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ORIGINAL RESEARCH ARTICLE

Quantitative Testing of Prescriber Knowledge Regarding the Risks and Safe Use of Albiglutide

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Abstract

Background The risk of pancreatitis and potential risk of medullary thyroid carcinoma associated with glucagon-like peptide-1 receptor agonists prompted the US Food and Drug Administration to require a Risk Evaluation and Mitigation Strategy for albiglutide, including education for prescribers and subsequent assessment of their knowledge of the risks and safe use of albiglutide via a quantitative survey.

Objective The objective of this study was to assess prescribers' knowledge of the risks related to medullary thyroid carcinoma, pancreatitis, and the appropriate patient population for albiglutide.

Methods Two Risk Evaluation and Mitigation Strategy surveys were conducted 18 months and 3 years after albiglutide was launched. Primary analyses evaluated correct response rates for each question. Secondary analyses evaluated the number of correct responses and the percentage of respondents scoring at/above the target comprehension thresholds (75% at 18 months; 80% at 3 years), which were selected based on discussion with the Food and Drug Administration and current standards for Risk Evaluation and Mitigation Strategy assessments, for each key risk message.

Results The correct response rate for individual questions ranged from 68.2 to 97.9% (18-month survey) and from 69.4 to 98.1% (3-year survey). For the secondary analysis, 79.5, 86.7, and 86.7% of respondents in the 18-month survey answered $\geq 75\%$ of the questions correctly and 70.8, 90.9, and 54.1% of respondents in the 3-year survey answered $\geq 80\%$ of the questions correctly for key risk messages related to medullary thyroid carcinoma, pancreatitis, and appropriate patient population, respectively.

Conclusions Survey results indicated most, but not all, prescribers are knowledgeable regarding the risks and safe use of albiglutide. Additional education to address gaps in knowledge could further improve risk mitigation.

Key Points

The correct response rate for individual questions ranged from 68.2 to 98.1%, indicating that most, but not all, prescribers are aware of the risks, safe use, and the appropriate patient population for albiglutide.

Prescribers were least knowledgeable (68.2% in the 18-month survey and 69.4% in the 3-year survey) regarding the appropriate patient population for whom albiglutide is indicated.

Additional education could be beneficial to help address gaps in knowledge and further improve risk mitigation.

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1 Introduction

Albiglutide is a long-acting, glucagon-like peptide-1 receptor agonist (GLP-1RA) approved by the US Food and Drug Administration (FDA) in April 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [1]. Like other GLP-1RAs, albiglutide stimulates glucose-dependent insulin secretion, resulting in reductive effects on glycemic parameters [2–4]. Glucagon-like peptide-1 receptor agonists are also associated with a low risk of hypoglycemia and the potential for weight reduction [3, 5].

An association between GLP-1RA treatment and acute pancreatitis was first suggested by post-marketing reports of acute pancreatitis in patients with T2DM who were treated with or had recently discontinued the GLP-1RA exenatide [6–10]. Subsequent animal studies did not consistently show an association between GLP-1RAs and pancreatitis [11–14], and observational and clinical trial data in humans remain inconclusive with regard to pancreatitis risk with GLP-1RAs [15–22]. In 2013, the FDA and the European Medicines Agency concluded that current pre-clinical and clinical data do not support a causal association between GLP-1RAs and pancreatitis or pancreatic cancer; however, no formal conclusion has been reached, and pancreatitis continues to be considered a risk of the treatment until further data are available [23]. Consequently, it is important that prescribers be aware of this risk.

Post-marketing cases of medullary thyroid carcinoma (MTC) have also been reported in patients treated with GLP-1RAs [24]. The carcinogenicity of albiglutide could not be assessed in rodents, but there is evidence of increased rates of thyroid C-cell abnormalities with other GLP-1 RAs in rodent models [25, 26]. It is unclear whether these results translate to humans because human thyroid C cells express lower levels of GLP-1 receptors. Clinical studies with GLP-1RAs have not shown an effect on MTC [26–29]. However, an effect of GLP-1RAs on the development of MTC cannot be excluded from available data. As such, treatment with albiglutide, or other long-acting GLP-1RAs, is not recommended in subjects at high risk for MTC. In 2014, the FDA mandated a class labeling change for all long-acting GLP-1RA products concerning a potential risk of MTC.

Based on the current evidence related to the risk of pancreatitis and the potential risk of MTC with GLP-1RAs, the FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary for albiglutide to ensure the benefits of the drug outweigh the risks. The goal of the albiglutide REMS is to provide prescribers with information to help them make appropriate treatment choices for individual patients, as well as to provide information on appropriate precautions and actions to take should issues be suspected or arise.

As part of standard practice, the FDA requires an assessment of physicians' knowledge regarding the risks and safe use of drugs with a REMS in place. An important component of this assessment is conducting a quantitative evaluation survey. The Tanzeum® (albiglutide) REMS evaluation survey was designed to assess prescribers' knowledge regarding the risk of acute pancreatitis and the potential risk of MTC associated with albiglutide, the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis, and appropriate albiglutide patient population characteristics. Additionally, prescriber awareness, access/receipt and review of the Tanzeum® prescribing information (PI), Tanzeum® REMS letter for healthcare providers, and Tanzeum® REMS factsheet, and awareness and use of the Tanzeum REMS® website, were assessed. The objective of this report is to present the findings from the 18-month and 3-year REMS quantitative evaluation surveys.

