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Evaluation of the Safety and Effectiveness of BELKYRA® Inj. for the Treatment of Patients with Submental Fullness due to Submental Fat: A Postmarketing Surveillance Study in Korea

Version 1.0, Date: 29 September 2017

Postmarketing Surveillance Protocol No.:	CMO-EPI-FAS-0537
Type of Postmarketing Surveillance:	Use-result Surveillance
Name of Study Drug:	BELKYRA (Deoxycholic acid) Inj.
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List of Abbreviations and Definition of Terms

ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CR-SMFRS	Clinician-Reported Submental Fat Rating Scale
EDC	electronic data capture
EMA	European Medicine Agency
IEC	independent ethics committee
MFDS	Ministry of Food and Drug Safety
MAH	marketing authorization holder
PMS	postmarketing surveillance
PR-SMFRS	Patient-Reported Submental Fat Rating Scale
SAE	serious adverse event
SM	submental
SMF	submental fat

1. General Particulars

Submental (SM) fullness associated with the accumulation of submental fat (SMF) can influence negative perception (Honigman 2006). Deoxycholic acid injection (KYBELLA in the United States and BELKYRA in Canada) is the first aesthetic injectable approved for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults. The deoxycholic acid in BELKYRA Inj. is identical to deoxycholic acid produced in the body to help fat absorption. (Rubin 2015).

This study is a prospective, observational postmarketing surveillance (PMS) conducted under the requirements of the Korean Ministry of Food and Drug Safety (MFDS) to evaluate the safety and effectiveness of BELKYRA Inj. in routine clinical settings when administered to patients in Korea for the improvement of moderate to severe convexity or fullness associated with SMF in adults. This study will be conducted on 600 Korean patients who were administered BELKYRA Inj. according to clinical practices, based on the instructions for use. Treatment information of BELKYRA Inj. will be collected during the Initial Treatment Visit and Evaluation Visits. Each patient may be administered BELKYRA Inj. at least once and the interval between treatments should be no less than 1 month apart. Safety information of all patients within 3 months after the last treatment will be collected at the Follow-up.

The study will sequentially enroll eligible Korean patients treated with BELKYRA Inj. at each of the selected clinic(s)/hospital(s) from the date of contract until 600 patients have completed the Follow-up during the study period. The decision to treat a patient with BELKYRA Inj. is determined by the investigator and patient prior to the decision to include the patient in the study.

Safety information and effectiveness, as assessed by the investigator and by the patient, will be collected during patient's follow-up from the initial treatment with BELKYRA Inj. to within three months after the last treatment. If the patient is unable to make in-office visit during the study period, safety information and the patient's assessment of effectiveness may be collected over the telephone. The investigator's assessment of effectiveness may not be collected over the telephone. This study will be analyzed through descriptive statistical analysis.

The study will start after the final PMS protocol is approved by the MFDS and will be completed within 6 years after the study drug and efficacy/effectiveness approval date 25 August 2017 (i.e., 24 August 2023) or when 600 patients have completed the study before the end of the 6-year period. Periodic and final reports will be sent to the MFDS according to the schedule per regulation.

The re-examination report will be submitted by 24 November 2023.

2. Drug and Indication Under Re-examination

2.1. Study Drug

BELKYRA (deoxycholic acid) Injection 10 mg/mL (containing Benzyl Alcohol), hereinafter "BELKYRA Inj.".

2.2. Efficacy and Effectiveness

Improvement of moderate to severe convexity or fullness associated with SMF in adults.

2.3. Re-examination Period

6 years from 25 August 2017- 24 August 2023

2.4. Authorization No.

No. 251-31

2.5. Date of Authorization

25 August 2017

2.6. Planned Market Launch Date

29 January 2018

3. Postmarketing Surveillance Study Protocol

3.1. Study Objectives

The purpose of this PMS study is to evaluate the safety and effectiveness of BELKYRA Inj. used according to the dose specified in the instructions for use, for the treatment of patients with SM fullness due to SMF, through active investigation under routine clinical practice. The specific study objective is to report on the following:

1. Serious Adverse Events and Adverse Drug Reactions;
2. Unexpected Adverse Events and Adverse Drug Reactions that are not reflected in the precautions;
3. Known Adverse Drug Reactions;
4. Non-serious Adverse Drug Reactions;

5. Other safety or effectiveness related information.

The specific objectives of this study are as follows:

1. To assess the safety profile of BELKYRA in routine clinical practice in adult patients treated for SM fullness due to SMF;

2. To assess the effectiveness of BELKYRA Inj. in routine clinical practice in adult patients treated for SM fullness due to SMF.

3.2. Study Population

This study will include adult patients (≥ 18 years of age) in South Korea treated with BELKYRA Inj. for the improvement of moderate to severe convexity or fullness associated with SMF in adults according to the approved label.

3.3. Number of Patients

In compliance with Article 6 Paragraph 3 of the [Standard for Re-examination of New Drugs, etc.], this study intends to assess 600 patients who were treated with BELKYRA Inj. at least once in accordance with dosage/usage in the Product Package Insert for the improvement of moderate to severe convexity or fullness associated with SMF and completed the Follow-up.

The actual number of patients enrolled into the study may be more than 600 patients to allow for patients who are lost to follow-up or withdraw from the study prior to providing any follow-up data, as these patients will be excluded from the safety and effectiveness assessments.

3.4. Planned Study Period

BELKYRA Inj., for the improvement of moderate to severe convexity or fullness associated with SMF in adults, was approved in South Korea on 25 August 2017. Pursuant to pharmaceutical regulations, this study will be completed within 6 years after the approval date, during the re-examination period from 25 August 2017- 24 August 2023. The study report will be submitted to the MFDS by 24 November 2023.

3.5. Planned Study Sites

BELKYRA Inj. is expected to be mainly used at clinics (specializing in dermatology, plastic surgery, and aesthetic medicine), university hospitals, and general hospitals with dermatology, plastic surgery, or aesthetic medicine departments; therefore, surveillance will be mainly conducted by collecting relevant information on treated patients from contracted clinicians at these locations.

The specific criteria for the selection of planned study sites are as follows:

1) Sites equipped with the equipment, facilities, and personnel to fully accomplish the objectives of the study;

2) Sites equipped with investigators who have professional knowledge about the target drug and indications, have received necessary training/education or have work experience for performing the study tasks;

3) Sites that are able to handle records containing the patients' personal information in a way that ensures their confidentiality;

4) Sites that are able to support the notification of investigators and their familiarization of the study protocol;

The active surveillance study will begin after a contract has been executed between the hospital or principal investigator and Allergan. In the event that a contracted principal investigator is changed during the agreed surveillance period, a qualified replacement will be identified to assume the role of principal investigator to ensure continuity of the surveillance study. For this purpose, a separate contract or an amendment to the contract will be executed with the new principal investigator, and the Independent Ethics Committee (IEC) will be notified of the changes.

Designated study personnel will participate in a BELKYRA Inj. training program. In addition, the clinical research associate (CRA) will provide training on the conduct of the study and provide overview of the approved label to the participating investigator and all site staff involved in the study.

3.5.1 Additional Particulars Regarding Patients

Allergan Korea shall deliver the product information, instructions for use, and precautions to the medical professionals prescribing/administrating BELKYRA Inj. and conduct training on product properties and usage methods.The medical professionals concerned shall be reminded of the injection site nerve damage that may affect patients with BELKYRA Inj. use, risks including unapproved uses, and all information included in the product information; and advised to educate all patients on product properties, possible risks, and information included in the product information before administration.

