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CONTOUR Australia: Condition of Submental Fullness and Treatment Outcomes Registry

Version 1.1; 27 September 2017

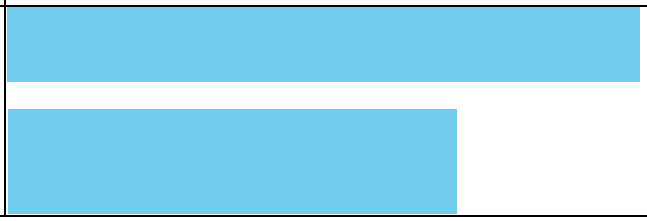
Emergency Telephone Number(s):	
Serious Adverse Event Reporting:	
Allergan Medical Safety Physician: Contact Information:	

PASS information

Title	CONTOUR Australia: **Con**dition of Submental Fullness and **T**reatment **Ou**tcomes **R**egistry
Protocol version identifier	CMO-AP-FAS-0505
Date of last version of protocol	15 December 2016
EU PAS register number	Study not registered
Active substance	Deoxycholic acid
Medicinal product	Belkyra™
Product reference	AUST R 233201
Procedure number	Not applicable
Marketing authorization holder(s)	Allergan Australia, 810 Pacific Hwy, Gordon, New South Wales 2072 Australia
Joint PASS	No
Research question and objectives	The primary objective of this registry is to develop a comprehensive understanding of how Belkyra™ is utilized in clinical practice in Australia, following its approval for the treatment of submental fullness due to submental fat, in order to further inform assessment of the risks and benefits associated with its treatment. This objective will be accomplished through the systematic collection of data on the following:

	• Characteristics of sites and physicians treating patients for SMF reduction with Belkyra™ in Australia • The population of patients who are eligible for SMF reduction treatment and elect SMF reduction treatment with Belkyra™ • Treatment procedures • Treatment outcomes • Belkyra™ safety profile through adverse event (AE) and serious adverse event (SAE) collection • Evaluate the incidence of the following safety concerns: Injection site nerve injury, Injection site ulceration, and Injury of structures at or near the injection site • Assess how Belkyra™ is utilized in Australia • Describe Belkyra™ off-label use
Country(-ies) of study	Australia
Author	

Marketing authorization holder(s)

Marketing authorization holder(s)	Allergan Australia, 810 Pacific Hwy, Gordon, New South Wales 2072 Australia
MAH contact person	

Investigator Signature Page

CONTOUR Australia: **Con**dition of Submental Fullness and **T**reatment **Ou**tcomes **R**egistry
Post-Authorization Safety Study of Belkyra™

I have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this study. My signature confirms my agreement that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, Good Pharmacoepidemiology Practices (GPP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an appropriate Independent Ethics Committee (IEC) prior to any subjects being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

Print Name

Signature Date

RETURN ORIGINAL TO THE SPONSOR AND/OR CRO AND RETAIN COPY

1. Table of contents

2. List of abbreviations

ADR	*adverse drug reaction*
AE	*adverse event*
ANCOVA	*analysis of covariance*
BMI	*body mass index*
CI	*confidence interval*
CMH	*Cochran-Mantel-Haenszel*
CR-SMFRS	*Clinician-Reported Submental Fat Rating Scale*
eCRF	*electronic case report form*
EDC	*electronic data capture*
GPP	*Good Pharmacoepidemiology Practices*
HCP	*healthcare provider*
ICF	*Informed Consent Form*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
ISPE	*International Society for Pharmacoepidemiology*
MedDRA	*Medical Dictionary for Regulatory Activities*
PGQ	*Patient Global Questions*
PR-SMFIS	*Patient-Reported Submental Fat Impact Scale*
PR-SMFRS	*Patient-Reported Submental Fat Rating Scale*
PT	*preferred term*
SAE	*serious adverse event*
SAP	*Statistical Analysis Plan*
SD	*standard deviation*
SM	*Submental*
SMF	*submental fat*
SMSLG	*Submental Skin Laxity Grade*
SOC	*system organ class*
SPA	*Self-perception of Age*
SSRS	*Subject Self Rating Scale*

3. Responsible parties

Name *[qualifications]*	Address	Title & Affiliation
Main Author(s) of Protocol		
Principal Investigator(s)		

4. Abstract

Study Title: CONTOUR Australia: **Con**dition of Submental Fullness and **T**reatment **Ou**tcomes **R**egistry

Version 1.1; 27 September 27, 2017

Ma n Protocol Author:

Rationale and background:

Submental (SM) fullness associated with the accumulation of submental fat (SMF) can influence negative self-perception. Until recently, only surgical interventions such as direct fat excision and liposuction have been available, which are not suitable or desired for all patients. Less invasive, energy-based approaches to reducing SMF (eg, laser lipolysis) have been investigated, but may still require accompanying surgery in more severe cases, and safety concerns remain. Recently, a pharmacologic treatment, deoxycholic acid injection, Belkyra™, was approved by the TGA for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

This registry will gather information on patterns of use and outcomes of treatments for Australian patients treated with Belkyra™ for SM fullness by reduction of SMF.

Research question and objectives:

The primary objective of this registry is to develop a comprehensive understanding of how Belkyra™ is utilized in clinical practice in Australia, following its approval for the treatment of submental fullness due to submental fat, in order to further inform assessment of the risks and benefits associated with its treatment with Belkyra™. This objective will be accomplished through the systematic collection of data on the following:

- Characteristics of sites and physicians treating patients for SMF reduction with Belkyra™ in Australia
- The population of patients who are eligible for SMF reduction treatment and elect SMF reduction treatment with Belkyra™
- Treatment procedures
- Treatment outcomes
- Belkyra™ safety profile through adverse event (AE) and serious adverse event (SAE) collection

- Evaluate the incidence of the following safety concerns: Injection site nerve injury, Injection site ulceration, and Injury of structures at or near the injection site
- Assess how Belkyra™ is utilized in Australia
- Describe Belkyra™ off-label use

Study design:

This is a Phase 4, prospective, observational, multi-center registry for patients receiving treatment with Belkyra™. Patients considering treatment to reduce SMF and who plan to pursue treatment with Belkyra™ will be recruited. Eligible patients will be enrolled in the registry, and patients who elect treatment with Belkyra™ will be followed until their SMF reduction treatment is completed or discontinued as indicated in Table 9.2 Data for Collection.