2 Methods

2.1 Reporting

The 18-month survey was conducted between 1 June, 2015 and 18 August, 2015 and the 3-year survey was conducted between 1 December, 2016 and 1 February, 2017. Survey timing was based on the timetable for submission of REMS assessments determined by the FDA [30]. Data from these surveys, together with other REMS metrics, were analyzed to determine prescribers' knowledge regarding the risks of albiglutide.

2.2 Survey Development

Prior to finalizing the 18-month survey, qualitative research was performed on a subset of questions with a representative sample of 12 prescribers who treat patients with T2DM to evaluate prescribers' understanding of the content, language, and format of the survey. Findings from the research were incorporated before the 18-month survey was fielded. Additionally, feedback received from the FDA on the draft survey protocol was incorporated as appropriate into the final 18-month survey before fielding. Some of the questions were reworded for the 3-year evaluation survey [Table 1 of the Electronic Supplementary Material (ESM)] to align with updates to the REMS materials. The desired response for key risk messages was generally "true" or "yes". However, some questions were formatted to have the respondent disagree with the statement ("false" or "no") to avoid an affirmative answer for all desired responses.

The following additional controls were implemented to minimize bias:

- A standardized script was used for telephone interviews and all interviewers were trained.
- Lists of responses within a multi-item question were randomized.
- The survey was programmed to ensure that questions were asked in the appropriate sequence.
- Automated skip patterns were included based on a participant's response to certain questions. No skip patterns were included for questions on key risk messages.
- Respondents could not go back to a question once answered and could not skip ahead. All questions had to be answered to complete a survey.
- Each respondent was given a unique code, which was required to access the system (online or via telephone). The code was inactivated after use.

2.3 Survey Population

Healthcare professionals who had prescribed albiglutide at least once since its launch in the USA were eligible for the 18-month assessment and those who had prescribed it at least once within the 12 months prior to survey administration were eligible for the 3-year assessment. An initial list of prescribers was obtained from GlaxoSmithKline (GSK) and a third party (QuintilesIMS) based on pharmacy claims for albiglutide. Subjects who had previously opted out of communications from GSK were not included. Prescribers from the eligible pool were randomly selected to complete the surveys via computer-generated samples, and invited to participate via e-mail or US postal mail ($n = 3500$ for the 18-month survey and $n = 8175$ for the 3-year survey). Prescribers who had participated in the qualitative research or a previous albiglutide knowledge survey were excluded. Prescribers who, or whose immediate family members, had ever worked for GSK, United BioSource Corporation, or the FDA were also excluded.

2.4 Survey Administration

The survey was administered via telephone or online. Responders used a secured website to complete the survey online. The telephonic survey was conducted by a trained interviewer using a computer-assisted telephone interviewing program. The data entry system used for both methods of survey administration was validated and secured for receiving and storing data. All data collected during the surveys were held confidential. The survey was designed, administered, and analyzed in collaboration with the United BioSource Corporation.

Invited prescribers were eligible to receive US $125 in compensation for their time participating in the survey, except for prescribers licensed and practicing in Massachusetts, Minnesota, or Vermont. Participants were asked 16 questions designed to measure prescribers' knowledge of key risk messages on the potential risks and safe use of albiglutide. After the key risk message questions, participants were asked which materials associated with albiglutide they had previously reviewed or were aware of including the PI, the REMS letter for healthcare providers, the Tanzeum® REMS factsheet, and the Tanzeum® REMS website (http://www.TANZEUMREMS.com). The survey was not designed to compare or evaluate the content of these materials. Following the survey, copies of the PI and REMS factsheet were mailed to respondents.

2.5 Sample Size

A sample size of 200 prescribers was planned for both assessments. The sample size was selected based on the precision of the estimated rate of comprehension so that at least two-thirds of respondents would fall within the confidence interval (CI) for the target comprehension threshold for each survey.

2.6 Questions and Statements Based on the Risk Evaluation and Mitigation Strategy Goal and Survey Objectives

The REMS survey was divided into three broad key risk messages, each of which included detailed questions relevant to the general topic. The questions were presented as multiple-choice options or respondents were asked to indicate agreement or disagreement using response options of "yes" or "true", "no" or "false", and "I don't know". The key risk messages are listed below and the full surveys can be found in Table 1 of the ESM.

- Key Risk Message 1: "There is a potential risk of medullary thyroid carcinoma (MTC) associated with Tanzeum®".
- Key Risk Message 2: "There is a risk of acute pancreatitis associated with Tanzeum®".
- Key Risk Message 3: "Prescribers should be aware of the characteristics of the appropriate patient population for which Tanzeum® should be prescribed".

2.7 Awareness, Receipt, and Use of Risk Evaluation and Mitigation Strategy Materials

Prescribers' awareness of the REMS program was assessed as part of the questionnaire. Participants were asked if they had ever received the Tanzeum® PI, the Tanzeum® REMS

letter for healthcare providers, and/or the Tanzeum® REMS factsheet, and whether they had reviewed these materials. Survey respondents were also asked if they were aware of the Tanzeum® REMS website (http://www.TANZEUMREMS.com). Finally, respondent demographics were collected, including provider type, specialty, years in practice, and number of patients prescribed albiglutide.