3.6. Surveillance Items and Surveillance Method

3.6.1 General Particulars

The investigator or his/her designee will collect the required information on enrolled patients utilizing the provided electronic case report forms. Paper case report forms will also be available in the event the site cannot access the electronic data collection (EDC) system. It is the investigator's responsibility to ensure the accuracy and completeness of all provided data entered/recorded on the CRFs and source documents by any site staff member trained for study data collection. Training on study data collection will be provided by Allergan. All data collection will be obtained in compliance with local ethical and privacy regulations.

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BELKYRA Inj. treatment information is collected from Initial Treatment Visits and up to Evaluation Visits. The patients can administer at least one BELKYRA Inj. and the treatment interval should be 1 month or longer. Safety information of all patients within 3 months after the last treatment will be collected through Follow-up. Data will be collected by interviewing patients and/or reviewing medical charts. If a patient cannot be reached or does not wish to answer questions, this patient will be considered as lost to follow-up and the reason will be recorded. Investigators shall report adverse events (AEs), adverse drug reactions (ADRs), and serious adverse events (SAEs) to Allergan without any delays in accordance with local regulatory requirements and Allergan's AE reporting policy. The definitions and reporting requirements for AEs, ADRs, and SAEs are presented in Section 3.6.3.2.

3.6.2 Surveillance Items

The following basic information will be collected (a summary of the study schedule is presented in Table 1):

- Information on study site
    - Site number
    - Site name (name of medical institution)
    - Department name
    - Investigator name
- Basic information of patients

  - Patient number
    - Basic information (Refer to section 3.6.2.1)

- Date of visit
- BELKYRA Inj. usage status
  - Usage/Dosage (dose, number of administrations, route of administration, etc.)
  - Administration period (Dates of start and end)
  - Indication
- [Other than study site] Presence or absence of additional BELKYRA Inj. treatment
- Other cosmetic/dermatologic treatments or procedure at current visit
- Concomitant medications (Refer to section 3.6.3.2)
- Evaluation visit and status at follow-up
- Safety assessment (Refer to section 3.6.3.1)
- Effectiveness assessment (Refer to section 3.6.3.3)
- CRF completion date and investigator's signature

Table 1. Study Schedule

Procedure	**Initial Treatment Visit**	**Evaluation Visit(s) (at least once)**	
Patient information/medical history/demography/ treatment history	X		
CR-SMFRS	X	X*	
PR-SMFRS	X	X	
BELKYRA Inj. treatment injection	X	X+	
Concomitant medications	X	X	
Adverse events	X	X	

*If Follow-up is conducted over the phone, CR-SMFRS will not be collected.
+Information collected at treatment.

3.6.2.1 Basic Information

The following patient background information and medical history will be collected after enrollment:

- Subject ID, Sex
- Date of birth (YYYY/MM/DD)
- Height and weight
- Collect a medical history, as judged by the investigator, including the following:
    - History of facial aesthetics procedures, including procedures to the SM area in the past 12 months
        - Collect the following information for previous (within the last 12 months) treatments for SMF, if any:
            - Name of treatment
            - Date of treatment
            - Type of treatment
            - Frequency of treatment
            - Site(s) of treatment
    - Surgical history
    - Comorbidities (includes diabetes and cardiovascular disease)
    - Other relevant medical history, including complications of underlying disease
    - Presence of hepatic/renal disorder
    - Presence of allergic history
    - Previous disease history
    - Pregnancy and breastfeeding status (for female patients)

3.6.2.2 Concomitant medications

Any concomitant medications (excluding BELKYRA Inj.) prescribed by any medical specialist, that patients are currently taking, will be recorded. The following information will be collected:

- whether other medications were concomitantly administered or used
- drug name (generic name or active ingredient)
- route of administration
- frequency
- dosage
- start date (YYYY/MM/DD)
- end date (YYYY/MM/DD) or check box if ongoing
- indication for drug use

3.6.3 Surveillance Method

3.6.3.1 Matters Related to Safety

The roles and responsibilities of study personnel for identifying, collecting, and reporting AE/ADR/SAE data to Allergan and relevant health authorities are presented in the Safety Management Plan.

All AEs that occur during and/or after administration of the initial BELKYRA Inj. treatment through the follow-up period will be collected regardless of causal relationship to the product. The safety assessment will include all undesirable changes in medical findings (including any laboratory or other test findings) and all AEs associated with the product.

The following information will be collected for all AEs:

- Investigator's comment on the SAEs and ADRs
- Descripton of any treatment given and the AEs
- Product administration date
- Relevant medical history

- Relevant concomitant medications
- Onset and resolution (if resolved) dates for the AEs
- Outcome of AEs
- Actions taken by the investigator or healthcare provider
- Presence of causal relationship to the product
- Site (body part) affected, if applicable
- Relationship to the administration procedure
- Severity of AEs
- Determination of whether the AE is serious or non-serious

3.6.3.2 Definition of Terms

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not related to the medicinal investigational product. This includes, but is not limited to, AEs that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure

Severity of Adverse Event

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed with the following definitions serving as guidelines:

- Mild Awareness of sign or symptom, but easily tolerated.
- Moderate Discomfort, enough to cause interference with usual activity.
- Severe Incapacitating, with inability to work or do usual activity.

Adverse Drug Reaction (ADR)

Regarding marketed medicinal products, a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases, or for modification of physiological function is considered an adverse drug reaction (ADR).

Serious Adverse Event (SAE)

An serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death or life-threatening AE;
- Inpatient hospitalization or prolonging of existing hospitalization;
- Resulting in persistent or significant disability/incapacity;
- Resulting in congenital anomaly or birth defect;
- Other medically significant issues.

Allergan considers all cancer AEs to be serious. In addition, miscarriage (spontaneous or non-spontaneous) is also considered an SAE.

Inpatient hospitalization or prolongation of existing hospitalization for “social reasons” without an associated AE (e.g., for convenience or for respite care when there is no one at home to care for the patient, prolonged hospitalization while appropriate social care is set up) is not considered reportable as an SAE.

Any preplanned surgery or procedure should be clearly documented in the patient's source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as an SAE and reported to Allergan.

Expected Adverse Event

Any adverse event or suspected adverse reaction that is mentioned in the investigator brochure or other reference safety information against which clinical trial expectedness is assessed.

Unexpected Adverse Event

An unexpected adverse event is an event, the nature or severity of which is not consistent with the applicable product information, which is the local label.

Causality of Adverse Event

As per the MFDS's guidelines for PMS, the following definitions will be used to assess causality:

- Certain: Considering the timing of medication administered and onset of an adverse event, there is a reasonable relationship between the adverse event and surveillance medication. The adverse event cannot be explained by other concurrent medication, chemicals, or other underlying disease. There is clinically reasonable response upon withdrawal of the drug. The same event recurred following rechallenge with the same drug alone.

- Probable/likely: Considering the timing of medication administered and onset of an adverse event, there is a reasonable relationship between the adverse event and the surveillance drug. The adverse event does not appear to be related to concurrent medication, chemicals, or other underlying disease, and shows a clinically reasonable response on stopping the surveillance drug. There is no information on rechallenge.

- Possible: Considering the timing of medication administered and onset of an adverse event, there is a reasonable relationship between the adverse event and the surveillance drug. However, the adverse event can be also explained by other concurrent medication, chemicals, or underlying disease. Information on response when stopping the surveillance drug is not sufficient or available.

- Unlikely: It is a transient adverse event that is unlikely to be related to the surveillance drug based on the timing of medication and onset of the adverse event. The adverse event can be reasonably explained by other concurrent medication, chemicals, or other underlying disease.

- Conditional/unclassified: More data is required for appropriate evaluation or additional materials are being reviewed.

