In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

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- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Final Study Report
Control: Not applicable

Title:	**Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™**
Phase:	IV
Compound Number:	GW582892
Effective Date:	26-AUG-2015
Description:	GlaxoSmithKline (GSK) launched a study to evaluate the impact of risk management communication activities, outside the United States. This related to the information added to the TROBALT (retigabine) Prescribing Information on retinal pigmentation in June 2013 to ensure prescribers' comprehension.

Subject: Prescriber survey of the understanding of specific risks associated with TROBALT, communicated in the Healthcare Provider letter and TROBALT Prescribing Information.

Author: [redacted] MD, PhD (GlaxoSmithKline)

Indication Studied: Anti-epileptic

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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POST-AUTHORISATION SAFETY STUDY INFORMATION

Title	**Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™**
Version identifier of the final study report	1.0
Date of last version of the final study report.	26 August 2015
EU PAS register number	ENCEPP/SDPP/4851
Active substance	Anti-epileptic, ATC code: N03AX21, retigabine
Medicinal product	TROBALT™ (retigabine)
Product reference	EU/1/11/681/001-002, EU/1/11/681/004-005, EU/1/11/681/007-012, EU/1/11/681/014
Procedure number	Not applicable
Marketing authorisation holder(s)	Glaxo Group Limited
Joint PASS	No
Research question and objectives	The objective of this study was to assess prescribers' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey.
Countries of study	Belgium, Hong Kong (China), Norway, Slovakia, Spain, Switzerland, and the United Kingdom
Author	[redacted] MD, PhD (GlaxoSmithKline)

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
MAH contact person	[redacted]

Table of Contents

1 ABSTRACT

Title

Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™

Keywords

TROBALT, anti-epileptic, risk, prescriber understanding

Rationale and Background

This survey of physicians was undertaken to evaluate the understanding of specific risks associated with TROBALT and to evaluate the effectiveness of the educational plan as specified in the European Risk Management Plan (RMP).

Research Question and Objectives

The objective of this study was to assess physicians' awareness and knowledge of the specific risks associated with TROBALT (retigabine) and their management and the appropriate patient population to be treated as evaluated by a survey.

Study Design

This was an on-line cross-sectional survey of a targeted sample of physicians who had prescribed an anti-epileptic drug (AED) at least once in the last 6 months, who were sent a TROBALT Dear Healthcare Professional (DHCP) letter in June 2013, and who practiced medicine in one of 7 countries that participated in the survey. The letter provided details to the physicians regarding the revised indication and wording in the summary of product characteristics (SmPC), a recommendation of ophthalmological examinations to be performed at baseline and at least six months thereafter during TROBALT treatment, and the need to assess the balance of benefits and risks when initiating or continuing treatment with TROBALT.

Setting

The survey was conducted across 7 countries (Belgium, Hong Kong [China], Norway, Slovakia, Spain, Switzerland, and the United Kingdom). A target sample of 400 physicians (200 prescribers and 200 non-prescribers) who had received a TROBALT DHCP letter in June 2013 was sought.

Approximately half (52.7%) of the Complete Respondents (the sum of the TROBALT Prescribers [physicians who currently manage patients on TROBALT] and TROBALT Non-prescribers [physicians who are not currently managing patients on TROBALT]) reported general neurology as their primary medical specialty, with an additional 38.2% reporting a specialty in neurology with an interest in the treatment of epilepsy. Additionally, 8.5% of prescribers were self-identified as epilepsy specialists/epileptologists.

Of the 7335 physicians who were sent invitation letters, there was a slower recruitment of TROBALT Prescribers than TROBALT Non-prescribers. Multiple follow-up reminder letters (N = 13,085) were sent to all non-responders (one letter to physicians in Norway and Hong Kong and two letters to physicians in all other countries). When the sample size was met for the TROBALT Non-prescribers, the survey was closed earlier (28 Oct 2014) for that group and extended for the TROBALT Prescribers (30 Jan 2015). Additional reminder letters were sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size. When the survey was completely closed, a total of 467 respondents had replied and were screened for participation, and 426 (91.2%) of these were considered eligible (not an employee of GSK, United BioSource Corporation [UBC], or a government official [GO]) for analysis. Of the 467 respondents who accessed the survey, 414 (88.7%) completed the survey (Complete Respondents) and were included in the analysis, (141 TROBALT Prescribers and 273 TROBALT Non-prescribers). Despite not meeting the target sample size for TROBALT Prescribers, the numbers of responders in each group were considered sufficient for analysis.

Variables and Data Sources

The questions comprising the survey were constructed to test the understanding of the significant risks associated with TROBALT. The survey was composed of multiple choice and close-ended questions. There were no open-ended questions. For statements or questions that used “true” or “yes” vs. “false” or “no” response options, the desired response for key risk messages was generally “true” or “yes” indicating knowledge of, or behaviour in accordance with, the objectives of the program. However, some questions were formatted to have the respondent disagree with the statement as written, by providing response options of “false” or “no” to avoid having the same affirmative answer for all desired responses. The full questionnaire is shown in (ANNEX 2, [Protocol, Appendix 3]).

Results

About three-quarters of Complete Respondents (74.2%; TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 72.5%) understood that the current labelling indicates that TROBALT is approved for use in adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.

Pigment changes (discolouration) of ocular tissues, including the retina: Overall, 81.9% of Complete Respondents (TROBALT Prescribers: 86.5% and TROBALT Non-prescribers: 79.5%) identified that the specific risks associated with TROBALT included pigment changes (discolouration) of ocular tissues, including the retina. Additionally, 81.6% of Complete Respondents (TROBALT Prescribers: 87.2% and TROBALT Non-prescribers: 78.8%) identified that according to the safety monitoring measures in the current product labelling, a comprehensive ophthalmological examination is required.