2.8 Statistical Analysis

All statistical analyses are descriptive; no formal hypothesis was tested. Descriptive statistics for categorical variables included counts, percentages, and frequency distribution of responses to each question. Exact two-sided 95% CIs were calculated by the Clopper–Pearson method [31]. No adjustment was made for multiplicity. Because skip patterns in the survey may have affected the number of respondents presented with each question, the percentages for questions were calculated based on respondents exposed to the question.

2.8.1 Primary Analysis

Primary analyses evaluated the correct response rates for each individual question/item defined by the key risk message.

2.8.2 Secondary Analysis

The secondary analysis evaluated the number of correct responses within each key risk message and the percentage of respondents who scored at/above, or below the target comprehension threshold. A target comprehension threshold of 75% was selected for the 18-month survey so that precision estimates of CIs in a fixed sample size of 195 would fall between 68 and 81%, indicating at least two-thirds of respondents know the tested information. Based on FDA advice, the target comprehension threshold was increased to 80% in the 3-year survey, with precision estimates of CIs for a fixed sample size of 200 falling between 74 and 85%. The target comprehension threshold for both surveys was based on current FDA standards for assessment of physicians' knowledge of the risks associated with a specific drug, and was not intended as a threshold for good medical knowledge standards for physicians. The secondary analysis included the exact binomial two-sided 95% CI for the rate of respondents at/above or below the specified respective threshold in both assessments.

2.9 Subgroup Analysis

Subgroup analyses were performed for the primary and secondary analyses of the key risk messages. The subgroup analyses included awareness of the REMS program, receiving/accessing/reading the PI, prescriber type, primary specialty, years practicing, and number of patients prescribed albiglutide within the past 12 months.

3 Results

3.1 Respondents

Out of 3500 invited, 242 respondents accessed the 18-month survey, and 296 out of 8195 invited respondents accessed the 3-year survey. The sample of respondents was self-selected, as they voluntarily responded to the invitation to participate. Reminder letters were sent to non-responders to reduce volunteer and non-response bias. Of those who responded, 205 (84.7%) were eligible to participate and 195 (80.6%) completed the 18-month survey. For the 3-year survey, among responders, 228 (77.0%) were eligible to participate and 209 (70.6%) completed the survey (Fig. 1). One out of three respondents from states where reimbursement of prescribers is not permitted (Massachusetts, Minnesota, or Vermont) completed the 18-month survey and zero out of two respondents completed the 3-year survey.

Respondents in both surveys consisted of more male (61.0% in the 18-month survey and 56.0% in the 3-year survey) than female prescribers, and more physicians (medical doctor or doctor of osteopathy, 67.1% in the 18-month survey and 65.0% in the 3-year survey) than nurse practitioners/advanced practice registered nurses or physician assistants (Table 1). Most physicians practiced family medicine or internal medicine, while fewer specialized in endocrinology. The majority (54.4% in the 18-month survey and 65.1% in the 3-year survey) reported prescribing albiglutide for six or more patients within the 12 months prior to survey completion. Just over half of respondents in both assessments had been practicing for >15 years.

3.2 Knowledge of Safe Use of Albiglutide

The correct response rate for individual questions about the safe use and appropriate patient population for albiglutide