Population:

- Adult male and female patients, aged 18 years and above, presenting with SM fullness due to the accumulation of unwanted SMF, and considered by their treating physician to be a candidate to receive treatment of SM fullness by reduction of SMF. If the patient decides to participate, then the following will be performed or assessed:
- Signed informed consent and medical records release
- No severe skin laxity, defined as superficial wrinkling, loose skin separated from deeper neck structures, and/or marked skin redundancy (draping and/or sagging), per the physician's judgment
- No other cause of fullness in the SM region (eg, thyroid enlargement, cervical adenopathy) other than localized SMF
- Not participating in an interventional clinical study, currently or within 30 days before enrollment
- Did not previously participate in an interventional clinical study involving ATX-101 (Belkyra™) or have received commercial Belkyra™ previously

Variables:

None

Data sources:

Physician Practice Profile

At each site, the physician will complete the Physician Practice Setting Questionnaire, including the following information:

- Physician characteristics:
  - Clinical history / specialty, including board certification
  - Years of aesthetic practice
  - Gender
  - Location of practice
  - Percent of practice focused on facial aesthetics
  - Number and roles of physicians and other healthcare providers (HCPs) in the practice
- Aesthetic treatment options, including options for reducing SMF, offered by the clinic: types and relative frequencies
- Consent and intake details pertaining to aesthetics and chin and neck (cervicomental) region.
- Percent of patients presenting with SMF concerns and percent receiving SMF reduction treatment
- Referral of patients for SMF reduction treatment to or from other physicians
- Date of Mandatory Physician Belkyra™ Training test completion

Patient Population (all patients)

Upon confirmation of eligibility and signed informed consent, the following information will be collected at the Enrollment visit for all patients:

- Informed consent / medical records release
- Demography & Clinical Information (birth date, sex, ethnicity, height, weight, lifestyle habits)
- Brief medical history (including diabetes, cardiovascular disease)
- Patient treatment history:
    - Previous facial aesthetic treatment(s) within past 24 months:
    - Treatment type (eg, toxins, fillers, devices, cosmetic surgery)
    - Location of treatment (eg, face, chin/neck)
- Patient Treatment Goals Questionnaire:
- History of SMF concern
- Patient's treatment goals in terms of aesthetic outcome
- Physician Treatment Goals Questionnaire
  - Physician's treatment goal in terms of aesthetic outcome
- Enrollment SMF assessments:
    - Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
    - Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
    - Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
    - Submental Skin Laxity Grade (SMSLG) score
    - Subject Self-Rating Scale (SSRS) score
    - Self-perception of age (SPA) scale score

Treatment Details (all patients)

At each site, the physician or designee will complete the following questionnaires and scales at every treatment session for all patients:

Treatment Details Questionnaire

Completed at the first Belkyra™ treatment session for all patients:

- Patient preparation for the procedure / specific instructions
- HCP who prepared the treatment materials/equipment, HCP who prepared the patient for the procedure, and HCP who performed the procedure
- Time spent with patients, by both the physician and qualified designee, discussing treatment details and expectations
- Total time spent by patients on treatment and post-treatment follow-up in office (including deviation from the scheduled time / other treatments given during the same appointment)
- Belkyra™ treatment schedule
- Other treatments (if any) combined in the same treatment session / area(s) where these treatments were administered
- Clinic scheduling procedures for treatment sessions
- Pre-treatment comfort regimen (if applicable); effectiveness of pre-treatment comfort regimen
- Total injection volume of Belkyra™; average volume of Belkyra™ per injection site; injection instrument used (needle, other); details of injection instrument (gauge, length)
- Was Belkyra™ used in areas other than the submentum? If yes, please specify.

- Total volume of Belkyra™ injected outside of the submental area
- What route was used for Belkyra™ administration?
- Volume per injection site outside of the submental area
- Post-treatment mitigation strategies used (in-office, at home), including instructed duration of use
- Was the patient evaluated for swallowing function and asymmetric smile prior to leaving the office?

Pain Numeric Rating Scale for Pain

All patients will be asked to provide a Pain Numeric Rating Scale score for maximum pain experienced post-treatment by the patient at every Belkyra™ treatment session.

Treatment Procedures Questionnaire

At each Belkyra™ treatment session, the site will complete the Treatment Procedures Questionnaire, including the following information:

- Did you identify and mark major anatomic landmarks surrounding the treatment area?

  Patient Grid Questionnaire (only if grid was used)

Adverse Events

The following information will be recorded in the Electronic Data Capture (EDC) system:

- Frequency, severity, duration, medication or other treatment required, and outcome of AEs during and after each Belkyra™ treatment session:
  - At each visit, patients will have treatment areas examined and be interviewed in an open-ended manner to solicit reports of AEs since the last visit.

    Patient calls to clinic with post-treatment concerns or symptoms that meet the definition of AEs (eg, pain, swelling, bruising, numbness) will be included in the AE record.

Treatment Outcomes and Follow-up

Following Belkyra™ treatment initiation, patients and physicians will be asked to complete SMF assessments and scales at the **Follow-up** time point for each treatment**:**

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG) score
- Subject Self-Rating Scale (SSRS) score
- Pain Numeric Rating Scale for Pain: maximum pain experienced post-treatment by the patient.