- Unassessable/unclassifiable: Information is insufficient or contradictory to such an extent that a judgment cannot be made and it is not possible to supplement or confirm such information.

3.6.3.3 Effectiveness Variables

The effectiveness of BELKYRA Inj. treatment for the improvement of moderate to severe convexity or fullness associated with SMF in adults will be assessed based on submental fat assessments.

Patients and investigators will complete SMF assessments at Initial treatment, all Evaluation Visits, consisting of the following:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) Score: A validated scale used by investigators to assess SM convexity/amount of SMF. Specifically, the CR-SMFRS ranges in whole number increments from 0 (absent submental convexity) to 4 (extreme submental convexity) (Table 2)

    - The investigator will record the date of the contact and their assessment. If the assessment of SM convexity/amount of SMF cannot be assessed, the investigator will record the reason the assessment cannot be performed (e.g., patient lost to follow-up, patient contacted via telephone, etc.). Investigator-assessed effectiveness data will only be collected by the investigator during in-house visits and will not be collected via telephone contact with the patient.

- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) Score: Validated scale used by patients to evaluate SM size. Specifically, the PR-SMFRS asks patients to assess how much fat they have under their chins by selecting options ranging from “no chin fat at all” to “a very large amount of chin fat” (Table 3).

    - The patient’s overall assessment of the effectiveness of BELKYRA Inj. treatment on SMF can be collected during house visits or via telephone contact.

CR-SMFRS is a validated scale used by investigators to assess SM convexity/amount of SMF. Specifically, the CR-SMFRS ranges in whole number increments from 0 (absent submental convexity) to 4 (extreme submental convexity) (Table 2). The PR-SMFRS is a validated scale used by patients to evaluate SM size. Specifically, the PR-SMFRS asks patients to assess how much fat they have under their chins by selecting options ranging from “no chin fat at all” to “a very large amount of chin fat” (Table 3).

3.6.3.4 Matters Related to the Selection of Patients

The investigators at the relevant sites will enroll patients who elect to receive treatment with BELKYRA Inj., from the first patient until required enrollment satisfied.

The investigators will enroll eligible and Korean patients suitable for BELKYRA Inj. administration at each of the contracted clinic(s)/hospital(s) to ensure appropriate enrollment of patients during the agreed surveillance period.

The decision to treat a patient with BELKYRA Inj. is determined by the investigator and patient prior to the decision to include the patient in the study. Per approved label, BELKYRA Inj. treatment is contraindicated in patients with infection at the injection sites. Patients presenting evidence of causes of enlarged SM area other than localized SMF (E.g.: thyroid enlargement, enlarged submental salivary glands, cervical lymphadenopathy, etc.) shall be excluded from the study Patients with severe laxity shall be excluded from the study according to the investigator’s judgment, as the reduction of SMF may result in medically and aesthetically unacceptable outcomes in such patients.

4. Evaluation Items, Assessment Methods and Analytical Methods

4.1. Evaluation item

4.1.1 Composition of Subjects

Different analysis sets will be defined and used for the statistical analyses. Tables for the composition of patients including the following analysis sets will be presented.

- Full analysis set - patients whose case report form were retrieved: the demographic data, baseline characteristics including diagnosis, treatment history, concurrent disease, etc., and concomitant medications will be analyzed for the full analysis set

- Safety analysis set – Subjects who have administered the study drug at least once and have been followed up

- Effectiveness analysis set – Among the safety analysis set, subjects whose effectiveness assessments were recorded as described in the study protocol

4.1.2 Matters Related to Safety

Safety assessment shall be conducted based on factors thought to affect AE incidence and safety.

4.1.3 Matters Related to Effectiveness

Effectiveness assessment will be carried out based on objective or subjective indexes to determine the effectiveness of BELKYRA Inj. treatment for excess SMF.

4.1.4 Matters Related to Special Patient Populations

Pediatrics are not included, and if there are geriatrics (aged 65 or higher), pregnant women, renal impairment patients, hepatic impairment patients or other special patient groups among patients who have been prescribed this product under the postmarketing use setting, such special patient groups shall be extracted, the incidence of AEs identified, and unexpected ADRs as well as other factors deemed to affect safety or effectiveness investigated for them.

4.2. Assessment Methods and Analysis

Statistical analyses to address the specific research objectives will be conducted according to a detailed statistical analysis plan that will be developed and finalized prior to database lock. Analyses will be performed on de-identified patient data. All analyses will be descriptive in nature; no statistical hypothesis testing will be performed. Results will be displayed in tabular format (i.e., summary statistics, frequency distribution of item responses, and incidence rates will be presented as applicable). No imputations for missing values will be performed.

All statistical tabulations and analyses will be performed using SAS® software, version 9.3 or later. Patient data will be presented in data listings.

Effectiveness and safety analyses will be based upon all enrolled patients who had at least 1 post enrollment visit. Additional groups also may be examined, as deemed appropriate, and will be defined in the Statistical Analysis Plan (e.g., sex, initial assessment scores, prior treatments received).

Statistical analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the samples studied. Continuous variables (e.g., age) will be summarized using the descriptive statistics including the number of non-missing

observations, mean, standard deviation, median, minimum, and maximum values by visit. Categorical variables (e.g., gender) will be summarized by the frequency counts and percentages in each category. Any missing category included in the case report form or generated from data collection will be treated as an independent category without imputation. Patients that use study treatment off-label will be analyzed separately.

A detailed statistical analysis plan (SAP) will be prepared prior to database lock. The key elements of analysis are summarized below in the sub-sections. Additional exploratory, descriptive, and inferential analyses of the data will be conducted as deemed appropriate. The SAP will be updated only if these additional analyses change a principal feature of the analyses described here.

4.2.1 Analytic Methods

4.2.1.1 Safety Analysis Methods

MedDRA version 19.0 or higher will be used to report data according to system organ class and preferred terms in the postmarketing surveillance. Descriptive statistics will be used to summarize AE (safety) data. Specifically, the frequency of AEs by system organ class and preferred term will be presented separately for SAEs, nonserious AEs, ADRs, and unexpected ADRs. The incidence rate of each type of AE will be calculated as the number of new events divided by the corresponding person-time at risk based on the time since the initial BELKYRA Inj. treatment session. For describing the incidence of AEs, the frequency, patient-time incidence rate, and 95% CI for the incidence measures will be displayed.

Concomitant medications and procedures will be summarized descriptively.

Pregnancy status will be summarized descriptively and/or presented in patient listings.

4.2.1.2 Effectiveness Analysis Methods

The following SMF assessments are planned at each visit:

- CR-SMFRS score (Table 2)
- PR-SMFRS score (Table 3)

Results for the CR-SMFRS and PR-SMFRS scores at baseline (before initial treatment) and Evaluation Visits will be summarized using descriptive statistics. The number and percent of patients for each parameter who are responders, i.e., have at least a 1-grade improvement, will be presented, along with the corresponding 95% confidence interval (CI).

5. Other

5.1. Case Report Form Completion and Retention

The investigator is responsible for ensuring that data is properly recorded on each patient's case report forms and related documents. An investigator who has signed the investigator signature page should personally sign for the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The case report forms are to be submitted to Allergan or Allergan's representative(s) in a timely manner at the completion of the study, or as otherwise specified by Allergan, and will be maintained in a central data repository.

All study related correspondence, patient records, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file after receipt by Allergan and retained for 3 years after completion and submission of the surveillance report.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

5.2. Protocol Amendment

When a significant change in administration, dosage, indications, or study conduct is required or anticipated during the active surveillance period of BELKYRA Inj., the protocol will be amended accordingly and submitted to the MFDS.