Pigment changes (discolouration) of the nails, lips, and/or skin: 71.5% of Complete Respondents (TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 68.5%)

identified that the specific risks associated with TROBALT included pigment changes (discolouration) of the nails, lips and/or skin.

Urinary retention: 67.4% of Complete Respondents (TROBALT Prescribers: 75.9% and TROBALT Non-prescribers: 63.0%) identified that the specific risks associated with TROBALT included urinary retention.

Psychotic disorders (including confusional state and hallucinations: 72.2% of Complete Respondents (TROBALT Prescribers: 78.7% and TROBALT Non-prescribers: 68.9%) identified that the specific risks associated with TROBALT included psychotic disorders (including confusional state and hallucinations).

QTc prolongation: 65.7% of Complete Respondents (TROBALT Prescribers: 75.2% vs. TROBALT Non-prescribers: 60.8%) identified that the specific risks associated with TROBALT included QTc prolongation.

Action taken in the event of retinal pigmentation or vision changes: 99.8% of Complete Respondents (TROBALT Prescribers: 100.0% and TROBALT Non-prescribers: 99.6%) correctly identified that action was required if retinal pigmentation or vision changes were detected in a patient taking TROBALT. Approximately half of Complete Respondents (53.1%; TROBALT Prescribers: 51.8% and TROBALT Non-prescribers: 53.8%) identified that patients who are currently on TROBALT require careful reassessment of the balance of benefits and risks before deciding whether TROBALT should be continued. Slightly less than half of Complete Respondents (48.6%; TROBALT Prescribers: 51.1% and TROBALT Non-prescribers: 47.3%) selected that TROBALT should be discontinued if other suitable treatment options are available, and 40.6% of Complete Respondents (TROBALT Prescribers: 38.3% and TROBALT Non-prescribers: 41.8%) selected that if TROBALT is continued, the patient should be monitored more closely.

Subgroup Analyses:

Primary specialty of the physician: The subgroup analysis of responses by the primary medical specialties of Epilepsy or Epileptology (N=35), Neuropsychiatry (N=2), and Neurosurgery (N=1) showed higher correct response rates than the main analysis results for Complete Respondents. The groups of physicians who specialized in Neurology with an interest in the treatment of epilepsy (N=158) and General Neurology (N=218) paralleled the main analysis results for Complete Respondents. The numbers of physicians in the medical specialties Neuropsychiatry and Neurosurgery were so small that any conclusions based on the results for these primary medical specialties would be meaningless.

Number of patients treated with epilepsy per month: An analysis was conducted comparing the knowledge of physicians by the numbers of patients with epilepsy per month they treated (1 to 10, 11 to 50, 51 to 100 and 101 or more). The results for the subgroup analysis by the number of patients with epilepsy treated per month showed an increase in the percentages of correct responses for physicians who treated more patients per month. The exception was for Question 13 regarding what should be done if retinal pigmentation or vision changes are detected in a patient taking TROBALT where the

responses were similar between the physicians no matter how many patients with epilepsy they treated per month.

Country of the physician respondents: A *post hoc* subgroup analysis by country of the physician respondents paralleled the main analysis results for Complete Respondents. Comparison of the results between countries revealed that overall, respondents from Slovakia had the lowest percentages of correct responses and respondents from Spain had the highest percentages of correct responses.

Discussion

This survey of HCPs was conducted across 7 counties and recorded the complete responses of 414 physicians who regularly treat patients with epilepsy. A total of 141 physicians were self-identified as current TROBALT Prescribers and 273 physicians as TROBALT Non-prescribers. Recruiting TROBALT Prescribers proved to be significantly more difficult than finding physicians who do not prescribe the medicine, reflecting the relatively modest current usage of the product internationally.

Approximately three quarters of all respondents identified that the current licensed indication for TROBALT now limits the adjunctive usage of this medicine to patients with partial onset seizures where other appropriate combinations have proven inadequate, or poorly tolerated. Over 80% of all respondents recognised the risk of ocular pigmentation events with TROBALT (including retinal) and understood that comprehensive ophthalmologic safety assessments were required. In the event of detecting either retinal pigmentation, or visual changes virtually all respondents understood that action was required. However, there was a high level of variability in the choice of action identified, potentially driven by a range of different hypothetical patient considerations and the way the question was presented.

Broadly this survey has demonstrated a satisfactory awareness of the most important safety issues associated with TROBALT, including the risk of pigmentation events. There was some evidence that HCP understanding was less satisfactory among physicians in Slovakia than for the other countries, although no clear rationale for this finding has yet been identified. Understanding was stronger for TROBALT Prescribers than TROBALT Non-prescribers, stronger for physicians with a greater speciality in the management of epilepsy than general neurologists and stronger for those HCPs who tend to treat a higher number of epilepsy patients per month.

Statistical Methods

Confidence intervals (CI) were calculated at the 95% level, and no adjustments were performed for multiplicity. Exact binomial two-sided 95% confidence intervals were calculated by the method of Clopper and Pearson. No formal hypotheses were tested.

Counts and percentages were calculated for each question/item in the questionnaire. Confidence intervals were only calculated for the percentage of physicians choosing the correct answer or answers to a given question. Only counts and percentages were calculated (no CI) for incorrect responses. Unless otherwise indicated, the percentages were based on the population to whom a specific question was presented.

