the study protocol on conducting and reporting this survey according to the rational summarized in the table below, and in line with the following plan:

- Recruitment for Wave 1 started in September 2019
- No limit on the number of patients recruited per HCP i.e. all patients an HCP can recruit will be included in this study
- Questionnaire collection is extended to 6 months

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Section # and Name	Description of Change	Brief Rationale
PASS information	Updated the list of candidate countries 'Wave 1 - Czech Republic, Hungary, Slovenia Wave 2 - Belgium, Croatia, Romania, United Kingdom Wave 3 - Countries will be selected based on the product launch and market uptake and the possibility for conducting Wave 3 will be revisited in November 2020 and communicated to PRAC (Pharmacovigilance Risk Assessment Committee) during Wave 2 interim report submission'.	The change describes the candidate countries included in Wave 1 and Wave 2 of this study. Countries for Wave 3 will be selected based on the product launch and market uptake. Clarification related to an assessment on possibility for conducting Wave 3 is also added.
Responsible parties	Name and educational qualification updated.	The name and educational qualification of the statistician and name of project manager fieldwork are added for information.
Section 4: Abstract (Study design)	Removed 'the number of countries to be determined' and changed to 'Wave 1: Hungary, Czech Republic, Slovenia, Wave 2: Belgium, Croatia, Romania, United Kingdom, and Wave 3: countries will be selected based on the product launch and market uptake'.	To provide clarity about the countries included in each wave of the study.
	Added 'Croatia is at risk and Italy has been dropped from this study due to challenges related to ethics committee (EC) approvals Latvia was planned as a candidate country for Wave 1 but was dropped from the survey due to difficulties to setup the study'.	Reasons for risk in inclusion of Croatia in Wave 2 and dropping Italy and Latvia from the study are provided.
	Removed 'Each wave will last for approximately 7 months from HCP/patient enrolment to the submission of a report' and added 'The possibility for conducting Wave 3 will be revisited in November 2020 and communicated to Pharmacovigilance Risk Assessment Committee (PRAC) during Wave 2 interim report submission'.	Clarification related to possibility of conducting Wave 3.
	Changed tense of the sentences and added information that patient and HCP questionnaires are included in the protocol as Annex 2 and 3.	HCP and patient questionnaires are included as Annex 2 and 3 in the study protocol.
Section 4: Abstract (population [HCP enrollment])	Added HCPs practice information i.e. 'diabetologist, nurse, geriatrist'.	Clarification related to HCPs practice information i.e. the types of specialists who will be participating in the study.
Section 4: Abstract (population [patient enrollment])	Removed 'No more than 2 patients will be recruited for the survey by the same HCP' and added 'There will be no limit on the number of patients recruited per HCP'.	To increase the chances of reaching 450 patients, the limit on the number of patients recruited per HCP is removed i.e. all patients a HCP can recruit will be included in this study.

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Section # and Name	Description of Change	Brief Rationale
Section 4: Abstract (Variables)	Added HCPs practice information i.e. 'diabetologist, nurse, geriatrist'	Clarification related to HCPs practice information i.e. the types of specialists who will be participating in the study.
	The below mentioned information '1.Collected through HCP questionnaire: • Variables related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate' is changed to 1. Collected/estimated through HCP questionnaire: • Information related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate'	Change made in language for better clarity and understanding.
Section 4: Abstract (Variables)	Below mentioned two points were removed from the subheading 'Variables related to the HCPs knowledge about the prescribing conditions and safety information/warnings of SULIQUA' and added as separate bullet points: • Receipt of SULIQUA pre-filled pen guide for HCPs (yes/no) • Distribution to patients/caregivers of the guide for patient treated with SULIQUA (yes/no)	Changes made for better clarity and understanding.
Section 4: Abstract (Study size)	Removed 'Considering that about 80-90% of all questions will be provided with an answer, approximately 400-450 HCPs shall be surveyed in total, providing a sample of 150 HCPs per wave' and added 'It is estimated that at least 85% of the questionnaires completed by HCPs will be analysable. Therefore, approximately 450 HCPs shall be surveyed in total. An overall sample of 150 HCPs will be needed for each wave'.	Clarification related to HCP sample size in each wave.
	Removed 'We will apply the same rule to patients to be recruited, assuming a maximum uncertainty (50%), for a confidence interval of 95% and a precision of 8%, a total of 150 analysable questionnaires will be needed for the overall sample in each wave, for a total study sample of 450 analysable questionnaires' and added 'Applying the same rule to patients to be recruited, the required sample size would be 150 per wave for a precision level of 8%'.	Change made to be consistent with section 9.5.1

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Section # and Name	Description of Change	Brief Rationale
Section 5: Amendments and Updates	Removed the word "None" and section updated as per amendment instructions in the template i.e. document history, and rationale for amending the protocol updated.	The actual launch schedules and the utilization of SULIQUA in EU are very different from the projections that were used to prepare the last version of the study protocol, so that the initial plan is not achievable. Therefore, MAH plans to amend the study protocol on conducting and reporting this survey as summarized below: • Recruitment for Wave 1 was started in September 2019 • No limit on the number of patients recruited per HCP i.e. all patients a HCP can recruit will be included in this study • Questionnaire collection is extended to 6 months
Section 6: Milestones	All study milestones updated.	The original plan was to start recruitment in April 2019 and submit the final report to EMA by July 2020. Now, MAH has started the recruitment in September 2019 and plans to submit the final study report by June 2022. Questionnaire collection is extended to 6 months.
Section 9.1: Study design	Added HCPs practice information i.e. 'diabetologist, nurse, geriatrist'.	Clarification related to HCPs practice information i.e. the types of specialists who will be participating in the study.
Section 9.2: Setting	Table 2 (i.e. list of countries to be included in different waves of study) is updated. Additional column for Wave 3 is added indicating that countries are yet to be determined along with a footnote mentioning that the details on countries to be included in wave 3 will be updated if Wave 3 is deemed feasible at the time of Wave 2 report submission. Added 'Croatia is at risk and Italy has been dropped from this study due to challenges related to ethics committee (EC) approvals Latvia was planned as a candidate country for Wave 1 but was dropped from the survey due to difficulties to setup the study'. Added ' Wave 3 countries are yet to be determined, and for this the MAH will continue monitoring which additional countries can be added and provide an update on the sales data (product launch and market uptake) in the interim reports.'	To clarify which countries are included in each wave of study. Reasons for risk in inclusion of Croatia in Wave 2 and dropping Italy and Latvia from the study are provided. Clarification related to Wave 3 countries.

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Section # and Name	Description of Change	Brief Rationale
Section 9.2: Setting	Information related to inclusion of countries in all waves of study based on distribution of EM is updated, see below 'The first wave of survey includes the countries in which EM were distributed from the end of Q4 2017. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 1. The second wave of the survey will include countries in which EM were distributed from Q3 2018. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 2. If the sample size is difficult to reach, the countries in which EM were distributed in a following quarter, i.e. Q3-Q4 2019 but which were not included in Wave 1, will be included in Wave 2. The third wave of the survey will include countries in which EM will be distributed from Q3 2019. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 3. If the sample size is difficult to reach, the countries in which EM were distributed earlier will be included in Wave 3'.	Clarifying information related to inclusion of countries in all waves of study based on distribution of EM is updated i.e. time period when EM was distributed.
Section 9.2.1: Duration of the study	Timelines for start of first wave of study, submission of interim report of Wave 1 to EMA and the final study report to EMA is updated.	Clarification on planned timelines: the first wave of survey started in September 2019 and interim report for Wave 1 will be submitted to EMA in November 2020. The final study report is planned to be submitted to EMA in June 2022.
Section 9.2.4.2: Patient selection	Removed 'No more than 2 patients will be recruited for the survey by the same HCP' and added 'There will be no limit on the number of patients recruited per HCP'.	To increase the chances of reaching 450 patients, the limit on the number of patients recruited per HCP is removed i.e. all patients a HCP can recruit will be included in this study.

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Section # and Name	Description of Change	Brief Rationale
Section 9.3:	Added HCPs practice information i.e. 'diabetologist, nurse, geriatrist'. The below mentioned information '1.Collected through HCP questionnaire: • Variables related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate' is changed to 1. Collected/estimated through HCP questionnaire: • Information related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate' Below mentioned two points were removed from the subheading 'Variables related to the HCPs knowledge about the prescribing conditions and safety information/warnings of SULIQUA' and added as separate bullet points: • Receipt of SULIQUA pre-filled pen guide for HCPs (yes/no) • Distribution to patients/caregivers of the guide for patient treated with SULIQUA (yes/no)	Clarification related to HCPs practice information i.e. the types of specialists who will be participating in the study. Change made in language for better clarity and understanding. Changes made for better clarity and understanding.
Section 9.5.1: Determination of sample size (HCPs to be enroled)	Removed 'Considering that about 80-90% of all questions will be provided with an answer, approximately 400-450 HCPs shall be surveyed in total, providing a sample of 150 HCPs per wave'. Added 'It is estimated that at least 85% of the questionnaires completed by HCPs will be analysable. Therefore, approximately 450 HCPs shall be surveyed in total. An overall sample of 150 HCPs will be needed for each wave'.	Clarification related to HCP sample size in each wave.
Section 9.5.2: Sample distribution	Table 4 and 5 deleted.	Clarification to describe the distribution of the specialties and patients involved in the survey per country given as an example (not actual) is deleted.
Section 9.6.1 Data collection schedule	The change made described that data collection period in each wave will last for 6 months.	Clarification related to questionnaire collection, which is extended to 6 months.

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Section # and Name	Description of Change	Brief Rationale
Section 9.6.2: Approaches for increasing response rates	'Recruiting HCPs will be provided with 10 kits (while only 2 patients can be recruited by the same HCP)' is changed to 'Recruiting HCPs will be provided with 10 patient kits (as there is no limit on number of patients recruited by a HCP, a refill will be done at HCP's request)'.	The change is made as now there is no limit on the number of patients recruited per HCP.
Section 9.6.3.1 HCP questionnaire	The below mentioned text: 'HCPs practice information: • Duration of practice • Specialty • Type of setting • Number of patients treated with SULIQUA pre-filled pen Information related to the HCP knowledge about the prescribing conditions and safety information/warnings of SULIQUA data include: • HCP knowledge about SULIQUA pre-filled pen guide for HCPs • Awareness of the responsibility to provide each patient with the guide for patient treated with SULIQUA • Knowledge of the instructions for appropriate utilization of SULIQUA pre-filled pen. • Appropriate labelling of dose range and strength of SULIQUA pre-filled pen and dose steps to be administered in prescription • Education of the patient with regard to dose steps required, design, features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information' is changed to 'HCPs practice information: • Duration of practice (years working with diabetic patients) • Specialty (GP, endocrinologist/diabetologist, pharmacist, internist, gastroenterologist, nurse, geriatrist) • Type of setting (office based, hospital based, both, outpatient pharmacy, hospital pharmacy, diabetes care clinic)	Section 9.6.3.1 made consistent with section 4 abstract (variables) and section 9.3.

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Section # and Name	Description of Change	Brief Rationale
Section 9.6.3.1 HCP questionnaire	• Past experience with SULIQUA (number of patients treated with SULIQUA pre-filled pen) Information related to the HCP knowledge about the prescribing conditions and safety information/warnings of SULIQUA data include: • HCP knowledge about SULIQUA pre-filled pen guide for HCPs • Awareness of the responsibility to provide each patient with the guide for patient treated with SULIQUA • Knowledge of the instructions for appropriate utilization of SULIQUA pre-filled pen (dose titration, pen choice, storage, adverse reactions) • Appropriate labelling of dose range and strength of SULIQUA pre-filled pen and dose steps to be administered in prescription (yes/no) • Education of the patient with regard to dose steps required, design, features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information • Number of recorded medication errors since EM distribution'	
Section 9.6.3.2 Patient questionnaire	The below mentioned text '• Patients characteristics (age, gender, location) • Treating physician (specialty) • Patient knowledge about SULIQUA pre-filled pen guide for patient • Patient knowledge about SULIQUA pre-filled pen conditions of use' is changed to '• Patients characteristics (age, gender, length of SULIQUA treatment) • Treating physician (GP, endocrinologist/diabetologist, internist, gastroenterologist, geriatrist) • Patient knowledge about SULIQUA pre-filled pen guide for patient (yes/no) • Patient knowledge about SULIQUA pre-filled pen conditions of use (features and appropriate utilisation of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information)'	Section 9.6.3.2 made consistent with section 4 abstract (variables) and section 9.3.