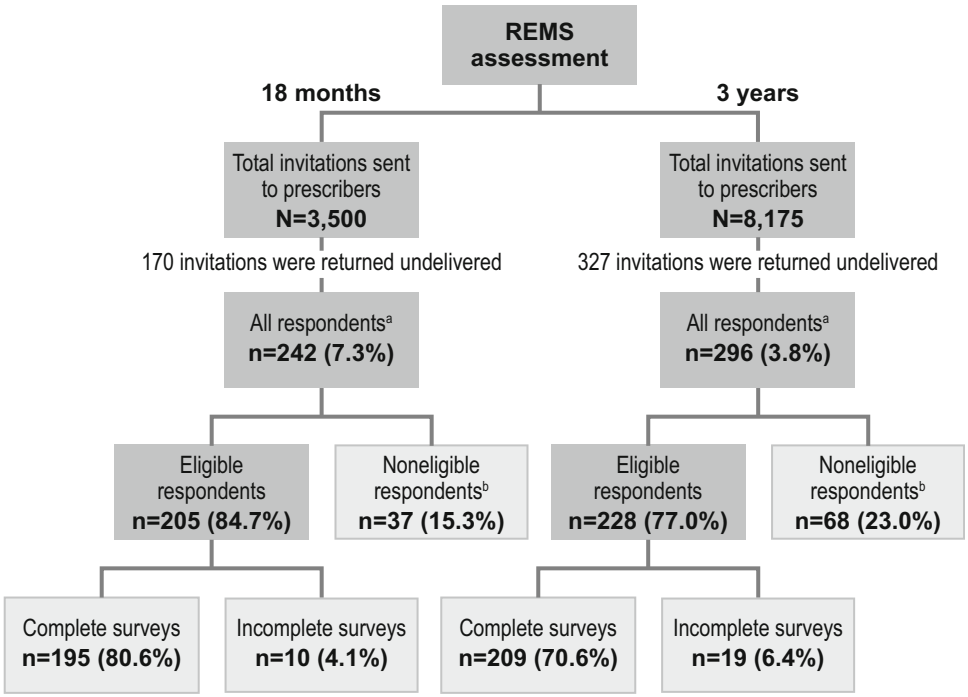

Fig. 1 Survey administration statistics. [a]Number of unique respondents who accessed the survey. Percentage is based on the number of invitations sent to prescribers excluding the invitations returned as undeliverable. [b]Number of respondents who did not meet eligibility criteria or did not complete eligibility questions. Percentages are based on the number of all respondents, unless otherwise specified. *REMS* Risk Evaluation and Mitigation Strategy

Table 1 Description of survey responders

Question	18-month survey Prescribers ($N = 195$) n (%)	3-year survey Prescribers ($N = 209$) n (%)
What is your gender?		
Male	119 (61.0)	117 (56.0)
Female	73 (37.4)	91 (43.5)
Prefer not to answer	3 (1.5)	1 (0.5)
What type of healthcare provider are you?		
Medical doctor (MD)	112 (57.4)	110 (52.6)
Doctor of osteopathy (DO)	19 (9.7)	26 (12.4)
Nurse practitioner/advanced practiced registered nurse	50 (25.6)	51 (24.4)
Physician assistant	14 (7.2)	22 (10.5)
What is your primary medical specialty (MDs or DOs)[a]		
Family medicine	51 (38.9)	58 (42.6)
Internal medicine	47 (35.9)	40 (29.4)
Endocrinology	32 (24.4)	38 (27.9)
For how many patients have you prescribed Tanzeum® within the last 12 months?		
1–5	86 (44.1)	70 (33.5)
6–10	56 (28.7)	49 (23.4)
11–20	24 (12.3)	44 (21.1)
More than 20	26 (13.3)	43 (20.6)
I don't know	3 (1.5)	3 (1.4)

[a]One MD/DO indicated other as their primary medical specialty

ranged from 68.2 to 97.9% in the 18-month survey and from 69.4 to 98.1% in the 3-year survey (Table 2). For the secondary analysis, 79.5, 86.7, and 86.7% of respondents in the 18-month survey answered $\geq 75\%$ of the questions correctly and 70.8, 90.9 and 54.1% of respondents in the 3-year survey answered $\geq 80\%$ of the questions correctly for key risk messages related to MTC, pancreatitis, and appropriate patient population, respectively.

Table 2 Primary analysis of responses to questions linked to key risk messages: completed surveys

	18-month survey Prescribers ($N = 195$) n (%), [95% CI][a]	3-year survey Prescribers ($N = 209$) n (%), [95% CI][a]
Key Risk Message #1		
Carcinogenicity of albiglutide could not be assessed in rodents, but other glucagon-like peptide-1 receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures[b]		
True	**173 (88.7), [83.4–92.8]**	**159 (76.1), [69.7–81.7]**
False	4 (2.1)	15 (7.2)
I don't know	18 (9.2)	35 (16.7)
It is unknown whether Tanzeum® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans		
True	**175 (89.7), [84.6–93.6]**	**185 (88.5), [83.4–92.5]**
False	7 (3.6)	7 (3.3)
I don't know	13 (6.7)	17 (8.1)
Prescribers should counsel patients regarding the potential risk for MTC and to report the symptoms of thyroid tumors[b]		
True	**177 (90.8), [85.8–94.4]**	**201 (96.2), [92.6–98.3]**
False	5 (2.6)	2 (1.0)
I don't know	13 (6.7)	6 (2.9)
Patients should be educated on the symptoms of thyroid tumors such as mass in the neck, dysphasia, dyspnea, and persistent hoarseness, when starting Tanzeum® therapy		
True	**173 (88.7), [83.4–92.8]**	**185 (88.5), [83.4–92.5]**
False	10 (5.1)	12 (5.7)
I don't know	12 (6.2)	12 (5.7)
Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation		
True	**177 (90.8), [85.8–94.4]**	**176 (84.2), [78.5–88.9]**
False	13 (6.7)	24 (11.5)
I don't know	5 (2.6)	9 (4.3)
Routine monitoring of serum calcitonin and thyroid ultrasound should be performed in patients treated with Tanzeum®		
True	23 (11.8)	29 (13.9)
False	**156 (80.0), [73.7–85.4]**	**163 (78.0), [71.8–83.4]**
I don't know	16 (8.2)	17 (8.1)
If serum calcitonin is measured and found to be elevated in a patient taking Tanzeum®, the patient should be referred to an endocrinologist for further evaluation		
True	**160 (82.1), [75.9–87.2]**	**163 (78.0), [71.8–83.4]**
False	14 (7.2)	25 (12.0)
I don't know	21 (10.8)	21 (10.0)
Key Risk Message #2		
There is a risk of acute pancreatitis associated with Tanzeum®		
True	**172 (88.2), [82.8–92.4]**	**192 (91.9), [87.3–95.2]**
False	14 (7.2)	9 (4.3)
I don't know	9 (4.6)	8 (3.8)
Patients should be counseled on the symptoms of acute pancreatitis when starting Tanzeum® therapy		
True	**173 (88.7), [83.4–92.8]**	**187 (89.5), [84.5–93.3]**
False	11 (5.6)	13 (6.2)
I don't know	11 (5.6)	9 (4.3)
Patients should be counseled to contact their healthcare provider promptly if they experience symptoms of pancreatitis while on Tanzeum® therapy		
True	**191 (97.9), [94.8–99.4]**	**205 (98.1), [95.2–99.5]**
False	2 (1.0)	1 (0.5)
I don't know	2 (1.0)	3 (1.4)

