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Name of Active Ingredient(s): Deoxycholic acid		
Title of Study: CONTOUR Australia: Condition of Submental Fullness and Treatment Outcomes Registry		
Protocol Number: CMO-AP-FAS-0505		
Study Period: **Date of first patient enrollment:** 20 March 2018 **Date of last patient completed study:** 02 Oct 2019	**Phase of Development:** IV	
Reporting Period: 20 March 2018 to 02 Oct 2019		
Study Center(s): A total of 6 sites/practices were involved in providing treatments, all these sites are in Australia at different cities: Fremantle, Box Hill, Brisbane, Hawthron and Subiaco (2 sites).		
Publication(s): None		
Background and Rationale for the Study: Submental (SM) fat (SMF) represents an aesthetic problem in both younger and older male and female patients. It can occur regardless of body mass. Submental (SM) fullness associated with the accumulation of SMF can influence negative self-perception. 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. Because surgery is associated with the risks of anesthesia, infection, bleeding, bruising, and scarring, as well as the possibility of poor outcome, discomfort, and the prolonged "downtime" for the patient, there is a demand for nonsurgical alternatives. The use of energy-based devices for lipolysis has been investigated as a less invasive approach but may still require accompanying surgery in more severely affected cases, and safety concerns remain. This registry gathered information on patterns of use and outcomes of treatment for Australian patients treated with Belkyra™ for SM fullness by reduction of SMF.		
Objectives: The primary objective of this registry was to develop a comprehensive understanding of how Belkyra™ is utilized in clinical practice in Australia, following its approval for the treatment of SM fullness due to SMF, in order to further inform assessment of the risks and benefits associated with its treatment.		
Endpoints: The primary objective was 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 were 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™ was utilized in Australia; • Describe Belkyra™ off-label use		

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Study Design: This was a Phase 4, prospective, observational, multi-center registry for patients receiving treatment with Belkyra™. Patients considering treatment to reduce SMF and who planned to pursue treatment with Belkyra™ were recruited. Eligible patients were enrolled in the registry, and patients who elected treatment with Belkyra™ were followed until their SMF reduction treatment was completed or discontinued.

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

The registry study had four phases:

- Enrollment Visit;
- Baseline Visit;
- Follow-up Visit;
- End-of-Treatment Visit.

At enrollment, relevant data on previous SMF and facial aesthetic treatments were 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 were recorded after site initiation. This included:

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

At Baseline (first treatment session), patient medical history data were updated, as appropriate and details of treatment were recorded. At subsequent post-baseline treatment visits or telephone contacts, information, including treatment procedures and outcomes, follow-up assessments of SMF, and AEs was recorded. A treatment details questionnaire and a treatment procedures questionnaire were completed at every Belkyra™ treatment session for all patients.

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

Number of Patients (planned and analyzed): A total of 100 patients were planned to be enrolled for the study. **Analyzed:** A total of 79 patients were analysed in the registry study.

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Diagnosis and Main Criteria for Inclusion and Exclusion: Patients must have met all of the following criteria for inclusion in the study:

Inclusion Criteria:

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 had confirmed plans with their treating physician to receive treatment with Belkyra™.

3.Signed informed consent by the patient, obtained before any study-related activities were 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.

Exclusion Criteria:

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 (e.g., 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 enrolment.

4.Participated previously in an interventional clinical study involving Belkyra™.

Test Product, Dose and Mode of Administration, and Lot Number(s): Belkyra™ was administered by a health professional specially trained in the use of this product. Belkyra™ was injected into the subcutaneous fat tissue in the SM area using an area adjusted dose of 2 mg/cm^2.

A single treatment consisted of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1 cm apart.

Lot Number: Not applicable as this is a registry study.

Control Product, Dose and Mode of Administration, and Lot Number(s): Not applicable

Duration of Treatment: Up to 6 single treatments could be administered at intervals no less than 1 month apart.

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Criteria for Evaluation: The **effectiveness** assessment criteria included:

Site Characteristics: Physician Practice Profile: This included collection of data on physician practice setting questionnaire.