All survey questions were programmed to ensure that questions were asked in a logical sequence. Some questions required a specific answer in order for the respondent to proceed to the next question. Skip patterns were clearly indicated where responses to one question resulted in the respondent to skip to a subsequent question. Respondents could not go back to a question once the question had been answered, and could not skip ahead if they did not meet the criteria to skip questions. With the exception of missing data from the skip pattern, no missing data were expected. All questions had to be answered in order for a survey to be considered complete. All lists of response options were randomised to minimise the potential for positional bias.

Responses to the questions related to the knowledge, attitudes and behaviours were categorised as "Correct response" or "Incorrect response" as detailed in the Correct Answers Document (Version 2, 01 Jul 2014 included in ANNEX 2). "I don't know" was categorised as an incorrect response.

Computer programming was reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey. All tables were produced using SAS Software Version 9.1 or higher.

Populations and Subgroup Analysis

Primary Population (Complete Respondents)

The primary population for the analysis was the Complete Respondent Population which includes all eligible respondents who completed the survey. This population was used for the entire analysis with exception of the participant screening results and the survey administration statistics.

For all the questions related to understanding the risks associated with TROBALT, the Complete Respondent Population was further segmented into two mutually exclusive and exhaustive groups. First, TROBALT Prescribers, which were defined based on Question 8 of the survey as physicians who currently had patients taking TROBALT, and secondly, TROBALT Non-prescribers which were defined as physicians who currently do not have patients taking TROBALT.

Subgroup Analysis

The questions about the risks associated with the use of TROBALT were additionally analysed by the primary specialty of the respondents (Epilepsy or Epileptology, Neurology with an interest in the treatment of epilepsy, General Neurology, Neuropsychiatry, Neurosurgery) and by the number of patients treated for epilepsy per month (1 to 10, 11 to 50, 51 to 100, 101 or more). These subgroup analyses were displayed as all physicians combined for the subgroup. The subgroup analysis was only to be performed if at least two of the subgroups had a sample size of 30 or more respondents. If two subgroups had a sample size of 30 or more respondents, all subgroups would be presented including the subgroups with less than 30 respondents. Confidence intervals were calculated for the correct response rate for each question and subgroup.

The *post hoc* subgroup analysis by country of the physicians who completed the survey was conducted. As the number of respondents from Switzerland, Hong Kong, and Norway were ≤ 30 respondents each, these data would not be included in the subgroup analysis. It was decided for this analysis to use a subgroup of at least 20 as to not exclude a non-EU country (Switzerland) that was only one below the group size for the cut-off.

2 LIST OF ABBREVIATIONS

AE	Adverse event
AED	Anti-epileptic drug
CI	Confidence interval
DHCP	Dear Healthcare Professional
EDC	Electronic data capture
EU	European Union
GO	Government Official
GSK	GlaxoSmithKline
MAH	Marketing authorisation holder
PASS	Post-Authorisation Safety Study(ies)
PI	Prescribing Information
RMP	Risk Management Plan
SmPC	Summary of product characteristics
UBC	United BioSource Corporation
UK	United Kingdom

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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NONE

3 INVESTIGATORS

This was a cross-sectional survey of 414 physicians across 7 countries that included Belgium, Hong Kong (China), Norway, Slovakia, Spain, Switzerland, and the United Kingdom.

4 OTHER RESPONSIBLE PARTIES

United BioSource Corporation (UBC) was the contract research organization that conducted the survey and analysed the data. When mandated by local requirements, UBC sought approval from ethics committees and regulatory approval from the Competent Authority to conduct the survey in the various countries that participated.

5 MILESTONES

The following table shows the survey milestones.

Milestone	Planned Date	Actual Date	Comments
Start of data collection	01-AUG-2014	24-SEP-2014	
End of data collection	10-OCT-2014	30-JAN-2015	
Registration in the EU PAS register	05-MAR-2014	28-FEB-2014	
Final report of study results	20-MAR-2015	13-JUL-2015	

6 RATIONALE AND BACKGROUND

6.1 Background

The goal of the survey was to evaluate the awareness and knowledge of physicians who had prescribed an AED at least once in the last 6 months and who were sent a TROBALT DHCP letter in June 2013 regarding the management of specific risks associated with TROBALT and the appropriate patient population to be treated, as revised on 31 May 2013. This is in alignment with the European RMP. In addition, the results of the survey will be used to determine whether any additional measures are required to optimise the benefit/risk profile for TROBALT™ (retigabine), later referred to as TROBALT.

6.2 Rationale

The European RMP describes the measures taken by the marketing authorization holder of TROBALT, to minimise the identified risks associated with TROBALT. As part of this RMP, GSK conducted a survey of physicians' understanding of specific risks associated with TROBALT, as described in the Prescribing Information (PI) and communicated to health care professionals. The goal of the survey was to assess

physicians' awareness of PI changes for TROBALT, and evaluate the effectiveness of the communication of recognised risks related to use of TROBALT (as outlined in a TROBALT DHCP letter sent in June 2013 regarding the management of specific risks associated with TROBALT and the appropriate patient population to be treated) in 6 European markets and the city of Hong Kong (China).

The results of this survey will be used to help decide whether any additional measures are needed to help ensure appropriate use of the product.

7 RESEARCH QUESTIONS AND OBJECTIVES

The objective of the study was:

- To assess physician respondents' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey.

8 AMENDMENTS AND UPDATES

The original protocol (dated 25 February 2014) for this survey was amended on 19 May 2014. The amendment included the following updates:

Number	Date	Section of study protocol	Amendment or update	Reason
1	19 May 2014	6.1 Analysis Populations	Revision of subpopulations	To look at physicians currently prescribing TROBALT, those physicians who may have prescribed TROBALT in the past and do not currently prescribe TROBALT, and those who have never prescribed TROBALT.
		Section 10.2, Appendix 2	Update contact email address	Administrative update
		Appendix 3 Questionnaire	Update wording	Following feedback from the comprehension exercise some questions were rephrased to clarify what was being asked.