Table 2 continued

	18-month survey Prescribers ($N = 195$) n (%), [95% CI][a]	3-year survey Prescribers ($N = 209$) n (%), [95% CI][a]
If acute pancreatitis is suspected, Tanzeum® should be promptly discontinued		
True	**186 (95.4), [91.4–97.9]**	**203 (97.1), [93.9–98.9]**
False	1 (0.5)	1 (0.5)
I don't know	8 (4.1)	5 (2.4)
If acute pancreatitis is confirmed, Tanzeum® can be restarted once it has resolved		
True	16 (8.2)	15 (7.2)
False	**147 (75.4), [68.7–81.3]**	**163 (78.0), [71.8–83.4]**
I don't know	32 (16.4)	31 (14.8)
Key Risk Message #3		
Tanzeum® is recommended as first-line therapy for adult patients with type 2 diabetes inadequately controlled on diet and exercise		
Yes	60 (30.8)	60 (28.7)
No	**133 (68.2), [61.2–74.7]**	**145 (69.4), [62.6–75.6]**
I don't know	2 (1.0)	4 (1.9)
Tanzeum® is contraindicated in patients with a personal or family history of MTC		
Yes	**182 (93.3), [88.9–96.4]**	**197 (94.3), [90.2–97.0]**
No	5 (2.6)	6 (2.9)
I don't know	8 (4.1)	6 (2.9)
Tanzeum® is contraindicated in patients with multiple endocrine neoplasia syndrome type 2		
Yes	**167 (85.6), [79.9–90.2]**	**187 (89.5), [84.5–93.3]**
No	7 (3.6)	9 (4.3)
I don't know	21 (10.8)	13 (6.2)
In patients with a history of pancreatitis, other diabetic treatments should be considered instead of Tanzeum®		
True	**168 (86.2), [80.5–90.7]**	**181 (86.6), [81.2–90.9]**
False	20 (10.3)	14 (6.7)
I don't know	7 (3.6)	14 (6.7)

CIs confidence intervals

Correct responses are shown as bold text

[a]95% exact two-sided CIs are calculated using the Clopper–Pearson method

[b]Questions were worded differently between the 18-month and 3-year surveys (see Table 1 of the Electronic Supplementary Material); however, the meaning remained the same. Wording from the 3-year survey is represented in the table

3.3 Potential Risk of Medullary Thyroid Carcinoma Associated with Albiglutide

3.3.1 Primary Analysis

There were slight differences in wording between the 3-year and 18-month surveys for two questions included in Key Risk Message 1. The questions are listed in Table 1 of the ESM. Most respondents were aware that GLP-1RAs have caused thyroid C-cell tumors in rodents at clinically relevant exposures (88.7% in the 18-month survey and 76.1% in the 3-year survey) (Table 2), and that it is unknown whether albiglutide causes thyroid C-cell tumors, including MTC, in humans (89.7% in the 18-month survey and 88.5% in the 3-year survey). Most respondents were also aware that prescribers should inform patients that thyroid C-cell tumors have been observed in rodents treated with some GLP-1RAs, but the relevance to humans is unknown (90.8% in the 18-month survey, not asked in the 3-year survey), and that prescribers should counsel patients about the potential risk for MTC and to report the symptoms of thyroid tumors (96.2% in the 3-year survey; not asked in the 18-month survey). Respondents were aware that they should educate patients on the symptoms of thyroid tumors when starting albiglutide therapy (88.7% in the 18-month survey and 88.5% in the 3-year survey), and that patients with thyroid nodules should be referred to an endocrinologist for further evaluation (90.8% in the 18-month survey and 84.2% in the 3-year survey). Additionally, most respondents were aware that routine monitoring of serum calcitonin and a thyroid ultrasound are not necessary during albiglutide therapy

(80.0% in the 18-month survey and 78.0% in the 3-year survey), but that if serum calcitonin is found to be elevated, the patient should be referred to an endocrinologist for further evaluation (82.1% in the 18-month survey and 78.0% in the 3-year survey) (Table 2).

3.3.2 Secondary Analysis

The secondary analysis of Key Risk Message 1 indicated that 79.5% of respondents in the 18-month survey and 70.8% in the 3-year survey demonstrated knowledge of the potential risk of MTC associated with albiglutide by answering ≥ 75% (18-month survey) or 80% (3-year survey) of the questions correctly (Table 3). For both surveys, correct answers to at least six out of the seven questions were needed to meet or exceed the target comprehension threshold.

