Research Article

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Evaluation of patient/caregiver and healthcare provider knowledge, attitudes and behavior for safety and use of pexidartinib

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Aim: Pexidartinib was approved for the treatment of tenosynovial giant cell tumors with a required Risk Evaluation and Mitigation Strategy (REMS) to ensure its safe use. As required by the REMS, a survey was conducted to document the knowledge, attitudes and behavior (KAB) of patients/caregivers and healthcare providers (HCPs) regarding the risk of serious and potentially fatal liver injury due to pexidartinib, the need for liver testing prior to and during treatment and the need for patient counseling about this risk. **Patients & methods:** The KAB survey was conducted among 40 patients and 18 HCPs enrolled in the pexidartinib REMS. **Results:** Among patients, 87.5% demonstrated understanding of key risk message (KRM) 1 (risk of serious liver injury), 87.5% demonstrated understanding of KRM2 (liver testing requirement) and 77.5% demonstrated understanding of both KRMs. Among HCPs, 83.3% demonstrated understanding of KRM1, 88.9% demonstrated understanding of KRM2, 100% demonstrated understanding of KRM3 (patient counseling) and 83.3% demonstrated understanding of all three KRMs. **Conclusion:** The KAB surveys demonstrated that the educational goals of the pexidartinib REMS were being achieved.

Lay abstract: Pexidartinib is a prescription medicine used to treat adults who have a tenosynovial giant cell tumor that is not likely to improve with surgery. Because of the risk of serious liver problems, pexidartinib is available only through a restricted program called a Risk Evaluation and Mitigation Strategy (REMS) that enrolls both patients and healthcare providers (HCPs). As part of the REMS, information is collected about their knowledge, attitudes and behavior (KAB) regarding the potential for pexidartinib to cause liver problems that may be severe and can lead to death. This KAB survey was conducted among 40 patients and 18 HCPs enrolled in the pexidartinib REMS. The results indicated that among patients, over three-quarters demonstrated understanding of the risk of serious liver injury and the need for regular liver testing. Among HCPs, 83.3–100% demonstrated understanding of the risk of serious liver injury, the need for regular liver testing and the requirement to counsel their patients about this risk. In conclusion, the KAB surveys demonstrated that the educational goals of the pexidartinib REMS were being achieved.

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Keywords: KAB • pexidartinib • quantitative research • REMS • survey • Turalio

Pexidartinib (TURALIO®) is a small molecule tyrosine kinase inhibitor for oral use that targets CSF1R, KIT proto-oncogene receptor tyrosine kinase and FLT3 harboring an internal tandem duplication mutation. It was approved on 2 August 2019 for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Pexidartinib is the first systemic therapy approved for this rare condition.

Future Medicine

In the pivotal Phase III ENLIVEN trial, the safety and efficacy of pexidartinib was compared with placebo in 120 patients with unresectable advanced TGCT [1]. Patients in the pexidartinib group received a loading dose of 1000 mg pexidartinib per day orally (400 mg morning; 600 mg evening) for the first 2 weeks, followed by 800 mg per day (400 mg twice a day) for 22 weeks. The overall response rate was significantly higher for pexidartinib than placebo at Week 25 (39 vs 0%) and the responses were durable (all 13 of responding patients who were followed for ≥12 months maintained the response). The most common side effects of pexidartinib were increased LDH, increased AST, hair color changes, increased ALT and increased cholesterol. Three patients given pexidartinib developed aminotransferase elevations 3 or more times the upper limit of normal with total bilirubin and alkaline phosphatase 2 or more times the upper limit of normal. In a more recent pooled long-term analysis of hepatic adverse reactions in 140 patients with TGCT taking pexidartinib, five patients (4%) experienced serious mixed or cholestatic injury; all five cases recovered 1–7 months following pexidartinib discontinuation [2]. The prescribing information includes a Boxed Warning advising healthcare providers (HCPs) and patients about the risk of serious and potentially fatal liver injury.

In accordance with section 505(1)(f)(3)(A) of the United States (US) Federal Food, Drug and Cosmetic Act, the US FDA determined that a Risk Evaluation and Mitigation Strategy (REMS), including a Communication Plan (which provides for the dissemination of information about the risk of serious and potentially fatal liver injury) and an Elements to Assure Safe Use (ETASU), was necessary to ensure that the benefits of pexidartinib outweighed the risk of serious adverse events [3]. A component of the pexidartinib REMS assessment plan was the conduct of a quantitative Knowledge, Attitudes and Behavior (KAB) evaluation survey with HCPs and patients to assess their knowledge of the risks associated with pexidartinib and of the requirements of the pexidartinib REMS.

The objective of the KAB surveys was to document the level of knowledge and assess the attitudes and behavior of patients/caregivers and HCPs regarding the following key risk messages (KRM): pexidartinib can cause serious and potentially fatal liver injury (KRM1); monitoring of liver tests is required prior to and during treatment with pexidartinib and HCPs must withhold, modify, or discontinue the dose based on the liver tests (KRM2); and HCPs must counsel patients on the risk of serious and potentially fatal liver injury, monitor liver tests prior to and during treatment with pexidartinib and report any signs and/or symptoms of liver injury during therapy (KRM3; HCPs only).

Methods

Participant recruitment

Patients were eligible for participation in the survey if they were enrolled in the pexidartinib REMS and were at least 18 years of age. For HCPs, the inclusion criterion was that they had received training and were certified in the pexidartinib REMS, regardless of whether they were actively treating patients for TGCT during survey execution. Patients or HCPs were ineligible if they were currently working for and/or who had immediate family members currently working for Daiichi Sankyo, UBC or the FDA; or if they reported having a potential conflict of interest. To join the pexidartinib REMS, prescribers were required to successfully complete the REMS training (with 100% correct responses).