The complete protocol is included in ANNEX 2.

After the survey went live, the inclusion/exclusion criteria were updated. In addition to the original exclusion of employees of UBC and GSK, it was decided to also exclude Government Officials (GOs) from the participation in the survey. Follow-up letters were sent to each physician who completed the survey before the electronic data capture (EDC) update to ask if physicians identified themselves as GOs.

9 RESEARCH METHODS

9.1 Study Design

The survey was conducted in two phases: a Screening Phase and an Assessment Phase. The cross-sectional study was designed to assess physicians' understanding of the appropriate patient population to treat with TROBALT and the new safety monitoring activities that were instituted.

The aim of this survey was to recruit a sample of physicians who treated epilepsy patients and then to subdivide them into physicians who were currently managing patients on TROBALT and those who were not. The physicians were taken from selected EU countries that included markets in which the medicine has been used comparatively frequently (the United Kingdom, Spain, Belgium, and Slovakia). Three non-EU countries (Switzerland, Norway, and Hong Kong [China]) were selected to represent markets where TROBALT is available outside the EU. Five additional countries (Austria, Belgium, Bulgaria, France, Italy and Poland) were initially planned to be included in the survey. However, due to administrative reasons, these countries were never initiated.

9.2 Setting

This was an on-line cross-sectional survey of a targeted sample of physicians who had prescribed an AED at least once in the last 6 months, who were sent a TROBALT DHCP letter in June 2013, and who practiced medicine in one of 7 countries (Belgium, Hong Kong [China], Norway, Slovakia, Spain, Switzerland, and the United Kingdom) (see Section 9.1). The DHCP letter provided details to the physicians regarding the revised indication and wording in the SmPC, a recommendation of ophthalmological examinations to be performed at baseline and at least six months thereafter during TROBALT treatment, and the need to assess the balance of benefits and risks when initiating or continuing treatment with TROBALT.

The survey was conducted from 24 September 2014 to 30 January 2015.

Physicians were recruited from lists of DHCP letter recipients who were considered as potential TROBALT prescribers in each country provided by GSK or by liaising with the prescriber list vendor. The healthcare providers were recruited through an invitation letter to participate in the survey. Invitations were sent by e-mail to those physicians for whom an e-mail address was available (Spain only) or by mail for those physicians without e-mail addresses (ANNEX 2, [Protocol]).

The invitation letter explained to physicians how to access and complete the survey on-line. Physicians were provided two unique codes each in the survey invitation letter; one to use if they were a current TROBALT prescriber and a second to use if they were not a current TROBALT prescriber. Respondents were asked to select the appropriate unique code to gain access to the online survey. The code was deactivated after use to minimise the possibility for fraud. All respondents completed the survey online.

The evaluation survey used a standard questionnaire (ANNEX 2, [Protocol, Appendix 3]).

9.3 Subjects

Of the 7335 physicians who were sent invitation letters, there was a slower recruitment of TROBALT Prescribers than TROBALT Non-prescribers. Multiple follow-up reminder letters (N = 13,085) were sent to all non-responders (one letter to physicians in Norway and Hong Kong and two letters to physicians in all other countries). When the target sample size was met for the TROBALT Non-prescribers, the survey was closed earlier (28 Oct 2014) for that group and extended for the TROBALT Prescribers (30 Jan 2015). Additional reminder letters were sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size. When the survey was closed, a total of 467 respondents had replied and were screened for participation, and 426 (91.2%) of these were considered eligible (not an employee of GSK, UBC, or a GO) for analysis. Of the 467 respondents who accessed the survey, 414 (88.7%) completed the survey (Complete Respondents) and were included in the analysis (141 TROBALT Prescribers and 273 TROBALT Non-prescribers). Despite not meeting the target sample size for TROBALT Prescribers, the numbers of responders in each group was considered sufficient for analysis.

9.4 Variables

The questions and statements comprising the survey were constructed to test the understanding of the significant risks associated with TROBALT. The survey was composed of multiple choice and close-ended questions. No open-ended questions were included. For statements or questions that used “true” or “yes” vs. “false” or “no” response options, the desired response for key risk messages was generally “true” or “yes” indicating knowledge of, or behaviour in accordance with, the objectives of the program. However, some questions were formatted to have the respondent disagree with the statement as written, by providing response options of “false” or “no” to avoid having the same affirmative answer for all desired responses. The full questionnaire for the physicians is shown in (ANNEX 2, [Protocol, Appendix 3]).

9.5 Data Sources and Measurement

The questionnaire (survey instrument) that was utilised for physicians who prescribe AEDs and to whom the TROBALT DHCP letter was sent is included at the end of the protocol (ANNEX 2, [Protocol, Appendix 3]).

9.6 Bias

Measures to Minimise Bias in the Survey Process

A number of controls were in place to ensure the survey was conducted in a professional manner and to minimise bias, including the following:

- All survey questions were programmed to ensure that questions were asked in a logical sequence.
- Some questions required a specific answer in order for the respondent to proceed to the next question.

- Skip patterns were clearly indicated where responses to one question resulted in the respondent to skip to a subsequent question.
- Respondents could not go back to a question once the question was answered and could not skip ahead if they did not meet the criteria to skip questions.
- With the exception of missing data from the skip pattern, no missing data were expected. All questions had to be answered in order for a survey to be considered complete.
- All lists of response options were randomised to minimise the potential for positional bias.