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Section # and Name	Description of Change	Brief Rationale
Section 9.6.6: Logistic aspects	'For patient questionnaires, each recruiting physician will hand over a kit to up to 10 patients. Considering the return rate would be about 70%, this will allow the recruitment of not more than 2 patients per HCP.' is changed to 'For patient questionnaires, each recruiting HCP will hand over a patient kit. Refill of patient kits will be done at HCP's request'.	The change is made as there is no limit on the maximum number of patients recruited per HCP.
Section 9.7.1: Primary analysis (definition of success)	For HCP, success factor 2 and 3 are updated: '2. Proportion of HCPs sufficiently understanding the key messages, i.e. providing at least 75% of correct answers (Questions Q3-Q4, Q7 of HCP questionnaire; at least 11 correct answers out of 14 sub-questions). 3. Proportion of HCPs adequately implementing the EM, i.e. providing at least 75% of answers that are correct or consistent with appropriate use of the EM (Questions Q2a-b, Q5-Q6 of HCP questionnaire; at least 12 correct or consistent answers out of 15 sub-questions)." For patient, success factor 2 and 3 are updated: '2. Proportion of patients/caregivers sufficiently understanding the key message, i.e. providing at least 75% of correct answers (Questions Q3 and Q4 of Patient/Caregiver questionnaire; at least 8 correct answers out of 10 sub-questions). 3.Proportion of patients/caregivers adequately implementing the EM, i.e. providing at least 75% of correct or appropriate answers (Questions Q6 and Q7 of Patient/Caregiver questionnaire; at least 6 correct or appropriate answers out of 8 sub-questions).'	Success factors for HCPs and patients is updated.

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Section # and Name	Description of Change	Brief Rationale
Section 9.7.2: Secondary analysis	Definition of "Contacted HCP" updated.	To clarify that contacted HCPs will be those who have received the e-mail or have answered the phone call.
	Ratios for participation rates of HCPs are revised as given below: 'Contact rate = Number of contacted HCPs divided by the total number of targeted HCPs Response rate = Number of HCPs who agreed to participate (in the survey or in recruitment of patients) divided by the total number of invited HCPs Cooperation rate = Number of HCPs with submitted questionnaire divided by the total number of HCPs who agreed to participate Refusal rate = (Number of contacted HCPs minus the number of HCPs who agreed to participate) divided by the total number of contacted HCPs'	Clarification related to definition of ratios (contact rate, response rate, cooperation rate and refusal rate) for participation rates of HCPs.
	Removed 'The reasons for non-response will be sought, especially from all observed variables. This will ensure that missing data are reported with enough detail to strengthen the results validity, as recommended by the STROBE guidelines (6).'	
Section 10.3.2 Ethics and Regulatory Considerations	Added 'Croatia is at risk due to challenges in ethics committee approvals. For Italy, as EC consultations provided conflicting advice on the study classification, it was advised that Italian Drug Agency's (AIFA) decision would supersede the EC consultations. AIFA decided that this study was 'observational', but no further details or definition had been given about its classification and, classification would determine the type of EC submissions required. In addition, AIFA asked for notification or submission but, in Italy there is no mechanism for a non-interventional study notification to EC. Furthermore, AIFA did not provide clear instructions on the submission. Due to these challenges Italy was dropped from this study. Latvia was dropped from the survey due to difficulties to setup the study.'	Reasons in detail for risk in inclusion of Croatia in Wave 2 and dropping Italy and Latvia from the study are provided.
Section 11.2: Safety observations	"NA" changed to "Not applicable"	Minor consistency change.

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Section # and Name	Description of Change	Brief Rationale
All sections in protocol	Few grammatical and consistency changes done. Capitalized "Suliqua" (brand name) to SULIQUA for consistency.	Minor consistency changes.
Section 13 (References)	Reference numbers updated.	Changes made for more clarity and understanding.
Annexes	Annex 1, 2 and 3 updated.	HCP and patient questionnaire are added. ENCePP checklist revised.

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6 MILESTONES

Milestone	Planned date
Start of data collection wave 1	01 September 2019
End of data collection wave 1	30 May 2020
Interim report 1	31 October 2020
Submission Interim report 1	30 November 2020
Start of data collection wave 2	01 January 2020
End of data collection wave 2	31 July 2020
Interim report 2	31January 2021
Submission Interim report 2	28 February 2021
Start of data collection wave 3	01 June 2021
End of data collection wave 3	31 December 2021
Final report of study results	01 April 2022
Submission final report	30 June 2022

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7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

SULIQUA is a fixed-ratio combination of insulin glargine, a basal insulin analogue, and lixisenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist. Insulin glargine binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin. Lixisenatide acts via enhancing glucose-dependent insulin secretion, reducing glucagon release and decreasing gastric emptying.

SULIQUA is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.

SULIQUA is available in two pens, providing different dosing options, i.e. SULIQUA (10-40) pen, SULIQUA (30-60) pen respectively. The differentiation between the pen strengths is based on the dose range of the pen.

7.2 RATIONALE

The European Commission granted a marketing authorisation valid throughout the European Union (EU) for SULIQUA in January 2017 (1). In the risk management plan (RMP) assessment report by the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (EMA-PRAC), dated 7 July 2016, the Marketing Authorization Holder (MAH) was requested to submit key safety messages for inclusion in a healthcare professional guide (Annex 4) and a patient guide (Annex 5), to address the potential risk of medication errors occurring at the prescribing, dispensing and patient level.

The educational materials (EM) were aimed at increasing awareness about the two available strengths of the product and at minimising the risk of medication errors including mix-ups between the different strengths of the product.

To measure the effectiveness of the EM, the Sanofi-Aventis Group was requested to conduct a prescriber/dispenser/patient survey as part of the RMP for SULIQUA in the EU.

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8 RESEARCH QUESTION AND OBJECTIVES

The research questions for this study is: Were the key safety messages in the healthcare professional guide and the patient guide, implemented as risk minimisation measures (RMM) beyond routine, effective in:

- Providing a good knowledge and understanding to health care professionals (HCPs) who prescribed or dispensed SULIQUA and to patients treated with SULIQUA
- Reducing the risk of medication errors when prescribing/delivering or using SULIQUA

The main objective of this study is to assess the knowledge and understanding of the key safety messages in the healthcare professional guide and patient guide among HCPs who prescribed or dispensed SULIQUA and patients treated with SULIQUA, respectively.

Specific objectives are to assess the proportion of:

- HCPs:
  - Who receive, understand and implement the safety messages conveyed by EM for SULIQUA
  - Who are aware that prescriptions for SULIQUA should state clearly the dose range and strength of SULIQUA in a pre-filled pen and the number of dose steps to be administered by the patient
  - Who advise patients with regard to dose steps required, design, features and appropriate utilization of SULIQUA pre-filled pen, close monitoring of blood sugar levels after initiation, and anticipated adverse reactions
  - Who noted medication errors in treated patients
- Patients/caregivers
  - Who acknowledge receiving SULIQUA pre-filled pen guide for patients and caregivers
  - Who read the patient guide before using SULIQUA pre-filled pen
  - Who implemented the safe utilisation of SULIQUA according to safety information for the SULIQUA pre-filled pen
  - Who were trained/advised by their HCP (physician or pharmacist) on how to use SULIQUA pre-filled pen

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9 RESEARCH METHODS

9.1 STUDY DESIGN

This survey will be cross-sectional, multinational, multichannel and conducted among HCPs as well as patients/caregivers in 3 waves.

There will be two questionnaires, one designed for the HCPs and another designed for patients/caregivers. These questionnaires include the following sections:

Table 1: Sections of HCP's and patient's questionnaires

HCP Questionnaire	Patient/Caregiver Questionnaire
Screening section (items S1-S3)	Screening section (items S1-S2)
HCP practice information (items D1-D3)	Questionnaire (items S3-S6, Q1-Q7)
Prescribing/delivery conditions and safety information (items Q1-Q10)	

The survey will be conducted primarily through a web questionnaire. Paper questionnaires will be additionally proposed to patients and phone questionnaires to HCPs who would not be able to answer the survey online.

In each country, HCPs will be identified according to their specialty (general practitioners [GP], endocrinologist/diabetologist, internists, gastroenterologists, pharmacists, nurse, geriatrists) as specified in OneKey lists (IQVIA). OneKey is the most comprehensive worldwide database of HCPs. It is constructed according to ISO 9001: 2015 Quality Management Systems Requirements. The lists are representative of the HCPs population in the selected countries.

For patients recruitment, HCPs to be contacted will be randomly selected according to the procedure described in the sampling plan section (Section 9.2.4). They will be sent patient kits for distribution to the patients.

9.2 SETTING

The survey will be conducted in selected European countries in 3 waves. Each wave will correspond to the sequential inclusion of the targeted countries according to the timing of SULIQUA launch and implementation of RMM in these countries. Furthermore, the selection of countries to be involved in each wave of the survey will take into account the following criteria:

- Where SULIQUA has been registered and both pens were marketed for at least 6 months at the start of the survey (Table 2)
- Where the HCPs have been targeted for the EM and direct healthcare professional communication (DHPC) at the start of the survey
- where SULIQUA availability and market penetration is sufficiently high to allow HCPs participation

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The MAH will therefore take into account the predicted market uptake to preselect the countries and will ensure that the study will be performed in countries where SULIQUA (both pens) is available and accessible to patients. The exact list of participating countries is currently being refined.

Table 2, below, shows the provisional timetable for commercial launch of SULIQUA in selected European countries. Dates are projections and may be subject to change during the course of the study. The list of countries participating in each wave will be finalized before each wave starts according to the effective launch date.

Table 2: List of candidate countries to be included in the successive waves according to SULIQUA provisional dates when both pens were made available to patients in EU (source Sanofi-Aventis Group)

Country	Available to patients (both pens)	Wave		
		1	2	3*
Hungary	09 October 2017	X	-	
Czech Republic	02 May 2018	X	-	
Slovenia	01 June 2018	X	-	To be determined
Romania	05 June 2018 (peach pen) 23 April 2019 (olive pen)	-	X	
Croatia	Q3 2019	-	X	
Belgium	01 November 2018	-	X	
United Kingdom	10 May 2019 (olive) 17 May 2019 (peach)	-	X	

X refers to candidate to be included in the present wave
*The details on countries will be updated if Wave 3 is deemed feasible at the time of Wave 2 report submission.

Essentially, countries selected will be different from one wave to the next wave based on the actual market penetration and product availability to patients. Croatia is at risk and Italy has been dropped from this study due to challenges related to the ethics committee (EC) approvals. Latvia was planned as a candidate country for Wave 1 but was dropped from the survey due to difficulties to setup the study. Wave 3 countries are yet to be determined, and for this the MAH will continue monitoring which additional countries can be added and provide an update on the sales data (i.e. product launch and market uptake) in the interim reports.

The first wave of survey includes the countries in which EM were distributed from the end of Q4 2017. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 1.

The second wave of the survey will include countries in which EM were distributed from Q3 2018. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 2. If the sample size is difficult to reach, the countries in which EM were distributed in a following quarter, i.e. Q3-Q4 2019 but which were not included in Wave 1, will be included in Wave 2.

The third wave of the survey will include countries in which EM will be distributed from Q3 2019. A total of 150 HCPs and 150 patients/caregivers will be included in Wave 3. If the sample size is difficult to reach, the countries in which EM were distributed earlier will be included in Wave 3.

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9.2.1 Duration of the study

The Wave 1 of the survey started in September 2019. The interim study report of Wave 1 will be submitted to EMA in November 2020. The final report of results of this study is planned to be submitted in June 2022 to EMA.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

The HCP survey will be conducted among HCPs meeting the following inclusion criteria:

- HCPs who prescribe/deliver SULIQUA

The patient survey will be conducted among patients (or their caregivers) meeting the following inclusion criteria:

- Respondents (patients or caregivers of a patient) who receive SULIQUA

9.2.2.2 Exclusion criteria

HCP survey

The following exclusion criteria will be checked at the beginning of the web questionnaire:

- HCPs who are not involved in patient treatment
- HCPs who may have conflicts of interest with the survey (i.e. HCPs employed by regulatory bodies, pharmaceutical industries)
- HCPs who have participated in the previous waves of the survey
- HCPs who have already 2 or more colleagues participating in the survey from the same practice in the same wave

Patient survey

The following exclusion criteria will be checked at the beginning of the web questionnaire:

- Patients (or caregivers) who may have conflicts of interest with the survey
- Patients (or caregivers) who have participated in the previous waves of the survey

9.2.3 Analysis population(s)

Analysable questionnaires are those submitted by the participant on the web, completed by phone or received by postal mail anonymously, and which do not have “I don’t know” as the answer to all questions. If the questionnaire is just filled on the web but not submitted, the questionnaire will be destroyed and will not be analysed.