3.4 Risk of Acute Pancreatitis Associated with Albiglutide

3.4.1 Primary Analysis

Most respondents knew that there is a risk of acute pancreatitis associated with albiglutide (88.2% in the 18-month survey and 91.9% in the 3-year survey), that patients should be counseled on the symptoms of pancreatitis when initiating albiglutide therapy (88.7% in the 18-month survey and 89.5% in the 3-year survey), and to contact their healthcare professional promptly if they experience such symptoms (97.9% in the 18-month survey and 98.1% in the 3-year survey) (Table 2). Respondents also knew that albiglutide should be promptly discontinued if acute pancreatitis is suspected (95.4% in the 18-month survey and 97.1% in the 3-year survey), and that it cannot be restarted, after resolution, if acute pancreatitis is confirmed (75.4% in the 18-month survey and 78.0% in the 3-year survey) (Table 2).

Table 3 Secondary analyses of responses to questions linked to key risk messages: complete surveys

Correct prescriber responses	Below threshold of 75% *n* (%)	At or above threshold of 75% *n* (%), [95% CI][a]
18-month survey, prescribers ($N = 195$)		
Key Message 1: There is a potential risk of medullary thyroid carcinoma associated with Tanzeum®	40 (20.5)	155 (79.5) [73.1–84.9][b]
Key Message 2: There is a risk of acute pancreatitis associated with Tanzeum®	26 (13.3)	169 (86.7), [81.1–91.1][c]
Key Message 3: Prescribers should be aware of the characteristics of the appropriate patient population for which Tanzeum® should be prescribed	26 (13.3)	169 (86.7), [81.1–91.1][d]
Correct prescriber responses	**Below threshold of 80% *n* (%)**	**At or above threshold of 80% *n* (%), [95% CI][a]**
3-year survey prescribers ($N = 209$)		
Key Message 1: There is a potential risk of medullary thyroid carcinoma associated with Tanzeum®	61 (29.2)	148 (70.8), [64.1–76.9][e]
Key Message 2: There is a risk of acute pancreatitis associated with Tanzeum®	19 (9.1)	190 (90.9), [86.2–94.4][f]
Key Message 3: Prescribers should be aware of the characteristics of the appropriate patient population for which Tanzeum® should be prescribed	96 (45.9)	113 (54.1), [47.1–61.0][g]

CI confidence interval

[a]95% exact two-sided CIs are calculated using the Clopper–Pearson method

[b]Threshold of 75% = 6 correct responses out of 7

[c]Threshold of 75% = 4 correct responses out of 5

[d]Threshold of 75% = 3 correct responses out of 4

[e]Threshold of 80% = 6 correct responses out of 7

[f]Threshold of 80% = 4 correct responses out of 5

[g]Threshold of 80% = 4 correct responses out of 4

3.4.2 Secondary Analysis

The secondary analysis of Key Risk Message 2 indicated that 86.7% of respondents in the 18-month survey and 90.9% in the 3-year survey demonstrated knowledge of the risk of acute pancreatitis associated with albiglutide by answering four of the five related questions correctly (Table 3).

3.5 Awareness of the Characteristics of the Appropriate Patient Population for Albiglutide

3.5.1 Primary Analysis

Most respondents were aware that albiglutide is contraindicated in patients with a personal or family history of MTC (93.3% in the 18-month survey and 94.3% in the 3-year survey) (Table 2). In the 18-month and 3-year survey, 85.6 and 89.5%, respectively, were aware that albiglutide is contraindicated in patients with multiple endocrine neoplasia syndrome type 2. Most were also aware that other diabetic treatments should be considered instead of albiglutide in patients with a history of pancreatitis (86.2% in the 18-month survey and 86.6% in the 3-year survey). Results showed that 68.2 and 69.4% in the 18-month survey and 3-year survey, respectively, responded correctly to the question that albiglutide is not recommended as first-line therapy for adult patients with T2DM inadequately controlled on diet and exercise (Table 2).

3.5.2 Secondary Analysis

In the secondary analysis of Key Risk Message 3, respondents demonstrated knowledge of the appropriate population for albiglutide therapy. In the 18-month survey, 86.7% of respondents met the 75% comprehension threshold. In the 3-year survey, 54.1% of respondents met the 80% target comprehension threshold (Table 3).

3.5.3 Subgroup Analysis

Descriptive subgroup analyses were performed to potentially identify influential factors among those assessed (Table 4). Specialization in endocrinology was potentially associated with better rates of knowledge for key risk messages related to pancreatitis, while awareness of the REMS program was potentially associated with better rates of knowledge for key risk messages on the potential risk of MTC and the appropriate patient type in the 18-month survey. No potential differences based on subgroup were observed in the 3-year assessment. Subgroup analysis results are descriptive, and no formal hypothesis was tested.