5.3. Reporting of Adverse Events

All SAEs and ADRs (serious or not) should be recorded in the study CRF and on the Allergan Noninterventional Study Adverse Event Form. Non-serious AEs with no causal relationship to BELKYRA Inj. will only be collected in the study CRF (i.e., these events will not be reported using the Noninterventional Study Adverse Event Form).

Each participating site will be trained on the recording and reporting of SAEs, serious and non-serious ADRs, and important identified risks, important potential risks, and missing information to the marketing authorization holder (MAH), or designee. Investigators will be instructed to follow the local regulations of reporting AEs, ADRs, and SAEs to local and national authorities. AEs, ADRs or SAEs include all events observed by site staff or reported to the site staff during and/or after administration of the initial BELKYRA Inj. treatment through the follow-up period (may or may not include treatment, and treatment is not included in the Evaluation Visits after final

treatment). The investigator or site staff shall instruct patients to report AEs during this time period.

At all study visits, the patients will be queried with simple, open ended questions and questions designed to collect information regarding specific outcomes of interest. If a patient is seen by a nonstudy physician, the investigator and/or trained site staff should make every effort to follow-up with the relevant concerned healthcare provider to obtain all information necessary for the accurate reporting of the event in a timely manner.

All SAEs and ADRs must be reported to the MAH within 24 hours of learning of the event as described within the Safety Management Plan. Upon receipt of an SAE or ADR report, the MAH or designated contract research organization staff member will initiate appropriate follow-up. All events reported on the AE CRF by the investigator will be confirmed by medical record review and or direct follow-up with the investigator/treating physician.

In the event of death, the cause of death will be recorded. In the event of any SAE, the investigator shall carry out the following:

1. Notify Allergan or its representatives immediately, but no later than 24 hours by fax or email using the PMS Adverse Event Form (contact details can be found on page 1 of the Noninterventional Study Adverse Event Form). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of this protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the AE(s) on the Noninterventional Study Adverse Event Form describing the event chronologically, including any treatment given (e.g., medications administered, procedures performed) for the AE(s). Summarize the relevant clinical information about the event: signs, symptoms, diagnosis, clinical course, and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality, which includes a statement as to whether the event was or was not related to the use of the investigational product.

4. Promptly inform the governing Independent Ethics Committee (IEC) of the SAE as required by the IEC, local regulations, and the governing health authorities.

Pregnancy is not considered an AE. However, in the case that a patient gets pregnant, the investigator shall take the following action:

5. Notify Allergan or the designee/contract clinical study institution within 24 hours of knowledge of the pregnancy via e-mail or telephone.

5.4. Protection of Human Subjects

When Independent Ethics Committee (IEC) is in place in the study site, approval from IEC in accordance with local regulations will be obtained. Prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., CRF and communication materials) to the responsible IEC for its review. The IEC's approval will be filed in the study master file managed by Allergan or its designee. Patient enrollment will not start at any site before the approval from the concerned IEC. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data by local laws and regulations. In the database and reports, each patient will be unambiguously identified by a study subject number, which links all the data reported for that specific patient.

To ensure the quality and integrity of research, the conduct of this study will be governed by the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines Reporting and Dissemination of Results.

5.5. Reporting and Dissemination of Results

As per the requirements of the MFDS, the results of this postmarketing surveillance shall be periodically summarized and reported to the MFDS according to the following schedule: every 6 months for the first 2 years and annually for the remaining 4 years. Each report will be submitted within 2 months of the end of each reporting period. At the end of the surveillance period (6 years after the product/indication approval date), a final report will be prepared and submitted to the MFDS.

6. References

Honigman R, Castle DJ. Aging and cosmetic enhancement. Clin Interv Aging. 2006; 1(2): 115–9.

Rubin R. FDA okays drug to reduce double chins. JAMA. 2015; 313(21): 2115.

7. Appendices

7.1. Rating Instruments

Clinician-Reported Submental Fat Rating Scale

The CR-SMFRS is presented in Table 2. The CR-SMFRS score is based on the investigator's clinical evaluation of the patient, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head. The score is determined using the definitions in the rating scale and representative photographs associated with each score. The final determination of the score will be made while the patient's head is in the Frankfort plane posture. The score will be recorded as a whole number. At the enrollment/index treatment visit, the score is determined in conjunction with protocol entry criteria (eg, absence of loose skin, diffuse submental fat, and prominent platysmal bands at rest that interfere with evaluation of localized fat).

Table 2. Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

Score	Submental Fat Description
0	Absent submental convexity: No localized submental fat evident
1	Mild submental convexity: Minimal, localized submental fat
2	Moderate submental convexity: Prominent, localized submental fat
3	Severe submental convexity: Marked, localized submental fat
4	Extreme submental convexity

Patient-Reported Submental Fat Rating Scale

Please look in the mirror at the area under your chin to help you answer the following question: How much fat do YOU have under your chin right now?

Patients will respond to the question using the scale shown in Table 3

Table 3. Patient-Reported Submental Fat Rating Scale (PR-SMFRS)

Mark ☒ in one box below.	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

7.2. Product Information (Korean)

Refer to product information for BELKYRA Inj.

7.3. Case Report Form

Evaluation of the Safety and Effectiveness of BELKYRA® for the Treatment of Patients with Submental Fullness due to Submental Fat: A Postmarketing Surveillance Study in Korea

Case Report Form (CRF):
1. Initial Treatment Visit

Site Number:		**Patient Number:**	
Name of Institution:		Date of Visit (yyyy/mm/dd):	_____ / _____ / _____
Department name:		Name of Investigator:	

1. Patient Eligibility

Does the patient meet the following criteria?	□ Yes □ No (If **no**, please exclude the patient from the study)
1. Patient is an adult (≥ 18 years of age) in South Korea treated with BELKYRA for the improvement of moderate to severe convexity or fullness associated with submental fat in adults according to the approved label. □ Yes □ No 2. Patient, per approved label, does not have an infection at the injection sites. □ Yes □ No 3. Patient does not have evidence of any cause of enlargement in the submental area (eg, thyroid enlargement, cervical adenopathy) other than localized SMF. □ Yes □ No 4. In the judgment of the investigator, patient does not have severe skin laxity for which reduction in SMF may result in an aesthetically unacceptable outcome. □ Yes □ No	

2. Basic Information: Patient background information

Sex □ Male □ Female	**Date of Birth (yyyy/mm/dd):** _____ / _____ / _____ Patients < 18 years old are not eligible	**Height** _____ cm **Weight** _____ kg
Currently pregnant or currently breastfeeding (if applicable):	□ No □ Yes (If **yes**, please exclude the patient from the study)	
Patient have BELKYRA administison history prior to this study		□ Yes □ No

3. Basic Information: History of facial aesthetics procedures

History of facial aesthetic procedure (other than SMF treatment) in the past 12 months:	Brow lift: □ No □ Yes Rhinoplasty: □ No □ Yes Chemical peel: □ No □ Yes Eyelid surgery: □ No □ Yes Face lift: □ No □ Yes Facial implants: □ No □ Yes Laser skin resurfacing: □ No □ Yes Dermal fillers: □ No □ Yes Botulinum Toxins: □ No □ Yes Others: □ No □ Yes(Specify _____)

4. Basic Information: History of Submental Fat (SMF) Treatments

History of SMF treatments in the past 12 months:		□ None □ Yes (If **yes**, please specify by completing the rest of this question)		
Type of Treatment	**Name of Treatment**	**Date of Treatment (yyyy/mm/dd)**	**No. of Treatments**	**Site(s) of Treatment**
☐ Energy Devices		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other
☐ Dermal Filler		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other
☐ Liposuction		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other
☐ Thread Lifting		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other

