Version 1.1

Injectors' Survey to Assess Effectiveness of BELKYRA (deoxycholic acid) Risk Minimisation Activities

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Medicinal product(s):	BELKYRA®
Product reference:	Not applicable
Procedure number:	[redacted]
Marketing authorisation holder(s):	Allergan Pharmaceuticals International Limited
Joint PAS:	N/A
Research question and objectives:	This study will assess Healthcare Professionals'' understanding of the Injector's Guide for the Safe Use of BELKYRA.
Countries of study:	At least 3 countries in the EU
Author:	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder (MAH):	[redacted]
MAH contact person:	[redacted]

Approval Page, Allergan

Project Title: Injectors' Survey to Assess Effectiveness of BELKYRA (deoxycholic acid) Risk Minimisation Activities

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The following people have reviewed the protocol and give their approval:

Allergan

[redacted]	*Signature*	*Date*
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[redacted]	*Signature*	*Date*

1. Table of Contents

Section **Page**

List of Tables

Table **Page**

2. List of Abbreviations

Abbreviation	Definition
aDCT	Annotated data collection tool
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CFR	Code of federal regulations
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CRO	Contract research organization
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
ICF	Informed consent form
ICH	International Council for Harmonization
ID	Used identification
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information technology
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
PAS	Post-authorization study
PASS	Post-authorization safety study
QC	Quality control
QPPV	Qualified person of pharmacovigilance
RMM	Risk minimisation measures
RUP	Repeat-use procedure
SAR	Suspected adverse reactions
SAP	Statistical analysis plan
SAS	Statistical analysis software
SDLC	System development life cycle
SmPC	Summary of product characteristics
SOP	Standard operating procedure

SQL	Structured query language
SSRS	SQL server reporting services
UAT	User acceptance testing
US	United States

3. Responsible Parties

Not applicable.

4. Abstract

Title: Injectors' Survey to Assess Effectiveness of BELKYRA® (deoxycholic acid) Risk Minimisation Activities.

Rationale and Background: The additional risk minimisation activity for BELKYRA consists of educational materials in the form of an Injector's Guide for the Safe Use of BELKYRA, which includes a patient selection checklist and a procedure checklist. The Injector's Guide will provide Healthcare Professionals (HCPs) with specific instruction on how to administer BELKYRA safely to minimise the risks of injection site nerve injury and injection site skin ulceration.

Research Questions and Objectives: This study will assess HCPs' understanding of the key safety messages contained in the Injector's Guide for the Safe Use of BELKYRA regarding injection site nerve injury and injection site skin ulceration.

Study Design: This study uses a multi-national, observational cross-sectional design. A survey will be administered to HCPs who are able to treat patients with BELKYRA to evaluate their comprehension of the safe use of the product and understanding of the key safety messages.

Population: The survey will be administered to HCPs in at least 3 EU countries based on market uptake. The targeted respondent population will be HCPs who are able to treat patients with BELKYRA**.** The timing of the survey initiation and implementation will vary according to the timing of the distribution of the Injector's Guide for the Safe Use of BELKYRA in each individual country. Screening questions will be used to determine respondent eligibility. Participants are ineligible if they have ever worked directly for, or whose immediate family members have ever worked directly for Allergan or any of its affiliates, *[CRO running the study]*, the European Medicines Agency (EMA) or any National Competent Authority (NCA).

Study Endpoints: The additional risk minimisation measure will be considered effective if at least 75% of respondents demonstrate their understanding of the key safety messages.

Variables: The survey will collect each participant's understanding of the key safety messages of BELKYRA as outlined in the Injector's Guide for the Safe Use of BELKYRA. The survey will also collect demographic characteristics for all respondents who complete all survey questions, which includes age-group, gender, speciality, geographical location, duration of their experience in undertaking aesthetic procedures and the number of patients they have treated with BELKYRA in the last six months.

Data Sources: Structured, self-administered surveys comprising closed-ended questions or statements with multiple response choices will be used to collect the survey data from a sample of HCPs who treat patients with BELKYRA.

Study Size: The study size will be dependent upon market uptake of BELKYRA and will target a completion of a minimum of 75 and a maximum of 150 surveys.

Data Analysis: Data collected from the survey will be reported as descriptive statistics. Survey data will also be analysed by country and speciality. Responses to each question relating to the risks will be categorised as "Correct response" or "Incorrect response". Frequency distributions with 95% confidence intervals (CIs) will be calculated for responses to the questions that address the survey objective (excluding demographic questions).

Milestones: The study will be initiated following protocol approval by the Medicines and Healthcare products Regulatory Agency (MHRA) and other relevant NCA and about 12 to 18 months after the beginning of distribution of the Injector's Guide for Safe Use of BELKYRA in the applicable countries. Findings from the survey results will be reported to the NCAs. The survey report will be completed 6 months after the completion of the survey in all countries.

