CONTOUR: CONDITION OF SUBMENTAL FULLNESS AND TREATMENT OUTCOMES REGISTRY (A REGISTRY OF SUBMENTAL FULLNESS, TREATMENT OPTIONS ADMINISTERED, AND ASSOCIATED OUTCOMES)

Title	CONTOUR: Condition of Submental Fullness and Treatment Outcomes Registry (A Registry of Submental Fullness, Treatment Options Administered, and Associated Outcomes)
Version identifier of the final study report	Final 2.0
Date of last version of the final study report	26 October 2017
Marketing Authorization Holder (MAH):	Kythera Biopharmaceuticals, Inc., an Allergan affiliate
Research question and objective:	The primary objective of this registry was to develop a comprehensive understanding of the condition of submental (SM) fullness due to submental fat (SMF), how it is treated in current clinical practice, and the risks and benefits associated with its treatment. This objective was accomplished through the systematic collection of data on the following: • Practice patterns of physicians with patients who had SMF concerns • The population of patients who were eligible for SMF reduction treatment • Eligible patients who elected SMF reduction treatment • Treatment procedures • Treatment outcomes • Safety profile through adverse event (AE) reporting of the SMF reduction treatments administered
Countries of study:	USA and Canada
Study dates	05 June 2015 to 29 December 2016
Report author:	[redacted]

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1. ABSTRACT

Study Title: CONTOUR: Condition of Submental Fullness and Treatment Outcomes Registry (A Registry of Submental Fullness, Treatment Options Administered, and Associated Outcomes)

Study Number: ATX-101-15-40M

Report Date: 26 October 2017

Marketing Authorization Holder (MAH): Kythera Biopharmaceuticals, Inc., an Allergan affiliate

Author:

Keywords: Submental fat, submental fullness, physician, non-interventional, safety, effectiveness.

Rationale and Background: Submental (SM) fullness associated with the accumulation of submental fat (SMF) can influence negative self-perception. Due to the psychological impact of SMF, patients often seek treatment. While the SM region is visually important, at present, current therapeutic options are limited to traditional aesthetic surgical options performed under general anesthesia (cosmetic surgery), targeted liposuction (performed under general or local anesthesia), or non-surgical therapies that have not undergone formal drug evaluation processes or been evaluated in appropriately controlled clinical studies. Not all patients are suitable candidates for, or willing to undergo, these invasive procedures and the potential complications. Currently available injectable products, i.e., Botulinum toxins and dermal fillers, are primarily employed in the aesthetic rejuvenation of the upper and mid-face and do not adequately address contouring the SM region. 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.

On 29 April 2015, a pharmacologic treatment consisting of an injectable form of a proprietary form of chemically-synthesized deoxycholic acid injection (Kybella®, AGN-241761-15-40M [formerly known as ATX-101]), was approved by the Food and Drug Administration as a treatment for moderate or submental fat in adults. Subsequent approvals globally have included Canada, Australia and in 29 European countries (approved in 21 countries and positive opinion in eight countries), Iceland and Norway for the same treatment (trade name: Belkyra®). AGN 241761, the proprietary chemically-synthesized deoxycholic acid, is approved and classified as a cytolytic drug with adipocytolytic activity when injected into subcutaneous fat.

Research Question and Objectives: The primary objective of this registry was to develop a comprehensive understanding of the condition of SM fullness due to SMF, how it is treated in current clinical practice, and the risks and benefits associated with its treatment. This objective was accomplished through the systematic collection of data on the following:

- Practice patterns of physicians with patients who had SMF concerns
- The population of patients who were eligible for SMF reduction treatment
- Eligible patients who elected SMF reduction treatment
- Treatment procedures
- Treatment outcomes
- Safety profile through AE reporting of the SMF reduction treatments administered

Study Design: This was a prospective, non-pre-specified non-interventional, observational, multi-center registry in North America. Patients enrolled in this study provided information related to the condition and treatments of interest and permitted their physicians to provide any available data concerning their condition status and treatment.

Patients: Adults presented 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 decided to enroll.