9.2.4 Modalities of recruitment

9.2.4.1 HCP selection

HCPs will be identified from OneKey lists. A random stratified sampling method will be applied. As a first step, all lists will be merged, and then the eligible HCPs will be divided into homogeneous

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groups, called strata, which are mutually exclusive (an HCP can only belong to one stratum). This stratification will be based on the following criteria:

Number of strata formed = number of countries * number of specialties

In order to fill-in each stratum of the sample survey from the IQVIA OneKey reference files, an independent sample will be selected per stratum through a simple random sampling without replacement.

In each specific stratum, HCPs will be contacted according to the order of draw in this stratum. If an HCP does not want to participate in the survey, the next one in order of draw will be contacted, and so on until the required number of HCPs is met. If the target for a stratum is not achieved after the end of the initial list, an additional randomly sampled list will be prepared, and the HCPs contacted until the goal is reached or no names are left in that stratum. If the complete list of the IQVIA OneKey reference files has been exhausted in any particular stratum, a strategy will be determined to adjust the sample size within stratum with associated weighting.

In web surveys, the number of HCPs to be contacted for reaching the required number of HCPs with analysable questionnaires is usually around ten times more than the expected final number.

9.2.4.2 Patient selection

Only HCPs (physicians) prescribing SULIQUA will be involved in patient recruitment. An invitation letter to participate in the study will be randomly given to patients treated with SULIQUA at physician offices. As in the case of HCPs, a patient can only participate in one wave of the survey. There will be no limit on the number of patients recruited per HCP. Patients' data will be anonymous when presented to the MAH.

The prescription of therapies is the sole responsibility of the patient's physician.

The patients who will be enrolled in the study, will be selected among the patients for whom the physician has decided to prescribe SULIQUA independently from study entry.

9.3 VARIABLES

Variables analysed will include:

9.3.1 Collected/estimated through the HCP questionnaire

- Information related to HCPs/patients participation: contact rate, response rate, cooperation rate, and refusal rate (section 9.7)

- Variables related to HCPs practice information:
  - Duration of practice (year working with diabetic patients)
  - Specialty (GP, endocrinologist/diabetologist, pharmacist, internist, gastroenterologist, nurse, geriatrist)
  - Type of setting (office based, hospital based, both, outpatient pharmacy, hospital pharmacy, diabetes care clinic)

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    - Past experience with SULIQUA (number of patients treated with SULIQUA pre-filled pen)
- Variables related to the HCPs knowledge about the prescribing conditions and safety information/warnings of SULIQUA data include:
    - HCP knowledge about SULIQUA pre-filled pen guide for HCPs
    - Awareness of the responsibility to provide each patient with the guide for patient treated with SULIQUA
    - Knowledge of the instructions for appropriate utilization of SULIQUA pre-filled pen (dose titration, pen choice, storage, adverse reactions e)
    - Appropriate labelling of dose range and strength of SULIQUA pre-filled pen and dose steps to be administered in prescription (yes/no)
    - Education/Advice of the patient with regard to dose steps required, design features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information
    - Number of recorded medication errors since EM distribution
- Receipt of SULIQUA pre-filled pen guide for HCPs (yes/no)
- Distribution to patients/caregivers of the guide for patient treated with SULIQUA (yes/no)

9.3.2 Variables collected through the patient questionnaire

Patient related variables include:

- Patients characteristics (age, gender, length of SULIQUA treatment)
- Treating physician (GP, endocrinologist/diabetologist, internist, gastroenterologist, geriatrist)
- Patient knowledge about SULIQUA pre-filled pen guide for patient (yes/no)
- Patient knowledge about SULIQUA pre-filled pen conditions of use (features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information)

9.4 DATA SOURCES

The survey is a primary data collection conducted through two questionnaires administered by web, phone or paper:

- A HCP questionnaire (administered by web or phone)
- A patient questionnaire (administered by web or paper)

HCPs will be identified from OneKey lists (IQVIA).

The HCP questionnaire was developed and tested among 6 HCPs for its comprehensibility, consistency and the appropriateness of medical terms. HCPs' comments were implemented in the final version. Likewise, a patient/caregiver questionnaire was tested among 6 non-HCPs for optimal readability by patients.

The translated versions of the questionnaire from English into local languages was done using the back and forth method (from English into local language and then from local language back into English) to ensure an accurate translation.

The HCP and patient questionnaire completion is estimated to take about 15-20 minutes.

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9.5 STUDY SIZE

9.5.1 Determination of sample size

The sample size formula based on the normal approximation to the binomial is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half the desired width of the confidence interval (CI), and $Z_{1-\alpha/2}$ is the standard normal Z value corresponding to a cumulative probability of 1– α/2. The following table provides the sample size for a margin error for 95% CI based on various half-widths and proportions of interest (Table 3).

Table 3: Sample size obtained for various precisions and various proportions

	Margin of error for 95% CI				
Proportion	**8%**	**5%**	**4%**	**3%**	**2%**
10%	55	139	216	384	864
30%	127	323	504	896	2017
50%	**150**	**384**	600	1067	2401
70%	127	323	504	896	2017
90%	55	139	216	384	864

The proportions of interest (p) are the proportions mentioned under specific objectives above. As p is not known in advance, we consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative i.e. the largest sample size for a specified margin of error.

HCPs to be enroled:

According to the above sampling formula, the required sample size for the study would be 384 for a precision level of 5%. This sample will be divided into 3 waves, each comprising 128 HCPs and providing a precision of 8.66% for each wave based on the same formula. It is estimated that at least 85% of the questionnaires completed by HCPs will be analysable. Therefore, approximately 450 HCPs shall be surveyed in total. An overall sample of 150 HCPs will be needed for each wave.

Patients to be enrolled:

Applying the same rule, the required sample size would be 150 per wave for a precision level of 8%.

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9.5.2 Sample distribution

Total sample of HCPs

A total sample of 450 HCPs is to be recruited for this study.

For the conduct of the survey, ideally the sample of 450 HCPs should be proportionally split between the selected countries based on the number of HCPs in each country. However, due to large variance of the number of HCPs in targeted countries such a distribution would yield to a number of participants in smaller countries and/or in specialties (such as endocrinologists) too small to allow the applicability of common statistical methods.

A pragmatic split will therefore be implemented in each wave to allocate a sufficient sub-sample size to the less represented countries based on the countries included in each wave of the survey.

To be representative, such a sample will necessitate that the results of the study be weighted back according to the real proportion of HCPs from IQVIA reference lists.

Total sample of patients

A total sample of 450 patients is to be recruited in the study.

With a similar line of reasoning as above, a pragmatic split will be implemented in each wave to allocate a sufficient sub-sample size to the less represented countries.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

The data collection period will last for 6 months in each wave.

As the EM might not have been approved in each of the participating countries at the same time, the EM will be disseminated at different time periods in each country. Consequently, in the same wave the field work will be conducted at different time periods in each country. Whenever possible, the countries will be grouped, but effort will be made to conduct the survey between 6 and 12 months after the dissemination of the EM in each country.

The survey will be conducted by IQVIA Primary Intelligence, a division of IQVIA specialised in the conduct of phone and web surveys for more than 20 years. IQVIA Primary Intelligence will create a web-based instance survey. The lists of HCPs will be loaded into separate databases for the management of the survey. HCPs' answers/data will be collected through a web questionnaire. The survey will collect data in an anonymous manner.

HCPs will be randomly contacted, mainly by e-mails, and according to their stratum by the IQVIA Primary Intelligence team. Their recruitment will be done as follows:

- HCPs will be invited to participate in the survey (via e-mails, letters or phone calls). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the HCPs at this step. The MAH will ensure that the compensation is in line with relevant guidelines of each country and that is only constitutes a compensation of the actual effort and time that is needed to fill-in the questionnaire.

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- If they agree to participate in the survey, they will receive a link to access the survey and the instructions for the web questionnaire completion.
- HCPs can also choose to participate in the survey by phone. In this case, an appointment for a phone interview will be scheduled with them.
- If the questionnaire is not completed and sent to IQVIA Primary Intelligence, the HCPs will be sent a reminder by e-mail one week after the start of the survey.
- If the target is not achieved in the stratum, a reminder by phone will be conducted 1.5 week after the start of the survey.
- If the questionnaire has been started but is still not completed and sent to IQVIA Primary Intelligence, the HCPs will be sent a last reminder by e-mail 2 weeks after the start of the survey.

If necessary, i.e. if the minimum number of needed responders is still not reached, the recruitment will be continued by phone to achieve the target in a specific stratum.

An HCP will be considered as contacted if he/she has:

- Answered the web questionnaire and sent it back to IQVIA Primary Intelligence
- Refused to participate,
- Been tentatively reached at least 3 times and up to 5 times.

An HCP will be considered as unreachable if he/she has been contacted between 3 and 5 times without any answer.

For each HCP of the sample, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. Recruitment in each stratum will be stopped when the target is reached. If the files have been exhausted in any particular stratum, recruitment in this stratum will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

9.6.2 Approaches for increasing response rates

People are increasingly contacted to participate in web or phone surveys. The overall response rate of participation remains low according to international studies (2) (3) (4). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (4). Van Geest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (5). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician response rates while non-monetary incentives were much less effective. These measures include the use of a short questionnaire, and questionnaires personalised, and approved by professional associations.

In order to increase the response rate among HCPs, three actions will be applied to this survey:

- A compensation fee will be proposed to HCPs for their participation in the survey
- All HCPs will be sent an e-mail or contacted by experienced operators of IQVIA Primary Intelligence with extensive experience in conducting health related surveys
- Each HCP will be emailed or called up to 3-5 times before being considered as “not reachable”, and reminders will be sent by email if IQVIA Primary Intelligence does not receive the web questionnaire

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For increasing the response rate among the patients:

- The survey will be explained clearly through the HCPs, and the documentation will also clearly explain the importance of the patients' participation
- It will be ensured that patients participate anonymously in the survey
- Patients will be given the option to take the survey by paper or web questionnaire
- Recruiting HCPs will be provided with 10 patient kits (as there is no limit on number of patients recruited by a HCP, a refill will be done at HCP's request)
- No monetary or material incentives will be provided to patients, but a compensation fee will be proposed to HCPs for each patient participating in the survey
- The response rate will be monitored throughout the data collection period. If at the end of the inclusion period, the number of participants is insufficient, the inclusion period will be extended. Reminder notices and additional kits will be sent to HCPs who have been invited to participate, but not yet recruited any patients.

9.6.3 Data collected

9.6.3.1 HCP questionnaire

HCPs practice information:

- Duration of practice (years working with diabetic patients)
- Specialty (GP, endocrinologist/diabetologist, pharmacist, internist, gastroenterologist, nurse, geriatrist)
- Type of setting (office based, hospital based, both, outpatient pharmacy, hospital pharmacy, diabetes care clinic)
- Past experience with SULIQUA (number of patients treated with SULIQUA pre-filled pen)

Information related to the HCP knowledge about the prescribing conditions and safety information/warnings of SULIQUA data include:

- HCP knowledge about SULIQUA pre-filled pen guide for HCPs
- Awareness of the responsibility to provide each patient with the guide for patient treated with SULIQUA
- Knowledge of the instructions for appropriate utilization of SULIQUA pre-filled pen (dose titration, pen choice, storage, adverse reactions)
- Appropriate labelling of dose range and strength of SULIQUA pre-filled pen and dose steps to be administered in prescription (yes/no)
- Education of the patient with regard to dose steps required, design, features and appropriate utilization of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information
- Number of recorded medication errors since EM distribution

9.6.3.2 Patient questionnaire

- Patients characteristics (age, gender, length of SULIQUA treatment)
- Treating physician (GP, endocrinologist/diabetologist, internist, gastroenterologist, geriatrist)
- Patient knowledge about SULIQUA pre-filled pen guide for patient (yes/no)

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- Patient knowledge about SULIQUA pre-filled pen conditions of use (features and appropriate utilisation of SULIQUA pre-filled pen, close blood sugar levels monitoring after initiation, safety information)

9.6.4 Site/Investigators questionnaire

Not applicable

9.6.5 Patient data

Not applicable

9.6.6 Logistic aspects

For patient questionnaires, each recruiting HCP will hand over a patient kit. Refill of patient kits will be done at HCP's request. In the kit, the patient will find the survey questionnaire with a prepaid envelope for sending the survey back to IQVIA. It will also include a simplified guide for taking the survey online according to the patient's personal choice.