Information from the pexidartinib REMS database was used to identify potential survey participants. In an effort to ensure maximum participation in the survey, all eligible patients and HCPs were sent a prenotification letter 1 week prior to survey launch explaining the purpose and details of the upcoming survey. An invitation letter was then sent, which included three methods (Internet, telephone, or paper) for accessing the survey. Those who did not respond to the survey were to be sent up to three reminder letters. In a further attempt to minimize sampling error and bias, outbound calling to nonresponders was utilized. Respondents who completed the entire survey and provided their contact information were sent a thank-you letter, a copy of the correct answers to important survey questions, a copy of the pexidartinib prescribing information (HCPs), copies of the Medication Guide and Patient Guide (patients) and compensation of US$25 (patients) or US$125 (HCPs).

Survey design & administration

The HCP and patient KAB surveys were designed in collaboration between Daiichi Sankyo and UBC, and the survey was administered by UBC.

The survey was administered via Internet, telephone or paper and participants were able to choose the method they preferred. The Electronic Data Capture (EDC) system used for all methods of survey administration was validated and secure for receiving and storing survey data. The system was developed in accordance with 21

Code of Federal Regulations (CFR) Part 11 and Health Insurance Portability and Accountability Act (HIPAA) requirements for information systems. Respondent identifying information was stored separately from survey data.

The questions and statements in the surveys addressed the goal, objectives and specific key risk messages of the pexidartinib REMS. They were written in several formats, which included the following: questions that required the respondent to choose from a defined list of possible answers (i.e., multiple choice questions); questions that required the respondent to 'select all that apply;' and statements where the respondent was asked to indicate agreement or disagreement using response options of 'yes' or 'true,' 'no' or 'false' and 'I don't know.' All answers for questions permitting multiple responses were tallied to provide a broad picture of the participant's knowledge, attitudes and behavior. Questions regarding the requirements of the pexidartinib REMS and participants' awareness, access to, receipt of, reading and use of educational materials were asked after the screening and key risk message questions, and were followed by the collection of demographic information.

A number of controls were in place to ensure that the survey was conducted in a professional manner and to minimize bias, including the following: respondents were required to provide a unique code (issued during the recruitment process) in order to gain access to the Internet-based survey or when calling, and the code was inactivated after use to minimize exposure bias and fraud; all questions were presented in a standard order to reduce exposure bias; response options within a multi-item question, where applicable, were randomized to minimize the potential for positional bias; respondents were instructed that they could not (Internet and telephone) and should not (paper) go back to a question once they had progressed to the next question and could not (Internet and telephone) and should not (paper) skip ahead; and a standardized script was used for telephone interviews, and all telephone interviewers were carefully trained in interview techniques to minimize interviewer bias.

Statistical analysis

No formal hypotheses were tested. Descriptive statistics were presented by counts and percentages. Counts and percentages were calculated for each question/item in the questionnaire. In cases where the estimated percentage was equal to 0 or 100%, the Clopper-Pearson method [4] was utilized to estimate the CIs using *proc freq* in SAS® [5]. All other estimated percentages and their confidence intervals (CIs) were calculated using 2-sided transformed logit 95% CIs calculated according to the method of Agresti [6]. *Proc surveyfreq* in SAS® [7] was used to estimate the transformed logit CIs.

Analysis populations include the 'All Respondents' population, which consisted of unique respondents who accessed the survey using a unique code. This population was used as the denominator for percentages in survey administration statistics, unless otherwise specified and in the survey eligibility results analysis. The 'Eligible Respondents' population consisted of all respondents who completed all eligibility questions, fulfilled all inclusion criteria and none of the exclusion criteria, regardless of whether or not they completed the survey. The 'Completed Surveys' population is a subset of the Eligible Respondents population. For Internet and telephone surveys, 'Completed Survey' was defined as one with no missing data with the exception of missing data due to skip patterns.

A primary analysis was performed for each key risk message. Responses for all questions/items within each key risk message were summarized by counts and percentages. The primary analysis for a key risk message evaluated the rate for each correct response to each individual question/item defined by the key risk message. Statements or questions asking the participant to select all that apply from a defined list of possible statements or answers ("*select all that apply*") were counted as correct if at least 80% of the correct responses were selected and no more than one incorrect response was selected.

Secondary analysis of each key risk message was also performed consisting of a frequency distribution of the number of correct responses to each key risk message (i.e., number and percentages are shown by the number of correct responses). 'Select all that apply' questions were counted as correct if at least 80% of the correct responses were selected and no more than one incorrect response was selected. Another secondary end point was the demonstrated understanding of each key risk message, defined as correctly answering 80% or more questions/items in a key risk message. The pre specified threshold of 80% aligns with the FDA general guidance that 80% or higher should be the general standard for each REMS key risk message [3].

All other questions, including those about demographics, inclusion/exclusion, counseling about the pexidartinib REMS and participant awareness of, access to, receipt of, reading and use of educational materials, were also analyzed. The responses to each question were summarized by frequency tables.

Table 1. Demographics of survey participants.