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	Planned Timeline
Start of data collection	About 12 to 18 months after the beginning of distribution of the Injector's Guide for Safe Use of BELKYRA in the applicable countries
End of data collection	When the target number of surveys have been completed
Registration in the EU PAS Register	Prior to start of data collection
Final study report	6 months after the end of data collection

7. Rationale and Background

BELKYRA is indicated for the treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has an important psychological impact for the patient. BELKYRA should only be administered by physicians with appropriate qualifications, expertise in the treatment and knowledge of the submental anatomy. When national guidance permits, BELKYRA may be administered by appropriately qualified healthcare professionals (HCPs) under the supervision of a physician.

BELKYRA was initially registered in 23 European Economic Area (EEA) countries via a decentralised procedure and the positive opinion was received on 29 June 2016. To register BELKYRA in 7 additional EEA countries, a repeat-use procedure (RUP) was initiated and the positive opinion was received on 08 May 2017. During the RUP, the Marketing Authorisation Holder, Allergan Pharmaceuticals International Ltd. agreed to fulfil several post-approval commitments related to the Risk Management Plan. It included the introduction of educational materials as additional risk minimisation measures (RMMs) to supplement the summary of product characteristics (SmPC).

Consequently, an Injector's Guide for the Safe Use of BELKYRA, which includes a patient selection checklist, as well as a procedure checklist, has been introduced as an additional risk minimisation measure to provide information on the recommended injection technique and how to minimise the important identified risks of injection site nerve injury and injection site skin ulceration.

This protocol refers to the survey that is designed to assess the effectiveness of the Injector's Guide for the Safe Use of BELKYRA with respect to the risks of injection site nerve injury and injection site skin ulceration and is part of the regulatory commitment to assess the effectiveness of the risk minimisation measure. The Injector's Guide for the Safe Use of BELKYRA will be distributed to HCPs who administer BELKYRA. The type of HCP will vary per country depending upon national guidance and local clinical practice, and will include, but not be limited to, plastic surgeons, aesthetic doctors, dermatologists and, other appropriately qualified HCPs (e.g. nurses) under the supervision of a physician.

User Testing will be performed on survey questions by sampling around 10 HCPs who are known to be actively treating patients with BELKYRA and who are independent of the sponsor and *[CRO running the study]*. Based on the feedback from this User Testing, the survey will be updated.

8. Research Question and Objectives

This study will assess HCPs understanding of the key safety messages of BELKYRA regarding injection site nerve injury and injection site skin ulceration as communicated in the Injector's Guide for the Safe Use of BELKYRA.

9. Research Methods

9.1. Study Design

This study is a multi-national, observational, cross-sectional survey design that will be conducted in at least 3 EU countries based on market uptake of BELKYRA.

9.2. Setting

The assessment survey will be initiated within about 12 to 18 months following the distribution of the Injector's Guide for the Safe Use of BELKYRA in at least 3 EU countries based on market uptake.

Selection bias will be minimised by standardised messaging and survey implementation methodology. The same survey will be used for all participating countries in order to ensure consistency in testing the target population.

[CRO running the study] will administer the survey to the eligible study population that responds to the invitation to participate in the study.

The survey will be administered via the internet, which will allow respondents to participate at a time and location that is convenient for them. The survey includes questions/statements that will assess the HCPs' understanding of the key safety messages as outlined in the Injector's Guide for the Safe Use of BELKYRA.

The targeted survey population will be HCPs who are able to treat patients with BELKYRA. The exact speciality of HCPs may vary per country depending upon local clinical practice and national guidance, and will include, but not be limited to, plastic surgeons, aesthetic doctors, dermatologists and other appropriately qualified HCPs (e.g. nurses) under the supervision of a physician. The number of respondents will be monitored throughout the data collection period.

The HCPs will receive an invitation letter via email (preferred) or postal mail (if email is not available) to participate in the survey. The invitation letter will include: an overview of the rationale for the survey, provide information on how to access the survey online, and provide a unique User Identification (ID) to ensure that the invitation is used only once. The ID will only be known by the CRO and will not be shared with the sponsor. Using the ID, the contract research organization (CRO) will be able to determine which HCPs have not completed the questionnaire.

The database of invited HCPs will be routinely updated by the CRO with respondents. After each invitation mailing, the database will be cross-checked with any correspondence that had an invalid address, had bounced back or had incorrect contact details. The target population for survey reminders is HCPs who received an invitation (that is, no reason for not receiving, such as invalid address) but did not respond within 2 weeks from the initial mailing. Using the updated database, at least one reminder will be sent via email and/or postal mail to the target population identified above 2 weeks after the initial mailing. The total number of reminders will be based on the number of respondents at predefined recruitment milestones. The interval between the reminders will be approximately 2 to 3 weeks from each reminder. Participants' identifying information will be collected for the purposes of providing compensation as allowed by local laws and country regulations.

9.2.1. Inclusion criteria

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

- HCPs currently treating patients with BELKYRA

9.2.2. Exclusion criteria

HCPs meeting the following criterion will be excluded from the survey:

- Current or past employment with Allergan or any of its affiliates, *[CRO running the study]*, the EMA or any NCA.