Patient and Treatment Characteristics: Enrolment Visit: This included collection of data on demography, clinical information, patient treatment history, patient treatment goals questionnaire, physician treatment goals Questionnaire, and baseline SMF assessment.

Patient and Treatment Characteristics Baseline Visit: This included collection of data on Treatment Details Questionnaire (Baseline), Pain Numeric Rating Scale (PNRS) for Pain, Treatment Procedures Questionnaire (Baseline), and AEs.

Patient and Treatment Characteristics: Post-Baseline Treatment Sessions: This included collection of data on Treatment Details Questionnaire (Follow-up), for Pain, Treatment Procedures Questionnaire (Follow-up) and AEs.

Patient and Treatment Characteristics: Follow-up Visit: This included data collection on PNRS for Pain, and AEs, Follow-up 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], Submental Skin Laxity Grade [SMSLG] score; Subject Self-Rating Scale [SSRS score]).

Patient and Treatment Characteristics: End-of-Treatment Visit: This included data collection on clinical information, AEs, PNRS, EOT SMF assessments, Physician End-of-Treatment Questionnaire, Patient End-of-Treatment Question (CR-SMFRS score, PR-SMFRS score, PR-SMFIS score SMSLG score, [SSRS] score, Self-Perception of Age [SPA] scale score, Patient Global Questions [PGQ]).

Safety: The safety assessment included all undesirable changes of medical findings and all AEs associated with the product. Assessment of AEs, including definition of seriousness, severity an adverse event of special interest.

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Statistical Methods:

Effectiveness: The effectiveness measurements and variables, which were of the primary interest included: Data on SMF assessments, including CR-SMFRS, PR-SMFRS, PR-SMFIS, SMSLG and SSRS, these were collected at the Enrollment Visit, the Follow-up visit and the EOT visit. Data on patient's SPA were collected at the enrollment visit and the EOT visit.

Summaries for each of the five SMF assessments (CR-SMFRS, PR-SMFRS, PR-SMFIS, SMSLG and SSRS) were provided using descriptive statistics for each of the three visits, namely the enrollment visit, the Follow-up visit and the EOT visit where data on the five assessments were collected. For the Follow-up visit and the EOT visit, mean change from baseline in each SMF assessment was analyzed using paired t-test. Estimates of the mean change along with the p-values from paired t-test were reported. Distribution-free 95% confidence intervals (CI) for the median change was presented. The number and proportion (and its associated 95% Clopper-Pearson CI) of patients with at least 1-grade improvement in the assessment were reported for CR-SMFRS, PR-SFRS, SMSLG and SSRS.

Summaries for patient's SPA assessment as frequency count and percentage were provided for each of the two visits, which were the Enrollment Visit and the EOT visit where data on patient's SPA were collected. The distribution-free 95% CI for the estimate of median or median change was calculated using SAS® procedure Proc Univariate.

Other Analyses of Effectiveness Variables: Data on PGQ, Patient EOT Questionnaire and Physician EOT Questionnaire were collected only at the EOT visit. For the categorical responses in each of the questionnaires, 95% CI for the proportion of the response categories of interest were presented.

Pain numeric rating scale: Raw numeric pain scores were summarized using descriptive statistics by session/visit. The maximum (worst) numeric pain scores at patient level was summarized for the study. Pain scores were categorized into four severity categories as follows: None (numeric pain score of 0), Mild (numeric pain scores of 1 to 3), Moderate (numeric pain scores of 4 to 6) and Severe (numeric pain scores of 7 to 10). The worse category of pain experienced at patient level throughout the study was summarized using frequency count and percentage.

Safety: All AEs were included by-patient AE listings. A separate listing was created with all the distinct levels of system organ class (SOC) and preferred term (PT), and the verbatim investigator description reported in the study. Sorting was by earliest observed SOC, PT within SOC and then verbatim description. An overall summary of frequency count and the binomial incidence proportion with associated 95% CIs were presented to evaluate the incidence of treatment-emergent AEs (TEAEs). 95% CIs of the binomial incidence proportion were presented for the overall summary analyses of TEAEs, and not for the by-visit analyses. Percentages and corresponding 95% CIs were displayed to one decimal place. Each type of AE was tabulated by SOC and PT within SOC. The incidence of all TEAEs by SOC and PT was presented for the following categories:

- Any TEAE;
- Any TEAE related to Belkyra™;
- Any TEAE related to Belkyra™ and leading to discontinuation of treatment with Belkyra™;
- Any TEAE by maximum severity;
- Any pre-treatment AE.
- Adverse drug reactions were analyzed and presented in a similar way to that of the AE described above.