Assessment of variables:
As part of site characteristics, physician practice profiles were assessed which included information about the practice setting, including Physician Practice Setting Questionnaire.
As part of patient and treatment characteristics, demographic and baseline assessments (demography, clinical information, and brief medical history; patient treatment goals questionnaire and physician treatment goals questionnaire), baseline treatment assessments (treatment logistics, questionnaire, Pain Numeric Rating Scale for pain, treatment procedures questionnaire and AEs), treatment outcomes and follow-up (Pain Numeric Rating Scale for pain and AEs) and End-of-Study assessments (clinical information, AEs and Pain Numeric Rating Scale for pain) were performed.
The SMF assessments were collected at baseline, follow-up and End-of-Treatment (EOT) 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 and patient global question

Statistical Methods: Up to 1000 patients were anticipated. No pre-specified statistical hypotheses were tested; therefore no formal power calculations were performed. Instead, the precision of 95% confidence intervals (CIs) around key response variables was estimated.
A formal statistical analysis plan (SAP) that provided detailed specifications of all analyses and presentation of registry data was approved prior to the study database lock.
Unless specified in the SAP, descriptive statistics were used to analyze all study endpoints. Descriptive statistics comprised of number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and n and percent for categorical variables.
No imputation for missing data was performed. Analyses were conducted using observed cases.
AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. AE and AE mitigation data were summarized with descriptive statistics, by type of SMF reduction treatment, system organ class, and preferred term, and presented in listings.

Demography and Baseline Characteristics: This multi-centered non-interventional study was conducted at 97 sites in the US and Canada between 05 June 2015 and 29 December 2016. A total of 1029 patients were enrolled in the study of whom 504 (49%) completed the study. Of the 1029 enrolled patients, 570 patients opted for ATX-101, 23 patients opted for surgery, five patients opted for laser liposuction, 77 patients opted for energy devices and nine patients opted for other treatments for SMF. A total of 353 patients did not elect for any treatment.
The majority of the patients who opted for ATX-101 (68.9% [393/570]) completed the study.
The overall mean (SD) age of patients was 49.9 (12.3) years majority of the patients were White (84.5% [870/1029]), females (85.8% [883/1029]), and between 31 and 65 years of age (81.6% [840/1029]).
The majority of the patients opting for ATX-101 treatment for their SMF fat reduction were White (83.7% [477/570]), female (83.2% [474/570]), and between the ages 31 and 65 years (82.3% [469/570]) with no history of diabetes (98.9% [564/570]) or cardiovascular diseases (93.7% [534/570]). Nearly a third of them (31.2% [178/570]) had undergone a previous facial aesthetic treatment which included injectable facial aesthetic treatment.
In the ATX 101 group, more than half of the patients (61.9% [353/570]) were non-smokers and lightly active or moderately active (79.6% [454/570]) in terms of exercise levels. In this ATX-101 group, 75.6% (431/570) had no SMSLG or mild SMSLG, 22.2% (127/570) had moderate SMSLG and 1.9% (11/570) had severe SMSLG. Nearly half of patients had moderate CR-SMFRS (49.1% [280/570]). More than half of patients in the ATX-101 group (59.3% [338/570]) had moderate PR-SMFRS. On a scale of zero to ten (zero being no impact and ten being highest impact) the overall mean (SD) PR-SMFIS was 6.9 (1.8). More than half of the patients (62.3% [355/570]) had a SSRS of slightly dissatisfied or dissatisfied. Nearly half of the patients (46.1% [263/570]) indicated that they looked their actual age and 15.3% (87/570) of the patients indicated that they looked older than their actual age on the SPA scale.

Results:

Physician Practice Characteristics:

A total of 94 physicians provided responses to the physician practice questionnaire at screening. Of these, 70 physicians indicated that their clinic had a general aesthetically-focused intake questionnaire. Overall, a mean percentage of 70.6 of physicians' practice focused on facial aesthetics. These physicians treating SMF were generally well experienced and focused on facial aesthetics. The treating physicians had a mean of 18.5 years of experience in aesthetic practice.

ATX-101 Treatment Practices:

In 92.8% (529/570) of the ATX-101 cases, the physicians reported that they identified and marked major anatomic landmarks surrounding the treatment area and used the supplied skin marking grid to facilitate treatment. The mean (SD) length of time spent by the physician and a qualified staff member performing the SMF reduction consultation in the ATX-101 treated group were similar (14.1 [8.2] and 14.6 [8.7] minutes, respectively). The mean (SD) length of time spent by the physician and a staff member administering the ATX-101 treatment were 7.9 (5.3) and 9.3 (5.2) minutes. In almost all cases (99.0% [564/570]), it was the physician (Investigator or Sub-Investigator) who administered the ATX-101 treatment. In order to mitigate the pain, in most of the cases, patients were instructed to use pain mitigation strategies immediately following treatment and at home.