- Comprehension testing was conducted among simulated users (User Acceptance Testing) to evaluate the draft survey questions and to assess the understanding of the questions (i.e., proper wording had been used) prior to implementing the survey.

The inclusion of a subpopulation of TROBALT Prescribers potentially biased the findings of the Complete Responders, through enrichment, since those physicians might reasonably be assumed to have a better understanding of the risks associated with TROBALT. Due to a low response of TROBALT Prescribers to the initial survey invitations and once enrolment to the TROBALT Non-prescriber subpopulation had completed, subsequent reminder letters were sent to physicians asking that only current TROBALT Prescribers complete the survey in an attempt to achieve the desired sample size.

The possibility also exists that TROBALT was prescribed by physicians who were not included on the mailing list for the DHCP. However, this was considered unlikely, due to the indication per the approved labelling indication for TROBALT to be restricted to a patient population normally treated by physicians who are specialists in treating epilepsy. Therefore, the results should be generalizable to the population of TROBALT prescribers and those who could use the product.

It is possible that a prescriber could have researched the answers to the questions while taking the test. There is no way to control this type of behaviour in an unmonitored, self-administered survey.

9.7 Study Size

A target sample of 400 (200 prescribers and 200 non-prescribers) who had received a TROBALT DHCP letter in June 2013 was sought. Precision of estimated comprehension rates for various sample sizes and proportion of correct responses are shown in Table 1 which summarises the margin of error at the 95% confidence level provided by varying sample sizes and estimates of percentage of physicians indicating a correct response. For example, if the estimate of the percentage of physicians indicating a correct response to an individual survey question is 60%, then a sample of 200 physicians will provide a margin of error of ± 7.0 percentage points of this estimate with a 95% confidence interval. The screening phase of the survey recruited potential prescribers of TROBALT (i.e., those who had prescribed any AED within the past 6 months). Despite not meeting

the target sample size for TROBALT Prescribers, the numbers of responders in each group was considered sufficient for analysis. A same size of 150 physicians only increases the margin of error to ± 8.0 percentage points of the estimate with a 95% confidence interval.

There was a slower recruitment of TROBALT Prescribers than TROBALT Non-prescribers. Multiple follow-up reminder letters (N = 13,085) were sent to all non-responders (one letter to physicians in Norway and Hong Kong and two letters to physicians in all other countries). When the sample size was met for the TROBALT Non-prescribers, the survey was closed earlier (28 Oct 2014) for that group and extended for the TROBALT Prescribers (30 Jan 2015). Additional reminder letters were specifically sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size. When the survey was closed, a total of 467 respondents had replied and were screened for participation, and 426 (91.2%) of these were considered eligible (not an employee of GSK, UBC, or a GO) for analysis. Of all respondents who accessed the survey, 414 (88.7%) completed the survey and were eligible for analysis (141 TROBALT Prescribers and 273 TROBALT Non-prescribers). These targeted numbers of physicians reflect a trade-off between what is practicable in terms of recruitment, given the relatively low prescribing of TROBALT, and providing sufficient precision around outcome estimates (proportion giving correct responses per question).

Table 1 Sample Size and Precision Estimates

Sample Size	Proportion of Correct Responses to Each Question						
	50	60	70	75	80	85	90
	Precision/ Margin of Error (±%) with 95% Confidence Interval						
50	14	14	12	11	10	9.0	8.0
100	10	10	9.0	8.0	8.0	7.0	6.0
150	8.0	8.0	7.3	7.0	6.7	5.7	4.7
200	7.0	7.0	6.5	6.0	5.5	5.0	4.0
250	6.0	6.0	5.6	5.4	4.8	4.6	3.6
300	5.7	5.7	5.3	5.0	4.7	4.0	3.3
350	5.1	5.1	4.9	4.4	4.3	3.9	3.1
400	5.0	4.8	4.5	4.3	4.0	3.5	3.0
450	4.7	4.4	4.2	3.9	3.8	3.2	2.7
500	4.4	4.2	4.0	3.8	3.6	3.2	2.6

9.8 Statistical Methods

9.8.1 Main Summary Measures

9.8.1.1 Screening Phase

The Screening Phase surveyed physicians to confirm eligibility by identifying the proportion of physicians who were currently managing patients with TROBALT (herein

defined as TROBALT Prescribers) and summarizing their medical specialty and their experience in prescribing TROBALT.

The screening phase of the survey recruited potential prescribers of TROBALT (i.e., those who had prescribed any AED within the past 6 months). A total of 7335 physicians were invited to take part in the survey across 7 countries. Five additional countries (See Section 9.1) were initially planned to be included in the survey. However, due to administrative reasons, these countries never initiated the survey. There was a slower recruitment of TROBALT Prescribers than TROBALT Non-prescribers. Multiple follow-up reminder letters (N = 13,085) were sent to all non-responders (one letter to physicians in Norway and Hong Kong and two letters to physicians in all other countries). When the sample size was met for the TROBALT Non-prescribers, the survey was closed earlier (28 Oct 2014) for that group and extended for the TROBALT Prescribers (30 Jan 2015). Additional reminder letters were specifically sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size.

The survey was composed of multiple choice and close-ended questions. No open-ended questions were included. As soon as a respondent was deemed ineligible by their answer to a question, the survey was immediately terminated. If ineligible, the respondent was notified with a “thank you” message that his/her survey participation had ended.

The screening questions included in the physician survey covered the following general areas:

1. Exclusion of GSK, UBC, or GO employees;
2. Agreement to take the survey;
3. Time since the last prescription written for any AED;
4. If the respondent had ever prescribed TROBALT;
5. If the respondent currently had patients who were taking TROBALT*; and
6. The last time a patient was initiated on TROBALT.