9.3. Variables

The PASS survey will collect participants' understanding of the key safety messages of BELKYRA as outlined in the Injector's Guide for the Safe Use of BELKYRA in member states where the educational materials are being introduced. In member states where the educational materials have not been introduced and BELKYRA has already been launched, participants' understanding of key safety messages without benefit of the educational materials will be assessed. Additionally, the survey will collect information on demographic characteristics including age, gender, speciality, geographical location, the duration of their experience in undertaking aesthetic procedures and the number of patients prescribed BELKYRA in the last 6 months.

9.4. Data Sources

User-testing of Survey Questionnaire

HCPs taking part in the survey may have different backgrounds and knowledge that could lead to differing levels of comprehension of the educational materials, and some HCPs may also become high prescribers of BELKYRAwhilst others may use it only rarely. User-testing the survey prior to the implementation of the aRMM to the full target population (in this case, HCPs) increases the likelihood that the survey will be more effective based on qualitative feedback from a sample of HCPs. The survey will therefore undergo cognitive user-testing in a sample of around 10 HCPs comprising an appropriate mix of specialties from different EU countries; this will help facilitate understanding of differences that may require local modification of survey content. Allergan will update the survey based on findings from the user testing.

In order to target the desired population, the data source will be a list of HCPs who are able to treat patients with BELKYRA. The exact speciality of HCPs may vary per country depending upon local clinical practice and national guidance, and will include, but not be limited to, plastic surgeons, aesthetic doctors, dermatologists and, other appropriately qualified HCPs (e.g. nurses) under the supervision of a physician.

The structured, self-administered survey will be used to collect the survey data (Appendix 14.1). It will be comprised of closed-ended questions, statements with multiple responses or true/false choices. To help assess source(s) of information, the survey includes a question that asks HCPs to provide sources of information (e.g., Summary of Product Characteristics

(SmPC), an HCP's pre-existing knowledge or commercial sources) other than the injector's guide, if any.

The survey is designed to be voluntary and anonymous. The participating HCPs will be informed that the collection of any personal identifying information (first name, last name, address) from respondents will only be used for the processing of the HCPs' compensation as allowed by local laws and country regulations and will be stored in a separate database.

Each participant will be given a unique code to access the survey. Each code is deactivated upon its use to prevent the code from being used to complete the survey multiple times. Each code is randomly assigned.

Each survey will begin with a screening module with questions to confirm eligibility.

Screening questions will include:

- *Agreement to participate*
- *HCPs who are currently treating patients with BELKYRA*
- *Current or past employment by Allergan, or any of its affiliates, [CRO running the study], the EMA, or any NCA*

Data on demographic characteristics will include:

- *Age group*
- *Gender*
- *Speciality*
- *Geographical location*
- *Duration of experience in undertaking aesthetic procedures*
- *Number of patients treated with BELKYRA in the last six months*

Data pertaining to evaluation of the effectiveness of the Injector's Guide for the Safe Use of BELKYRA regarding:

- *Prevention of injection site nerve injury*
- *Prevention of injection site skin ulceration*

Knowledge questions will focus on the following areas:

- *General knowledge*
- *Eligibility Criteria*
- *Contra-indications*
- *Treatment*
- *Injection procedure*
- *Post-treatment*

9.5. Study Size

The study size will be dependent upon market uptake of BELKYRA and will target a completion of a minimum of 75 and a maximum of 150 surveys. Precision estimates based on sample sizes of 75, 100 and 150 using a level of understanding of 75%, 80% and 85% are set out in Table 1 below.

Table 1. Precision estimates based on sample sizes of 75, 100 and 150 using a level of understanding of 75%, 80% and 85% based on the method by Clopper and Pearson

Sample size	Estimated level of understanding	Estimated CI
75	75%	63.6% - 84.3%
75	80%	69.2% - 88.4%
75	85%	74.8% - 92.3%
100	75%	65.3% - 83.1%
100	80%	70.8% - 87.3%
100	85%	76.5% - 91.3%
150	75%	67.3% - 81.7%
150	80%	72.7% - 86.1%
150	85%	78.3% - 90.3%

9.6. Data Management

All data collected during the survey will be confidential. The Electronic data capture (EDC) system used for data collection does not collect any respondent identifying information. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses.

The survey is programmed to ensure respondents cannot skip ahead. Statements requiring response and response options are presented in a list and are randomised to minimise positional bias. In addition, the ability to mark only one response is part of the programming for the survey administration and will minimise the occurrence of data entry errors. There will be no queries to respondents for this project.

9.7. Data Analysis

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for responses to questions that address the survey objectives (i.e. excluding demographic questions). Survey data will also be analysed by country and speciality (if number of respondents will be sufficient). Data will also be analysed by countries in which the Injector's Guide has been introduced vs. those countries that have not. Responses will be categorised as "Correct response" and "Incorrect response". Each question will be assessed individually.