☐ Other Injectable		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other
☐ Other: Please specify _____		Date of Treatment ____/___/___	No. of Frequency _____	☐ Chin/Neck ☐ Face ☐ Other

5. Basic Information: Medical history

Medical history, Surgical history, Comorbidities (includes hepatic disorder, renal disorder, diabetes and cardiovascular disease) and other relevant medical history (including complications of underlying disease and allergic history):		□ None □ Yes (If **yes**, please specify by completing the rest of this question)
Category	**Disease/Surgery/Complications**	**Ongoing at the time of BELKYRA treatment**
☐ Hepatic Disorder ☐ Renal Disorder ☐ Allergic History ☐ Other	1)	□ Yes □ No
☐ Hepatic Disorder ☐ Renal Disorder ☐ Allergic History ☐ Other	2)	□ Yes □ No
☐ Hepatic Disorder ☐ Renal Disorder ☐ Allergic History ☐ Other	3)	□ Yes □ No
☐ Hepatic Disorder ☐ Renal Disorder ☐ Allergic History ☐ Other	4)	□ Yes □ No
☐ Hepatic Disorder ☐ Renal Disorder ☐ Allergic History ☐ Other	5)	□ Yes □ No

6. Investigator SMF Assessment: Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score

Was the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) completed:	□ No □ Yes
Evaluation Date (yyyy/mm/dd):	_____ / _____ / _____

SMF score based on investigator's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head. The final determination of the score will be made while the patient's head is in the Frankfort plane posture as described in the CR-SMFRS. The score will be recorded as a whole number. At enrollment, the score is determined in conjunction with protocol entry criteria (e.g. absence of loose skin, diffuse submental fat, and prominent platysmal bands at rest that interfere with evaluation of localized fat).

Using the validated submental fat rating scale, **select the patient's CR-SMFRS score (Check one):**

SMF Description		
☐	**0**	Absent Submental Convexity: No localized submental fat evident
☐	**1**	Mild Submental Convexity: Minimal, localized submental fat
☐	**2**	Moderate Submental Convexity: Prominent, localized submental fat
☐	**3**	Severe Submental Convexity: Marked, localized submental fat
☐	**4**	Extreme Submental Convexity

7. ***[To be evaluated by the Patient]*** Patient SMF Assessment: Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score

Did the patient complete the Patient -Reported Submental Fat Rating Scale (PR-SMFRS)?	□ No □ Yes
Evaluation Date (yyyy/mm/dd):	_____ / _____ / _____

Please look in the mirror at the <u>area under your chin</u> to help you answer the following question:

How much fat do you have under your chin right now?	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

8. BELKYRA Treatment Administration for Fullness of Submental Fat:

Date of injection (yyyy/mm/dd):	_____ / _____ / _____
Please enter number of injections (number) and total dose (mL):	_____ points X 0.2ml = _____ mL

The following section on BELKYRA administration is provided in the Dosage section of the approved label.

BELKYRA is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2.

- *A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1-cm apart.*
- *Up to 6 single treatments may be administered at intervals no less than 1 month apart.*

9. Other facial aesthetic or dermatologic treatment at current visit:

Other facial aesthetic or dermatologic treatment at current visit:	□ None □ Yes (If **yes**, please specify facial aesthetic or dermatologic treatment that the patient is currently taking by completing the rest of this question)	
Name of Treatment	**Site of Treatment**	**Comment**
1)		
2)		
3)		
4)		
5)		

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Case Report Form (CRF):
2. Evaluation Visit

Evaluation Date (yyyy/mm/dd):	_____ / _____ / _____
Type of Follow-up:	□ In-Office □ Phone □ Loss to follow-up, reason (explain number of telephone call attempts made, whether patient could not be reached, or patients was not willing to answer questions, etc.): _____

1. Pregnancy:

Has the patient become pregnant since the index BELKYRA treatment?	□ No □ Yes (If **yes**, please notify Allergan or its representatives by completing GPSE-PVOPS-F-02-06 and email to [redacted] within 24 hours.)

2. [Except Research Institution] BELKYRA Treatment received for improvement of Submental Fat between Initial Treatment or Last Evaluation Visit and current visit:

Received additional BELKYRA treatment for SMF since Initial Treatment or Last Evaluation Visit:	□ None □ Yes (If **yes**, please complete the rest of this question)
Date of injection (yyyy/mm/dd): (Depending on the permit, the treatment interval should be at least 1 month)	_____ / _____ / _____ □ Unknown

3. Other facial aesthetic or dermatologic treatment at current visit:

Other facial aesthetic ordermatologic treatment at current visit:	□ None □ Yes (If **yes**, please specify facial aesthetic or dermatologic treatment that the patient is currently taking by completing the rest of this question)

Name of Treatment	Site of Treatment	Comment
1)		
2)		
3)		
4)		
5)		

4. Investigator SMF Assessment: Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score

Was the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) completed:	□ No □ Yes
Evaluation Date (yyyy/mm/dd):	_____ / _____ / _____

SMF score based on investigator's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head. The final determination of the score will be made while the patient's head is in the Frankfort plane posture as described in the CR-SMFRS. The score will be recorded as a whole number. At enrollment, the score is determined in conjunction with protocol entry criteria (e.g. absence of loose skin, diffuse submental fat, and prominent platysmal bands at rest that interfere with evaluation of localized fat).

Using the validated submental fat rating scale, **select the patient's CR-SMFRS score (Check one):**

SMF Description		
☐	**0**	Absent Submental Convexity: No localized submental fat evident
☐	**1**	Mild Submental Convexity: Minimal, localized submental fat
☐	**2**	Moderate Submental Convexity: Prominent, localized submental fat
☐	**3**	Severe Submental Convexity: Marked, localized submental fat
☐	**4**	Extreme Submental Convexity

5. [***To be evaluated by the Patient]*** Patient SMF Assessment: Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score

Did the patient complete the Patient -Reported Submental Fat Rating Scale (PR-SMFRS)?	□ No □ Yes
Evaluation Date (yyyy/mm/dd):	_____ / _____ / _____

Please look in the mirror at the <u>area under your chin</u> to help you answer the following question:

How much fat do you have under your chin right now?	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

6. BELKYRA Treatment Administration for Fullness of Submental Fat:

Was BELKYRA Treatment preformed at this visit:	□ No(If **No**,go to question 7) □ Yes (If **yes**, please complete the rest of this question)
Date of injection (yyyy/mm/dd):	_____ / _____ / _____
Please enter number of injections (number) and total dose (mL):	_____ points X 0.2ml = _____ mL

The following section on BELKYRA administration is provided in the Dosage section of the approved label, which will be linked to the eCRF.

BELKYRA is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2.