The patient questionnaire completion is estimated to take 15-20 minutes.

9.7 DATA ANALYSIS

The statistical analyses will be described and further detailed into a Statistical Analysis Plan (SAP). The described analysis below might be revised, and adjustments might occur. The final SAP version will include (empty) table shells to be populated for the clinical study report (CSR).

General considerations:

The statistical analysis will be conducted using the SAS® software V9.4 on Windows™ (SAS Institute, North Carolina, US).

Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, median, Q1, Q3, minimum and maximum. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals of 95% will be evaluated, when relevant. The number of missing data will be indicated. Since, missing values are expected to be few and distributed at random, no replacement or imputation will be performed. Missing values will not be considered in the denominators for proportions.

For HCP questionnaire measures, results will be stratified by country and physician's specialty. For patient questionnaire measures, results will be stratified by country and treating physician's specialty. In tables "Overall - unweighted" columns and lines will show the results observed on the sample while "Overall weighted" columns and rows will show the results weighted according to the distribution of HCPs in the general population by country and specialty, respectively.

Two interim and 1 final analysis corresponding to 3 waves of survey will be performed according to timelines (Section 6) in selected European countries.

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9.7.1 Primary analysis

Distribution of all possible answers

As some questions may have multiple choices or be opened fields, the proportion of HCPs/patients having provided each possible answer will be described (Table 4).

Table 4: Mock table: Distribution of HCPs/patients answers to Question XX by country and physician specialty

Speciality	Answer	Country			Overall unweighted n(%)	Overall weighted * %
		Country 1 (N=XX)	Country 2 (N=XX)	…		
GP (N=XX)	**Answer 1**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	Answer 2	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	…	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	Missing	xx	xx	xx	xx	-
Endocrinologist (N=XX)	**…**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
Internist (N=XX)	**…**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
Gastroenterologist (N=XX)	**…**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
Other (N=XX)	**…**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
Overall unweighted (N=XX)	**Answer 1**	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	Answer 2	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	…	xx (xx.xx)	xx (xx xx)	xx (xx xx)	xx (xx xx)	xx xx
	Missing	xx	xx	xx	xx	-
Overall weighted	**Answer 1**	xx xx	xx xx	xx xx	xx xx	xx xx
	Answer 2	xx xx	xx xx	xx xx	xx xx	xx xx
	…	xx xx	xx xx	xx xx	xx xx	xx xx

* According to the distribution of HCPs in the general population by country and specialty, respectively.
Note: This template might be modified, final table shells will be presented in the statistical analysis plan (SAP).

Definition of success

Three success factors for professionals treating patients with SULIQUA will be defined:

1. Proportion of HCPs receiving the EMs (Question Q1 of HCP questionnaire).

2. Proportion of HCPs sufficiently understanding the key messages, i.e. providing at least 75% of correct answers (Questions Q3-Q4, Q7 of HCP questionnaire; at least 11 correct or consistent answers out of 14 sub-questions).

3. Proportion of HCPs adequately implementing the EMs, i.e. providing at least 75% of answers that are correct or consistent with appropriate use of the EMs (Questions Q2a-b, Q5-Q6 of HCP questionnaire; at least 12 correct or consistent answers out of 15 sub-questions).

Three success factors for patients/caregivers will be as follows:

1. Proportion of patients/caregivers receiving the EM (Question Q5 of Patient/Caregiver questionnaire).

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2. Proportion of patients/caregivers sufficiently understanding the key message, i.e. providing at least 75% of correct answers (Questions Q3 and Q4 of Patient/Caregiver questionnaire; at least 8 correct answers out of 10 sub-questions).

3. Proportion of patients/caregivers adequately implementing the EM, i.e. providing at least 75% of correct or appropriate answers (Questions Q6 and Q7 of Patient/Caregiver questionnaire; at least 6 correct or appropriate answers out of 8 sub-questions).

In order to allow better decision making on the eventual subsequent actions, the success rates will be evaluated separately for HCPs and patients/caregivers. The RMM will be deemed as effective based on the following definitions:

- For HCPs: if at least 2 of the 3 pertaining proportions above are equal to or above 80%
- For patients/caregivers: if at least 2 of the 3 pertaining proportions above are equal to or above 80%

Profile of HCPs with incorrect answers

The profile of HCPs with incorrect answers to the questions related to the 3 success factors will be described using all available and relevant HCPs characteristics collected in the survey (country, specialty, duration of practice, type of setting) and past experience with SULIQUA.

Profile of patients with inappropriate answers

The profile of patients with inappropriate answers to the questions related to the 3 success factors will be described using all available and relevant HCPs characteristics collected in the survey (country, treating physician's specialty, gender, age, location).

9.7.2 Secondary analysis

Analysis of Participation rate

The following cases of total response and non-response will be identified and described for HCPs:

- Targeted HCPs: HCPs reached to whom an e-mail or e-mail has been sent or have been called
- Contacted HCPs: HCPs who have received the e-mail or have answered the phone call.
- HCPs who agreed to participate: HCPs willing to participate in the survey (e.g. by phone or by clicking on the link provided in the recruitment e-mail) or in the patient's recruitment
- HCPs with submitted questionnaire: HCPs who actually answered the questionnaire through the end and submitted it. (One or some missing answers are allowed across the questionnaire.)
- HCPs who recruited patients: HCPs with at least 1 patient having actually answered the questionnaire and submitted it by paper or web

For patients/caregivers, more simplified definitions will be calculated based on the following definitions:

- Contacted patients/caregivers: those who have been asked by HCPs to participate
- Patients/caregivers who agreed to participate: those who accepted the questionnaire
- Patients/caregivers with submitted questionnaire: those who actually answered the questionnaire and submitted it by paper or web

The participation rates of HCPs will be examined via the following ratios:

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- Contact rate = Number of contacted HCPs divided by the total number of targeted HCPs
- Response rate = Number of HCPs who agreed to participate (in the survey or in recruitment of patients) divided by the total number of invited HCPs
- Cooperation rate = Number of HCPs with submitted questionnaire divided by the total number of HCPs who agreed to participate
- Refusal rate = (Number of contacted HCPs minus the number of HCPs who agreed to participate) divided by the total number of contacted HCPs

The participation rates will be presented by country and specialty.

The screening log which includes the HCPs' characteristics will enable to compare the participating and non-participating HCPs' profile to check if there is a selection bias.

Effect of EMs variations among targeted countries on success factors:

There could be variations between country affiliates of the MAH regarding the communication plan for EMs, including the route of distribution, target audience and layout or content of EMs as approved by national competent authorities. In order to take into account variations between member states concerning HCP specialties targeted, distribution routes and potential local adaptation to EMs, the success of EMs will be presented by country, distribution routes, version changes and HCPs targeted."

Analysis of the differences between paper or web responding patients:

Differences in demographic characteristics, participation rate, completeness of reported data and success factors, between the paper and web respondents will be described.

9.7.3 Interim analysis

Two interim and 1 final analysis corresponding to 3 waves of survey will be performed (Section 6).

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at IQVIA level

Data will be collected using a web or paper questionnaire.

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

For web version of the questionnaires, data will be collected using an electronic data capture system developed following a full validation process. A rigorous System Development Life Cycle (SDLC) is used for validation that complies with internal IT SOPs of Primary Intelligence (IQVIA). 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 management-related applications. The internet-based repository will be used to store survey data and, other relevant program information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimise positional bias. Programming will be reviewed by quality control and simulated users (User Testing) prior to implementation.

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For the paper questionnaire, respondents will be asked to complete questionnaire thoroughly with a ball-point pen and will be informed that responses modified (deletion, overprint) by participants will be considered as missing. Questions will be ordered in a way that no response to one question is available later in the questionnaire. The questionnaire will use multiple visual elements together to improve skip pattern compliance.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by the merging of databases of each country. HCP identifying information will be stored separately from survey data.
Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non admissible values
- Cross-check the consistency of data for related variables (if feasible)

The study database will be locked once validated.

9.8.2 Data quality control at site level

Not applicable

9.8.3 Approaches for validating the questionnaires

Both the HCPs and patient questionnaires will be user tested for their comprehensibility, consistency and the appropriateness of terms used (Section 9.4). The questionnaires will be translated from English into local language using the back and forth method to ensure an accurate translation of the local versions of the questionnaire will be validated by the MAH. Translation and back translation will be performed by IQVIA Primary Intelligence personnel.

9.8.4 Approaches for validating the results

The quality control for validating the results will be conducted at 5 levels:

1. At IQVIA Primary Intelligence management level, every effort will be undertaken to collect complete and validate data:
    - Verification of the reliability and security of the web questionnaire interface by a qualified web-master for each country
    - Validation of the quality of data entry for a random sample of $\sqrt{n+1}$ of the total paper questionnaires will be performed by a qualified data manager according to a Data Validation Plan
    - Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web questionnaire, real-time checks of the answers provided by the respondents will be developed. Non admissible answers (i.e. incorrect or unusual values, outlying values) will be detected and queries sent to the HCP
2. At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond the data management process):
    - Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage,

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- Identification and count of non-analysable questionnaires
- Estimation of the percentage of non-submitted questionnaires

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. Once the data is validated and quality checked, the database will be locked.

3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented and quality checked. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data, in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions.

The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the survey results and report will be conducted by a person who was not in charge of their preparation.

9.8.5 Safeguards, security and traceability of contacts

Operators of the call centre specialised in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The e-mails contacts and phone calls will be traced using the management software. All survey aspects from protocol development to the reporting of the results will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions. These SOPs can be consulted on site (6).

9.9 LIMITATIONS OF THE RESEARCH METHODS

1. Selection bias

   The potential for selection bias of HCPs participating in a survey is an inherent bias/limitation to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of HCPs (country, specialty, and the other available characteristics present in the screening log) will be compared between participants and non-participants.

   There is also a potential selection bias related to patient participation in the survey. The patient selection is susceptible to cluster sampling bias. In addition, if a bias occurs in the selection of HCPs, the sample of patients will be skewed. Because the characteristics of the general SULIQUA patient population are not available, it is impossible to compare patients surveyed in the study to those general SULIQUA patients.

2. Limits inherent to web surveys

   In such surveys, the generalisation and external validity of the results is restricted to HCPs who have an active e-mail address and are willing (and able) to answer a questionnaire online. These HCPs may not be fully representative of the whole targeted population (7) (8).

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Among non-response bias, targeted HCPs may also have activated filters in their mail box in order to block spams and unsolicited e-mails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple e-mail addresses could also be a critical situation. If the one used is not the primary address or if the HCPs do not check their e-mail box frequently, they will not receive the invitation during the recruitment period. Some HCPs who were sent a letter may not have received it. To overcome these potential limitations, HCPs will also be contacted by phone.

3. Limits inherent to paper questionnaires

Patient-reported outcomes are in general equivalent for both paper- and computer-collected questionnaires (9). However, data record and entry errors may occur when paper questionnaires are used. Such errors can be avoided when an electronic device is used for data collection (10). In this study, the paper-based option is provided because previous reports indicate that patients may prefer paper questionnaires (11).

9.10 OTHER ASPECTS

Strengths of the research methods:

1. The information contained in the file of each country is updated constantly with proactive updates. Quality controls are implemented on a regular basis.
2. The sampling of HCPs follows a stratified randomized method which guarantees the representativeness of the contacted population in order to limit selection bias due to voluntary participation. Batches of HCPs will be contacted up to five times before moving forward to other HCPs in the lists.
3. The questionnaires include general questions followed by specific ones in order to limit a learning process during the survey. As the HCPs may understand the right answer in subsequent questions, it will not be possible to go back in the questionnaire and edit answers in former questions.
4. The questionnaires are tested for clarity. It is also checked whether there are questions which would suggest a specific answer for any reason e.g. social desirability. The translations of the questionnaires are tested before implementation.
5. The study is conducted by an experienced team specialised in the design and conduct in such survey in safety area. The study follows IQVIA SOPs as well as the methodological guidelines from European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and EMA GVP.