Treatment effectiveness

CR-SMFRS Response: At least 1 grade improvement in CR-SMFRS was reported for 39.7% (161/406) of patients at the follow up visit and 66.8% (253/379) of patients at the EOT visit among those who opted for ATX-101.

The best post-baseline response was defined as best response status among the post-baseline CR SMFRS measures and the worst post-baseline response was defined as the worst status among the post-baseline CR-SMFRS measures. Among patients who were treated with ATX 101, the best and worst post-baseline responses were observed in 61.9% (286/462; 95% CI: 57.3–66.4) and 42.9% (198/462; 95% CI: 38.3–47.5) of patients, respectively.

PR-SMFRS Response: The PR-SMFRS response was fairly similar to the CR-SMFRS response where at least 1-grade improvement in PR-SMFRS was reported by 40.8% (167/409) of patients during the follow-up visit and by 59.3% (227/383) of patients at the EOT visit among patients who opted for ATX 101 treatment.

SSRS Response: A positive response relative to the SSRS's neutral option (i.e., "slightly satisfied", "somewhat satisfied", or "extremely satisfied" where neutral is "neither satisfied nor dissatisfied") was reported for 45.3% (185/408) of patients at follow-up visit and 73.9% (283/383) of patients at the EOT visit among ATX-101-treated patients.

SMSLG Response: The proportion of patients who remained at the same SMSLG score or who demonstrated improvement in their SMSLG score relative to baseline at follow-up visit and EOT visit was 88.2% (358/406) and 91.8% (348/379), respectively in the ATX-101 treatment group.

Patient assessment of ATX-101 treatment effectiveness:

During the study, 34.6% (197/570) of the patients ended the ATX-101 treatment after having met their treatment goal. The Patients Global Questionnaire indicated that 70.1% (269/384) of patients felt that the fat under the chin was better, 63.0% (242/384) of the patients felt that there was better definition between the chin and neck and 72.9% (280/384) of the patients felt that they were satisfied with the treatment they received.

Physician EOT questionnaire:

In the physician EOT questionnaire, responses from physicians who treated 376 of the 570 ATX-101 administered patients responded to whether the ATX-101 injection training adequately prepared them to administer the treatment and for side effects their patients experienced during and after the treatment. Of these, 99.5% (374/376) indicated the ATX-101 injection training adequately prepared them to administer the treatment and 100% (376/376) indicated that the training adequately prepared them for side effects their patients experienced during and after the treatment.

Furthermore, responses from physicians who treated 373 of the 570 ATX-101 administered patients were received for the EOT questionnaire 'would you use the grid routinely in future clinical practice.' Of these, 85.8% (320/373) of the physicians responded that they would use the grid routinely in clinical practice.

Safety:

Treatment exposure:

Of the 570 patients who opted for ATX-101 treatment, 49.1% (280/570) received a single treatment session, 38.2% (218/570) received two treatment sessions, 10.7% (61/570) received three treatment sessions, 1.6% (9/570) received four treatment sessions and 0.4% (2/570) received five treatment sessions. On average, each patient received a total of 6.1 (SD=4.0) mL of ATX-101 in the study. The overall median (range) number of injections received by all patients opting for ATX-101 treatment was 27.0 (2–146), across five treatment sessions, giving an average of 20.0 (2–125) injections per session. The overall median (range) volume of drug injected for the treatment was 5.0 (0.4–29.2) mL.

In addition, off-label use of ATX-101 (in areas other than submentum) was reported in 11 patients of which nine patients received one treatment session and two patients received two treatment sessions. The areas of off-label administration of ATX-101 included lateral to submental area, bilateral proximal dorsal arms, lateral right and left of submental area, area adjacent to submentum, area lateral to submentum, areas more laterally, lateral infundibular sulcus, submandibular neck, area lateral to submental chin, jowls, upper arms and area lateral to submental chin.