After completion/discontinuation of treatment with Belkyra™ or at study closure, patients and physicians will be asked to complete the following SMF assessments, questionnaires, and scales for **End-of-Treatment** time point:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG) score
- Subject Self-Rating Scale (SSRS) score
- Patient Self-Perception of Age (SPA) scale score
- Patient Global Questions
- Patient End-of-Treatment Questionnaire, including the following information:

- After treatment, would the patient undergo the treatment again? (eg, was the benefit greater than the risk)
- After treatment, would the patient recommend this treatment to a friend?
- Overall, is the patient aesthetically satisfied with the treatment outcome?
  - Did the patient's friends, spouse or co-workers notice a positive/negative aesthetic change?
- Physician End-of-Treatment Questionnaire, including the following information: Physician's treatment goal in terms of aesthetic outcome: was the physician's treatment goal achieved?
- Pain Numeric Rating Scale for Pain: maximum pain experienced post-treatment by the patient.
- Clinical Information (height, weight)

Study size:

Approximately 100 patients will be enrolled from approximately 10 sites in Australia.

Data analysis:

Full Analysis Population (FAP) consists of all enrolled patients who have had at least one efficacy assessment at baseline or a post-baseline visit. FAP will be used to analyse the patient disposition, demographic and baseline characteristics and efficacy parameters.

Safety population (SP) consists of all patients who receive at least one injection of Belkyra™ treatment injection. This will be used to analyse all the safety parameters. Data will be summarized using descriptive statistics, and presented in listings.

Results for SMF assessments will be summarized with descriptive statistics at each time point. Changes from baseline will be summarized descriptively at each post-baseline assessment. The change in the SMF assessment scores from baseline at follow-up and end-of-treatment will be analyzed using t-test. For the categorical responses, 95% confidence interval of the proportion of response out comes will be presented.

AE and AE mitigation data will be summarized with descriptive statistics, by system organ class (SOC), and preferred term (PT), and presented in listings. The duration (days) and severity of pain, swelling, and bruising will be summarized by treatment session, and overall. When a patient has an occurrence of a PT more than once, the patient's average duration for the PT will be computed for the overall summary. Pain scores from the Pain Numeric Rating Scale will be summarized with descriptive statistics by time point. In addition, the registry will evaluate the incidence of the following safety concerns: Injection site nerve injury, Injection site ulceration, and Injury of structures at or near the injection site. Off-label use will also be described.

Milestones:

Milestone	**Planned date**
Start of data collection	01 March 2018
End of data collection	30 March 2019
Study progress report 1	N/A
<Study progress report 2>	N/A
<Registration in the EU PAS register>	15 February 2018
Final report of study results	30 July 2019

- May change based on the date of approval from TGI

5. Amendments and updates

None

6. Milestones

Milestone	Planned date
Start of data collection	01 March 2018
End of data collection	30 March 2019
Study progress report 1	N/A
<Study progress report 2>	N/A
<Registration in the EU PAS register>	15 February 2018
Final report of study results	30 July 2019

- May change based on the date of approval from TGI

7. Rationale and background

Submental (SM) fullness associated with the accumulation of submental fat (SMF) can influence negative self-perception.[1,2] While the SM region is visually important, at present, only surgical options (cosmetic surgery, liposuction) are available for addressing SM fullness through SMF reduction, and not all patients are suitable candidates for, or willing to undergo, these invasive procedures and the potential complications.[3-8] The use of energy-based devices for lipolysis has been investigated as a less invasive approach,[9] but may still require accompanying surgery in more severely affected cases,[10] and safety concerns remain.[11] Recently, a pharmacologic treatment, deoxycholic acid injection (Belkyra™), was approved by the TGA for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.[12]

This registry will gather information on use patterns and outcomes of treatments for patients treated with Belkyra™ for submental fullness by reduction of SMF.

8. Research question and objectives

The primary objective of this registry is to develop a comprehensive understanding of how Belkyra™ is utilized in clinical practice, following its approval for treatment of submental fullness due to submental fat, in order to further inform assessment of the risks and benefits associated with its treatment. This objective will be accomplished through the systematic collection of data on the following:

- Characteristics of sites and physicians treating patients for SMF reduction with Belkyra™ in Australia
- The population of patients who are eligible for SMF reduction treatment and elect SMF reduction treatment with Belkyra™
- Treatment procedures
- Treatment outcomes
- Belkyra™ safety profile through adverse event (AE) and serious adverse event (SAE) collection

- Evaluate the incidence of the following safety concerns: Injection site nerve injury, Injection site ulceration, and Injury of structures at or near the injection site
- Assess how Belkyra™ is utilized in Australia
- Describe Belkyra™ off-label use

9. Research methods

9.1. STUDY DESIGN

This is a Phase 4, prospective, observational, multi-center registry for patients with submental fullness due to submental fat (SMF) planning on treatment with Belkyra™. Each participating physician will prescribe Belkyra™ treatment based on his or her usual clinical practice.

Study visits, procedures, and evaluations are summarized in Table 9.2 Data for Collection and described in detail in Section 9.2.

Patients considering treatment to reduce SMF and who plan to pursue treatment with Belkyra™ will be recruited. Eligible patients will be enrolled in the registry, and patients who elect treatment with Belkyra™ will be followed until their SMF reduction treatment is completed or discontinued.

Enrolled patients will be assessed regularly by their treating physician according to usual clinical practice. Data collection is anticipated to continue for approximately 15 months after enrolment. The duration of individual patient participation will vary depending on the treatment characteristics and individual requirements.

At Enrollment, relevant data on previous SMF and facial aesthetic treatments will be collected from the patients, and as necessary, from their medical records, along with patient demography, clinical information, baseline treatment goals questionnaires and baseline assessments of SMF. Details of the investigator's practice setting will be recorded after site initiation, and details of treatment details will be recorded at the first treatment session for all patients. Information, including treatment procedures and outcomes, follow-up assessments of SMF, and adverse events (AEs) will be recorded at subsequent clinic visits or telephone contacts. Patient medical history data will be updated, as appropriate, at the first treatment session (Baseline Visit).