Patient Disposition: A total of 86 patients were enrolled in the registry study, of these, 79 patients (91.9%) received at least one injection of Belkyra™ treatment. The majority of the enrolled patients (n=75 patients; 87.2%) completed the study. Eleven patients (12.8%) did not complete the study. The reasons for not completing the study were lost to follow-up: 7 patients (8.1%); patient's decision: 3 patients (3.5%): and pregnancy; 1 patient (1.2%).

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Demography and Baseline Characteristics: The median age of the patients at enrollment was 44 years (range: 24 to 66 years). Most of the patients were in the age category 31 to 50 years (57 patients; 66.3%). The majority of patients were female (82 patients; 95.3%). Most of the patients were White (62 patients; 72.1%). The median body mass index (BMI) was 24.9 kg/m^2 (range: 16.6 to 34.8 kg/m^2), Male patients had a slightly higher BMI (27.8 kg/m^2) than female patients (24.8 kg/m^2) patients. The majority of patients (79 patients; 91.9%) were non-smokers.

Effectiveness Results:

Clinician-Reported Submental Fat Rating Scale: At baseline, mean CR-SMFRS was 1.7. At the EOT, a total of 72 patients were evaluated, the mean CR-SMFRS was 0.9 (standard deviation [SD=0.6). A decrease in the mean CR-SMFRS from baseline through Follow-up visit 1 to Follow-up visit 3 and at the EOT visit indicated an improvement in moderate to mild fullness associated with SMF following Belkyra™ treatment. A greater proportion of the evaluated patients had at least a 1-grade improvement on the CR-SMFRS across the visits. The mean number of treatment sessions for patients with at least a 1-grade improvement on the CR-SMFRS was 1.6.

Patient-Reported Submental Fat Rating Scale: At baseline visit, mean PR-SMFRS was 3.1. At the EOT visit, a total of 72 patients were evaluated, the mean PR SMFRS was 2.1 (SD=0.5). A decrease in the mean PR-SMFRS from baseline through Follow-up visit 1 to Follow-up visit 3 and at the EOT visit suggested a reduction in SMF following the Belkyra™ treatment. The mean change from baseline across the visits in the PR-SMFRS was significant. A greater proportion of the evaluated patients had at least a 1-grade improvement on the PR-SMFRS across visits. The mean number of treatment sessions for patients with at least a 1-grade improvement on the PR-SMFRS was 1.7.

Patient-Reported Submental Fat Impact Scale: At baseline visit, mean PR-SMFIS total score was 6.0. At the Follow-up visit 1, the mean PR SMFIS total score decreased to 4.4. Decrease in the mean PR SMFIS total score continued until the EOT visit. A decrease in the mean PR-SMFIS total score from baseline through Follow-up visit 1 to Follow-up visit 3 and at the EOT visit suggested an improvement in SMF-associated physiological impact in patient from a reduction in SMF following Belkyra™ treatment. This mean change from baseline across the visits in the PR-SMFIS total score was significant. The individual components of PR-SMIFS also showed significant mean change from baseline across the visits, except for one component of how embarrassed; at the Follow-up visit 3 (n=7) for this characteristic, mean change from baseline was found to be not significant.

Clinician-Reported Submental Skin Laxity Grade: At baseline, the mean SMSLG was 2.0. At the Follow-up visit 1, the mean SMSLG decreased to 1.6. Decrease in the mean SMSLG continued until the EOT visit. This decrease in the mean SMSLG from baseline through Follow-up visit 1 to Follow-up visit 3 and at the EOT visit indicated no worsening in the SMSLG after receiving the Belkyra™ treatment. This mean change from baseline across the visits in the SMSLG was significant.