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10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE INVESTIGATOR /HEALTH CARE PROVIDERS

The Investigator/Health Care Provider will perform the study in accordance with this protocol, local regulations and international guidelines applicable to the conduct of Healthcare Market Research (HMR) including professional codes of conduct.

10.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH representative is responsible for:

- Ensuring compliance with local and international applicable guidelines and regulations
- Ensuring compliance with Data Protection requirements including General Data Protection Regulation (GDPR) compliance; collection and maintenance of the survey data
- Analysis of the survey data
- Providing deliverables to the Sanofi-Aventis Group

10.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

HMR does not require clinical research ethics committee or independent review board approval (IRB). Although the study is a post-authorization safety study, it is not designed and conducted as a Non-Interventional Study. This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

10.3.1 Laws and regulations

The study is post-authorization safety study (PASS) category III which aims to evaluate RMM implemented as part of the product RMP. The study will be conducted in accordance with the Good Pharmacovigilance Practices (GVP), more specifically with Module XVI (*Risk minimization measures: selection of tools and effectiveness indicator*) ad Module VIII (*Post-Authorization Safety Studies*).

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (12). Given the study is a HMR, the MAH will also comply with the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines (13) as well as the charter from Association of Opinion and Behaviour in Health Field Research Companies (ASOCS). Finally, the study will be conducted in accordance with the National codes of EFPIA Member Associations.

10.3.2 Ethics and Regulatory considerations

Although HMR does not require IRB/IEC approval as per EphMRA code of conduct, IQVIA on behalf of the MAH, will be responsible for any submission to local EC/IRB if requested by the participating site (e.g. hospital direction or HCP).

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Croatia is at risk due to challenges in ethics committee approvals. For Italy, as EC consultations provided conflicting advice on the study classification, it was advised that Italian Drug Agency's (AIFA) decision would supersede the EC consultations. AIFA decided that this study was 'observational', but no further details or definition has been given about its classification, and classification would determine the type of EC submissions required. In addition, AIFA asked for a notification or submission, but in Italy there is no mechanism for a non-interventional study notification to EC. Furthermore, AIFA did not provide clear instructions on the submission. Due to these challenges Italy was dropped from this study. Latvia was dropped from the survey due to difficulties to setup the study.

The study protocol will be notified to Member State Competent Authority as per GVP module VIII addendum I and local requirements.

10.3.3 Incentive for Healthcare Professionals

HCPs will be offered a compensation for the time spent participating in this survey (that they may refuse). For HCPs involved in the HCP survey, the time to complete the questionnaire is estimated between 15 to 20 minutes. For HCPs recruiting patients, time for each patient/caregiver recruitment is estimated to be to 5 minutes. The amount of this compensation will be determined according to local applicable codes of conduct and guidelines, the EphMRA recommendations and the Association of Opinion and Behaviour in Health Field Research Companies (ASOCS) charter which states:

"When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws".

10.3.4 Data protection

The study will comply with local applicable Data Protections laws (including GDPR in EU). Data collected from the HCPs and from the patients are anonymous and will remain confidential. Only aggregated data will be analysed and communicated in a report.

HCPs and patients participating in the survey will have to consent and will be informed about the purpose of the survey, the nature of the data collected, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data.

The patient's personal data and Investigator's personal data which may be included in IQVIA database will be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the HCPs and/or to the patients, IQVIA will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. Participating HCPs/patients will access the website (https secured site) via a secure link unique to each HCP/patient. The answers provided will be collected in an anonymous way, only aggregated data and presented as a synthesis will be transmitted to the MAH.

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10.3.5 Insurance

Participating countries may contract insurance according to local specific requirements.

10.3.6 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the HCPs (or any action carried out by the Sanofi-Aventis Group/IQVIA on their behalf), including the present protocol and the questionnaires, are exclusive property of the Sanofi-Aventis Group.

These materials or information (both global and partial) cannot be given or disclosed by the HCPs or by any person of her/his group to unauthorized persons without the prior formal written consent of the Sanofi-Aventis Group.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

10.3.7 Record retention

The study documentation will be stored in the study master file. The web questionnaires data will be stored on the survey database for 5 years. Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted. All documentation pertaining to the study, including paper and electronic records will be retained for a minimum of 5 years after the end of the study, in accordance with IQVIA Standards.

10.3.8 Discontinuation of the study

Not applicable

10.3.9 MAH/MAH representative audits and inspections by competent authorities

Not applicable

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11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of EM implemented as RMM. This survey does not involve data collection on clinical endpoints on individual patients. However, any safety information for an individual patient that is volunteered by a study participant (e.g. HCP) during the course of this research must be reported as described below.

11.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

11.1.1 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or
- Is life-threatening or
- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect
- Is a medically important event
- Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (e.g. product contamination)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.1.2 Collection of Overdose and Pregnancy

Overdose*:*

Any case of accidental or intentional overdose, even in the absence of an AE (asymptomatic), is to be reported to the representative of the Sanofi-Aventis Group (within 30 days) and recorded accordingly on the corresponding page(s) in the questionnaire as explained below.

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Pregnancy*:*

Pregnancy occurring in the patient or the female partner of a male patient exposed to a Sanofi-Aventis Group medicinal product will be reported to the representative of the Sanofi-Aventis Group (within 24 hours) and recorded immediately on the corresponding page(s) in the questionnaire as explained below.

11.1.3 Obligations regarding safety reporting

11.1.3.1 Adverse Events collection

Any AE information received will be documented and reported following the EMA Guideline on Good Pharmacovigilance Practices Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (12) and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004) (14).

Study participants will complete the survey online via a secure website. The survey does not include questions that could potentially identify a safety event and does not provide an opportunity (e.g. free text field) where study participants could provide information that may constitute a safety event. Further, routine communication with participants via e-mail or phone with the IQVIA Programme staff may not be expected during the conduct of the survey. However, it is possible that a study participant may provide information that could constitute a safety event (e.g. serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to the IQVIA Programme staff while in conversation about the survey for any reason (e.g. seeking information about the purpose of the survey).

All staff involved in data collection, quality control and AE identification and reporting is trained to AE Reporting procedures.

11.1.3.2 Adverse event reporting to MAH/MAH representative

There will be no collection of AEs in this study.

In the event that a study participant reports a safety event associated with a Sanofi-Aventis Group product, the IQVIA Programme staff will complete an AE Report Form and submit to the Sanofi-Aventis Group within one business day of becoming aware of the safety event. Included in the completion of the AE Report Form is the study participant's contact information as the reporter; complete contact information should be obtained so that, once the AE Report Form is transferred to Sanofi-Aventis Group pharmacovigilance unit in the country of report, the AE Report Form can be assessed and processed according to Sanofi-Aventis Group's SOPs, including requests for follow-up to the study participant.

11.2 SAFETY OBSERVATIONS

Not applicable

11.3 OBLIGATIONS OF SANOFI

During the course of the study, the Sanofi-Aventis Group will report safety data to health authorities according all applicable local and global regulations (e.g. All serious AE within 15 days (calendar)

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from the date of receipt of the reports to the health authorities; All non-serious AE within 90 days (calendar) from the date of receipt of the reports to the health authorities for some European countries) and to Directive 2001/83/EC.

The MAH will report all safety observations made during the conduct of the study in the final study report.

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12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the Sanofi-Aventis Group/IQVIA conducting the study.

12.2 PUBLICATIONS

The Sanofi-Aventis Group can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. Any publication has to be disclosed onto the ENCePP site within two weeks of acceptation by a Journal.

A Publication Committee responsible for the overall publication plan can be set up upon needs. Its main mission could be:

- To define the overall publication plan including the primary publications reporting new scientific findings/data from the study
- To review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications

Interim reports including the results of the first two waves of the survey and a final survey report including the results for all the surveyed countries will be written in English, using MAH or IQVIA template (which is based on the template included in the GVP module VIII) and following STROBE recommendations in MS Word format (15).

Two interim reports and a final survey report validated by the MAH will be communicated to EMA.

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ANNEXES

Annex 1 ENCePP checklist for study protocols

European Network of Centres
for Pharmacoepidemiology
and
Pharmacovigilance

Doc.Ref.
EMA/540136/2009

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ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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:
SURVEY TO EVALUATE THE KNOWLEDGE AND UNDERSTANDING OF THE KEY SAFETY MESSAGES IN THE HEALTHCARE PROFESSIONAL GUIDE AND THE PATIENT GUIDE FOR

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS register	☐	☐	☐	EUPAS23920
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

[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**	**Section Number**
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 management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which 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**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4

4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2.4
4.2.3 Country of origin?	☒	☐	☐	9.2.4
4.2.4 Disease/indication?	☒	☐	☐	9.2.4
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population?	☒	☐	☐	9.2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, 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?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☐	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4, 9.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
9.1.3 Covariates?	☐	☐	☒	

9.2 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)	☒	☐	☐	9.4, 9.6
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4, 9.6
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6

11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 17/02/2020

Signature: _____

Annex 2 HCP survey questionnaire

SURVEY TO EVALUATE THE KNOWLEDGE AND UNDERSTANDING OF THE KEY SAFETY MESSAGES IN THE HEALTHCARE PROFESSIONAL GUIDE AND THE PATIENT GUIDE FOR SULIQUA

- HCP questionnaire -

SURVEY TO EVALUATE THE KNOWLEDGE AND UNDERSTANDING OF THE KEY SAFETY MESSAGES IN THE HEALTHCARE PROFESSIONAL GUIDE AND THE PATIENT GUIDE FOR SULIQUA

1. Invite/ Recruitment

IF CATI:

"Good morning/afternoon, my name is.....from IQVIA, a company specialised in epidemiological and observational studies and surveys in the field of health and drug safety, are contacting you on behalf of the Sanofi-Aventis Group.

IF CAWI:

Dear Doctor [INSERT NAME & SURNAME HCP]

IQVIA is a company specialised in epidemiological and observational studies and surveys in the field of health and drug safety, are contacting you on behalf of the Sanofi-Aventis Group.

We are currently conducting a survey among Healthcare Practitioners (HCPs) and patients in selected European countries, of which objective is to: assess the knowledge and understanding of the key safety messages in the HCP and patient guides among HCPs who prescribed or dispensed Suliqua and to patients treated with Suliqua, respectively. The survey has been requested by the European Medicines Agency (EMA) and it is funded by the Marketing Authorisation Holder (MAH).

Participation in this study will involve completion of a [INSERT LENGTH OF INTERVIEW] online survey designed to capture your current practice, opinions and perceptions related to the treatment of [INSERT DISEASE/INDICATION]. You can complete the online survey in more than one sitting should you want to, and at a time which is most convenient / appropriate for you. As an appreciation of your time you will receive an honorarium of [INSERT AMOUNT] (options may include IQVIA™ HEALTHCARE RESEARCH PARTNER PROGRAM, bank transfer or vouchers).*

During the course of this survey, you might be asked to provide anonymized data from some of your [INSERT DISEASE/INDICATION] patients' medical records [**For NORDICS**: During the course of this survey, you will be asked to ***recall*** anonymized information about recent [INSERT DISEASE/INDICATION] patients you have treated].

Please be assured that we act in accordance with applicable laws and regulations, including those related to protection of personal data, as well as the British Healthcare Business Intelligence Association (BHBIA), Market Research Society (MRS), European Pharmaceutical Marketing Research Association (EphMRA) and ESOMAR market research codes and guidelines.

Your responses and any personal contact information you provide in completing the survey will be processed by the IQVIA group of companies ("IQVIA") on a strictly need-to-know basis, for purposes of informing IQVIA and its client(s) of current and on-going trends in the management of [INSERT DISEASE/INDICATION] and for any follow-up contact that you have consented to. Your responses may also be used by IQVIA to create non-identifiable information that we may use, alone or in aggregate with information obtained from other sources, in order to gain greater insights in this area.

Your data will not be disclosed to the Study sponsor except in aggregated or non-identified form, provided however that your identity may be disclosed to the Study sponsor and the applicable national regulatory authority if you give your consent for your personal details to be passed on in the event of adverse events, product complaints or special situations reporting, or if the Study Sponsor is required to do so by applicable law to meet mandatory regulatory reporting requirements

Participating in this research does not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any Medicine.

You can withdraw from the research at any time. If you wish to withdraw consent to our processing of your personal information as outlined herein, please contact [INSERT EMAIL CONTACT].