Parameter	n (%)
Patients	40
Age, years	
– 18–29	1 (2.5)
– 30–39	6 (15.0)
– 40–49	12 (30.0)
– 50–59	10 (25.0)
– 60–69	7 (17.5)
– 70 or older	4 (10.0)
Sex, n (%)	
– Male	12 (30.0)
– Female	28 (70.0)
Education, n (%)	
– High School/GED	5 (12.5)
– Some college	11 (27.5)
– Associate's Degree	2 (5.0)
– Bachelor's Degree	11 (27.5)
– Master's Degree	8 (20.0)
– Professional or Doctoral Degree	2 (5.0)
– Prefer not to answer	1 (2.5)
Race, n (%)	
– Asian	7 (17.5)
– Black or African American	1 (2.5)
– White	28 (70.0)
– Two or more races	1 (2.5)
– Other	1 (2.5)
– Prefer not to answer	2 (5.0)
Time taking pexidartinib, n (%)	
– <1 month	2 (5.3)
– 1–6 months	28 (73.7)
– 7–12 months	8 (21.1)
– Have not taken at least 1 dose	2 (5.0)
Healthcare providers	18
Type of provider, n (%)	
– Doctor of Medicine (MD)	15 (83.3)
– Advanced Practice Registered Nurse (APRN)	2 (11.1)
– Physician Assistant (PA)	1 (5.6)
Practice setting, n (%)†	
– Group Practice	7 (38.9)
– Hospital	8 (44.4)
– Independent Practice	1 (5.6)
– Outpatient clinic	4 (22.2)
– Other	1 (5.6)
Primary medical specialty, n (%)	
– Oncology	14 (77.8)
– Orthopedics	4 (22.2)
Years as an HCP, n (%)	
– <1 year	1 (5.6)

†More than one response can be selected, so percentages may not sum to 100%.
GED: General educational development; HCP: Healthcare professional.

Table 1. Demographics of survey participants (cont.).

Parameter	n (%)
– 1–3 years	3 (16.7)
– 3–5 years	5 (27.8)
– 6–10 years	0
– 11–15 years	2 (11.1)
– 16–20 years	2 (11.1)
– >20 years	5 (27.8)
Last time prescribing pexidartinib, n (%)	
– <1 month ago	5 (27.8)
– 1–3 months ago	8 (44.4)
– 4–6 months ago	1 (5.6)
– I don't remember	1 (5.6)
– Never	3 (16.7)

†More than one response can be selected, so percentages may not sum to 100%.
GED: General educational development; HCP: Healthcare professional.

Results

Survey participants

Information from the pexidartinib REMS database as of 3 Mar 2020 was used to identify all HCPs who were certified in the pexidartinib REMS and patients who were enrolled in it. The survey was administered from 8 Apr 2020 to 7 Jun 2020.

For the HCP survey, 187 invitation letters and 484 reminder letters were sent and 197 outbound calls were made to nonresponders. Of the 26 HCPs who accessed the survey, 19 (73.1%) were eligible to participate and of those, 18 (94.7%) completed the survey. For the patient survey, 96 invitation letters and 206 reminder letters were sent and 68 outbound calls were made. Of the 45 patients who accessed the survey, 41 (91.1%) were eligible to participate and of those, 40 (97.6%) completed the survey.

Characteristics of the eligible patients and HCPs who completed the survey are presented in Table 1. Of the 40 patients, the majority (55%) were 40–59 years of age, 70.0% were female, 70.0% were white and 73.7% had been receiving pexidartinib for 1–6 months.

HCPs were 66.7% male and included medical doctors (83.3%), advanced practice nurses (11.1%) and physician assistants (5.6%) specializing in oncology (77.8%) or orthopedics (22.2%). HCPs most commonly reported they had practiced for 3–5 years (27.8%) or more than 20 years (27.8%). Almost all HCPs reported working in a hospital (44.4%), group practice (38.9%) or outpatient clinic (22.2%; respondents could select more than one type of healthcare facility). Most (72.2%) reported having most recently prescribed pexidartinib 1 to 3 months (44.4%) or <1 month (27.8%) prior to participation.

Key Risk Message 1

Key Risk Message 1 for patients states that pexidartinib can cause serious liver problems which may be severe and can lead to death. The HCP version is slightly reworded to state that pexidartinib "*can cause serious and potentially fatal liver injury.*"

Primary analysis of the patient surveys indicated that almost all participants (39, 97.5%) were aware that pexidartinib is a prescription medication used to treat adults who have TGCT that is not likely to improve with surgery (Table 2). Almost all patients (39, 97.5%) knew pexidartinib can cause serious and potentially fatal liver injury and that liver problems can occur at any time during treatment with pexidartinib. Almost all respondents (90.0%) knew the statement that "*you are not required to have blood testing done to monitor your liver while receiving treatment with pexidartinib*" is false. All respondents (100%) knew that they should tell their HCP right away if they have any symptoms of liver problems, at any time, while taking pexidartinib, including lack or loss of appetite (90.0%), abdominal pain or tenderness (90.0%), feeling overly tired (95.0%), nausea (97.5%), vomiting (95.0%), fever (90.0%), rash (87.5%) and itching (87.5%). Most patients were also aware that they should stop taking pexidartinib immediately and call their HCP if any of the following occur: yellowing of the skin (87.5%), dark urine (85.0%) or yellowing of the whites of the eyes (87.5%). The secondary analysis of Key Risk Message 1

Table 2. Primary analysis of patient responses to questions linked to Key Risk Message 1.