Allergan considers the risk minimisation measures to be successful if the majority (at least 75%) of HCPs understand the key messages being communicated.

Source of Data.

The source(s) of information will be assessed based on the question in the survey that asks HCPs to provide sources of information (e.g., Summary of Product Characteristics (SmPC), an HCP's pre-existing knowledge or commercial sources) other than the injector's guide, if any. Data will be presented as frequency counts for the respective source(s) of information.

The following information will be analysed descriptively:

- *Survey administration*
    - *The number of survey invitations issued (i.e., by country)*
    - *The number of survey invitations/reminders returned due to incorrect mailing/emailing address of HCPs invited to participate in the survey*
    - *The number of HCPs who responded to the invitation to participate in the survey*
    - *The number of HCPs eligible for participation in the survey*
    - *The number of ineligible HCPs along with the reasons for ineligibility*
    - *The number of eligible HCPs who completed the survey*
- *Demographic characteristics of participants*
    - *Age-group*
    - *Gender*
    - *Speciality*
    - *Country*
    - *Duration of experience in undertaking aesthetic procedures*

  - *Number of patients treated with BELKYRA in the last 6 months*

- *Characteristics of responders and non-responders using:*
  - *Country*
  - *Speciality of HCPs*
  - *Gender of HCPs*
- *Responses to questions pertaining to the survey objectives:*
  - *Awareness and understanding of the Injector's Guide for the Safe Use of BELKYRA which outlines the risks of injection site nerve injury and injection site skin ulceration*
  - *Questionnaire scores will be presented by 'domain' (i.e., questions pertaining to):*
    - *General knowledge*
    - *Eligibility criteria*
    - *Contra-indications*
    - *Treatment*
    - *Injection procedure*
    - *Post-treatment*

Responses to questions pertaining to survey objectives will be analysed based on responses to speciality, number of patients treated with BELKYRA in the last 6 months, and by country, if sufficient responses.

Evaluation of the Effectiveness of the Educational Materials

To evaluate the effectiveness of the BELKYRA educational materials in terms of outcome, i.e. risk minimisation for injection site nerve injury and injection site skin ulceration, a trend analysis will be presented, based on spontaneous reporting rates of these events, post implementation of the aRMM in selected countries.

Since the aRMM will be implemented concurrent with product launch in some EU markets (e.g. in Germany & the UK), suitable reference values for direct comparison cannot be defined, and the results obtained will need to be interpreted with caution. For example, a reduction in suspected ADRs reported over time following the launch of a product may be due to a variety of confounding factors and cannot be easily credited to risk minimisation (e.g. the Weber effect). Although risk minimisation will prevent some occurrences of an ADR, a decrease in occurrence may also be attributed to HCPs having gained knowledge from other sources, such as the SmPC or product training from the Company.

BELKYRA was launched in March 2017 in some EU member states, but educational materials have not yet been introduced into these member states. However, with the assumption that prescriber injecting habits for BELKYRA are similar across all EU member states, data from these member states will provide an opportunity for comparison of rates and trends based on spontaneous event reporting in these specific member states with those states where the educational materials are being newly introduced. This will help provide information on the usefulness of the educational materials and whether the materials may have contributed to the observed trends in outcome in the respective member states.

9.8. Quality Control

Data will be collected using a secure and validated online EDC system. Spontaneous events will be collected utilising the Allergan Argus Global Safety Database. A System Development Life Cycle (SDLC) is used for validation that complies with *[CRO running the study]* internal Information Technology (IT) Standard Operating Procedures (SOPs). The SDLC is fortified with SOPs addressing validation for all clinical and risk minimisation-related applications. The internet-based repository will be used to store survey data and other relevant programme information. The system is EudraLex Annex 11 (and 21 Code of Federal Regulations (CFR) Part11 in the United States (US)) compliant for the entry, storage, handling, analysis and transmission of electronic information. This platform ensures compliance with all relevant regulatory guidelines. Respondent-identifying information is stored separately from survey data.

Programming will be reviewed by *[CRO running the study]*, Allergan, Quality Control (QC) and simulated users [User Acceptance Testing (UAT)] prior to implementation.

At the completion of data collection, data will be extracted from the EDC and mapped to Statistical Analysis Software (SAS) datasets (SAS V9.1.3 or higher). The mapping of raw data will be validated, as will the programming of the analysis tables created from the raw EDC data. The raw EDC data is used to populate analysis tables that are programmed by Structured Query Language (SQL) Server Reporting Services (SSRS) according to the Survey Analysis Plan (SAP). Additionally, the EDC data will also be mapped to SAS datasets by a SSRS programmer as defined in the annotated Data Collection Tool (aDCTs) and validated by the *[CRO running the study]* QC team.