If you wish to participate online, please click the link below or copy it into your browser:

[INSERT UNIQUE URL]

*Payment method is determined by local EphMRA guidelines for individual countries and participant preferences, where possible. IQVIA™ Healthcare Research Partner Program is our IQVIA-branded doctor payment system, which utilizes virtual and plastic MasterCard® debit cards and guarantees your prompt payment for participation in our studies. For more information about IQVIA™ Healthcare Research Partner Program, please click here.

** We are now being asked to pass on to our client details of adverse events, product complaints or special reporting situations, that are mentioned during the course of this post-authorisation safety study (PASS). Although what you say will, of course, be treated in confidence, should you raise during the discussion/survey an adverse event, product complaint or special reporting situation in a specific patient or in a specific number of patients, we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities using the normal reporting processes.

1. Introduction, Terms & Conditions and Consent [UNIQUE URL]:

Thank you for your interest in this post-authorisation safety study (PASS) on [INSERT TOPIC/DISEASE AREA] ("Study").

This form constitutes a privacy notice explaining how **IQVIA Medical Radar AB and/or its group affiliates** ("IQVIA"/ "we", "our", "us") will process your personal data for purposes of the Study and a consent declaration form for you to give your consent to this use, should you so choose.

If you choose to participate in the Study, you will need to read the following information carefully and provide your consent at the end of this form.

Purpose of Personal Data Processing:

IQVIA will serve as the Controller of personal data collected, and processing of such personal data will relate to conducting the Study and any follow-up contact that you have consented to. [Add other use purposes as relevant].

Your responses and any personal contact information you provide in participating in the Study (i.e.: name, business address, email address, and phone number) will be processed by the IQVIA group of companies ("IQVIA") on a strictly need-to-know basis, for purposes of informing IQVIA and its client(s) of current and on-going trends in the management of [INSERT DISEASE/INDICATION]. Your responses may also be used by IQVIA to create non-identifiable information that we may use alone or in aggregate with information obtained from other sources, in order to gain greater insights in this area.

[FRANCE ONLY]: IQVIA is committed to ensuring compliance with the Loi Bertrand (decree implementing French Law No. 2011-2012 on the Strengthening of Health Protection for Medicinal and Health Products, issued on 21 May 2013, also known as the French Sunshine Act).

Third Party Transfers

In order for IQVIA to conduct the Study, IQVIA may need to transfer your data to third party companies providing services to IQVIA. IQVIA shall ensure adequate contractual terms are in place with such third parties in order to ensure there are protections for your data.

If such third parties are located outside the EEA which may not benefit from a European Commission adequacy decision, IQVIA shall ensure Standard Contractual Clauses approved by the European Commission are in place with such third parties in order to ensure an adequate level of protection.

Your data will not be disclosed to the Study sponsor except in aggregated or non-identified form, provided however that your identity may be disclosed to the Study sponsor and the applicable national regulatory authority if you give your consent for your personal details to be passed on in the event of adverse event, product complaint or special situations reporting, or if the Study Sponsor is required to do so by applicable law to meet mandatory regulatory reporting requirements. **

How we store your information and your rights

We retain your data for no longer than is necessary for the purposes for which your personal data is collected. Your responses in the Study and your associated personal data will be maintained for **12 months** except to the extent required to comply with a legal obligation.

You may contact us to request access to your personal data or to be provided with information on your personal data stored by us, object to the processing of it and request that we correct or delete it. If you have any queries or wish to know more about the information we hold, you can call us on [insert phone number] or email us on [insert email address], mentioning the name of the Study and one of our team will be happy to assist. You may also contact our Data Protection Officer at eu.dpo@iqvia.com (for EU studies only), as well as our Privacy Officer at privacyofficer@iqvia.com (in the case of non-EU studies).

You also have the right to complain to a data protection authority in the country where you live, work, or where you believe data protection laws have been breached.

The granting of your consent is voluntary and may be revoked at any time without any detrimental effect to you. You will not suffer any detriment should you choose not to participate in the Study.

****ADVERSE EVENTS REPORTING:** We are now being asked to pass on to our client details of adverse events, product complaints or special reporting situations that are mentioned during the course of this post-authorisation safety study (PASS). Although what you say will, of course, be treated in confidence, should you raise during the discussion/ survey an adverse event, product complaint or special reporting situation in a specific patient or in a specific number of patients, we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities using the normal reporting processes.

[**NOT IN GERMANY**] In the event of an adverse event/side effect, product complaint or special reporting situation, being found during the analysis of this research, are you willing to waive the confidentiality given to you under the Market Research Codes of Conduct specifically in relation to that adverse event? Please note that if you consent to a follow up of the Adverse Event, product complaint or special reporting situation, your name will not be linked in any way to your responses given during the survey, other than in relation to the adverse event.

☐ Yes

☐ No

Confidentiality Agreement:

You acknowledge that in the course of the Study, proprietary information regarding products and product development, and other trade secrets and know-how may be disclosed, and by participating in the Study you agree to hold all such information confidential and to not disclose it to any third party or use it for any other purpose whatsoever. You also agree not to disclose any part of the following pages, which are proprietary material of IQVIA and its clients. You are required to accept the above confidentiality agreement in order to participate in this survey.

Please indicate whether or not you accept our conditions and start now :

Please select:

- ☐ **YES,** I want to take part in the Study and confirm my consent to the collection, storage and use of my personal data as outlined above.
- ☐ **NO,** I do not want to take part in this Study.

Before Passing on the main survey we will first ask some screener questions to ensure you can participate in this survey.

Introduction

The aim of this survey is to assess the effectiveness of the additional Educational Materials (EM) regarding the safety information about Suliqua provided to healthcare professionals. The survey has been requested by the European Medicines Agency (EMA) and it is funded by the Marketing Authorisation Holder (MAH).

The information will be collected anonymously and will only be used for the purposes of this survey. The results obtained will be presented to the MAH and regulatory agencies in an aggregated form.

We greatly appreciate your participation in this research survey.

The questionnaire will take 15-20 minutes to complete.
As appreciation for the time you will dedicate to complete the questionnaire you will be compensated with *[to be adapted to the specialty and country]*.

You may also choose not to accept the monetary compensation.

❒ **Please check this box only if you do not want to be paid.**

Thank you for your interest in participating in this survey.

Kind regards,
IQVIA Team

Section 1: Screener

S1. Are you currently employed by a pharmaceutical company or contracted by regulatory bodies (e.g. EMA *= ZVA, Hungary = OGYEI, Italy = AIFA, Czech Rep =SUKL, Slovenia =JAZMP)***?**

1	No	( )
2	Yes	( )

Data: single punch

If S1=2 then THANK&CLOSE

S2. Have you ever prescribed / dispensed Suliqua?

1	Yes	( )
2	No	( )

Data: single punch
If S2=2 then THANK&CLOSE

S3. Approximately how many patients have you treated with /delivered Suliqua in the last 3 months?

…. .. …….

Data: Open numeric 0-500
If 0 => STOP then THANK&CLOSE
If>0 => continue

Section 2: HCP Practice information

D1. For how many years have you been working with patients with diabetes?

1	≤ 5 years	( )
2	6 to 10 years	( )
3	> 10 years	( )

Data: single punch

D2a. What is your main medical specialty?

1	General practice (GP)/ family physician	( )
2	Endocrinology/ Diabetology (Medical doctors or nurse practitioners)	( )
3	Pharmacist	( )
4	Internist	( )
5	Gastroenterologist	
6	Geriatrics	
7	Other	( )

Data: single punch
If D2=7 then THANK&CLOSE

(For UK questionnaires: Replace " Internist" by "Internal Medicine"; remove Gastroenterologists in UK as they do not prescribe antidiabetic drugs)

D2b. For how long have you been working in this specialty?

For |__|__| years

Data: open numeric, 2 digits

D3. In which type of setting do you work in? (you can select more than one answer)

1	Office	( )
2	Hospital	( )
3	Diabetes care clinic	( )
4	Community Pharmacy	( )
5	Hospital Pharmacy	( )

Data: multiple punch
If D2a = 1,2,4,5 then ask i1,i2,i3
If D2a = 3 then ask i4,i5
(For UK: in the UK the term "Office" is not used: would rephrase to "Private Practice")

Section 3: Prescribing conditions and safety information/warnings of Suliqua 10-40 or 30-60 pen

Explanatory text
Please answer the following general questions about the prescribing conditions and safety information of Suliqua

Q1.Which educational materials (EM) related to Suliqua have you received ?

1	Guide for Heathcare professionals	☐ Yes ☐ No ☐ I do not remember
2	Guide for patients and/or caregivers	☐ Yes ☐ No ☐ I do not remember
3	Letter - Important prescribing information	☐ Yes ☐ No ☐ I do not remember

Data: single punch per row
Ask Q2a only if response to 1 is yes
Ask Q2b only if response to 2 is yes

Key message:
Sanofi should deliver educational material to Healthcare professionals according to the additional risk minimization measures described in the Suliqua Risk Management Plan.

Q2a. Please answer to the following questions related to the use of the Guide for Healthcare Professionals:

	Use of educational materials	
1	Do you review the HCP guide checklist when prescribing/dispensing Suliqua to a patient for the first time ?	☐ Never ☐ Occasionally ☐ Frequently
2	Do you review the HCP guide checklist when changing Suliqua pen strength to a patient for the first time ?	☐ Never ☐ Occasionally ☐ Frequently
3	Do you review each point of the checklist?	☐ Never ☐ Occasionally ☐ Frequently

Data: single punch per row
Key message:
HCPs should review the checklist that is in the guide to Heathcare professional when you prescribe /deliver Suliqua pens.

Q2b. Please answer to the following question related to the use of the Guide for patients and/or caregivers:

	Use of educational materials	
	Do you provide patients with patient guide prior initiating Suliqua	☐ Never ☐ Occasionally ☐ Frequently

Data: single punch per row

Key message:

HCPs should provide patients with the patient guide prior to prescribing or dispensing Suliqua.

Q3. According to your knowledge about the dose titration of Suliqua, which of the following statements are true and which are false?

	Prescription /Patient first daily dose/ dosage titration	TRUE	FALSE
1	Insulin-naive patients (on oral antidiabetic only), should start with 10 dose steps daily.	( )	( )
2	Patients who received between 20 and 30 units of insulin, should start with 30 dose steps daily.	( )	( )
3	Patients who received insulin or insulin glargine twice a day, should have a reduction of total daily dose of Suliqua by 10%.	( )	( )
4	For doses >40 dose steps/day titration must be continued with Suliqua (30-60) pen.	( )	( )
5	For total daily doses >60 dose steps/day, Suliqua must not be used.	( )	( )

Data: single punch per row

Answer:
Option 2 is wrong (patient had insulin before between 20 and 30 units, patient should start with 20 dose steps
Option 3 is wrong (Patients who received insulin or insulin glargine twice a day, should have a reduction of total daily dose of Suliqua by 20%)

Key message:

Prescriber /Pharmacist should understand and know the table in HCP guide for starting dose

Q4. According to your knowledge about the two different Suliqua pens, which of the following statements are true and which are false?

	Prescription/ Pen choice	TRUE	FALSE
1	Patient can use the colour of pen of his/her choice	( )	( )
2.	The Suliqua (10-40) pen allows a daily injection of doses between 10 and 40 dose steps	( )	( )
3	The Suliqua (30-60) pen allows a daily injection of doses between 30 and 60 dose steps	( )	( )
4	The Suliqua pen (30-60) is olive coloured with a brown button	( )	( )
5	Both pre-filled pens contain insulin glargine in a strength of 100 Units/mL	( )	( )

Data: single punch per row

Answer:
Option 1 is wrong (patient should use the pen according to the dose steps that he/she will be prescribed).

Key message:

Prescriber /Pharmacist should understand and know the table in HCP guide for starting dose

Q5. According to your knowledge related to the communication with the patients, what important message(s) should be provided to the patient? (you can select more than one answer)

	Education of patient	
1	Patients should use the same needle for **several injections**	( )
2.	Patients should closely monitor their blood sugar level when starting Suliqua which contains insulin glargine 100U/ml and lixisenatide (non insulin substance)	( )
3	The dose pointer shows the number of dose steps to be injected	( )
4	Patients should read the patient guide and the patient information leaflet, as well as the leaflet provided in Suliqua Solo Star packaging carefully.	( )
5	Patients who are blind or have low vision should be helped by another person who has been trained on Suliqua use	( )
6	The peach colour pen and the olive colour pen contain the same concentration of insulin	( )
7	Patients should report any side effect/medication error to their doctor or pharmacist	( )

Data: multiple punch
Option 1 incorrect

Key message:
HCP should refer to the HCP material and checklist to inform patient about specificities of the pen use.