Question	Patients (n = 40)[†] n (%) (95% CI)[‡]
Question 6: Please answer True, False, or I don't know. TURALIO can cause serious liver problems which may be severe and can lead to death.	
– True (Correct)	39 (97.5) (88.9–99.5)
– False	0
– I don't know	1 (2.5)
Question 7: Please answer True, False, or I don't know. You are not required to have blood testing done to monitor your liver while receiving treatment with TURALIO.	
– True	3 (7.5)
– False (Correct)	36 (90.0) (79.8–95.3)
– I don't know	1 (2.5)
Question 8: Please answer Yes, No, or I don't know. You should tell your healthcare provider right away if you have any symptoms of liver problems, at any time, while taking TURALIO.	
– Yes (Correct)	40 (100.0) (91.2–100.0)
– No	0
Question 9: Please answer True, False, or I don't know. You should tell your healthcare provider right away if you experience any of the following symptoms while taking TURALIO.	
9A: Lack or loss of appetite	
– True (Correct)	36 (90.0) (79.8–95.3)
– False	3 (7.5)
– I don't know	1 (2.5)
9B: Right upper stomach-area (abdomen) pain or tenderness	
– True (Correct)	36 (90.0) (79.8–95.3)
– False	2 (5.0)
– I don't know	2 (5.0)
9C: Feeling overly tired	
– True (Correct)	38 (95.0) (86.0–98.3)
– False	1 (2.5)
– I don't know	1 (2.5)
9D: Nausea	
– True (Correct)	39 (97.5) (88.9–99.5)
– False	1 (2.5)
9E: Vomiting	
– True (Correct)	38 (95.0) (86.0–98.3)
– False	2 (5.0)
9F: Fever	
– True (Correct)	36 (90.0) (79.8–95.3)
– False	3 (7.5)
– I don't know	1 (2.5)
9G: Rash	
– True (Correct)	35 (87.5) (76.9–93.6)
– False	4 (10.0)
– I don't know	1 (2.5)
9H: Itching	
– True (Correct)	35 (87.5) (76.9–93.6)
– False	3 (7.5)
– I don't know	2 (5.0)

Percentages are calculated based on the number not missing for each question. Question 10 is counted as a correct response if all three correct items have been selected.
[†]Total number of eligible respondents completing the survey.
[‡]Logit-transformed CIs will be used to take into account the finite population. Clopper-Pearson will be used for proportion estimates of zero and 100.
[§]If 'All of the above' is selected, the response is counted in each category except 'None of the above' and 'I don't know'. Therefore, 'All of the above' is not presented as a category.
[¶]More than one response can be selected, so percentages may not sum to 100%.

Table 2. Primary analysis of patient responses to questions linked to Key Risk Message 1 (cont.).

Question	Patients (n = 40)[†] n (%) (95% CI)[‡]
Question 10: Please select all that apply. You should stop taking TURALIO immediately and call your healthcare provider if any of the following occur:[§],[¶]	
– Yellowing of the skin (Correct)	35 (87.5) (76.9–93.6)
– Dark urine (Correct)	34 (85.0) (74.0–91.9)
– Yellowing of the whites of the eyes (Correct)	35 (87.5) (76.9–93.6)
– None of the above	3 (7.5)
– I don't know	2 (5.0)
– Correct response to Question 10	34 (85.0) [74.0–91.9]
Question 11: Please answer Yes, No, or I don't know. TURALIO is a prescription medication used to treat adults who have tenosynovial giant cell tumor (referred to as TGCT) that is not likely to improve with surgery.	
– Yes (Correct)	39 (97.5) (88.9–99.5)
– No	0
– I don't know	1 (2.5)
Question 13: Please answer True, False, or I don't know. Liver problems can occur at any time during treatment with TURALIO.	
– True (Correct)	39 (97.5) (88.9–99.5)
– False	0
– I don't know	1 (2.5)

Percentages are calculated based on the number not missing for each question. Question 10 is counted as a correct response if all three correct items have been selected.
[†]Total number of eligible respondents completing the survey.
[‡]Logit-transformed CIs will be used to take into account the finite population. Clopper-Pearson will be used for proportion estimates of zero and 100.
[§]If 'All of the above' is selected, the response is counted in each category except 'None of the above' and 'I don't know'. Therefore, 'All of the above' is not presented as a category.
[¶]More than one response can be selected, so percentages may not sum to 100%.

Table 3. Primary analysis of healthcare providers responses to questions linked to Key Risk Message 1.

Question	HCPs (n = 18)[†] n (%) (95% CI)[‡]
Question 8: Please answer True, False or I don't know. TURALIO can cause serious and potentially fatal liver injury.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0
Question 9: Please answer True, False or I don't know. Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with TURALIO. Ductopenia refers to reduction in the number of intrahepatic bile ducts (pathology finding), a process that ultimately leads to cholestasis.	
– True (Correct)	– 15 (83.3) (57.5–94.9)
– False	– 0
– I don't know	– 3 (16.7)
Question 10: Please answer True, False or I don't know. The mechanism of cholestatic hepatotoxicity associated with the use of TURALIO is unknown and its occurrence cannot be predicted.	
– True (Correct)	– 12 (66.7) (41.6–84.9)
– False	– 1 (5.6)
– I don't know	– 5 (27.8)
Question 11: Please answer True, False or I don't know. Liver function testing is not required for patients receiving treatment with TURALIO if the patient reports not having any history of liver injury.	
– True	– 1 (5.6)
– False (Correct)	– 17 (94.4) (67.0–99.3)
Question 12: Please answer Yes, No or I don't know. According to the TURALIO REMS, healthcare providers must report adverse events of serious and potentially fatal liver injury by submitting the Liver Adverse Event Reporting Form to the TURALIO REMS.	
– Yes (Correct)	– 17 (94.4) (67.0–99.3)
– No	– 0
– I don't know	– 1 (5.6)
Question 13: Please answer True, False or I don't know. Baseline liver testing should be obtained prior to patients receiving treatment with TURALIO.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0

Percentages are calculated based on the number not missing for each question.
[†]Total number of eligible respondents completing the survey for the given category.
[‡]Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson is used for proportion estimates of 0 and 100.