Subject Self-Rating Scale: Across all the visits, the mean SSRS increased from baseline, except at the Follow-up visit 4 as only 1 patient was evaluated. An increase in the mean SSRS from baseline across all visits (except at the Follow-up visit 4) showed patients' satisfaction with the appearance of their face/chin after receiving the Belkyra™ treatment. The mean SSRS change from baseline across all visits (except at the Follow-up visit 4) was significant. A total of 5/53 patients (9.4%) at the Follow-up visit 1, 2/22 patients (9.1%) at the Follow-up visit 2 and 2/73 (2.7%) patients at the EOT visit had at least a 1-grade improvement on the SSRS from baseline.

Self-Perception of Age Scale: At the baseline, more than half of the evaluable population; 44/77 patients (57.1%) reported that they appeared as their actual age. At the EOT visit, an increase in the number of patients was observed who reported that they appeared younger than their actual age (21 patients; 27.3%).

Patient Global Questions: For Patient's rating of fat under chin; Of the 77 evaluable patients, 27 patients (35.1%) rated the fat under their chins as being a great deal better, 28 patients (36.4%) rated the fat under their chin as being moderately better. Patient's Rating of the Definition Between their Chin and Neck: Of the 77 evaluable patients, 25 patients (32.5%) rated definition between their chin and neck as being a great deal better and 29 patients (37.7%) patients rated the definition between their chin and neck as being a moderately better. Patient's satisfaction with treatment they received: Most of the evaluable population expressed that they were extremely satisfied (35 patients; 45.5%) or moderately satisfied (23 patients; 29.9%) with the treatment they received.

Patient EOT Questionnaire: Of the 77 patients in the Evaluable Population, a majority of the patients (49 patients; 63.6%) reported that they achieved treatment goals. More than half of the evaluated patients (41 patients; 53.2%) reported that meeting the treatment goal was the main reason for ending SMF reduction treatment. A majority of the patients (60 patients; 77.9%) reported that after ending treatment they would undergo treatment again.

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Physician EOT Questionnaire: Physician administered treatment to 77 patients. For the majority of these patients (65 patients; 84.4%), physicians achieved the treatment goal and were satisfied with SMF treatment outcome. For the majority of patients (72 patients; 93.5%), physicians believed Belkyra™ injection training adequately prepared them to administer treatment and prepared them for side effects.

Site/physician characteristics: A total of 6 sites/practices were involved in providing treatments. Mean number of years site treated aesthetics was 13.2 years. The median number of physicians at sites that focused on aesthetics was 2. Mean percentage of practices that focused on facial aesthetics was 72.5%. The mean percentage of patients who had SM fullness due to SMF in the past week was 31.5%. All 6 sites (100%) used injectables.

Patient Treatment Goals: Top 4 ranked goals were listed for the assessment (I want a more defined jawline, to look younger, to look thinner, and to feel more confident). Of the 77 patients in the Evaluable Population, 40 patients (46.5%) wanted a more defined jaw line, 18 patients (20.9%) wanted to look younger, 12 patients (14.0%) wanted to look thinner and 6 patients (7.0%) wanted to feel more confident. The mean amount of time that patients were concerned about their double chins was 65.0 months.

Physician Treatment Goals: Physician's top 2 ranked goals were listed (to achieve a more defined jawline and to achieve an ideal SMl contour). For 34 patients (39.5%), the physicians' goal was to achieve a more defined jawline and for 31 patients (36.0%), the physicians' goal was to achieve an ideal SM contour.

Treatment Procedure: At baseline visit (first Belkyra™ treatment), for most of the patients (54 patients; 68.4%) the skin marking grid was used by physician. The mean time to apply treatment was 2.8 minutes. For the majority of the patients (69 patients; 87.3%), no other treatment was given along with the Belkyra™ treatment. The mean number of other treatments given along with Belkyra™ injection was 1.5 and frequently reported treatments given was botulinum toxin (5 patients; 6.3%). Post-baseline visit 1: A total of 33 patients were evaluated at this visit. For almost all patients (31 patients; 93.9%), skin marking grid was used by physician. The mean time to apply treatment was 5.2 minutes. For the majority of the patients no other treatments were given along with Belkyra™ injection (30 patients; 90.9%). Post-Baseline visits 2, 3 and 4: Most of the treatment procedures performed at these visits were reported to be similar to that of post-baseline 1. Of note, the number of patients evaluated during these visits was low: post-baseline visit 2 (n=10), visit 3 (n=3) and visit 4 (n=1).