9.1.1 Patient Discontinuation and Study Site or Study Termination

A patient may be withdrawn from the registry prior to completion for any of the following reasons:

- Withdrawal of patient consent
- Any other reason, including lack of willingness to complete assessment questionnaires, the patient's best medical interest, patient decision to not proceed with Belkyra™ treatment, or decisions made by the investigator or the sponsor

If a patient withdraws or is withdrawn, the reason should be documented in the electronic case report form (eCRF) and all End-of-Treatment assessments completed, if possible.

The Sponsor reserves the right, at any time, to discontinue enrollment of additional patients into the registry, at any site; or to discontinue the registry, for medical or administrative reasons.

9.2. SETTING

9.2.1 Inclusion Criteria

A patient must meet all of the following criteria to be eligible for participation in the registry.

1. Adult male and female patients, aged 18 years and above, presenting with SM fullness due to the accumulation of unwanted SMF, and considered by their treating physician to be a candidate to receive SMF reduction treatment with Belkyra™
2. Patient has confirmed plans with their treating physician to receive treatment with Belkyra™
3. Signed informed consent by the patient, obtained before any study-related activities are undertaken
4. Willing to complete all patient assessment questionnaires
5. Signed release form by the patient, permitting abstraction of the patient's medical records at baseline and during participation in the registry

9.2.2 Exclusion Criteria

A patient who meets any of the following criteria is not eligible for participation in the registry.

1. Severe skin laxity, defined as superficial wrinkling, loose skin separated from deeper neck structures, and/or marked skin redundancy (draping and/or sagging), per the physician's judgment
2. Any other cause of fullness in the SM area (eg, thyroid enlargement, thyromegaly, cervical adenopathy, cervical lymphadenopathy, pronounced submandibular glands, lymph nodes, and muscles) other than localized SMF
3. Participating in an interventional clinical study, currently or within 30 days before enrollment
4. Participated previously in an interventional clinical study involving Belkyra™

9.2.3 Site Enrollment, Training and Questionnaires

The Sponsor or designee will invite qualified investigators who have completed mandatory training to participate in the registry study. Investigators will be required to obtain approval from the appropriate Independent Ethics Committee (IEC), and will be responsible for maintaining all related documents, before enrollment of any patient into the registry.

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure collection of high-quality data for this registry. All sites will be trained on the protocol, registry logistics, and the electronic data capture (EDC) system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse events (AEs), serious adverse events (SAEs), and other information.

The investigator or designee at each initiated site will complete the following questionnaires regarding practices at that site:

- **Physician Practice Setting Questionnaire:** to be completed once for each site at the beginning of study participation
- **Treatment Details Questionnaire:** to be completed at every Belkyra™ treatment session for all patients
- **Treatment Procedures Questionnaire:** to be completed at every Belkyra™ treatment session for all patients

Patients planning on treatment of SM fullness by reduction of SMF with Belkyra™ will be recruited. After written informed consent is obtained, each screened patient will be assigned a unique study identification number. Eligibility will be determined by review of the inclusion/exclusion criteria.

Enrollment Visit

Patients who are eligible and sign informed consent will be enrolled in the registry will have information abstracted from their medical records, complete baseline questionnaires and assessments of SMF.

Baseline Visit

Information about the patient's treatment procedures, any adverse events (AEs), and treatment outcomes will be recorded at the first Belkyra™ treatment session for all patients who elect treatment for SMF reduction with Belkyra™.

Follow-up Visit

The follow-up visit will take place after the patient's first Belkyra™ treatment session or Baseline Visit at the treatment mid-point. Depending on the number of Belkyra™ treatment sessions (to be determined by physician and patient), the timing of the follow-up visit may vary according to the mid-point of their treatment. Information on adverse event (AE), serious adverse events (SAEs) and treatment outcomes will be recorded.

End-of-Treatment Visit

The patient's end-of-treatment visit will take place either at the last scheduled follow-up visit after completion of all Belkyra™ treatment(s), within 3 months of the last treatment session, when a patient elects to discontinue treatment with Belkyra™, or prior to study closure. Information on adverse events (AEs), serious adverse events (SAEs), treatment outcomes, and end-of-treatment assessments will be recorded

9.2.4 Study Assessments

9.2.4.1 Site Characteristics: Physician Practice Profile

At each site, the investigator or designee will provide information about the practice setting, including the following:

<u>Physician Practice Setting Questionnaire:</u>

- Characteristics of physicians:
  - *Clinical practice history and specialty, including board certification*
  - *Years of aesthetic practice*
  - *Physician gender*
  - *Location of practice*
  - *Percent of practice focused on aesthetics versus medical or reconstructive*
  - *Number and roles of physicians and other healthcare providers (HCPs) in the practice*
- Aesthetic treatment options, including options for treating SM fullness through SMF reduction, offered by the clinic: types and relative frequencies
- Consent and intake details pertaining to aesthetics and chin and neck (cervicomental) region.
- Percent of patients in the practice who present with SMF concerns, and percent of these patients who elected to receive treatment of SM fullness through SMF reduction
- Referral of patients for (SMF reduction treatment to and from other physicians

- Date of Mandatory Physician Belkyra™ Training Test Completion

9.2.4.2 Patient and Treatment Characteristics: Enrollment Visit

The following information will be collected at the Enrollment visit time point:

Demography:

- Birth date
- Sex
- Ethnicity

Clinical Information:

- Height
- Weight
- Lifestyle habits (eg, smoking)
- Brief medical history (including diabetes, cardiovascular disease)

Patient Treatment History:

- Previous facial aesthetic treatment(s) within past 24 months:
  - Treatment type (eg, toxins, fillers, devices, cosmetic surgery)
  - Location of treatment (eg. face, chin/neck)