[CRO running the study] has an IT Quality Assurance Group that is responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

9.9. Limitations of the Research Methods

Low response rates from HCPs' surveys may not achieve the desired level of response for assessing knowledge of HCPs on the key safety messages pertaining to the use of BELKYRA. A low response rate will also result in a small sample size which may not provide a representative picture of the full target population, and results may not be generalizable to the wider HCP population in Europe. A potential impact of this type of bias is that non-responders may systematically differ from participating HCPs for the outcome measured. Although non-response bias will be assessed by comparing characteristics of responders and non-responders, there are limitations to this approach as only a limited number of non-respondent characteristics (e.g. geographic location of HCP, speciality and perhaps gender) may be available. In addition, the study will not be able to compare other factors that could have influenced some participants to respond versus non-responders. Caution is therefore needed when interpreting outcomes from surveys with a low response rate, evidence of non-response bias and directionality of any such bias.

The survey recruitment strategies are intended to recruit HCPs who are identified as treating patients with BELKYRA. The participants will be self-selected since they will voluntarily respond to the invitation to participate; however, those who read the invitation to participate

are more likely to be attentive to all BELKYRA information, and therefore more aware of the key safety messages.

Inherent in survey research is the reliance on the respondent's recall for whether or not the Injector's Guide for the Safe Use of BELKYRA was received/ read. If the respondent says she/he did not receive/read the Injector's Guide for the Safe Use of BELKYRA, the risk minimisation programme is evaluated as not optimally disseminating material. It is possible, however, that respondents may simply not recall receiving/reading the Injector's Guide for the Safe Use of BELKYRA that was, in fact, received.

It is also possible that the respondents have acceptable understanding of the key safety messages despite not receiving, reading or recalling the Injector's Guide for the Safe Use of BELKYRA. Hence, although the survey can assess the HCPs' understanding of the key safety messages, it may not clearly identify via which channel the HCPs gained the information. This is a common issue with survey results whereby they often do not reveal where information was gleaned. This makes it somewhat difficult to determine whether relevant knowledge about safety messages arose due to the aRMM, in this case - the injector's guide, or from another source, such as the Summary of Product Characteristics (SmPC), an HCP's pre-existing knowledge or commercial sources. To help assess source(s) of information, the survey includes a question that asks HCPs to provide sources of information, other than the injector's guide, if any. Importantly, the general consideration is for HCPs to understand important key safety information on BELKYRA, irrespective of the source.

BELKYRA

All data from the survey are self-reported and therefore susceptible to possible reporting bias.

9.9.1. Controls to minimise bias

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

- Lists of response options will be randomised to minimise the potential for positional bias.
- The surveys will be programmed to ensure that questions will be presented in a random order to reduce exposure bias. Respondents cannot skip ahead or go back to a question once the question has been answered. All questions presented must be answered in order to complete a survey.
- Respondents will be provided with a unique code during the recruitment process in order to gain access to the Internet-based systems. The code will be inactivated after use to minimise exposure bias and fraud.

9.10. Other Aspects

Not applicable

10. Protection of Human Subjects

10.1. Personal Information and Consent

All data collected during the survey will be held confidentially by *[CRO running the study]* and used only for the purposes stated in the survey instructions. Respondent names and addresses are collected for the purposes of mailing a thank you letter and payment, if applicable, after the survey is completed. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses. The EDC system used for data collection of the survey responses does not collect any identifiable information. Allergan will not have access to any personal information collected, in relation to this survey.

By answering the first question of the survey ("*Do you agree to participate in this survey?*"), respondents are providing informed consent for participation in the research study.

10.2. Respondent withdrawal

Respondents can decline to participate or stop taking the survey at any time. Only complete surveys will be included in the analysis. This will be made clear to participants as they commence the survey.

10.3. Ethics Committee (EC)

Approval of this protocol by the respective local EC will be sought prior to initiating the survey in each country, where applicable.

10.4. Ethical Conduct of the Study

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

11. Management and Reporting of Adverse Events/Adverse Reactions

Adverse Events

Adverse events will not be actively collected as this study is assessing the knowledge of HCPs on the key safety messages pertaining to the use of BELKYRA and therefore is not relevant to this survey. Survey respondents and other study personnel are requested to report any suspected adverse reactions (SARs) with BELKYRA to the regulators as they would in normal practice as required by applicable laws, regulations, and practices.

Product Complaints

HCPs are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

The study will be registered in the PAS Register hosted by ENCePP. The final report of the study results will be submitted as described in Section 6. Additionally, the study findings may be presented at a scientific congress and/or submitted to a peer-reviewed journal.

13. References

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika 1934;* 26, 404–413.

EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology.*

Guideline on Good Pharmacovigilance Practices (GVP) Module XVI- Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators.

Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

International Ethical Guidelines for Epidemiological Research issued by the Council for International Organisations of Medical Sciences (CIOMS).

US Food and Drug Administration (FDA) Guidance for Industry: *Good Pharmacovigilance and Pharmacoepidemiologic Assessment*.