* Used to ensure that the sample identified current TROBALT prescribers.

Physician demographic information was collected in order to further characterise the respondent population. This included country, type of medical practice, and number of patients with epilepsy being treated. The first 200 TROBALT Prescribers and the first 200 TROBALT Non-prescribers were allowed by the EDC system to transition to the Assessment Phase of the survey.

9.8.1.2 Assessment Phase

The Assessment Phase surveyed physicians to confirm their understanding of specific risks and the appropriate patient population for TROBALT. The outcome of this survey was to determine the proportion of physicians who correctly responded to individual survey questions concerning risks associated with TROBALT. The proportion who responded correctly was tabulated separately for each question in the survey. The risks that were evaluated in the survey are listed below:

1. Pigment changes (discolouration) of ocular tissues, including the retina;
2. Pigment changes (discolouration) of the nails, lips and/or skin;
3. Urinary retention;
4. Psychotic disorders (including confusional state and hallucinations); and
5. QTc prolongation.

9.8.2 Main Statistical Methods

The Statistical Analysis Plan is included in ANNEX 2. No formal hypotheses were tested. Confidence intervals (CI) were calculated at the 95% level, and no adjustments were performed for multiplicity. Exact binomial two-sided 95% confidence intervals were calculated by the method of Clopper and Pearson, (1934). Confidence intervals were only calculated for the percentage of physicians choosing the correct answer or answers to a given question. Only counts and percentages were calculated (no CI) for incorrect responses. Counts and percentages were calculated for each question/item in the questionnaire. Unless otherwise indicated, the percentages were based on the population to whom a specific question was presented.

All survey questions were programmed to ensure that questions were asked in a logical sequence. Some questions required a specific answer in order for the respondent to proceed to the next question. Skip patterns were clearly indicated where responses to one question resulted in the respondent to skip to a subsequent question. Respondents could not go back to a question once the question had been answered, and could not skip ahead if they did not meet the criteria to skip questions. With the exception of missing data from the skip pattern, no missing data were expected. All questions had to be answered in order for a survey to be considered complete. All lists of response options were randomised to minimise the potential for positional bias.

Responses to the questions related to the knowledge, attitudes and behaviours were categorised as “Correct response” or “Incorrect response” as detailed in the Correct Answers Document (Version 2, 01 Jul 2014, ANNEX 2). “I don’t know” was categorised as an incorrect response.

All tables were produced using SAS Software Version 9.1 or higher.

9.8.3 Missing Values

All questions had to be answered in order for a survey to be considered complete. Only completed surveys were analysed.

9.8.4 Sensitivity Analyses

No sensitivity analyses were conducted.

9.8.5 Amendments to the Statistical Analysis Plan

The statistical analysis plan was amended on 04 Mar 2015 to state that data from GOs completing the survey prior to the implementation of an update to the online survey tool to exclude GOs would be included in the analysis.

9.8.6 Quality Control

This report underwent a quality control review of the data prior to its finalisation.

9.9 Study Management

9.9.1 Ethical Approval and Subject Consent

Survey participation was voluntary. The survey began with a question indicating the physician's agreement to participate in the survey. If the individual did not agree, the survey was ended.

Ethics approval was sought as required by individual countries, as well as regulatory approval or notification where applicable.

9.9.2 Subject Confidentiality

All data collected during the survey were held confidentially. The EDC system that was validated and used for data collection encrypted all identifier information; respondent identifiers were stored separately from the survey responses.

Respondent names and addresses were collected in order to mail a thank you letter and an honorarium after the survey was completed. All GSK employees remained blinded to the names and addresses of all physicians who participated in the survey.

9.9.3 Reporting of Adverse Events

The reporting of Adverse Event (AE) was not expected or requested during the survey, because answers were closed-ended, i.e., there are no free-text fields into which the respondent could enter AE information. However, as reporting suspected adverse reactions after authorisation of the medicinal product is important to allow continued monitoring of the benefit/risk balance of the medicinal product, physicians were provided with a link at the end of the survey to report any suspected AEs via the national reporting system.

10 RESULTS

10.1 Survey Administration Results

The invitation letter was sent to 7335 physicians to complete the online survey (Table 2). There was a slower recruitment of TROBALT Prescribers than TROBALT Non-prescribers. Multiple follow-up reminder letters (N = 13,085) were sent were sent to all non-responders (one letter to physicians in Norway and Hong Kong and two letters to physicians in all other countries). When the sample size was met for the TROBALT Non-prescribers, the survey was closed earlier (28 Oct 2014) for that group and extended for the TROBALT Prescribers (30 Jan 2015). Additional reminder letters were specifically sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size. When the survey was closed, a total of 467 respondents had replied and were screened for participation, and 426 (91.2%) of these were considered eligible (not an employee of GSK, UBC, or a GO) for analysis. Of all respondents who accessed the survey, 414 (88.7%) completed the survey and were eligible for analysis (141 TROBALT Prescribers and 273 TROBALT Non-prescribers). Despite not meeting the target sample size for TROBALT Prescribers, the numbers of responders in each group was considered sufficient for analysis.

Table 2 Survey Administration Statistics

Survey Invitee Results	All Respondents	
	N	%[1]
Number of invitation letters issued to physicians	7335	
Number of reminder letters issued to physicians	13085	
Number of respondents screened for participation[2]	467	100.0
Number of eligible and ineligible respondents[3]	459	98.3
Number of respondents eligible for participation[4]	426	91.2
Number of respondents eligible who completed the survey (Complete Respondents)	414	88.7

[1] Percentages are calculated based on the number of screened respondents.
[2] Screened respondents are all respondents who assessed the online survey with the unique code and answered at least the first question with any response.
[3] All respondents are the respondents who answered all inclusion / exclusion questions.
[4] Not an employee of GSK, UBC, or a GO.
Source: Table 1.1, Appendix A.