- *A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1-cm apart.*
- *Up to 6 single treatments may be administered at intervals no less than 1 month apart.*

7. Treatment completion

Is the treatment completed?	□ No (If **NO**, please complete the rest of this question) □ Yes
Next visit date (yyyy/mm/dd):	_____ / _____ / _____

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Case Report Form (CRF):
4. Concomitant Medication

Concomitant medications (excluding BELKYRA) prescribed by any medical specialist, that the patient is currently taking during the Initial Treatment or Last Evaluation Visit.	□ No □ Yes (If **yes**, please specify all medications that the patient is currently taking after Initial Treatment or Last Evaluation Visit by completing the rest of this question)

Medical Name (Trade Name)	Route of Administration	Frequency	Dosage	Date Started (yyyy/mm/dd)	Date Ended (yyyy/mm/dd)	Reason/ Indication
1)				____ / ___ / ___	____ / ___ / ___ □ Ongoing	□ Medical History(_____) □ Adverse Event(_____) □ Prevention □ Others(_____)
2)				____ / ___ / ___	____ / ___ / ___ □ Ongoing	□ Medical History(_____) □ Adverse Event(_____) □ Prevention □ Others(_____)
3)				____ / ___ / ___	____ / ___ / ___ □ Ongoing	□ Medical History(_____) □ Adverse Event(_____) □ Prevention □ Others(_____)
4)				____ / ___ / ___	____ / ___ / ___ □ Ongoing	□ Medical History(_____) □ Adverse Event(_____) □ Prevention □ Others(_____)
5)				____ / ___ / ___	____ / ___ / ___ □ Ongoing	□ Medical History(_____) □ Adverse Event(_____) □ Prevention □ Others(_____)

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Case Report Form (CRF):
5. Adverse Event

Did patient experience any adverse event since the index BELKYRA treatment and/or at Evaluation Visit:	□ No □ Yes □ Unknown (If subject is lost to follow-up, check Unknown)
Adverse event description **(***diagnosis***):**	
Onset of event (yyyy/mm/dd):	_____ / _____ / _____
Stop date (yyyy/mm/dd):	_____ / _____ / _____ □ Ongoing
Severity	□ Mild □ Moderate □ Severe
Was the reaction serious?	□ No (if **no**, continue to complete outcome) □ Yes (if **yes**, please complete seriousness criteria)
In the event of a Serious Adverse Event, notify Allergan or its representatives immediately, but no later than 24 hours by completing online eCRF or email [redacted] the Adverse Report Form GPSE-PVOPS-F-02-03 (Non-Interventional Studies Serious Adverse Event Non-Serious Adverse Drug Reaction Form)). By checking 'YES' for 'was the reaction serious?' using online eCRF, an automatic alert will be sent immediately from the EDC system to Allergan PV mailbox.	
Seriousness criteria (if reaction was serious, *select all that apply):*	☐ Death
	☐ Life-threatening
	☐ Hospitalization – initial or prolonged
	☐ Disability or permanent damage
	☐ Congenital anomaly/birth defect
	☐ Other important medical event
Outcome (*select one):*	☐ Recovering/resolving/improved
	☐ Recovered/resolved with sequelae
	☐ Recovered/resolved without sequelae
	☐ Not recovered/not resolved/unchanged
	☐ Fatal
	If Subject died, enter date of death (yyyy/mm/dd): _____ / _____ / _____
	Was an autopsy performed? □ No □ Yes □ Unknown
	☐ Unknown

Action taken with Study Drug (*select one):*	☐ Dosage maintained	
	☐ Dosage increased	
	☐ Dosage reduced	
	☐ Drug discontinued	
	If patient was withdrawn permanently from the trial, enter date of withdrawal (yyyy/mm/dd):	_____ / _____ / _____
	☐ Temporarily discontinued	
	☐ Not Applicable	
	☐ Unknown	
Treatment	□ No □ Yes (Specify:_____)	
Was diagnostic tests performed?	□ No □ Yes (If Yes, please update **6. Diagnostic Test page**)	
comments		
Causal Relationship (is there a reasonable possibly that the event/reaction may have been caused by (select 'yes' or 'no' for each option))		
Study drug?	□ No (Not Related or Unlikely) □ Yes (if **yes**, please assess causality)	
	If **yes**, assess causality:	□ Certain □ Probable/likely □ Possible □ Conditional/unclassified □ Unassessable/unclassifiable
Study drug administration procedure?	□ No □ Yes	
Present Disease?	□ No □ Yes (Specify:_____)	
Medical or surgical procedures?	□ No □ Yes	
Other known or suspected cause?	□ No □ Yes (Specify:_____)	
Concomitant drug(s)?	□ No □ Yes	

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Case Report Form (CRF):
6. Diagnostic Test

Was diagnostic tests related to AE/SAE performed?	□ No □ Yes					
Test Performed	**Date (yyyy/mm/dd)**	**Results**	**Unit**	**Normal Range (if applicable)**	**Unit**	**Comment**
	_____ / ___ / ___					
	_____ / ___ / ___					
	_____ / ___ / ___					

8. [Addendum Form Number 2] Post-Marketing Surveillance and Special Surveillance (Amended) Protocol

8.1. Product Development Issues

Product Development Issues

Deoxycholic acid (DCA) is a well-characterized endogenous secondary bile acid in humans and other animals that serves to emulsify and solubilize dietary fat, thereby aiding in its breakdown and absorption within the gut. ATX-101 (deoxycholic acid injection) is a potential first-in-class adipocytolytic, submental contouring, subcutaneous (SC) injectable drug that has been developed for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF), ie, SC fat in the area below the chin, in adults.

ATX-101, when injected into localized subcutaneous fat, physically disrupts the cell membrane of adipocytes and causes adipocytolysis, the destruction of fat cells. The destruction of adipocytes elicits a tissue response in which macrophages are attracted to the area to eliminate cellular debris and lipids, which are then cleared through natural processes. This is followed by the appearance of fibroblasts and observed thickening of fibrous septa suggesting an increase in total collagen (ie, neocollagenesis). The activity of deoxycholic acid is attenuated by protein, making protein-poor tissues such as SC fat more sensitive to its cytolytic effects. When injected into fat tissue, nearby protein-rich tissues such as skin and muscle are largely unaffected.

ATX-101 contains 10 mg/mL of DCA formulated in a sterile solution of sodium hydroxide, dibasic sodium phosphate, sodium chloride and water for injection, with 0.9% benzyl alcohol as a preservative. ATX-101 is intended to be administered as a 2 mg/cm2 dose in 0.2-mL injections, spaced 1-cm apart. The maximum intended dose in a treatment session is 100 mg (ie, 10 mL; 50 injections). ATX-101 may be given in up to 6 treatment sessions, at intervals at least 4 weeks apart. The number of injections in each treatment and the number of treatment sessions are tailored to the individual patient based on the amount and distribution of their SMF, as well as their desired result.

A comprehensive nonclinical and clinical development program has been conducted to support the approval of ATX-101 for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults.

The nonclinical pharmacology data have demonstrated in vitro and in vivo adipocytolytic activity of ATX-101. Safety pharmacology studies assessed cardiovascular, respiratory and CNS effects of ATX-101 with no adverse findings. The toxicological profile of ATX-101 was evaluated in rats and dogs with most findings attributable to the local pharmacologic action of the drug and ensuing local inflammatory reaction. The toxicology studies, along with the toxicokinetic data, support the safe use of ATX-101 for the clinical reduction of SMF. In addition, it was concluded that there is negligible carcinogenic risk to patients associated with SC administration.

The clinical program includes 23 Phase 1 to 3 clinical studies, 19 of which supported the SMF indication. More than 2800 subjects have been enrolled to date, of whom more than 1800 were treated with ATX-101. The overall adverse event experience with ATX-101 presents a favorable safety profile, without apparent effect on ECG parameters, and the results of the adequate and well-controlled studies indicate that ATX-101 is effective for the proposed indication. Based on this information, ATX-101 represents a nonsurgical treatment for submental contouring and may serve as a less invasive alternative to liposuction with or without necklift.

Clinical overview

Summary

The safety evaluation program for ATX-101 was comprehensive. It included both spontaneously reported and elicited AEs, acute and late-onset events, ECGs, and clinical laboratory evaluations.

Particular attention was also given to a large set of special interest AEs that might be expected to occur given the mode of administration (injection), mechanism of drug action, or the resulting tissue response; and that are typical for an elective facial injectable. In terms of demographic and baseline characteristics, the subject population enrolled in the SMF studies was consistent with the intended population for the marketed drug.