Overall Treatment-Emergent Adverse Events:

At least one treatment-emergent adverse event (TEAE) was reported in 12.0% (81/676) of patients. In the ATX-101 treatment group, 13.2% (75/570) of patients reported at least one TEAE. All TEAEs were assessed as related to study treatment. The reported TEAEs were either mild or moderate in intensity. There were no serious TEAEs or deaths. The mean (SD) value of Pain Numeric Rating Scale (scale of 1 to 10) in the ATX-101-treated patients was 3.5 (2.2) at baseline, 3.5 (2.3) at follow-up visit and 3.4 (2.4) at the EOT visit.

TEAEs by patients' medical history and existing medical conditions (ATX-101 treatment group):

A total of six (1.1%) patients treated with ATX-101 had diabetes. Only one of the six (16.7%) patients experienced TEAEs which included injection site bruising, injection site hypoesthesia and injection site swelling.

Thirty six (6.3%) patients treated with ATX-101 had cardiovascular disease. Of these, nine patients experienced TEAEs. The most commonly reported (≥5% of patients) TEAEs among the patients with cardiovascular disease at baseline were injection site swelling (22.2% [8/36]), injection site bruising (16.7% [6/36]) and injection site hypoesthesia (11.1% [4/36]).

Summary of TEAEs by types of healthcare professionals who performed the injection procedure (ATX-101 treatment group):

A total of 547 (95.9%) patients were administered with ATX-101 by the Principal Investigators. Among these patients, 71 experienced TEAEs. The most commonly reported (≥5% of patients) TEAEs among patients who were administered ATX-101 by Principal Investigators were injection site swelling (10.4% [57/547]), injection site hypoesthesia (6.6% [36/548]) and injection site bruising (6.2% [34/547]).

A total of 17 (2.9%) patients were administered with ATX-101 by the Sub-Investigators. Among these, four patients experienced TEAEs: injection site bruising (17.6% [3/17]), injection site hypoesthesia (11.8% [2/17]), injection site pain (11.8% [2/17]) and injection site swelling (11.8% [2/17]).

Summary of TEAEs by the number of years of experience in aesthetic practice (ATX-101 treatment group):

Injection site hypoesthesia and injection site swelling were reported in one patient (2.2% [1/45]) who was administered ATX-101 by physician with 0–5 years' experience in aesthetic practice.

Among patients who were administered ATX-101 by physicians with 11–15 years' experience in aesthetic practice (n=121), 50 patients experienced TEAEs. The most commonly reported (≥5% of patients) TEAEs were injection site swelling (39.7% [48/121]), injection site bruising (24.8% [30/121]), injection site hypoesthesia (24.0% [29/121]) and injection site pain (6.6% [8/121]).

Among patients who were administered ATX-101 by physicians with 16–20 years' experience in aesthetic practice (n=88), six patients experienced TEAEs. The most commonly reported (≥5% of patients) TEAE was injection site swelling (3.4% [3/88]).

Among patients who were administered ATX-101 by physicians with 21–25 years' experience in aesthetic practice (n=145), six patients experienced TEAEs. The most commonly reported (≥2% of patients) TEAE was injection site swelling (2.8% [4/145]).

For patients who were administered ATX-101 by physicians with >25 years' experience in aesthetic practice (n=63), 11 patients experienced TEAEs. The most commonly reported (≥5% of patients) TEAEs were injection site pain (14.3% [9/63]), injection site edema (12.7% [8/63]), injection site bruising and injection site hypoesthesia (7.9% [5/63], each). *TEAEs by off-label use:* Among patients who received ATX-101 in areas other than submentum, three patients reported six TEAEs (injection site swelling [four events], injection site bruising [one event] and injection site hypoesthesia [one event]). All TEAEs were assessed as related to study treatment. Of these, five were moderate and one was mild in severity.
Conclusion: ATX-101 treatment is the most commonly selected treatment option for SMF reduction among the physicians and patients. ATX-101 treatment is administered by experienced physicians who generally focus on facial aesthetic treatments. Overall, patients seem to be satisfied with the ATX-101 treatment for SMF reduction. The data indicates that ATX-101 is safe in the treatment of SMF reduction in adults in the post-approval, clinical setting. Results from this study are consistent with the known safety profile of ATX-101. No new safety signals were identified.