14. List of Stand-alone Documents

Number	Document reference number	Date	Title
1	Appendix 14.1		Survey
2	Appendix 14.2		Sample Survey Invitation letter for HCPs
3	Appendix 14.3		Injector's Guide for the Safe Use of BELKYRA
4	Appendix 14.4		ENCePP checklist

14.1. Survey questions

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

1. Do you agree to take part in this survey about BELKYRA?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you or any of your immediate family members ever worked directly for Allergan or its affiliates, [*CRO conducting the survey*], the European Medicines Agency (EMA), or any National Competent Authority (NCA)?

   - ○ Yes **[TERMINATE]**
   - ○ No

3. Are you a healthcare professional currently treating patients with BELKYRA?

   - ○ Yes
   - ○ No **[TERMINATE]**

4. Have you treated at least one patient with BELKYRA?

   - ○ Yes
   - ○ No **[TERMINATE]**

5. Approximately how many patients have you treated in the last six months with BELKYRA?

   - ○ None **[TERMINATE]**
   - ○ 1-5
   - ○ 6-10
   - ○ More than 10

[END SCREENING QUESTIONS]

6. In total, how many years have you been undertaking aesthetic procedures?

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

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

   - ○ Less than 40
   - ○ 40-59
   - ○ 60 or older
   - ○ Prefer not to answer

8. What is your gender?

   - ○ Male
   - ○ Female
   - ○ Prefer not to answer

9. In which country do you practice?

   - ○ Country 1 TBD
   - ○ Country 2 TBD
   - ○ Country 3 TBD
   - ○ Prefer not to answer

10. Please answer True/False/I do not know for the following statements			
	True	False	I do not know

BELKYRA is indicated for the treatment of mild convexity or fullness associated with submental fat in adults.			
BELKYRA should not be used in patients that are obese (Body mass index (BMI) ≥ 30).			
BELKYRA can be used in patients who have body dysmorphic disorder.			

11. Please answer True/False/I do not know for the following statements			
	True	False	I do not know
Caution should be exercised in patients aged 55 and over as it is not known whether they respond differently than younger patients.			
Caution should be exercised in patients who have excessive skin laxity, prominent platysmal bands or other conditions for which reduction in submental fat may result in an undesirable outcome.			
Prior to using BELKYRA, patients should be screened for other potential causes of submental convexity/fullness (e.g. thyromegaly and cervical lymphadenopathy).			

12. Please answer True/False/I do not know for the following statements			
	True	False	I do not know
If the patient has an infection at the injection site, BELKYRA can be used so long as antibiotics are started.			

13. Caution should be exercised when using BELKYRA in patients with (please mark one only)	
Inflammation or induration at the proposed injection site.	○
Symptoms of dysphagia.	○
Prior surgical or aesthetic treatment of the submental area.	○
All of the above.	○

14. Please answer True/False/I do not know for the following statements			
	True	False	I do not know
The time interval between treatment sessions should be at least 4 weeks.			
Up to a maximum of 4 treatment sessions can be performed.			

15. Please answer True/False/I do not know for the following statements			
	True	False	I do not know
Do not inject above the inferior border of the mandible.			
Inject BELKYRA only within the target submental fat treatment area.			

16. Please answer True/False/I do not know for the following statements			
	True	False	I do not know
Patients may be provided with pre-treatment analgesia.			
Injections should consist of 0.4ml (4mg) per injection site, 2cm apart.			
The maximum dose of 10 ml (100 mg equivalent to 50 injections) should not be exceeded in one treatment session.			

17. In which sites should you NOT inject BELKYRA? (please mark one only)	
Into post-platysmal fat.	○
Intradermally to avoid risk of skin ulceration	○
In the "No treatment zone" to avoid injury to the marginal mandibular nerve.	○

Into or in close proximity (1-1.5 cm) to thyroid gland, salivary gland, lymph nodes, and muscle.	○
All of the above.	○

18.Please answer True/False/I do not know for the following statements			
	True	False	I do not know
Do not apply an ice pack			
Assess smiling and swelling for nerve injury and dysphagia			

19. Did you receive the Injector's Guide for the Safe Use of BELKYRA

- ○ Yes
- ○ No

20. Did you read the Injector's Guide for the Safe Use of BELKYRA

- ○ Yes
- ○ No

21. Please indicate your other sources of information (other than the Injector's Guide for the Safe Use of BELKYRA), if any

- ○ The Injector's Guide was the only source of information
- ○ The Summary of Product Characteristics (SmPC)
- ○ HCP's pre-existing knowledge
- ○ The literature
- ○ A conference (s)
- ○ Via communication with another HCP
- ○ Commercial sources

- Other

14.2. SAMPLE INVITATION LETTER FOR HCPS

[Date]

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

Re: Invitation to Participate in a BELKYRA® (Deoxycholic acid**) Survey**

Dear HCP [insert HCP LAST NAME],

On behalf of Allergan, we would like to invite you to participate in a voluntary research survey about BELKYRA® **(**Deoxycholic acid**)** which is indicated for the treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has an important psychological impact on the patient.