The 414 physicians completed the online survey in a mean time of 11.1 ± 21.83 minutes (Table 3). Approximately half (48.1%) of the physicians took between 5 and 10 minutes to complete the survey (Table 4).

Table 3 Time to Complete Survey (Minutes) for Completed Surveys

Summary Statistic	Time (min)
N	414
Mean (SD)	11.1 (21.83)
Minimum	2
Median	7.2
Maximum	375

Source: Table 1.3, Appendix A.

Table 4 Number of Responders Who Completed Surveys per Category of Time

Category	N (%)
0 to <5 Minutes	87 (21.0)
5 to <10 Minutes	199 (48.1)
10 to <15 Minutes	76 (18.4)
15 to <20 Minutes	27 (6.5)
20 to <25 Minutes	7 (1.7)
25 to <30 Minutes	4 (1.0)
30 Minutes or More	14 (3.4)

Source: Table 1.3, Appendix A.

10.2 Participants

Description of Survey Participants

Table 5 displays the survey screening results of the physicians who received the invitation letters to participate in the survey. Of the 414 eligible physicians (defined as those who were not a member of GSK, UBC, or a GO) who completed the survey, 84.1% had prescribed anti-epileptic drugs within the previous week preceding the survey. Approximately half (52.7%) of Complete Respondents (the sum of the TROBALT Prescribers [physicians who currently manage patients on TROBALT] and TROBALT Non-prescribers [physicians who are not currently managing patients on TROBALT]) treated between 11 and 50 patients with epilepsy per month.

Table 5 Survey Participant Screening Results

Question	Eligible and Ineligible Respondents N=459		Complete Respondents N=414	
	n/N	%	N	%
Question 1: Are you an employee of GlaxoSmithKline or UBC or a Government Official?				
Yes[1]	6/459	1.3		
No	453/459	98.7	414	100.0
Question 2: This survey is voluntary. Do you agree to take part in this survey?				
Yes	453/453	100.0	414	100.0
Question not asked [2]	6			
Question 5: On a monthly basis, how many patients with epilepsy do you manage in your practice?				
I do not treat patients with epilepsy [1]	20/453	4.4		
1 – 10	109/453	24.1	100	24.2
11 – 50	244/453	49.4	218	52.7
51 – 100	76/453	16.8	73	17.6
101 or more	24/453	5.3	23	5.6
Question not asked [2]	6			
Question 6: When was the last time you prescribed an anti-epileptic drug for a patient with epilepsy?				
In the last week	357/433	82.4	348	84.1
In the last month	54/433	12.5	52	12.6
In the last 3 months	8/433	1.8	8	1.9
In the last 6 months	7/433	1.6	6	1.4
More than 6 months ago [1]	7/433	1.6		
Question not asked [2]	26			

[1] Ineligible to participate in the survey.
[2] Question not asked due to a previous question elimination.
Source: Table 1.2, Appendix A.

Table 6 summarises the background of the physicians who completed the survey. Approximately half (52.7%) of the Complete Respondents reported general neurology as their primary medical specialty, with an additional 38.2% reporting a specialty in neurology with an interest in the treatment of epilepsy. Additionally, 8.5% of prescribers were self-identified as epilepsy specialists/epileptologists. The countries with the highest response of eligible physicians who completed the survey were Spain (44.9%), Slovakia (15.9%), United Kingdom (15.2%), and Belgium (12.3%). Almost half (48.9%) of

TROBALT Prescribers reported that they had initiated a patient on TROBALT within the past 6 months and more than a quarter (28.3%) had done so within the last month through the last 3 months.

Table 6 Responses to Physician Questions

Question	Current TROBALT Prescribers N=141		Current TROBALT Non-prescribers N=273		Complete Respondents N=414	
	n	%	n	%	n	%
Question 3: How would you classify your primary medical specialty?						
Epilepsy or Epileptology	27	19.1	8	2.9	35	8.5
Neurology with an interest in the treatment of epilepsy	56	39.7	102	37.4	158	38.2
General Neurology	57	40.4	161	59.0	218	52.7
Neuropsychiatry	0	0.0	2	0.7	2	0.5
Neurosurgery	1	0.7	0	0.0	1	0.2
Question 4: In what country is your primary medical practice?						
Spain	56	39.7	130	47.6	186	44.9
Slovakia	28	19.9	38	13.9	66	15.9
United Kingdom	13	9.2	50	18.3	63	15.2
Belgium	23	16.3	28	10.3	51	12.3
Switzerland	12	8.5	17	6.2	29	7.0
Norway	7	5.0	10	3.7	17	4.1
Hong Kong	2	1.4	0	0.0	2	0.5
Question 9: When was the last time you initiated a patient on TROBALT (retigabine)?						
In the last month	13	9.2	0	0.0	13	3.1
In the last 3 months	27	19.1	5	1.8	32	7.7
Between 3 to 6 months	29	20.6	6	2.2	35	8.5
Between 6 to 12 months	39	27.7	32	11.7	71	17.1
More than 12 months ago	33	23.4	61	22.3	94	22.7
Question not asked (Answered ***No*** or ***I don't know*** to Question 7)			169	61.9	169	40.8

Source: Table 2, Appendix A.

10.3 Descriptive Data

The descriptive data regarding the physicians who completed the survey are discussed in Section 10.2 above.