Table 4. Secondary analysis of responses to questions linked to Key Risk Message 1.

Correct Responses	Patients (n = 40)† n (%) (95% CI)‡	HCPs (n = 18)† n (%) (95% CI)‡
0 correct responses	0	0
1 correct response	0	0
2 correct responses	0	0
3 correct responses	0	0
4 correct responses	0	3 (16.7)
5 correct responses	0	5 (27.8)
6 correct responses	0	10 (55.6)
7 correct responses	0	N/A
8 correct responses	2 (5.0)	N/A
9 correct responses	0	N/A
10 correct responses	2 (5.0)	N/A
11 correct responses	1 (2.5)	N/A
12 correct responses	4 (10.0)	N/A
13 correct responses	9 (22.5)	N/A
14 correct responses	22 (55.0)	N/A
Demonstrated Understanding of Key Risk Message 1	35 (87.5) (76.9–93.6)§	15 (83.3) (57.5–94.9)¶

†Total number of eligible respondents completing the survey.
‡Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson CIs are used for proportion estimates of 0 and 100.
§Demonstrated understanding of Key Risk Message 1 for patients is defined as 12 or more correct responses.
¶Demonstrated understanding of Key Risk Message 1 for HCPs is defined as five or more correct responses.
HCP: Healthcare provider; N/A: Not applicable.

indicated that 35 (87.5%) patients demonstrated understanding that pexidartinib can cause serious and potentially fatal liver injury by correctly answering at least 12 of the 14 questions linked to the key risk message (Table 4).

Primary analysis of the HCP surveys indicated that all respondents (100.0%) knew pexidartinib can cause serious and potentially fatal liver injury and most (83.3%) knew hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with pexidartinib (Table 3). The majority of HCPs (66.7%) knew the mechanism of cholestatic hepatotoxicity associated with the use of pexidartinib is unknown and its occurrence cannot be predicted. Almost all respondents (94.4%) knew the statement that "*liver function testing is not required for patients receiving treatment with pexidartinib if the patient reports not having any history of liver injury*" is false. Almost all HCPs (94.4%) knew that according to the pexidartinib REMS, they must report AEs of serious and potentially fatal liver injury. All respondents (100.0%) knew baseline liver testing should be obtained prior to patients receiving treatment with pexidartinib. The secondary analysis of Key Risk Message 1 indicated that 83.3% of HCPs demonstrated understanding that pexidartinib can cause serious and potentially fatal liver injury by correctly answering at least five of the six questions linked to the key risk message; over half answered all six questions correctly (Table 4).

Key Risk Message 2

Key Risk Message 2 for patients states that "*it is important for patients to have blood testing performed to check their liver health before starting and while taking*" pexidartinib. Similarly, for HCPs, Key Risk Message 2 states that "monitoring of liver tests is required prior to and during treatment with pexidartinib. HCPs must modify the pexidartinib dose based upon liver tests."

Almost all patients (80.0%) were aware that they must agree to be enrolled in the pexidartinib REMS to receive treatment with pexidartinib (Table 5). All 40 respondents knew that before taking pexidartinib, their HCP is required to discuss with them the frequency of blood testing and that they must have blood tests to check their liver as directed by their HCP. Almost all patients (92.5%) knew that blood testing for liver problems should occur before starting treatment with pexidartinib, every week for the first 8 weeks during treatment with pexidartinib and every 2 weeks for the next month, then every 3 months thereafter while taking pexidartinib. Almost all respondents (90.0%) knew that the statement "*if liver problems develop during treatment with pexidartinib, no blood testing will be required*" was false. Similarly, if liver problems are identified during treatment with pexidartinib, most respondents (87.5%) knew that their HCP may do more frequent blood testing. The secondary analysis of Key Risk Message 2

Table 5. Primary analysis of patient responses to questions linked to Key Risk Message 2.

Question	Patients (n = 40)[†] n (%) (95% CI)[‡]
Question 12: Please answer True, False or I don't know. Before taking TURALIO, your healthcare provider is required to discuss with you the frequency of blood testing.	
– True (Correct)	– 40 (100.0) (91.2–100.0)
– False	– 0
Question 14: Please answer True, False or I don't know. I must have blood tests to check my liver as directed by my healthcare provider.	
– True (Correct)	– 40 (100.0) (91.2–100.0)
– False	– 0
Question 15: Please answer True, False or I don't know. Your healthcare provider will do blood testing to check for liver problems: Before starting treatment with TURALIO, every week for the first 8 weeks during treatment with TURALIO and every 2 weeks for the next month, then every 3 months thereafter while taking TURALIO.	
– True (Correct)	– 37 (92.5) (82.9–96.9)
– False	– 2 (5.0)
– I don't know	– 1 (2.5)
Question 16: Please answer True, False or I don't know. If liver problems develop during treatment with TURALIO, no blood testing will be required.	
– True	– 0
– False (Correct)	– 36 (90.0) (79.8–95.3)
– I don't know	– 4 (10.0)
Question 17: Please answer True, False or I don't know. I must agree to be enrolled in the TURALIO REMS (Risk Evaluation and Mitigation Strategy) to receive treatment with TURALIO.	
– True (Correct)	– 32 (80.0) (68.4–88.1)
– False	– 1 (2.5)
– I don't know	– 7 (17.5)
Question 18: Please answer True, False or I don't know. If liver problems are identified during treatment with TURALIO, my healthcare provider may do more frequent blood testing.	
– True (Correct)	– 35 (87.5) (76.9–93.6)
– False	– 0
– I don't know	– 5 (12.5)

Percentages are calculated based on the number not missing for each question.
[†]Total number of eligible respondents completing the survey.
[‡]Logit-transformed CIs were used to take into account the finite population. Clopper-Pearson was used for proportion estimates of 0 and 100.

indicated that 87.5% of patients demonstrated understanding that it is important for patients to have blood testing performed to check their liver health before starting and while taking pexidartinib by correctly answering at least 5 of the 6 questions linked to the key risk message (Table 7).