Treatment Details: Baseline Visit (first Belkyra™ treatment session): The mean time spent with patients during consultation for SMF reduction treatment was 20.3 minutes. For the majority of the patients (71 patients; 89.9%), physicians administered Belkyra™. The mean time to administer Belkyra™ treatment was 10.0 minutes. For all 79 patients (100.0%), SM region was the location of treatment administration. Post-baseline 1, 2, 3, 4 and 5. The treatment details reported during these visits were similar to that of details reported during Baseline Visit (first Belkyra™ treatment session). The number of patients evaluated during these visits was low; post-baseline visit 1 (n=33), visit 2 (n=10) 3 (n=3), visit 4 and visit 5 (n=1).

Pain Numeric Rating Scale: At Baseline Visit (index treatment), the mean numeric PNRS was 4.1. At the EOT, a total of 71 patients were evaluated and the mean numeric PNRS was 2.6. Overall in the study period, the mean numeric PNRS was 4.6. An equal number of patients reported worst pain experienced as mild and moderate (28 patients; 36.4% for each category). Twenty patients (26.0%) reported worst pain experienced as severe.

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Safety Results: A total of 31 TEAEs were reported in 18 patients (22.8%), all these TEAEs reported were assessed as related to the Belkyra™ treatment by the Investigator. In the majority of patients, the TEAEs were reported during session 1 of the Belkyra™ treatment; 17 patients (21.5%) reported injection site swelling and 3 patients (3.8%) reported injection site bruising. Injection site bruising had the longest average duration of 137.0 days, followed by injection site swelling, which had an average duration of 58.8 days. All other TEAEs reported had an average duration of 3 days. No severe or serious TEAEs including death were reported in the registry study. The most frequently reported TEAE was injection site swelling in 17 patients (21.5%). All the TEAEs reported in 18 patients were mild in severity. The TEAE of special interest reported was arterial injury in 1 patient (1.3%). In 1 patient (1.3%), 2 TEAEs were reported; heart rate decreased, and lethargy assessed as related to the Belkyra™ treatment that led to discontinuation from treatment.

Conclusions:

- The primary effectiveness outcome measures used in this study (CR-SMFRS, PR SMFRS, PR-SMFIS, CR-SMSLG, and SSRS) suggested that Belkyra™ treatment reduced SMF severity and increased patient satisfaction with the appearance of the chin in the Australian patient population. Belkyra™ treatment was associated with improvement in the psychological impact of patients' SMF, and patients were happier, less bothered, less self-conscious, and less embarrassed about their SMF and looked younger and less overweight after receiving the Belkyra™ treatment. No overall worsening of skin laxity was reported. The majority of patients reported that they were satisfied with the treatment they received and achieved the treatment goals.
- All the 31 TEAEs reported in 18 patients were mild in severity and resolved by the end of the registry study. All these TEAEs reported were assessed as related to Belkyra™ treatment. Injection site TEAEs were the most frequently reported TEAEs. In the majority of patients, TEAEs were reported during session 1 of the Belkyra™ treatment. In only 1 patient, TEAE of special interest: arterial injury was reported. In 1 patient (1.3%), 2 TEAEs were reported; heart rate decreased, and lethargy assessed as related to the Belkyra™ treatment that led to discontinuation from the treatment.
- Overall, the safety profile of the Belkyra™ treatment is consistent with known safety profile of the product and no new safety findings were reported in the registry study.
- The effectiveness measurement used in the registry study suggested clinically meaningful, statistically significant outcomes and further supported the Belkyra™ treatment as an effective alternative to aesthetic surgical procedures and liposuction for SMF reduction in the Australian patient population.

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