The results from all of these sources present a consistent and favorable safety profile for ATX-101. The results from the Pivotal Studies group are similar to those of the individual studies (Study 22 and Study 23), which were in close agreement with each other. This similarity provides a substantial basis on which conclusions are made in the integrated analysis of the Pivotal Studies group. The results of 2 other integrated analyses (the Randomized, Controlled Studies in SMF group and the All SMF Studies group) provide strong confirmation of the primary analysis. The results of the LTFU group analyses provide confirmation of the durability of the treatment effect and long-term safety of ATX-101.

The safety profile of ATX-101 used in adults for improvement in the appearance of moderate to severe convexity or fullness associated with SMF is well characterized. ATX-101 is an acute, elective, and safe treatment, with mostly transient and mild or moderate AEs related to the treatment area that typically resolve without intervention or sequelae, and that can be managed by the practitioner. Moreover, these types of events are typical for facial injectables, and therefore are consistent with the expectations of clinicians and patients for such a product and procedure.

Non-Clinical Overview

Summary

Deoxycholic acid, the active pharmaceutical ingredient in ATX-101, is structurally identical to the endogenous deoxycholate found in the bile of humans and other mammals. Deoxycholic acid, BA, and other excipients (sodium phosphate and sodium chloride) are FDA-approved inactive ingredients for SC and or IV administration. The to-be-marketed ATX-101 drug product is a 10 mg/mL (1% w/v) DCA solution in PBS with 0.9% BA as a preservative.

The nonclinical pharmacology and PK data for ATX-101 have demonstrated its potential for cytolytic activity in the reduction of SMF. In particular, the data have shown that attenuation of DCA's cytolytic effect tracked closely with the relative protein content of tissues and DC is rapidly absorbed into the systemic circulation where it appears to exhibit the same PK characteristics as the endogenous molecule.

Safety pharmacology studies were conducted to assess potential cardiovascular, respiratory and CNS effects of ATX-101. In vitro, ATX-101 was not shown to inhibit the Ikr current in a hERG assay. In vivo, there were no effects on cardiovascular function or evidence of QT/QTc prolongation, or adverse effects on respiration, at doses of $\leq$ 20 mg/kg in Beagle dogs. There were no adverse effects on CNS parameters in SD rats at doses of $\leq$ 5 mg/kg.

In a comprehensive battery of in silico, in vitro and in vivo genotoxicity assays conducted for ATX-101, there was no evidence of structural-activity relationships, or mutagenic or clastogenic potential.

Overall, the toxicologic profile of ATX-101 has been well characterized over a range of concentrations up to the locally tolerated maximum doses in rats, dogs and minipigs. The toxicology program followed ICH M3(R2) guidelines with additional studies conducted as necessary to address specific issues including bridging toxicity studies in rats. In all studies,

most findings were attributed to the pharmacologic action of the drug and ensuing inflammatory reaction. Observations were consistent with effects observed following exposure to an adipocytolytic agent. Additionally, potential drug substance and drug product impurities were considered in accordance with regulatory guidelines ICH Q3A(R2), ICH Q3B(R2) and draft ICH M7. It was concluded that there is no concern of unacceptable carcinogenic risk to patients associated with SC administration of ATX-101.

Deoxycholic acid, the active drug substance in ATX-101, is structurally identical to the endogenous deoxycholate found in the bile of humans and other mammals and it has a long history of clinical use as an FDA-approved inactive ingredient for IV administration. The toxicology studies, along with the toxicokinetic data, support the safe use of ATX-101 for the clinical reduction of SMF in the area of the neck and face.

In Vitro Primary Pharmacology Studies

The nonclinical pharmacology data for DCA has demonstrated its potential for clinical reduction of SMF (Table 2.6.3.1). Using cytolytic activity as an established pharmacodynamic marker for efficacy in vitro, DCA has demonstrated a concentration-dependent cytotoxicity in multiple cell lines (Studies 003; 0008). Although there were small differences in the ability of DCA to lyse different cells, clinical concentrations of DCA were cytotoxic to all tested cells in vitro. Based on LC50 [lethal concentration to 50% of cells] values, human keratinocytes, immortalized human cervical cancer (HeLa) cells and immortalized human thyroid cancer (DRO) cells were most sensitive to DCA effects (LC50 0.01%-0.02%). Primary human fibroblasts and A375M melanoma cells demonstrated the least susceptibility (0.05%-0.06%). An LC50 value of 0.045% was shown for human adipocytes while human skeletal muscle cells LC50 values varied from 0.025%-0.05% between the two studies. These results are in agreement with Gupta et al., 2009 where DCA displayed similar sensitivities for cultured 3T3-L1 adipocytes, foreskin fibroblasts, neonatal dermal endothelial cells and fetal skeletal muscle cells in vitro.

In fresh porcine tissues (fat, muscle and skin) in vitro, the impact of tissue pre-exposure on the extent of DCA induced cytolysis showed that the reduction in cytolytic potency was proportional to the protein concentration of the tissue samples (Study 0007). Cytolysis caused by DCA solutions exposed to protein rich skin and muscle was 2- to 4-fold less than that of protein poor adipose tissue. Additionally, pre-incubation with purified collagen reduced DCA cytolytic activity in a concentration-dependent manner in A375M cells (Study 005) which is consistent with the known binding affinity of DCA to hydrophobic proteins (Helenius and Simons 1972; Makino et al., 1973). Thus, binding of DCA onto the hydrophobic surfaces of protein rich tissues may reduce the amount of free DCA available for cytolysis. This effect renders adipose tissue, which has lower protein content, more susceptible to DCA induced cell damage.

The localization of DCA-induced cytolysis following injection into adipose tissue may be

explained by the inactivation of DC by interstitial serum albumin which has been shown to vary by tissue type (Bert et al., 1982; Ellmerer et al., 2000). In separate studies, A375M melanoma cells and primary human adipocytes were incubated with bovine serum albumin (BSA) (0-4%) containing varying concentrations of DCA (Studies 006; 0009). Based on cell viability, a complete attenuation of DCA cytolytic effects was observed in the presence of 4% BSA, while at lower levels DCA activity was only partially attenuated.

The results of these primary in vitro studies indicate that albumin is protective and along with other hydrophobic proteins may be responsible for controlling the extent of cytolysis caused by DCA in vivo.

A bridging pharmacology study was conducted to compare the relative cytotoxicity of animalderived NaDC to synthetic DCA in the same PBS-based vehicle (PBS with 0.9% BA) (Study 0026). MDA-kb2 human breast cancer cells were incubated with varying concentrations of NaDC or DCA and cell viability was measured using the MTS assay. Superimposable cell survival curves were generated for the two formulations and the LC50 for each was 0.05%. Thus there

were no pharmacologically important differences in cytolytic potential between the two drug substances.