All HCP respondents (100.0%) knew that they are required to order liver tests for patients receiving pexidartinib prior to initiating treatment and all (100.0%) knew they are required to obtain liver tests for patients receiving pexidartinib during treatment; overall, 100.0% of respondents selected both correct items (Table 6). Almost all HCPs (94.4%) knew that they must assess the patient by obtaining liver function tests weekly for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months. Most respondents (88.9%) knew prescriptions should be limited to a 30-day supply for each of the first 3 months of treatment. For Question 17, a "*select all that apply*" question that tested knowledge about which initial actions HCPs should do if a patient presents with an increased ALT and/or AST greater than three- to five-times upper limit of normal (ULN), most HCPs (88.9%) knew that they should withhold pexidartinib and monitor liver tests weekly for the first month if a patient presents with an increased ALT and/or AST greater than 3 to 5 times ULN. The majority of HCPs (66.7%) knew that they should permanently discontinue pexidartinib in patients who are unable to tolerate 200 mg orally twice daily. Almost all HCPs (94.4%) knew it is true that "*If a patient presents with an increased ALT and/or AST greater than 10 times ULN, pexidartinib should be permanently discontinued. Monitor liver test twice weekly until AST or ALT is less than or equal to 5 times ULN, then weekly until less than or equal to three-times ULN.*" All HCPs (100.0%) knew that they should withhold and dose reduce or permanently discontinue pexidartinib based on severity of hepatotoxicity. The secondary analysis of Key Risk Message 2 indicated that 88.9% of respondents demonstrated understanding that monitoring of liver tests is required prior to and during treatment with pexidartinib and that HCPs must modify the pexidartinib dose based upon liver tests by correctly answering at least six of the seven questions linked to the key risk message (Table 7).

Table 6. Primary analysis of healthcare providers responses to questions linked to Key Risk Message 2.

Question	HCPs (n = 18)[†] n (%) (95% CI)[‡]
Question 14: Please select all that apply. Healthcare providers are required to obtain liver tests for patients receiving TURALIO[§],[¶]	
– Prior to initiating treatment (Correct)	18 (100.0) (81.5–100.0)
– During treatment (Correct)	18 (100.0) (81.5–100.0)
– After treatment for 3 years.	5 (27.8)
– At no time during treatment.	0
– None of the above	0
– I don't know	0
Question 15: Please complete the sentence below by selecting the best option. HCPs must assess the patient by obtaining liver function tests ----------	
– Weekly for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months. (Correct)	17 (94.4) (67.0–99.3)
– Weekly for the first 2 weeks, then once a month thereafter.	1 (5.6)
– Weekly for the first 4 months.	0
Question 16: Please answer True, False or I don't know about the following statement. Prescriptions should be limited to a 30 day supply for each of the first 3 months of treatment.	
– True (Correct)	16 (88.9) (63.0–97.4)
– False	0
– I don't know	2 (11.1)
Question 17: Please select all that apply. HCPs should do which of the following initial actions if a patient presents with an increased ALT and/or AST greater than 3 to 5 times upper limit of normal (ULN)?[¶]	
– Withhold TURALIO and monitor liver tests weekly for the first month (Correct)	16 (88.9) (63.0–97.4)
– Withhold TURALIO and monitor monthly for the first 6 months.	2 (11.1)
– Permanently discontinue TURALIO.	1 (5.6)
– None of the above	0
– I don't know	0
Question 18: Please answer Yes, No, or I don't know. HCPs should permanently discontinue TURALIO in patients who are unable to tolerate 200 mg orally twice daily.	
– Yes (Correct)	12 (66.7) (41.6–84.9)
– No	5 (27.8)
– I don't know	1 (5.6)
Question 19: Please answer True, False, or I don't know. If a patient presents with an increased ALT and/or AST greater than 10 times ULN, TURALIO should be permanently discontinued. Monitor liver test twice weekly until AST or ALT is less than or equal to 5 times ULN, then weekly until less than or equal to 3 times ULN.	
– True (Correct)	17 (94.4) (67.0–99.3)
– False	0
– I don't know	1 (5.6)
Question 21: Please answer True, False, or I don't know. HCPs should withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity.	
– True (Correct)	18 (100.0) (81.5–100.0)
– False	0
– I don't know	0

Percentages were calculated based on the number not missing for each question. Question 14 was counted as a correct response if both correct items and no more than one incorrect item have been selected. Question 17 was counted as a correct response if the correct item and no more than one incorrect item have been selected.
[†]Total number of eligible respondents who completed the survey for the given category.
[‡]Logit-transformed CIs were used to take into account the finite population. Clopper-Pearson was used for proportion estimates of zero and 100.
[§]If 'All of the above' was selected, the response was counted in each category except 'None of the above' and 'I don't know'. Therefore, 'All of the above' was not presented as a category.
[¶]More than one response option can be selected, so percentages can sum to >100%.
HCP: Healthcare provider.

Key Risk Message 3

Key Risk Message 3 is intended for HCPs only and states that HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with pexidartinib and to report any signs and/or symptoms of liver injury during therapy.