The survey is part of a post-marketing commitment between Allergan and European Regulatory Agencies to assess HCPs' knowledge on the safe use of BELKYRA and should take approximately 10-15 minutes to complete. *If you complete the survey and provide your contact information, you have the opportunity to receive compensation representing our appreciation of your time, subject to local rules and regulations [adapt depending upon country regulations]*.

You may be eligible to participate if you are currently treating patients with BELKYRA. For your convenience, the survey can be completed online at **[www.surveyURL.com].**

You will need the following code when completing the survey: **[UNIQUE CODE]**.

When participating online, you must take the survey on a desktop or laptop computer. The survey will not function correctly on other devices (such as: tablets, smart phones or e-notebooks).

Participating in this survey is entirely voluntary. All information that is collected during the course of the survey will be kept strictly confidential. Results will be reported in aggregate only. Your participation in the survey and your answers to the survey questions will not affect your ability to prescribe or treat patients with BELKYRA. You will not be contacted for marketing purposes. Neither Allergan nor its contractors will sell, transfer, or rent your information.

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

Sincerely,

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

14.3. INJECTOR'S GUIDE FOR THE SAFE USE OF BELKYRA

INJECTOR'S GUIDE FOR THE SAFE USE OF BELKYRA

IMPORTANT SAFETY INFORMATION

This guide provides important information on the safe and effective use of BELKYRA in order to minimise the risk of injection site nerve injury and associated motor neuropraxia and injection site skin ulceration in patients.

Please read this guide carefully and refer to the Summary of Product Characteristics for further information.

BELKYRA is indicated for the treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has an important psychological impact for the patient.

The safe and effective use of BELKYRA outside the submental fat area or at higher than recommended doses has not been established. BELKYRA should not be used in patients who are obese (BMI $\geq$ 30) or in patients who have body dysmorphic disorder.

BELKYRA should only be administered by physicians* with appropriate qualifications, expertise in the treatment, and knowledge of the submental anatomy.

*Where national guidance permits, BELKYRA may be administered by appropriately qualified healthcare professionals, under the supervision of a physician.

Injection site nerve injury
To avoid the potential for injection site nerve injury (motor neuropraxia), BELKYRA should not be injected into or in close proximity to the marginal mandibular branch of the facial nerve. Motor neuropraxia manifests as an asymmetric smile or facial muscle weakness. In clinical trials, nerve injury occurred in 3.6% of patients and was temporary and in all cases resolved with a mean time to resolution of 53 days (range 1 to 334 days).

Injection site skin ulceration
Care should be taken to avoid inadvertent intradermal or intramuscular injection. BELKYRA should be injected mid-way into the preplatysmal subcutaneous fat tissue in the submental area. Do not withdraw the needle from the subcutaneous fat during injection, as this could increase the risk of intradermal exposure and potential skin ulceration. In clinical trials, skin ulceration occurred in 1 patient (0.1%) and resolved in 23 days.

Reporting of suspected adverse drug reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Physicians and other healthcare professionals are asked to report any suspected adverse drug reactions via the national adverse event reporting system.

Anatomical structures of the neck

Figure 1
(slide 1)

Posterior to the facial artery
The marginal mandibular nerve runs along the inferior border of the mandible at a level which is deep to the platysma muscle; however, relative to the mandibular border, it:

- Is 1 – 2 cm below in most cases
- Has been described up to 4 cm below

Anterior to the facial artery
The marginal mandibular nerve passes above the mandibular border in 100% of cases.

Figure 2
(slide 2)

The Cervicomental Region Defined

Key Anatomic Landmarks of the Cervicomental Region

Figure 3
(slide 3)

Figure 4
(slide 4)

Figure 5
(slide 5)

Figure 6
(slide 6)

Checklist for BELKYRA™ (deoxycholic acid injection)

To administer BELKYRA™, you must be a physician* with appropriate qualifications, expertise in the treatment, and knowledge of the submental anatomy.

* Where national guidance permits, BELKYRA may be administered by appropriately qualified healthcare professionals, under the supervision of a physician.

Patient Name:	Patient Date of Birth:
Date of Treatment:	Person Administering Treatment and Credentials:
Treatment Number: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 *Note: A maximum of 6 treatments may be performed.*	