Patient Treatment Goals Questionnaire, including the following information:

- History of SMF concern
- Patient's treatment goal in terms of aesthetic outcome

Physician Treatment Goals Questionnaire, including the following information:

- Physician's treatment goal in terms of aesthetic outcome

Baseline SMF assessments:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG) score
- Subject Self-Rating Scale (SSRS) score
- Self-perception of age (SPA) scale score

9.2.4.3 Patient and Treatment Characteristics: Baseline Visit

At the Baseline time point, the investigator or designee will provide information about treatment details within the practice, and patients will be asked to provide post-treatment data, including the following information:

Treatment Details Questionnaire (Baseline):

Completed by the physician/investigator or designee at the first treatment session with Belkyra™ (for all patients)

- Patient preparation for the procedure / specific instructions
- HCP who prepared the treatment materials/equipment, HCP who prepared the patient for the procedure, and HCP who performed the procedure
- Time spent with patients, by both the physician and qualified designee, discussing treatment details and expectations
- Total time spent by patients on treatment and post-treatment follow-up in office (including deviation from the scheduled time / other treatments given during the same appointment)
- Belkyra™ treatment schedule
- Other treatments (if any) combined in the same treatment session / area(s) where these treatments were administered
- Clinic scheduling procedures for treatment sessions
- Pre-treatment comfort regimen (if applicable); effectiveness of pre-treatment comfort regimen
- Total injection volume of Belkyra™; average volume of Belkyra™ per injection site; injection instrument used (needle, other); details of injection instrument (gauge, length)
- Was Belkyra™ used in areas other than the submentum? If yes, please specify.
- Total volume of Belkyra™ injected outside of the submental area
- What route was used for Belkyra™ administration?
- Volume per injection site outside of the submental area
- Post-treatment mitigation strategies used (in-office, at home), including instructed duration of use
- Was the patient evaluated for swallowing function and asymmetric smile prior to leaving the office?

Pain Numeric Rating Scale for Pain:

- At each treatment time point (Baseline, Follow-up, End-of-Treatment), all patients will be asked to provide a Pain Numeric Rating Scale score for the maximum pain experienced post-treatment by the patient.
    - All patients will also be asked to provide a Pain Numeric Rating Scale score for maximum pain experienced post-treatment by the patient at every Belkyra™ treatment session.

Treatment Procedures Questionnaire (Baseline):

Completed by the physician/investigator or designee at the first treatment session with Belkyra™ (for all patients):

- Did you identify and mark major anatomic landmarks surrounding the treatment area?
- Patient Grid Questionnaire (only if grid was used)

Adverse Events:

Frequency, severity, duration, medication or other treatment required, and outcome of AEs during and after each treatment session with Belkyra™

- At the Baseline visit, patients will have treatment areas examined and be interviewed in an open-ended manner to solicit reports of AEs since the last visit.

- Patient calls to clinic with post-treatment concerns /symptoms that meet the definition of AEs (eg, pain, swelling, bruising, numbness) will be included in the AE record.

9.2.4.4 Patient and Treatment Characteristics: Post-Baseline Treatment Sessions

Following the Baseline time point, the investigator or designee and patients will be asked to provide post-treatment data at every Belkyra™ treatment session post-baseline, beginning at the 2nd treatment session through completion of Belkyra™ treatment:

Treatment Details Questionnaire (Follow-up):

Completed by the physician/investigator or designee at every post-baseline treatment session with Belkyra™ (for all patients)

- HCP who performed the procedure
- Other treatments (if any) combined in the same treatment session / area(s) where these treatments were administered
- Pre-treatment comfort regimen (if applicable); effectiveness of pre-treatment comfort regimen
- Total injection volume of Belkyra™; average volume of Belkyra™ per injection site; injection instrument used (needle, other); details of injection instrument (gauge, length)
- Was Belkyra™ used in areas other than the submentum? If yes, please specify.
- Total volume of Belkyra™ injected outside of the submental area
- What route was used for Belkyra™ administration?
- Volume per injection site outside of the submental area

Pain Numeric Rating Scale for Pain:

- At each Belkyra™ treatment session, all patients will be asked to provide a Pain Numeric Rating Scale score for the maximum pain experienced post-treatment by the patient.

Treatment Procedures Questionnaire (Follow-up):

Completed by the physician/investigator or designee at every post-baseline treatment session with Belkyra™ (for all patients):

- Did you identify and mark major anatomic landmarks surrounding the treatment area?
- Patient Grid Questionnaire (only if grid was used)

Adverse Events:

Frequency, severity, duration, medication or other treatment required, and outcome of AEs during and after each treatment session with Belkyra™

- At each Belkyra™ treatment session, patients will have treatment areas examined and be interviewed in an open-ended manner to solicit reports of AEs since the last visit.
- Patient calls to clinic with post-treatment concerns /symptoms that meet the definition of AEs (eg, pain, swelling, bruising, numbness) will be included in the AE record.
- Evaluate the incidence, severity and duration of the following adverse events of special interest: injection site nerve injury, injection site ulceration, and injury of structures at or near the injection site

9.2.4.5 Patient and Treatment Characteristics: Follow-up Visit

The following information will be collected at the Follow-up time point, which should occur after the first treatment session with Belkyra™ (Baseline Treatment Visit) at the treatment mid-point. Depending on the number of Belkyra™ treatment sessions (to be determined by the treating physician and patient), the timing of the follow-up visit may vary.

The following information will be captured at the Follow-up time point (Follow-up):

Pain Numeric Rating Scale for Pain:

- At each treatment time point (Baseline, Follow-up, End-of-Treatment), all patients will be asked to provide a Pain Numeric Rating Scale score for the maximum pain experienced post-treatment by the patient.
    - All patients will also be asked to provide a Pain Numeric Rating Scale score for maximum pain experienced post-treatment by the patient at every Belkyra™ treatment session.