Most HCPs (83.3%) knew that they should provide patients with the Patient Guide with each new or refill prescription (Table 8). All respondents knew that prior to initiating treatment with pexidartinib, HCPs should

Table 7. Secondary analysis of responses to questions linked to Key Risk Message 2.

Correct Responses	Patients (n = 40)[†] n (%) (95% CI)[‡]	HCPs (n = 18)[†] n (%) (95% CI)[‡]
0 correct responses	0	0
1 correct response	0	0
2 correct responses	0	0
3 correct responses	1 (2.5)	0
4 correct responses	4 (10.0)	0
5 correct responses	9 (22.5)	2 (11.1)
6 correct responses	26 (65.0)	8 (44.4)
7 correct responses	–	8 (44.4)
Demonstrated Understanding of Key Risk Message 2	35 (87.5) (76.9–93.6)[§]	16 (88.9) (63.0–97.4)[¶]

[†]Total number of eligible respondents completing the survey.
[‡]Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson CIs are used for proportion estimates of 0 and 100.
[§]Demonstrated understanding of Key Risk Message 2 for patients is defined as five or more correct responses.
[¶]Demonstrated understanding of Key Risk Message 2 for HCPs is defined as six or more correct responses.
HCP: Healthcare provider.

Table 8. Primary analysis of healthcare providers responses to questions linked to Key Risk Message 3.

Question	HCPs (n = 18)[†] n (%) (95% CI)[‡]
Question 20: Please answer Yes, No or I don't know. HCPs should provide patients with the Patient Guide with each new or refill prescription.	
– Yes (Correct)	– 15 (83.3) (57.5–94.9)
– No	– 1 (5.6)
– I don't know	– 2 (11.1)
Question 22: Please answer True, False or I don't know. Prior to initiating treatment with TURALIO HCPs should counsel their patients on which of the following:	
22A: The risk of serious and potentially fatal liver injury.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0
22B: Liver test monitoring prior to and during treatment with TURALIO.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0
22C: Immediately reporting any signs and/or symptoms of liver injury during therapy.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0
Question 23: Please answer True, False, or I don't know. To receive TURALIO, HCPs must counsel patients on the risks associated with TURALIO and enroll them in the TURALIO REMS prior to receiving treatment.	
– True (Correct)	– 18 (100.0) (81.5–100.0)
– False	– 0
Question 24: Please answer Yes, No, or I don't know. Prior to receiving treatment with TURALIO, patients should be counseled about the required liver function monitoring associated with TURALIO.	
– Yes (Correct)	– 18 (100.0) (81.5–100.0)
– No	– 0

Percentages are calculated based on the number not missing for each question.
[†]Total number of eligible respondents completing the survey for the given category.
[‡]Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson is used for proportion estimates of 0 and 100.
HCP: Healthcare provider.

counsel their patients on the following: the risk of serious and potentially fatal liver injury (100.0%), liver test monitoring prior to and during treatment with pexidartinib (100.0%), and immediately reporting any signs and/or symptoms of liver injury during therapy (100.0%). All HCPs (100.0%) knew that to receive pexidartinib, HCPs must counsel patients on the risks associated with pexidartinib and enroll them in the pexidartinib REMS prior to receiving treatment. All respondents (100.0%) knew that prior to receiving treatment with pexidartinib, patients should be counseled about the required liver function monitoring associated with pexidartinib. The secondary

Table 9. Secondary analysis of responses to questions linked to Key Risk Message 3.

Correct Responses	HCPs (n = 18)[†] n (%) (95% CI)[‡]
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	0
4 correct responses	0
5 correct responses	3 (16.7)
6 correct responses	15 (83.3)
Demonstrated Understanding of Key Risk Message 3[§]	18 (100.0) (81.5–100.0)

[†]Total number of eligible respondents completing the survey.
[‡]Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson is used for proportion estimates of 0 and 100.
[§]Demonstrated understanding of Key Risk Message 3 is defined as five or more correct responses.
HCP: Healthcare provider.

Table 10. Demonstrated understanding of all key risk messages.

Number of correct key risk messages	Patients (n = 40) n (%) (95% CI)[†]	HCPs (n = 18) n (%) (95% CI)[†]
Demonstrated Understanding of 0 Key Risk Messages	1 (2.5)	0
Demonstrated Understanding of 1 Key Risk Message	8 (20.0)	2 (11.1)
Demonstrated Understanding of 2 Key Risk Messages	31 (77.5) (65.6–86.1)	1 (5.6)
Demonstrated Understanding of 3 Key Risk Messages	–	15 (83.3) (57.5–94.9)

A respondent is counted as having demonstrating understanding if he/she correctly answered 80% or more of the questions/items in each key risk message.
[†]Logit-transformed CIs are used to take into account the finite population. Clopper-Pearson is used for proportion estimates of 0 and 100.
HCP: Healthcare provider.

analysis of Key Risk Message 3 indicated that 100.0% of respondents demonstrated understanding that HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with pexidartinib and to report any signs and/or symptoms of liver injury during therapy by correctly answering at least five of the six questions linked to the key risk message (Table 9).

Demonstrated understanding of all key risk messages

Table 10 presents the percentages of respondents who understood 0, 1, 2, or 3 key risk messages, including 95% CIs for the respondents who understood all 3 key risk messages. Most respondents (77.5% of patients and 83.3% of HCPs) demonstrated understanding of all the key risk messages.