PATIENT SELECTION

CHECKLIST		REMINDER
Does the patient have moderate to severe convexity or fullness associated with submental fat?	Yes ☐ No ☐	BELKYRA is only indicated for the treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has an important psychological impact on the patient.
Is the patient an adult (≥ 18 years)?	Yes ☐ No ☐	
Does the presence of submental fat have an important psychological effect on the patient?	Yes ☐ No ☐	
Is the patient aged 65 or above?	Yes ☐ No ☐	Caution should be exercised in patients aged 65 years or above as it is not known whether they respond differently than younger patients.
Does the patient have excessive skin laxity, prominent platysmal bands or other conditions for which reduction in submental fat may result in an undesirable outcome?	Yes ☐ No ☐	Careful consideration should be given to the use of BELKYRA in these patients.
Has the patient been screened for other potential causes of submental convexity/fullness (e.g. thyromegaly and cervical lymphadenopathy)?	Yes ☐ No☐	Patient should be screened prior to BELKYRA treatment.
Is the patient obese with a BMI ≥ 30?	Yes ☐ No☐	BELKYRA should not be used in obese patients with a BMI ≥ 30.
Does the patient have body dysmorphic disorder?	Yes ☐ No☐	BELKYRA should not be used in patients with body dysmorphic disorder.
Does the patient have any infection at the injection site?	Yes ☐ No☐	Presence of infection at the injection site is a contraindication.
Does the patient have inflammation or induration at the proposed injection site?	Yes ☐ No☐	Caution should be exercised in these patients.
Does the patient have any symptoms of dysphagia?	Yes ☐ No☐	Caution should be exercised in these patients.
Has the patient had prior surgical or aesthetic treatment of the submental area?	Yes ☐ No☐	Changes in anatomy/landmarks or the presence of scar tissue may impact the ability to safely administer BELKYRA or to obtain the desired result.
Have at least 4 weeks lapsed since previous treatment with BELKYRA?	Yes ☐ No☐ 1st Exposure ☐	At least 4 weeks should lapse between treatments.

PROCEDURE CHECKLIST

	PROCEDURE	REMINDER
EVALUATE	Evaluate and define treatment area: ☐Identify the marginal mandibular nerve area (see Figure 1)	To avoid injury to the marginal mandibular nerve: • Do not inject above the inferior border of the mandible. • Do not inject within a region defined by a 1-1.5 cm line below the inferior border (from the angle of the mandible to the submentum). • Inject BELKYRA only within the target submental fat treatment area.
	☐Identify the platysma	Prior to each treatment session, palpate the submental area to ensure sufficient submental fat and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) within the target treatment area. See Figure 5.
	☐Plan treatment area	Outline the planned treatment area with a surgical pen (see Figure 4) and apply a 1 cm^2 injection grid to mark the injection sites (see Figure 6). Do not inject BELKYRA outside the defined parameters.
APPLY	☐Mark treatment area landmarks, including the "No treatment zone!"	Landmarks are as follows (see Figures 2, 3, and 4): • Inferior border of mandible, anterior borders of sternocleidomastoid muscles, and thyroid notch • Anterior, posterior, and lateral borders of submental fat compartment • "No treatment zone!" to avoid risk of injury to the marginal mandibular nerve
	☐Apply skin marking grid	Do not inject BELKYRA outside the defined parameters. See Figures 4 and 6.
SELECT	☐Determine the number of 1 ml syringes needed	Injections should consist of 0.2 ml (2 mg) per injection site, 1 cm apart. The maximum dose of 10 ml (100 mg equivalent to 50 injections) should not be exceeded in one treatment session. Use a 30 guage (or smaller) 0.5 inch needle.
	☐Prepare the syringes	
INJECT	☐Consider use of the pinch and pull technique. Within the target treatment area, inject perpendicularly to the skin until the needle is midway into the pre-platysmal subcutaneous fat tissues.	• DO NOT inject into post-platysmal fat. • DO NOT inject intradermally to avoid risk of skin ulceration. • DO NOT inject in the "No treatment zone!" to avoid injury to the marginal mandibular nerve. • DO NOT inject into or in close proximity (1-1.5 cm) to thyroid gland, salivary gland, lymph nodes, and muscle. See Figures 3, 4, and 5.
	Post-treatment: ☐Assess smiling and swelling for nerve injury or dysphagia	Injection site nerve injury (motor neuropraxia) manifests as an asymmetric smile or facial muscle weakness.

	Post-treatment: ☐Remind patient about anticipated treatment reactions	In clinical trials, nerve injury occurred in 3.6% of patients and was temporary and in all cases resolved with a mean time to resolution of 53 days (range 1 to 334 days). Skin ulceration occurred in 1 patient (0.1%) and resolved in 23 days.
	Post-treatment: ☐Remember to report adverse drug reactions	All healthcare professionals and patients should report suspected adverse drug reactions via the national adverse event reporting system.

14.4. ENCePP Checklist

Study title:
Study reference number:

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15-16

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	18

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2 Is the planned study population defined in terms of:	☒	☐	☐	16
4.2.1 Study time period?	☒	☐	☐	16
4.2.2 Age and sex?	☒	☐	☐	16
4.2.3 Country of origin?	☒	☐	☐	16
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	15

Comments:

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

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

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

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

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

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	16
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	17
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐ ☐	☐ ☐	☒ ☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Are sample size and/or statistical power calculated?	☒	☐	☐	17

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	17
10.4 Are stratified analyses included?	☒	☐	☐	17

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	18
11.3 Are methods of quality assurance described?	☒	☐	☐	19
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:	☒	☐	☐	20

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	19

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	21
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	20

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	23
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	23

Comments:

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

Date: / /

Signature: _____