8.2. Comparison with similar products

Comparison with similar products

No similar product or compound was approved in Korea

8.3. Licensing / sales status of each country and AE cases

Licensing / sales status of each country and AE cases

1. Licensing / sales status of each country

Region	Country	Submission Date	Approval Date	Market Status/ Launch date
North America	US	**13-May-14**	29-Apr-15	Marketed
North America	Canada	**8-Aug-14**	24-Jul-15	Marketed
Europe	Austria	**17-Aug-15**	25-Aug-16	Pending
Europe	Bulgaria	**17-Aug-15**	28-Sep-16	Pending
Europe	Cyprus	**17-Aug-15**	Pending Received Positive Opinion 29- June-2016	Pending
Europe	Czech Republic	**17-Aug-15**	19-Oct-16	Pending
Europe	Estonia	**17-Aug-15**	13-Sep-16	Pending
Europe	Finland	**17-Aug-15**	9-Nov-16	Pending
Europe	France	**17-Aug-15**	Pending Received Positive Opinion 29- June-2016	Pending
Europe	Greece	**17-Aug-15**	02 Feb 2017	Pending
Europe	Hungary	**17-Aug-15**	29-Jul-16	Pending
Europe	Iceland	**17-Aug-15**	29-Jul-16	Pending
Europe	Italy	**17-Aug-15**	14-Jan-17	Pending
Europe	Latvia	**17-Aug-15**	13-Sep-16	Pending
Europe	Lithuania	**17-Aug-15**	9-Sep-16	Pending
Europe	Luxembourg	**17-Aug-15**	Pending Received Positive Opinion 29- June-2016	Pending
Europe	Malta	**17-Aug-15**	28-Oct-16	Pending
Europe	Norway	**17-Aug-15**	11-Oct-16	Pending
Europe	Poland	**17-Aug-15**	28-Nov-16	Pending

Region	Country	Submission Date	Approval Date	Market Status/ Launch date
Europe	Portugal	**17-Aug-15**	Pending Received Positive Opinion – 29- June-2016	Pending
Europe	Romania	**17-Aug-15**	14-Sep-16	Pending
Europe	Slovakia	**17-Aug-15**	7-Nov-16	Pending
Europe	Slovenia	**17-Aug-15**	22-Dec2016	Pending
Europe	Spain	**17-Aug-15**	18-Jan-2017	Pending
Europe	Sweden (RMS)	**17-Aug-15**	5-Oct-16	Pending
Europe	Belgium	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Croatia	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Denmark	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Germany	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Ireland	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Netherlands	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	United Kingdom	**19-Jan-17**	Pending Received Positive Opinion – 08 May 2017	Pending
Europe	Switzerland	**20-Jan-17***	Pending	Pending
Emerging Market	Egypt	Planned	Planned	Planned
Emerging Market	Lebanon	Planned	Planned	Planned
Emerging Market	Saudi Arabia	**18-May-17**	Planned	Planned
Emerging Market	South Africa	**10-Nov-16**	Pending	Pending
Emerging Market	United Arab Emirates	Planned	Planned	Planned
Emerging Market	Kuwait	Planned	Planned	Planned
Emerging Market	Qatar	Planned	Planned	Planned
Emerging Market	Oman	Planned	Planned	Planned
Emerging Market	Bahrain	Planned	Planned	Planned

Region	Country	Submission Date	Approval Date	Market Status/ Launch date
Emerging Market	Jordan	Planned	Planned	Planned
Emerging Market	Israel	Planned	Planned	Planned
Emerging Market	Turkey	**31-Mar-17**	Pending	Pending
Emerging Market	Serbia	Planned	Planned	Planned
Emerging Market	Ukraine	Planned	Planned	Planned
Emerging Market	Russia	**31-Mar-17**	Pending	Pending
AsiaPacific	Australia	**29-Jan-15**	21-Jul-16	Pending
AsiaPacific	China (CTA)	**27-Feb-17**	Pending	Pending
AsiaPacific	Hong Kong	**30-Jun-16**	Pending	Pending
AsiaPacific	India	**31-Mar-17**	Pending	Pending
AsiaPacific	Indonesia	**31-Mar-17**	Pending	Pending
AsiaPacific	Japan	Planned	Planned	Planned
AsiaPacific	Malaysia	Planned	Planned	Planned
AsiaPacific	Philippines	Planned	Planned	Planned
AsiaPacific	New Zealand	**30-Nov-16**	Pending	Pending
AsiaPacific	Singapore	**17-Oct-16**	Pending	Pending
AsiaPacific	Taiwan	**29-Jun-16**	01-Jun-17	Pending
AsiaPacific	S. Korea	**27-Jun-16**	25-Aug-17	Pending
AsiaPacific	Thailand	**17-Mar-17**	Pending	Pending
AsiaPacific	Vietnam	**27-Jun-16**	Planned	Planned
Latin America	Brazil	**30-Aug-16**	Pending	Pending
Latin America	Argentina	**30-Aug-16**	Pending	Pending
Latin America	Chile	**30-Aug-16**	Pending	Pending
Latin America	Colombia	**28-Jun-16**	Pending	Pending
Latin America	Mexico	**14-Jul-16**	Pending	Pending
Latin America	Venezuela	**Planned**	Planned	Planned

*Swiss MAA was initially submitted in October 2014 and subsequently withdrawn on 22 July 2016 to align the indication and formulation with European Economic Area (EEA). As a result, the approved EU MAA was resubmitted in Switzerland on 20 Jan 2017

2. AE cases reported after marketing

Belkyra Periodic Benefit-Risk Evaluation Report (PBRER) (Period:2016.10.30~2017.04.29)

Summary

This is from the third Periodic Safety Update Report (PSUR) for deoxycholic acid (DCA) 1.0% weight/volume (w/v) and was the second report written in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report (Rev 1) and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E2C(R2). This summarizes safety information received by Allergan from worldwide sources between 30-October-2016 and 29-April-2017. Deoxycholic acid 1.0% w/v was first approved as KYBELLA® on 29-April-2015 in the United States of America (USA) and is currently marketed in the USA, Canada, Australia, and European Union (EU) countries[1].1 This PSUR references the internationally licensed brand name BELKYRA® (first approved on 24-July-2015 in Canada) throughout, and includes safety data for BELKYRA and reports on DCA products in which the manufacturer is not identified or in cases where the strength is not specified.

BELKYRA is a cytolytic, submental contouring, injectable drug that has been developed for the treatment of moderate to severe convexity or fullness associated with submental fat (SMF) (i.e., subcutaneous [SC] fat) in the area below the chin.

In the EU, BELKYRA is indicated for the treatment of moderate to severe convexity or fullness associated with SMF in adults when the presence of SMF has a psychological impact for the patient. In the USA, Canada, and Australia, BELKYRA is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults. BELKYRA is supplied as a sterile solution in single-use vials containing 2 mL of a 10 mg/mL (1.0% w/v) solution in phosphate buffered saline with or without 0.9% benzyl alcohol (BA) as a preservative.

During the 6-month reporting period covered by this PSUR, approximately 46,288 units (185,152 vials) of BELKYRA have been distributed worldwide. In Canada, a patient receives between 2 and 3 treatment sessions with an average of 3 mL per treatment session. In the USA, EU, and

[1] Hungary, Sweden, Norway, Italy, Lithuania, Finland, Czech Republic, and Slovakia.

Australia, a patient receives between 2 and 4 treatment sessions with an average of 3.5 mL per treatment session. Therefore, during the reporting period, the estimated patient exposure is approximately between 23,399 and 46,288 patients.

Cumulatively, between product launch and the end of this PSUR reporting period 29-April-2017, approximately 127,763 units (511,052 vials) of BELKYRA have been distributed worldwide, resulting in an estimated patient exposure between approximately 64,616 and 127,763 patients. In clinical studies of any phase in the SMF program, approximately 3300 patients are estimated to have been exposed to BELKYRA.

The EU Summary of Product Characteristics (SmPC; approved through positive conclusion of the EU decentralized procedure on 29-June-2016) was used as reference safety information (RSI) during the previous PBRER reporting period and at the beginning of the current reporting period. The first version of the deoxycholic acid Company Core Data Sheet (CCDS) was approved in March-2017 and will be used as RSI moving forward.

The safety review from completed clinical studies during this PSUR review period as well as cumulative clinical safety experience suggests that the safety data remain in accord with the safety information presented in the CCDS. In addition, a medical review of post-marketing adverse drug events received during this PSUR period was performed.

Based on the safety and efficacy reviews, it is concluded that the overall benefit-risk profile of BELKYRA remains positive and unaltered.

In light of the above worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BELKYRA be allowed to continue.