3.6 Awareness, Receipt, and Use of Risk Evaluation and Mitigation Strategy Materials

Approximately one-third of respondents (31% in the 18-month survey and 33.5% in the 3-year survey) were aware that there is a REMS for albiglutide. More than 95% of respondents were aware of the albiglutide PI prior to participation in both the 18-month and 3-year surveys. Most respondents refer to the PI (81% in the 18-month survey and 76.1% in the 3-year survey) and obtain information from sales professionals (81% in the 18-month survey and 73.2% in the 3-year survey) for albiglutide risk information. Most respondents were not aware of the Tanzeum® REMS letter for healthcare providers (74% in the 18-month survey and 77% in the 3-year survey) and Tanzeum® REMS factsheet (75% in the 18-month survey and 79% in the 3-year survey). Finally, 88% of respondents in the 18-month survey and 87% of respondents in the 3-year survey were not aware of the Tanzeum® REMS website.

4 Discussion

Limited data are available on the effectiveness of REMS to reduce serious risks associated with certain medications. Moreover, the non-uniform nature of REMS, which vary in terms of content, scope, and complexity depending on the safety issue(s) in question and extent of risk management required, makes a generalization about the findings from REMS difficult. A 2013 report by the Office of the Inspector General of the Department of Health and Human Services found that, of 49 REMS reviewed by the FDA, only seven met all of their goals, 21 did not meet all goals, a determination on whether all goals were being met could not be made for 17, and the FDA did not determine whether four were meeting their goals. Of the 21 REMS that the FDA determined were not meeting their goals, inadequate prescriber awareness of risks (12 of 21 assessments) was among the most common determining factors [32].

Here, we report the results of a REMS survey designed to assess prescriber knowledge of risks and safe use of albiglutide, one key component of the overall REMS assessment. To our knowledge, this is the first report publishing the results of a REMS survey on a GLP-1RA. Overall, survey results suggest that most, but not all, albiglutide prescribers are knowledgeable regarding the risk of acute pancreatitis, the potential risk of MTC, and the patient population for whom treatment with albiglutide is appropriate. Additionally, some gaps in knowledge exist,

Table 4 Secondary analyses of responses to questions linked to key risk messages: complete surveys

Category[a]	18-month survey prescribers ($N = 195$)			3-year survey prescribers ($N = 209$)		
	Key risk message 1 %, (95% CI)[b]	Key risk message 2 %, (95% CI)[b]	Key risk message 3 %, (95% CI)[b]	Key risk message 1 %, (95% CI)[b]	Key risk message 2 %, (95% CI)[b]	Key risk message 3 %, (95% CI)[b]
Awareness of the Tanzeum® REMS Program						
Respondents who were aware of the REMS Program	91.8, (81.9–97.3)[c]	91.8, (81.9–97.3)	96.7, (88.7–99.6)[c]	80.0, (68.7–88.6)	94.3, (86.0–98.4)	61.4, (49.0–72.8)
Respondents who were not aware of the REMS Program	73.9, (65.6–81.1)[c]	84.3, (77.0–90.0)	82.1, (74.5–88.2)[c]	66.2, (57.7–74.0)	89.2, (82.8–93.8)	50.4, (41.8–58.9)
Receipt/access/read the Tanzeum® PI						
Respondents who received/accessed/read all or most of the PI	83.7, (74.5–90.6)	92.4, (84.9–96.9)	90.2, (82.2–95.4)	77.6, (67.3–86.0)	95.3, (88.4–98.7)	60.0, (48.8–70.5)
Respondents who did not receive/access or did not read at least most of the PI	79.2, (69.7–86.8)	86.5, (78.0–92.6)	84.4, (75.5–91.0)	68.1, (58.9–76.3)	89.1, (82.0–94.1)	51.3, (41.9–60.5)
Type of provider						
Medical doctor	80.4, (71.8–87.3)	85.7, (77.8–91.6)	84.8, (76.8–90.9)	74.5, (65.4–82.4)	91.8, (85.0–96.2)	54.5, (44.8–64.1)
Nurse practitioner/advanced practiced registered nurse	74.0, (59.7–85.4)	92.0, (80.8–97.8)	84.0, (70.9–92.8)	78.4, (64.7–88.7)	96.1, (86.5–99.5)	54.9, (40.3–68.9)
Medical specialty (medical doctor, doctor of osteopathy)						
Family medicine	74.5, (60.4–85.7)	74.5, (60.4–85.7)[c]	86.3, (73.7–94.3)	60.3, (46.6–73.0)	86.2, (74.6–93.9)	43.1, (30.2–56.8)
Internal medicine	83.0, (69.2–92.4)	89.4, (76.9–96.5)	83.0, (69.2–92.4)	75.0, (58.8–87.3)	97.5, (86.8–99.9)	52.5, (36.1–68.5)
Endocrinology	93.8, (79.2–99.2)	100, (89.1–100.0)[c]	93.8, (79.2–99.2)	84.2, (68.7–94.0)	92.1, (78.6–98.3)	68.4, (51.3–82.5)
Volume of prescriptions						
1–5 patients	76.7, (66.4–85.2)	87.2, (78.3–93.4)	93.0, (85.4–97.4)	62.9, (50.5–74.1)	88.6, (78.7–94.9)	47.1, (35.1–59.4)
6–10 patients	73.2, (59.7–84.2)	89.3, (78.1–96.0)	83.9, (71.7–92.4)	73.5, (58.9–85.1)	95.9, (86.0–99.5)	53.1, (38.3–67.5)
11–20 patients	–	–	–	65.9, (50.1–79.5)	88.6, (75.4–96.2)	63.6, (47.8–77.6)
>20 patients	–	–	–	83.7, (69.3–93.2)	90.7, (77.9–97.4)	55.8, (39.9–70.9)

CI confidence interval, *PI* prescribing information, *REMS* Risk Evaluation and Mitigation Strategy

[a]Only group populations with at least 30 respondents are included in this table

[b]95% exact two-sided CIs are calculated using the Clopper–Pearson method

[c]Non-overlapping CIs indicating potentially different rates of knowledge

particularly in terms of appropriate patient population, highlighting the need to evaluate whether additional education is warranted.