Q6. According to your knowledge what should be the important information to be indicated in the prescription for Suliqua? (you can select more than one answer)

	Prescription	
1	Number of dose steps to be injected	( )
2	Strength of pen	( )
3	Name of product	( )
4	Associated dose range /strength	( )

Data: multiple punch
Answer: mandatory: 1,3,4;

Key message
The prescription should mention which pre-filled pen type you need (the SULIQUA [100 units/mL + 50 micrograms / mL] pen or the SULIQUA [100 units/mL + 33micrograms / mL] pen) and the number of dose steps to be injected.

Q7. According to your knowledge, which of the following Suliqua safety messages should be communicated to patients treated with Suliqua ? (you can select more than one answer)

	Safety messages	
1	Patients may experience side effects and should talk to their doctors or pharmacists	( )
2	Patients may develop osteosarcoma and should be monitored for bone pain and swelling	( )
3	Medication errors are the most common cause of adverse events and patients should ask, if needed, clarifications on how to use their pen and on how many dose steps they require	( )

4	Patients may experience dysglycemia and should measure their blood sugar more frequently in the weeks after the shift to Suliqua	( )

Data: multiple punch
Answer: Option 2 is wrong
Key message:
HCPs should explain that the patient should anticipate dysglycemia and potential adverse reactions.

Q8. According to your experience, which of the following are the most relevant sources of information that should guarantee appropriate use of Suliqua by patients? (you can select more than one answer)

	Source of information	
1	Patient guide	( )
2	Patient leaflet and instructions for use accompanying the pen	( )
3	Explanations from prescribing physician	( )
4	Explanations from delivering pharmacist	( )
5	Explanations from a nurse	( )
6	Other (ie: Patient group experience, internet, ..)	( )

Data: multiple punch

Q9 and Q10 for prescribers [D2a=1 or 2 or 4 or 5]

Q9. How many prescriptions for Suliqua have you been queried about or have been returned for clarification by dispensers / pharmacists in the last 3 months?

1	None (0)	( )
2	1-5	( )
3	6-10	( )
4	11-20	( )
5	>20	( )

Data: Single punch

Q10 How many prescriptions for Suliqua have you been queried about or have you been asked for clarification by patients in the last 3 months?

1	None (0)	( )
2	1-5	( )
3	6-10	( )

4	11-20	( )
5	>20	( )

Data: Single punch

Q9 and Q10 for dispensers [D2a=3]

Q9 How many prescriptions for Suliqua have you been queried about or returned for clarification by the prescriber in the last 3 months?

1	None (0)	( )
2	1-5	( )
3	6-10	( )
4	11-20	( )
5	>20	( )

Data: Single punch

Q10 How many prescriptions for Suliqua have you been queried about for clarification by patients in the last 3 months?

1	None (0)	( )
2	1-5	( )
3	6-10	( )
4	11-20	( )
5	>20	( )

Data: Single punch

Another survey will be conducted to assess the knowledge and understanding of the key safety messages in the Patient Guide among patients treated with Suliqua. Would you like to help us, by giving the survey questionnaire to your patients? They will then complete an online/paper questionnaire anonymously without your involvement. You will be paid: XX € / completed patient/caregiver questionnaire. IQVIA will re-contact you in order to make the necessary arrangements for patient survey distribution.

1. Yes, I would like to distribute the patient survey among my patients. I agree to be contacted again for this purpose.
2. No

Data: Single punch

If yes, display :

1. I would like to be contacted by IQVIA using the default contact information
2. I would like to provide different contact information

Data: Single punch
If item 2 selected then show:
Please confirm your details:

YOUR NAME:	
E-MAIL ADDRESS:	
ADDRESS:	

Note:
Blue is for data and will not appear in questionnaire,
Green is for internal use and will not appear in questionnaire,
Black will be in the questionnaire.

Annex 3 Patient/caregiver survey questionnaire

SURVEY TO EVALUATE THE KNOWLEDGE AND UNDERSTANDING OF THE KEY SAFETY MESSAGES IN THE HEALTHCARE PROFESSIONAL GUIDE AND THE PATIENT GUIDE FOR SULIQUA

- Patient / Caregiver questionnaire -

Introduction:

Together with your treating physician, you have decided to start therapy with Suliqua.

The aim of this survey is to assess your knowledge and understanding of the recent educational materials about Suliqua provided to the patients.

This survey has been requested by the European Medicines Agency and it is funded by the pharmaceutical company Sanofi. For the purposes of applicable EU data protection laws and the processing of your information in connection with this survey, the Sanofi-Aventis Group is the sponsor of the study and the data controller. The Sanofi-Aventis Group has appointed IQVIA as a processor for the purposes of conducting and evaluating the survey responses for and on its behalf.

Your feedback is important for all patients already treated or to be treated with Suliqua

Please be assured that this study will comply with all [to be adapted to the COUNTRY, e.g. French] laws in protecting your personal data, and will be in accordance with the EphMRA Code of Conduct and any other local pharmaceutical codes of conduct. The survey will be conducted in an anonymous way, meaning neither the survey sponsor nor its contractors will collect, use or process any of your personally identifiable information. The information collected will remain absolutely confidential and will only be used for the purposes of this survey. The results obtained will be presented in aggregated form to the Sanofi-Aventis Group and regulatory agencies, mainly the European Medicines Agency. No connections will be made between your identity and your answers to the survey.

You may at any time exercise the rights you have under applicable data protection laws including to request access to your personal data or to be provided with information on your personal data stored by the survey sponsor or its contractors, to object to the processing of it and request that your information be corrected or deleted. However, as the survey sponsor and its contractors will only receive anonymous data and/or data in aggregated from your survey responses, they will only be able to respond to your requests to the extent that they process any of your personal data.

The data you provide through this survey is retained for no longer than is necessary for the study purposes, including data analysis, evaluation and results reporting, except where a longer period is required for compliance with a legal or regulatory obligation.

If you have any queries or wish to know more about how your data is used, please contact your treating physician or study staff who, in order to protect your anonymity, will also be pleased to refer any questions you may have to the Sanofi-Aventis Group. If you feel that any queries or concerns you have remain unresolved, you have the right to complain to the data protection authority in the country where you live, work, or where you believe data protection laws may have been breached.

The survey does not involve any promotional material and you will not be contacted for marketing purposes based on your answers to the survey. Neither the survey sponsor nor its contractors will sell or rent your information.

The core questionnaire will take 15-20 minutes to complete.

You can choose to complete this paper questionnaire or to use a web questionnaire using the following link [link to be inserted]. When completing the survey, please **do not** enter individual names in any part of the survey where open text options are permitted, as this survey is not intended to collect any individually identifiable information.

In case you decide to participate though the web, you will have to enter the physician number in the web questionnaire so that you can be linked to your treating physician. Your treating physician will provide this number to you.

Thank you for responding to the survey. The survey is entirely voluntary. If you agree to take it, you can stop and withdraw from the survey at any time

Do you agree to participate in this survey on this basis?

1	Yes	( )
2	No	( )

Data: single punch
If 2 then THANK&CLOSE

SCREENER

S1. Do you - or the person you take care of - work for any pharmaceutical company or advertising/research agency? Please select one answer

1	Yes	( )
2	No	( )

Data: single punch
If S1=1 then THANK&CLOSE

S2. Are you - or the person you take care of - treated with Suliqua for diabetes? Please select one answer

1	Yes	( )
2	No	( )

Data: single punch
If S2=2 then THANK&CLOSE

S3. How long have you - or has the person you take care of - been treated with Suliqua? Please select one answer

1	Less than 3 months	( )
2	From 3 to 6 months	( )
3	From 7 to 12 months	( )
4	More than 12 months	( )

Data: single punch

S4. What kind of pen are you - or is the person you take care of - using? Please select one answer

1	Peach (Suliqua 10-40)	( )
2	Green (Suliqua 30-60)	( )
3	I do not know	( )

Data: single punch

S5. What is your gender/ what is the gender of the person you take care of? Please select one answer

1	Female	( )
2	Male	( )

Data: single punch

S6. What is your age/ what is the age of the person you take care of? Please select one answer

1	< 30 years old	( )
2	31- 40 years old	( )
3	41- 50 years old	( )
4	51- 60 years old	( )
5	61- 70 years old	( )
6	71-80 years old	( )
7	>80 years old	( )

Data: single punch

QUESTIONNAIRE

Q1. Which of the following categories of doctors do you – or does the person you take care of - see for the management of diabetes? You can select more than one answer.

1	General practice (GP) / family physician	( )
2	Endocrinologist	( )
3	Gastroenterologist	( )
4	Diabetologist	( )
5	Geriatrician	( )
6	Internist /(BE, UK): Internal medicine	( )
7	Diabetes specialist nurse	( )
8	Other	( )

Data: multiple punch

Q2. Who has trained you - or the person you take care of - on the use of Suliqua? You can select more than one answer.

1	General practitioner (GP) / family physician	( )
2	Another physician, please select the specialty in the following list:	( )
3	Nurse	( )
4	Pharmacist	( )
5	No one	( )

Data: multiple punch
List: Endocrinologist, gastroenterologist, internist, geriatrician, diabetes care clinic physician

Q3. According to your knowledge, which of the following statements are true and which are false? Please select one answer per row.

		TRUE	FALSE
1	The dose pointer of the pen shows the number of dose steps to be injected	( )	( )
2	1 dose step of Suliqua contains 1 unit of insulin glargine 100U/ml plus a corresponding amount of lixisenatide	( )	( )
3	Even when the needle is changed, the pen should not be used by another person	( )	( )
4	You cannot use a syringe to withdraw Suliqua from a pre-filled pen	( )	( )
5	It is important to closely monitor your blood sugar level when starting Suliqua	( )	( )
6	One dose step of Suliqua only states the amount of lixisenatide	( )	( )

Data: single punch per row

Answer: Option 6 is false.

Q4. According to your knowledge, which of the following statements are true and which are false? Please select one answer per row.

		TRUE	FALSE
1	The prescription should mention which pre -filled pen you should use	( )	( )
2	The Suliqua (10-40) pen allows a daily injection of doses between 10 and 40 dose steps	( )	( )
3	The Suliqua (30-60) pen allows a daily injection of doses between 30 and 60 dose steps	( )	( )
4	If my total daily dose is more than 60 dose steps, then I should not use any of the Suliqua pens	( )	( )

Data: single punch per row
If S4=1 then skip item 3
If S4=2 then skip item 2
If S4= 3 then keep item 2 and item 3

Answer: All is true

Q5. Have you - or has the person you take care of - received the Suliqua Patient Guide from your physician or pharmacist? Please select one answer

□ Yes □ No

Data: single punch

Q6. Have you - or has the person you take care of - read the following educational materials (EM) related to Suliqua before using Suliqua? Please select one answer per row.

1	Suliqua Patient Guide (information that you may have received from your physician or pharmacist)	□ Yes □ No
2	Patient Information Leaflet (information available in each pack of Suliqua pre-filled pen)	□ Yes □ No

Data: single punch per row
If Q5=2 then skip item 1

Q7.Where would you - or the person you take care of - look for additional information if you have difficulties in understanding the prescription or use of the Suliqua pen ? You can select more than one answer.

	Prescription/ missing information	
1	Ask a physician	( )
2	Ask a pharmacist	( )
3	Ask a nurse	( )
4	Read the Information Leaflet from the Suliqua package	( )
5	Read the Suliqua Patient Guide	( )
6	Read on the web	( )

Data: multiple punch
If Q5=2 then skip item 5

Answer: all is true

Note :
Blue is for data and will not appear in questionnaire
Green is for internal use and will not appear in questionnaire
Black will be in questionnaire

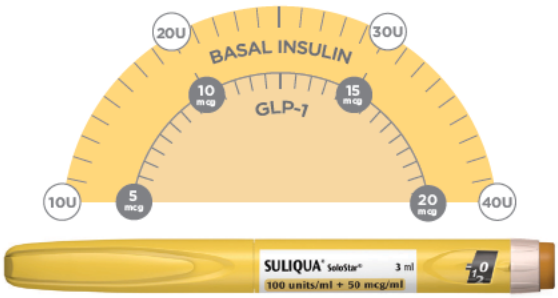
Annex 4 HCP guide

GUIDE FOR HEALTHCARE PROFESSIONALS

INTRODUCING SULIQUA™ (INSULIN GLARGINE 100 UNITS/mL + LIXISENATIDE)–AVAILABLE IN 2 PRE-FILLED PENS CONTAINING DIFFERENT DOSAGE STRENGTHS.