Adverse Events:

Frequency, severity, duration, medication or other treatment required, and outcome of AEs during and after each treatment session with Belkyra™

- At the Follow-up visit, patients will have treatment areas examined and be interviewed in an open-ended manner to solicit reports of AEs since the last visit.
- Patient calls to clinic with post-treatment concerns /symptoms that meet the definition of AEs (eg, pain, swelling, bruising, numbness) will be included in the AE record.
- Evaluate the incidence, severity and duration of the following adverse events of special interest: injection site nerve injury, injection site ulceration, and injury of structures at or near the injection site

Follow-up SMF assessments:

The following SMF assessments will be performed at the Follow-up visit (Follow-up) for all patients:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG) score
- Subject Self-Rating Scale (SSRS) score

These assessments were developed by Allergan for use in premarketing trials. The SMFIS and SSRS have been used in multiple Phase 3 trials, the CONTOUR North America study and have produced aligned results with respect to satisfaction with the SMF reduction treatment and positive impacts on visual and emotional aspects of treatment.

9.2.4.6 Patient and Treatment Characteristics: End-of-Treatment Visit

The following information will be collected at the End-of-Treatment visit, which should occur within 3 months after the last Belkyra™ treatment session, at the discontinuation visit, or prior to study closure in order to capture patient and physician feedback regarding treatment decisions.

The following information will be captured at the End-of-Treatment visit for all patients:

Clinical Information:

- Height
- Weight

Adverse Events:

- Frequency, severity and duration of adverse events, any intervention, medication or other treatment required, and outcome of AEs (resolved, ongoing) at the End-of-Treatment visit.
    - At the End-of-Treatment visit, patients will have treatment areas examined and be interviewed in an open-ended manner to solicit reports of AEs since the last visit. If a patient discontinues from the study and does not complete their End-of-Treatment visit, the outcome of any reported AEs (resolved, ongoing) will be confirmed per last available medical documentation.
    - Patient calls to clinic with post-treatment concerns /symptoms that meet the definition of AEs (eg, pain, swelling, bruising, numbness) will be included in the AE record.
    - Evaluate the incidence of the following adverse events of special interest: Injection site nerve injury, Injection site ulceration, and Injury of structures at or near the injection site

Pain Numeric Rating Scale for Pain:

- At each treatment time point (Baseline, Follow-up, End-of-Treatment), all patients will be asked to provide a Pain Numeric Rating Scale score for the maximum pain experienced post-treatment by the patient.
    - All patients will also be asked to provide a Pain Numeric Rating Scale score for maximum pain experienced post-treatment by the patient at every Belkyra treatment session.

End-of-Treatment SMF assessments:

The following SMF assessments will be performed at the End-of-Treatment for all patients:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG) score
- Subject Self-Rating Scale (SSRS) score
- Self-Perception of Age (SPA) score
- Patient Global Questions (PGQ)

Physician End-of-Treatment Questionnaire:

Completed by the physician/investigator or designee at the End-of-Treatment visit for all patients:

- Physician's treatment goal in terms of aesthetic outcome: was the physician’s treatment goal achieved?
- Treatment Adverse Events:
    - Does the physician feel that any training received for the treatment procedure accurately informed them of the adverse effects their patients experienced during and following treatment?
    - What could have been done better?

Patient End-of-Treatment Questionnaire:

Completed by the patient at the End-of-Treatment visit for all patients:

- After treatment, would the patient undergo the treatment again? (eg, was the benefit greater than the risk)
- After treatment, would the patient recommend treatment to a friend?

- Treatment Adverse Events:
    - Does the patient feel their physician accurately prepared them for the adverse effects that occurred during and following treatment?
    - What could have been done better?
- Overall, is the patient aesthetically satisfied with the treatment outcome?
- Did the patient's friends, spouse/significant other or co-workers notice a positive/negative aesthetic change

TABLE 9.2 DATA FOR COLLECTION

	Site Screening	**Enrollment** (all patients)	**Baseline** (all patients)	**Post-Baseline Treatment Session** (all patients) [d]	**Follow-up** (all patients)	**End-of-Treatment** (all patients)[e]
Physician Practice Setting Questionnaire[a]	X					
Patient Population						
Informed consent/medical records release/brief medical history		X				
Demography & Clinical Information		X[b]				X[b]
Patient Treatment History		X				
Patient Treatment Goals Questionnaire		X				
Physician Treatment Goals Questionnaire		X				
Treatment Details:						
Treatment Details Questionnaire (Baseline)			X			
Treatment Details Questionnaire (Follow-up) [d]				X		
Pain Numeric Rating Scale			X[c]	X	X[c]	X[c]
Treatment Procedures Questionnaire (Baseline)			X			
Treatment Procedures Questionnaire (Follow-up) [d]				X		
Adverse Events:						
Adverse Event Log			X	X	X	X
Treatment Outcomes & Follow-up:						
SMF assessments:						
Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score		X			X	X
Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score		X			X	X
Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score		X			X	X
Submental Skin Laxity Grade (SMSLG)		X			X	X
Subject Self Rating Scale (SSRS)		X			X	X
Patient Self-Perception of Age (SPA) scale		X				X
Patient Global Questions (PGQ)						X
Patient End-of-Treatment Questionnaire						X[e]
Physician End-of-Treatment Questionnaire						X[e]

a: Physician Practice Setting Questionnaire is to be completed once for each site at the start of the study (following site initiation).
b: Demography (birth date, sex, ethnicity) & Clinical Information (height, weight, lifestyle habits) to be collected at Enrollment; Clinical Information (height, weight) to be collected at End-of-Treatment for all patients.
c: To be completed at every Belkyra™ treatment session and at the following applicable time points: Baseline, Follow-up, and End-of-Treatment.
d: To be completed at every Belkyra™ treatment session post-baseline (starting at the 2nd treatment session).
e: End-of-Treatment Questionnaires are to be completed for all patients (where possible), including those who exit the study early (i.e. prior to completion of Belkyra™ treatment, withdraw consent, etc.)