Discussion

Pexidartinib was approved in 2019 in the US with a REMS to ensure that its benefits outweighed the risk of serious and potentially fatal liver injury in patients with TGCT. A component of the pexidartinib REMS assessment plan was the conduct of a quantitative KAB evaluation survey with HCPs and patients to assess their knowledge of the risks associated with pexidartinib and of the requirements of the REMS. The key risk messages were that pexidartinib can cause serious and potentially fatal liver injury (KRM1); monitoring of liver tests is required prior to and during treatment with pexidartinib (and HCPs must withhold, modify, or discontinue the dose based on the liver tests) (KRM2); and HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with pexidartinib and to report any signs and/or symptoms of liver injury during therapy (KRM3; HCPs only).

Although the number of survey responders was smaller than targeted, a sample size of 40 patients and 18 HCPs was achieved. A total of 175 prenotification letters, 186 invitation letters and 484 reminder letters were sent, and 197 outbound calls were made, to potentially eligible HCPs, which resulted in an HCP survey response rate of 13.5% (26/193) and a completion rate of 94.7% (18/19). Note that HCPs who were considered eligible were trained and certified in the pexidartinib REMS but not necessarily actively treating patients during survey execution. Although this participation rate was lower than desired despite aggressive recruitment, including numerous US mail, email and outbound calling outreach efforts, the use of three survey modalities (Internet, telephone and

paper) and inviting all available HCPs to participate, it is consistent with the low rates typically seen with this population. A systematic review of FDA KAB surveys of physicians from 2000 to 2014 (n = 75) found that half of the surveys had response rates between 34 and 68% [8].

The pexidartinib REMS is considered to be meeting its goals if the point estimates of all key risk message achieve a demonstrated understanding of 80% or above. The prespecified threshold of 80% is the minimum knowledge rate that, if achieved, indicates the REMS met the goal of communicating the REMS key risk message. Among patients, 87.5% demonstrated understanding of KRM1, 87.5% demonstrated understanding of KRM2 and 77.5% demonstrated understanding of both KRMs by meeting or exceeding the 80% knowledge threshold. Among HCPs, 83.3% demonstrated understanding of KRM1, 88.9% demonstrated understanding of KRM2, 100% demonstrated understanding of KRM3 and 83.3% demonstrated understanding of all 3 KRMs.

The KAB survey recruitment strategies were intended to recruit patients and HCPs who were trained and enrolled in the REMS as identified by the pexidartinib REMS database. Participants were self-selected because they voluntarily responded to the invitation to participate, so the potential exists that there may have been differences in understanding of important safety information between those who chose to respond to the survey versus those who elected not to participate. This is a common limitation of all studies that rely on voluntary participation. Another limitation is that the survey can assess respondents' understanding of the important safety information but cannot clearly determine via which channel the respondents gained the information. Among those who volunteer to respond to the survey, recall of information is critical. Inherent in survey research is the reliance on the respondent's recall of whether or not the REMS educational materials (e.g., Prescribing Information) was received and read. It is possible that the respondents had an acceptable understanding of the important safety information associated with the use of pexidartinib despite not recalling that he/she received and or read the REMS educational materials prior to completing the survey.

The complexity of an assessment plan depends on the complexity of the REMS [9]. The pexidartinib REMS is complex and includes a medication guide, communication plan, restricted distribution, certification of pharmacies, certification of HCPs and more. The KAB surveys were required to measure prescriber and patient knowledge and understanding of serious risks and safe use conditions, and prescriber knowledge of proper patient selection. Nonetheless, despite the complexity, the KAB surveys demonstrated that both patients who were prescribed pexidartinib and HCPs who prescribed pexidartinib had a good understanding of the KRMs, indicating that the educational goals of the pexidartinib REMS were being achieved. The knowledge acquisition is expected to support the REMS in the mitigation of the risk of serious and potentially fatal liver injury by ensuring patients and HCPs are informed about the risks associated with the use of pexidartinib and the requirement for baseline and periodic monitoring during treatment, the need to report and stop therapy for concerning signs or symptoms and the need to intervene with appropriate dose modification including permanent discontinuation.

Conclusion

Based on the results of these KAB surveys, the TURALIO REMS is meeting its goal to increase patient and HCPs' understanding of the risk of serious and potentially fatal liver injury of pexidartinib. Furthermore, our experience with the patient and HCP surveys indicates that the KAB survey is an appropriate and informative way to test the effectiveness of REMS.

Summary points

- Pexidartinib, a kinase inhibitor, is approved in the USA for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
- Due to potential hepatotoxicity, pexidartinib is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) Program.
- As part of the REMS, a quantitative survey of the knowledge, attitudes and behavior of pertaining to the key risk messages (KRMs) of patients/caregivers and healthcare providers (HCPs) was conducted.
- Forty patients (including 1 caregiver) and 18 HCPs enrolled in the REMS completed the survey via Internet, paper or phone.
- For KRM1 (pexidartinib can cause serious and potentially fatal liver injury (KRM1), 87.5% of patients and 83.3% of HCPs demonstrated understanding.
- For KRM2 (monitoring of liver tests is required prior to and during treatment with pexidartinib, and HCPs must withhold, modify or discontinue the dose based on the liver tests), 87.5% of patients and 88.9% of HCPs demonstrated understanding.
- For KRM3 (HCPs must counsel patients on the risk of serious and potentially fatal liver injury, monitor liver tests prior to and during treatment with pexidartinib and report any signs and/or symptoms of liver injury during therapy), 100% of HCPs demonstrated understanding.
- Overall, 77.5% of patients and 83.3% of HCPs demonstrated understanding of all KRMs.
- The KAB surveys demonstrated that both patients who were prescribed pexidartinib and HCPs prescribing pexidartinib have a good understanding of the KRMs, indicating that the REMS is effective in educating stakeholders about the risk of serious and potentially fatal liver injury.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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