Based on feedback from the FDA and similar REMS assessment studies, a correct response rate of $\geq 80\%$ is generally accepted as a suitable cut-off for a REMS assessment survey (although the FDA is currently re-evaluating knowledge assessment practices) [33]. It is important to note that the focus of this study, the REMs survey, is just one part of the overall assessment of REMS effectiveness, and that this threshold is not intended as a cut-off for good medical knowledge standards for physicians. In this report, two questions in the 18-month survey and five questions in the 3-year survey did not achieve this cut-off (Table 2). In particular, only 68.2% (18-month survey) and 69.4% (3-year survey) of respondents correctly answered that albiglutide is not recommended as first-line therapy in adults with T2DM inadequately controlled on diet and exercise, suggesting additional education on this topic could be beneficial. Additionally, only 75.4% (18-month survey) and 78.0% (3-year survey) of respondents correctly responded that if acute pancreatitis

is confirmed, albiglutide cannot be restarted after its resolution. In the 3-year survey, a correct response rate > 80% was also seen regarding the need for routine monitoring of serum calcitonin and a thyroid ultrasound in patients treated with albiglutide (78.0% correct), the need to refer a patient to an endocrinologist if calcitonin was found to be elevated (78.0% correct), and knowledge that GLP-1RAs have caused thyroid C-cell tumors in rodents (76.1% correct).

For the secondary analysis, while most prescribers achieved the target comprehension threshold by answering ≥ 75% (18-month survey) or ≥ 80% (3-year survey) of the questions within a key risk message correctly, between 10 and 45% of prescribers did not achieve this goal depending on the survey and key risk message in question (Table 3). Although the target comprehension threshold was increased from 75% in the 18-month survey to 80% in the 3-year survey based on recommendations from the FDA, only Key Risk Message 3 (appropriate patient population) was affected by this increase. For key risk messages related to MTC and pancreatitis, the number of questions respondents needed to answer correctly to meet or exceed the 80% threshold was the same as to meet or exceed the 75% threshold.

This report also assessed prescriber awareness and access to the albiglutide REMs. To ensure broad dissemination, it is important to provide information through multiple platforms (i.e., written letters, web-based sources, sales representatives), as different prescribers may have different preferences. In both surveys, prescriber awareness of the albiglutide PI and REMS was similar, and the PI and sales representatives were the most frequent sources of information regarding risks associated with albiglutide. Although ≥ 74% of prescribers were unaware of the REMS materials, 70–80% obtained information from sales representatives, which could indicate a preference to receive information verbally vs. through leave-behind materials or accessing a website.

Several strengths contributed to the integrity of this knowledge survey. First, to minimize bias, respondents who have or whose immediate family members ever worked for GSK, United BioSource Corporation, or the FDA were not eligible. Second, the response order within multi-item questions was randomized. Third, respondents could not change a response once answered and could not skip ahead. Additionally, each respondent was provided with a unique code that was required to gain access to the survey, minimizing the chance of duplicate participation. Finally, the use of a standard comprehension threshold consistent with FDA guidance could facilitate future comparisons of REMS assessments for other GLP-1RAs.

In an attempt to survey the appropriate population of prescribers, invited participants were randomly selected from a database of healthcare professionals that had prescribed albiglutide. The randomized selection process suggests that the results are generalizable to all prescribers of albiglutide. However, a limitation to the survey results may include bias in the sample of respondents who completed the survey because of the voluntary nature of participation. The proportion of respondents answering questions correctly in the population that chose to participate may not precisely represent the knowledge of all albiglutide prescribers. Additionally, the large number of questions with true/yes correct responses may have impacted the results. For example, the questions with the lowest response rates were those requiring the respondent to disagree (select "false" or "no") with the statement. Correction for guessing was also not included in the analysis. The survey was developed with feedback from the FDA, but did not undergo formal validation beyond qualitative research of a subset of questions for content, language, and format. Finally, the survey did not assess how well prescribers communicated the information on the risks and safe use of albiglutide to patients.

5 Conclusions

The results from the survey suggest that some gaps exist in prescribers' knowledge of the risks and safe use of albiglutide, particularly that albiglutide is not recommended as first-line therapy. However, a majority of prescribers demonstrated knowledge about mitigating the risk of pancreatitis and the potential risk of MTC. Continued assessment of the effectiveness of the albiglutide REMS in meeting its goals and identifying ways in which the comprehension of important key risk messages can be improved will be instrumental to ensure that prescribers continue to have the necessary information regarding the risks and safe use of albiglutide.

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Compliance with Ethical Standards

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