9.3. VARIABLES

None

9.4. DATA SOURCES

None

9.5. STUDY SIZE

Approximately 100 patients will be enrolled from approximately 10 sites in Australia.

9.6. DATA MANAGEMENT

All data collected in the context of this registry study will be stored and evaluated in accordance with regulatory requirements and applicable guidance for electronic records.

Electronic case report forms (eCRFs) will be used. Data will be extracted from the patient's medical record and entered into the EDC system as summarized in Table 9.2 Data for Collection. Patients will be identified by use of the ID number assigned to them when they enroll in the registry.

Before the first patient's medical record is abstracted, the Sponsor and/or designee will meet with the investigator and the study center's personnel to train them on recording the data on the eCRFs using the EDC system.

Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with instructions from the Sponsor and/or designee. Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

Online logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) as well as the investigator's approval of all changes performed on the data will be collected.

The investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

9.7. DATA ANALYSIS

Data will be summarized with descriptive statistics, and presented in listings.

Demographic and baseline characteristics will be summarized. Post-baseline values and change from baseline in selected outcome variables will be summarized with descriptive statistics, and, where appropriate, graphical presentations, and presented in listings.

All statistical tests will be tested on two-sided significance level of 0.05 and will be considered exploratory.

Main Efficacy Endpoint: Submental Fat (SMF) Assessments

The following SMF assessments are planned at each visit:

- Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) score
- Patient-Reported Submental Fat Rating Scale (PR-SMFRS) score
- Patient-Reported Submental Fat Impact Scale (PR-SMFIS) score
- Submental Skin Laxity Grade (SMSLG)
- Subject Self-Rating Scale (SSRS)
- Patient Self-Perception of Age (SPA) scale

Overall and individual component summaries for each scale, where applicable, will be provided using descriptive statistics at each time point. Changes from baseline will be summarized descriptively at each post-baseline assessment. The SMF assessments change from baseline at the end-of-treatment follow-up will be analyzed using paired t-test. If normality assumptions are not met, the Wilcoxon signed-rank test will be used to test for the median change from baseline and the distribution-free 95% confidence interval will be presented. For the categorical responses, 95% confidence interval of the response outcomes will be presented.

Other Efficacy Endpoints: Physician and Patient Questionnaires

The categorical responses observed for the physician and patient questionnaires will be summarized using counts, percents, and 95% CIs of the proportion of each response outcome will be presented.

Safety Analysis

AEs will be coded using MedDRA Version 18.0 or later. AE and AE mitigation data will be summarized with descriptive statistics, system organ class (SOC), and preferred term (PT), and presented in listings.

The duration (days) and severity of pain, swelling, and bruising will be summarized by treatment session, and overall. When a patient has an occurrence of a PT more than once, the patient's average duration for the PT will be computed for the overall summary. Pain scores from the Pain Numeric Rating Scale will be summarized with descriptive statistics by time point.

9.8. QUALITY CONTROL

Informed Consent

Before any protocol-specified procedures are carried out, the investigator or designee will explain details of the protocol and procedures to patients. Patients will be informed that they are free to withdraw from the registry at any time.

Each patient must sign an informed consent form (ICF), approved by the IEC, indicating their consent to participate. ICFs will conform to the requirements of the International Society for Pharmacoepidemiology (ISPE) code of Good Pharmacoepidemiology Practices (GPP). The original signed ICFs must remain in the patient's file in the clinic. Each patient will receive a copy of the signed ICF.

Each patient enrolled in the registry also must sign a medical records release form permitting abstraction of medical data for entry in the registry EDC system. Individual patient data included in the registry database will be treated in compliance with all applicable laws and regulations regarding privacy protection.

Independent Ethics Committee Approval

The protocol and the ICF must be reviewed and approved by the site's IEC before the registry is initiated. The investigator is then responsible for informing the IEC of the completion of the registry and should provide any required status and/or safety report(s).

Adherence to the Protocol

The registry must be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the patient requires intervention. Any significant deviation from the protocol must be reported immediately to the Sponsor and IEC.

Protocol Amendment

Any amendment to the protocol will be created by the Sponsor or designee, and subsequently submitted by the site to the IEC and appropriate regulatory authority for approval. If the protocol amendment substantially alters the registry design or increases the potential risk or discomfort to the patients, updated written consent for continued participation in the registry must be obtained.

Monitoring of the Study

The Sponsor and its representatives will monitor the registry at the site according to the Monitoring Plan. At the monitoring visits, the progress of the registry and any procedural or data issues will be discussed with the investigator and/or designee. Patient source documents should be available for review; the investigator will permit the Sponsor, representatives of the Sponsor, the IEC, or regulatory authorities to inspect facilities and original records relevant to this registry.

9.9. LIMITATIONS OF THE RESEARCH METHODS

Selection Bias

Sites will be selected from practices that see a large number of aesthetic patients with a variety of issues, including SMF. Physicians will attempt to consecutively enroll all patients who consent and meet the selection criteria, regardless of demography, health status, or other considerations.

Confounding Bias

An objective of this study is to better understand characteristics of practices, providers, and patients that influence the selection and outcomes of aesthetic treatments. The intent is to collect sufficient data to evaluate these predictors and adjust for them, as applicable, in the

analyses. The collection of retrospective and baseline information will permit outcomes to be compared in light of differences prior to treatment selection.

Effect Modification

Characteristics such as obesity, age, skin laxity, etc. will be associated not only with treatment routing (selection bias) but also with outcomes. Again, this information will be used as appropriate in evaluating outcome data.