SULIQUA™ 10-40 PEN

SULIQUA™ 100 UNITS/mL + 50 MICROGRAMS/mL
SOLUTION FOR INJECTION IN A PRE-FILLED PEN



FIXED RATIO 2:1

- Insulin glargine (100 Units/mL): 10 – 40 Units/day
- Lixisenatide (50 mcg/mL): 5 – 20 mcg/day

SULIQUA™ 30-60 PEN

SULIQUA™ 100 UNITS/mL + 33 MICROGRAMS/mL
SOLUTION FOR INJECTION IN A PRE-FILLED PEN

FIXED RATIO 3:1

- Insulin glargine (100 Units/mL): 30 – 60 Units/day
- Lixisenatide (33 mcg/mL): 10 – 20 mcg/day

- This document is supplied only as a guide. Please refer to the summary of product characteristics before prescribing and dispensing either of the SULIQUA™ SoloStar® pens.
- Please provide your patients with the patient guide prior to prescribing or dispensing SULIQUA™ to ensure that your patients and their caretakers are adequately informed on how to use SULIQUA™.

SANOFI

IMPORTANT INFORMATION ON DOSING

SULIQUA™ is available in 2 pre-filled pens containing different strengths of lixisenatide and different dose ranges of insulin glargine 100 U/mL, to treat patients with different insulin needs up to 60 Units:

- Both SULIQUA™ SoloStar® pens simultaneously deliver insulin glargine 100 U/mL and the prandial glucagon-like peptide-1 receptor agonist (GLP-1 RA) lixisenatide in 2 different fixed-ratio solutions for a single, once-daily injection.
- Both pre-filled pens contain insulin glargine in a strength of 100 Units/mL.
- The SULIQUA™ (10-40) pen allows a daily injection of doses between 10 and 40 dose steps (strength: insulin glargine 100 Units/mL and lixisenatide 50 mcg/mL; dose range: 10 to 40 Units of insulin glargine in combination with 5 to 20 mcg lixisenatide). This pen is peach colored with an orange injection button.
- The SULIQUA™ (30-60) pen allows a once- daily injection of doses between 30 and 60 dose steps (strength: insulin glargine 100 Units/mL and lixisenatide 33 mcg/mL; dose range: 30 to 60 Units insulin glargine in combination with 10 to 20 mcg lixisenatide). This pen is olive colored with a brown injection button.

STARTING DOSE TABLE

- The dose must be individualised based on clinical response and is titrated based on the patient's need for insulin.

		PREVIOUS THERAPY		
		Oral antidiabetic treatment (insulin-naive patients)	Insulin glargine (100 Units/mL)* ≥20 to <30 Units	Insulin glargine (100 Units/mL)* ≥30 to ≤60 Units
Starting dose and pen	SULIQUA™ (10-40) Pen	10 dose steps (10 Units/5 mcg)**	20 dose steps (20 Units/10 mcg)**	
	SULIQUA™ (30-60) Pen			30 dose steps (30 Units/10 mcg)**

*If a different basal insulin was used:
- For twice daily insulin or insulin glargine (300 Units/mL), the total daily dose previously used should be reduced by 20% to choose the SULIQUA™ starting dose.
- For any other basal insulin, the same rule as for insulin glargine (100 Units/mL) should be applied.

**Units insulin glargine (100 Units/mL)/mcg lixisenatide.

- The prescription must state the dose range and strength of the SULIQUA™ pre-filled pen and the number of dose steps to be administered.
- The maximum daily dose is 60 dose steps (60 Units insulin glargine and 20 mcg lixisenatide).

DOSAGE TITRATION

SULIQUA™ is to be dosed in accordance with the individual patient's need for insulin. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. Close glucose monitoring is recommended during the transfer and in the following weeks.

- For doses >40 dose steps/day titration must be continued with SULIQUA™ (30-60) pen.
- For total daily doses >60 dose steps/day, SULIQUA™ must not be used.

STORING THE SULIQUA™ PENS

- Unopened SULIQUA™ pens can be stored in the refrigerator until expiration date; once opened, discard after 14 days. The shelf-life is 24 months.

UNOPENED PEN

- Store, in the refrigerator with pen cap on at temperature between 2 °C and 8 °C, in the box it came in*
- Can be refrigerated until expiration date
- Do not freeze† Keep in the outer carton to protect from light
- Discard after expiration date has passed

OPENED PEN

- Keep at room temperature below 30 °C
- Do not refrigerate or freeze an opened SoloStar® pen
- Keep out of direct heat and light Put pen cap back on the pen after each injection
- Discard 14 days after opening

*Before injecting SULIQUA™, remove it from the refrigerator for at least one hour–cold insulin can be painful to inject.

†Do not allow SULIQUA™ to freeze. Do not put it in a freezer or next to a freezer pack. If you see frost or ice crystals in the SULIQUA™ solution, throw it away.

PHARMACIST GUIDANCE

- Pharmacists are encouraged to check that patients and caretakers are able to read the strength of SULIQUA™, the dose range of the pre-filled pen, and the dose pointer of the pre-filled pen before dispensing SULIQUA™.
- Pharmacists should also check that patients have been trained on how to use the pen.
- Pharmacists should clarify with the prescriber any incomplete prescription.

While both pens are available for use, the individual needs of your country may lead you to hear about only one pen from your sales representative.

SULIQUA™
insulin glargine (100 U/mL) & lixisenatide

A CHECKLIST FOR HEALTHCARE PROFESSIONALS

EXPLAIN TO YOUR PATIENT

- ☐ You are prescribing a number of dose steps that corresponds to a set number of Units of insulin glargine 100 U/mL plus a corresponding amount of lixisenatide.
- ☐ For SULIQUA™, one dose step always contains one Unit of insulin glargine 100 U/mL, regardless of the SULIQUA™ pre-filled pen being used (the SULIQUA™ [10-40] pen or the SULIQUA™ [30-60] pen).
- ☐ The dose pointer shows the number of dose steps to be injected.
- ☐ If your patient has been transferred from a different pre-filled pen device, highlight the differences in design between the two devices (focus on color differentiation and warning statements on packaging/label).
- ☐ Explain what the patient should anticipate regarding dysglycaemia and potential adverse reactions. For a complete list of adverse events, please refer to the SULIQUA™ Summary of Product Characteristics.
- ☐ Patients who are blind or have poor vision must be instructed to always get assistance from another person who has good vision and is trained in the SULIQUA™ SoloStar® pen device.
- ☐ Instruct your patients to always use a new needle before each use and to never use a syringe to remove the solution from the pen to avoid dosing errors and potential overdose.
- ☐ Recommend that your patients read the patient guide and the patient information leaflet carefully, as well as the instructions for use leaflet provided in the SULIQUA™ SoloStar® packaging.
- ☐ Tell patients to closely monitor their blood sugar levels when starting SULIQUA™, which contains insulin glargine 100 U/mL and a non-insulin active substance (lixisenatide).

IMPORTANT SAFETY INFORMATION

SULIQUA™ is supplied in a pre-filled pen and must only be used with this device; healthcare professionals must never use a syringe to withdraw SULIQUA™ from a pre-filled pen or dosing errors and serious harm can result.

Refer to the SULIQUA™ Summary of Product Characteristics for additional prescribing recommendations.

Reporting adverse events: Please report medication errors or any side effects suspected to be associated with the use of the SULIQUA™ SoloStar® pen to Sanofi, either by telephone <XX XXXXXXXXX> or by email XXXXXX@sanofi.com.

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Annex 5 Patient Guide

GUIDE FOR PATIENTS AND/OR CAREGIVERS

THIS CARD IS PROVIDED ONLY AS A GUIDE. BEFORE USING SULIQUA™, YOU MUST BE TRAINED ON HOW TO USE THE SULIQUA™ SOLOSTAR® PEN BY YOUR HEALTHCARE PROFESSIONAL, AND YOU MUST CAREFULLY READ THE PATIENT LEAFLET AND THE INSTRUCTIONS FOR USE ACCOMPANYING THE PEN.

Keep this card. You may need to refer to it again. Write your name on this card: _____

SULIQUA™ 10-40 PEN

SULIQUA™ 100 UNITS/mL + 50 MICROGRAMS/mL
SOLUTION FOR INJECTION IN A PRE-FILLED PEN

SULIQUA™ 30-60 PEN

SULIQUA™ 100 UNITS/mL + 33 MICROGRAMS/mL
SOLUTION FOR INJECTION IN A PRE-FILLED PEN

SULIQUA™ is available in 2 pre-filled pens containing 2 different strengths of lixisenatide, and different dose ranges of insulin glargine 100 U/mL. Your healthcare professional has prescribed the pen that is right for your insulin needs.

SULIQUA™ pre-filled pens simultaneously deliver insulin glargine and lixisenatide in a single, once-daily injection.

- Both pre-filled pens contain insulin glargine in a strength of 100 Units/mL.
- The SULIQUA™ (10-40) pen allows a daily injection of doses between 10 and 40 dose steps (strength: insulin glargine 100 Units/mL and lixisenatide 50 mcg/mL; dose range: 10 to 40 Units of insulin glargine in combination with 5 to 20 mcg lixisenatide). This pen is peach colored with an orange injection button.
- The SULIQUA™ (30-60) pen allows a daily injection of doses between 30 and 60 dose steps (strength: insulin glargine 100 Units/mL and lixisenatide 33 mcg/mL; dose range: 30 to 60 Units insulin glargine in combination with 10 to 20 mcg lixisenatide). This pen is olive colored with a brown injection button.
- The prescription should mention which pre-filled pen type you need (the SULIQUA™ [10-40] pen or the SULIQUA™ [30-60] pen) and the number of dose steps to be injected.
- Your Pharmacist should clarify with your prescriber any incomplete prescription.
- One dose step contains one unit of insulin glargine 100 U/mL plus a corresponding amount of lixisenatide. Before you use SULIQUA™, be clear on how many dose steps you require. Your healthcare professional provided you with this information.
- The dose pointer of the pre-filled pen device shows the number of dose steps to be injected.

GUIDE FOR PATIENTS AND/OR CAREGIVERS

TAKE NOTE:

- **SULIQUA™ is supplied in a pre-filled pen and must only be used with this device. Patients, caregivers, and healthcare professionals must never use a syringe to withdraw SULIQUA™ from a pre-filled pen or dosing errors and serious harm can result. A new needle must always be attached before each use. Needles must not be re-used.**
- For SULIQUA™, one dose step always contains one unit of insulin glargine 100 U/mL, regardless of the SULIQUA™ pre-filled pen being used (the SULIQUA™ [10-40] pen or the SULIQUA™ [30-60] pen).
- Your healthcare professional can explain the design and features of your SULIQUA™ SoloStar® pen, including how the dose counter of the pre-filled pen device shows the number of dose steps to be injected.
- During the switch to this type of combination medicine and in the weeks after the switch, you should measure your blood sugar levels more frequently.
- If you have any questions about your treatment, speak to your healthcare professional.

STORING THE SULIQUA™ PENS

- Unopened SULIQUA™ pens can be stored in the refrigerator until expiration date; once opened, discard after 14 days. The shelf-life is 24 months.

UNOPENED PEN


Store, in the refrigerator with pen cap on at temperature between 2°C and 8°C, in the box it came in*


Can be refrigerated until expiration date


Do not freeze†
Keep in the outer carton to protect from light

Discard after expiration date has passed

OPENED PEN


Keep at room temperature below 30°C


Do not refrigerate or freeze an opened SoloStar® pen


Keep out of direct heat and light
Put pen cap back on the pen after each injection

Discard 14 days after opening

*Before injecting SULIQUA™, remove it from the refrigerator for at least one hour—cold insulin can be painful to inject.

†Do not allow SULIQUA™ to freeze. Do not put it in a freezer or next to a freezer pack. If you see frost or ice crystals in the SULIQUA™ solution, throw it away.

BEFORE INJECTING SULIQUA™


Carefully read the instructions for use and the patient information leaflet that come with the package leaflet.


If you do not follow all of these instructions, you may get too much or too little medication.

If you experience any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed on this leaflet.

You can also report side effects to Sanofi by telephone <XXXXXXXXXXX> or by email XXXXXX@sanofi.com.

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