Patients Lost to Follow-Up

Some proportion of patients may discontinue the study. Investigators will be encouraged to share the patient's data with him/her, in an effort to encourage the patient to remain involved in the study. Steps may be taken to evaluate the presence of, and ameliorate, potential bias associated with differential attrition. Details will be provided in the Statistical Analysis Plan.

Registry Reports

Study results may be summarized periodically for presentation at professional conferences and sessions

9.10. OTHER ASPECTS

9.10.1 Source Documents

The physician should maintain source documents for each patient enrolled in the study. Source documents such as patient charts and doctors' notes will be kept as part of the patients' medical records. Patient files including medical records and signed patient ICFs must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after completion of the study.

Data recorded into the e-CRF should also be downloaded and stored on local computers at the site. Should this not be possible, a secondary option is to allow sites to print a date-stamped version of the completed CRF for each patient to be signed by the study physician and stored in files at the site.

9.10.2 File Retention and Archiving

The physician and trained staff at the study sites will maintain a record of each enrolled patient. Physicians will be instructed on source documentation that must be available to substantiate patient identification, eligibility and participation, proper informed consent procedures, dates of data collection, adequate reporting and follow-up of adverse events, concomitant medication, and drug administration. Specific items required as source documents will be reviewed with the physician before the study. The physician will be instructed to notify the Sponsor or its representative before any destruction of medical records of study participants.

10. Protection of human subjects

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 (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

11. Management and reporting of adverse events/adverse reactions

11.1 DEFINITIONS

Adverse Event

An adverse event (AE) is any undesirable medical occurrence or worsening of an existing condition that occurs after SMF reduction treatment, irrespective of whether the event is considered treatment related. Abnormal laboratory values should not be reported as AEs; however, any clinical consequences of an abnormality must be reported as such. Safety reporting of non-serious AEs and /or serious adverse events (SAEs) will be performed for all patients beginning at the Baseline Visit and through AE resolution.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Allergan considers all cancer adverse events as serious adverse events. In addition, an abortion (spontaneous or non-spontaneous) is also considered a serious adverse event.

Elective hospitalizations for conditions that existed before Belkyra™ treatment are not considered serious adverse events (SAEs). Also, inpatient hospitalization or prolongation of existing hospitalization for “social reasons” without an associated adverse event (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 a serious adverse event (SAE). Any pre-planned surgery or procedure should be clearly documented in the site 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 a serious adverse event and reported to Allergan.

Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event (AE) is at least a reasonable possibility [EMA 2004]. In this study, an adverse drug reaction (ADR) is any untoward medical occurrence in a patient administered Belkyra and is ‘related to’ either Belkyra™ or Belkyra™ injection procedure.

Special Situations

The following are considered special situations:

- Use of a medicinal product during pregnancy or breastfeeding
- Use of a medicinal product in a pediatric or elderly population
- Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

- Lack of therapeutic efficacy

Severity of Adverse Event

A clinical determination will be made of the intensity of an adverse event. The severity assessment for an AE must be completed using the following definitions 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.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

All *SAEs and non-serious ADRs* that occur during and/or after administration of Belkyra™ during the follow-up period will be collected regardless of causal relationship to Belkyra™. The safety assessment will include all undesirable changes of medical findings and all AEs associated with the product.

The following information will be collected for adverse events:

- Presence or absence of an adverse event
- If AE is present, the following detailed information will be collected using the Non-interventional Study Adverse Event Form
  - Description of adverse event including investigator's comments on the reported AE, including treatment given for AE
  - Product administration date
  - Relevant medical history
  - Relevant concomitant medications
  - Start and stop date of adverse event
  - Outcome of adverse event
  - Actions taken by healthcare provider
  - Causal relationship to the product
  - Site (body part) affected if applicable
  - Relationship to procedure
- Severity of adverse event
- Seriousness criteria met

All SAEs and ADRs (serious or not) should be recorded on the study CRF and the AGN NIS AE Form. However, non-serious AEs will only be collected on the study AE CRF (not on the NIS Study AE Form that gets sent to SIMR). A safety management plan, describing roles and responsibilities for identifying, collecting and reporting of adverse event data to Health Authorities as required, will be developed to train investigators on reporting AEs and SAEs.

Each participating site will be trained on the recording and reporting of serious adverse events, non-serious adverse drug reactions, special situations and adverse events of special interest to the Sponsor, or designee. Investigators will be instructed to follow the local regulations of reporting AEs of special interest and SAEs to local and national authorities. AEs of special interest, special situations, Non-Serious ADRs or SAEs include those that are observed by or reported to site personnel by the patient from the time of enrolment through end of follow-up or early discontinuation from the study. The physician or site staff should instruct patients to report SAEs and reportable AEs during this time period.

Each patient interview will begin with simple open-ended questions and questions designed to collect information regarding specific outcomes of interest. If a patient is seen by a non-study physician, the study physician and/or trained site staff should make every effort to follow-up with the relevant concerned health care provider to obtain all information necessary for the accurate reporting of the event in a timely manner.

All serious adverse events or reactions must be reported to the Sponsor within 24 hours of the learning of the event by fax or e-mail to:

Upon receipt of an SAE or an AE of special interest, the Sponsor or designated CRO staff will initiate appropriate follow-up. All events reported on the AE eCRF by the study physician will be confirmed by medical record review and or direct follow-up with the treating physician. In the event of a death, cause of death will be recorded.

All non-serious adverse drug reactions or special situations must be reported to the Sponsor within 10 business days.

In the event of an SAE, the investigator must:

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 Non-Interventional Study Adverse Event Form). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of 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 adverse event(s) on the Non-interventional Study Adverse Event Form describing the event chronologically, including any treatment given (e.g., medications administered, procedures performed) for the adverse event(s). Summarize 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 drug.

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

12. Plans for disseminating and communicating study results

12.2 PUBLICATIONS OF STUDY RESULTS

Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

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Annex 1. List of stand-alone documents

None.