10.4 Outcome Data

The survey was a voluntary data collection tool to gather information. This was not a study with outcomes that were to be tested. The results are described in Section 10.5, below.

10.5 Main Results

10.5.1 Complete Respondents

Table 7 displays the responses by Complete Respondents to all questions related to the understanding of the risks associated with TROBALT. About three-quarters of Complete Respondents (74.2%; TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 72.5%) understood that the current labelled indication for TROBALT is "approved for use in adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated".

Overall, 81.9% of Complete Respondents (TROBALT Prescribers: 86.5% and TROBALT Non-prescribers: 79.5%) identified that the specific risks associated with TROBALT included pigment changes (discolouration) of ocular tissues, including the retina. Additionally, 81.6% of Complete Respondents (TROBALT Prescribers: 87.2% and TROBALT Non-prescribers: 78.8%) identified that according to the safety monitoring measures in current product labelling, a comprehensive ophthalmological examination is required. Similar percentages of Complete Respondents identified that the specific risks associated with TROBALT included pigment changes (discolouration) of the nails, lips and/or skin (71.5%; TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 68.5%), urinary retention (67.4%; TROBALT Prescribers: 75.9% and TROBALT Non-prescribers: 63.0%), psychotic disorders (including confusional state and hallucinations, 72.2%; TROBALT Prescribers: 78.7% and TROBALT Non-prescribers: 68.9%), and QTc prolongation (65.7% TROBALT Prescribers: 75.2% vs. TROBALT Non-prescribers: 60.8%). The results analysed by TROBALT Prescribers and TROBALT Non-prescribers were similar to the overall analysis of Complete Respondents (Table 7) but with a trend indicating a better level of understanding amongst the TROBALT Prescribers.

Overall 99.8% of Complete Respondents (TROBALT Prescribers: 100.0% and TROBALT Non-prescribers: 99.6%) correctly identified that action was required if retinal pigmentation or vision changes were detected in a patient taking TROBALT. Approximately half of Complete Respondents (53.1%; TROBALT Prescribers: 51.8% and TROBALT Non-prescribers: 53.8%) identified that patients who are currently on TROBALT require careful reassessment of the balance of benefits and risks before deciding whether TROBALT should be continued. Slightly less than half of Complete Respondents (48.6%; TROBALT Prescribers: 51.1% and TROBALT Non-prescribers: 47.3%) selected that TROBALT should be discontinued if other suitable treatment

options were available and 40.6% of Complete Respondents (TROBALT Prescribers: 38.3% and TROBALT Non-prescribers: 41.8%) selected that if TROBALT were continued, the patient should be monitored more closely. The results analysed by TROBALT Prescribers and TROBALT Non-prescribers were similar to the overall analysis of Complete Respondents (Table 7).

Table 7 Responses to all Questions Related to Understanding the Risks Associated with TROBALT

Question	Current TROBALT Prescribers N=141		Current TROBALT Non-prescribers N=273		Complete Respondents N=414	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 10: According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:						
Monotherapy of partial onset seizures	1	0.7	1	0.4	2	0.5
Adjunctive treatment of partial onset seizures	30	21.3	60	22.0	90	21.7
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated [1]	109	77.3 (69.5, 83.9)	198	72.5 (66.8, 77.7)	307	74.2 (69.7, 78.3)
Status epilepticus	0	0.0	0	0.0	0	0.0
I don't know	1	0.7	14	5.1	15	3.6
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no", or "I don't know" for each of the following:						
Pigment changes (discolouration) of ocular tissues, including the retina						
Yes [1]	122	86.5 (79.8, 91.7)	217	79.5 (74.2, 84.1)	339	81.9 (77.8, 85.5)
No	7	5.0	20	7.3	27	6.5
I don't know	12	8.5	36	13.2	48	11.6
Pigment changes (discolouration) of the nails, lips and/or skin						
Yes [1]	109	77.3 (69.5, 83.9)	187	68.5 (62.6, 74.0)	296	71.5 (66.9, 75.8)
No	14	9.9	33	12.1	47	11.4
I don't know	18	12.8	53	19.4	71	17.1

Question	Current TROBALT Prescribers N=141		Current TROBALT Non-prescribers N=273		Complete Respondents N=414	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
c. Respiratory distress						
Yes	9	6.4	12	4.4	21	5.1
No [1]	90	63.8	155	56.8	245	59.2
I don't know	42	29.8	106	38.8	148	35.7
Urinary retention						
Yes [1]	107	75.9 (68.0, 82.7)	172	63.0 (57.0, 68.7)	279	67.4 (62.6, 71.9)
No	20	14.2	33	12.1	53	12.8
I don't know	14	9.9	68	24.9	82	19.8
Ischaemic colitis						
Yes	6	4.3	2	0.7	8	1.9
No [1]	82	58.2	141	51.6	223	53.9
I don't know	53	37.6	130	47.6	183	44.2
Psychotic disorders (including confusional state and hallucinations)						
Yes [1]	111	78.7 (71.0, 85.2)	188	68.9 (63.0, 74.3)	299	72.2 (67.6, 76.5)
No	11	7.8	16	5.9	27	6.5
I don't know	19	13.5	69	25.3	88	21.3
QTc prolongation						
Yes [1]	106	75.2 (67.2, 82.1)	166	60.8 (54.7, 66.6)	272	65.7 (60.9, 70.3)
No	12	8.5	31	11.4	43	10.4
I don't know	23	16.3	76	27.8	99	23.9
Rhabdomyolysis						
Yes	6	4.3	13	4.8	19	4.6
No [1]	69	48.9	110	40.3	179	43.2
I don't know	66	46.8	150	54.9	216	52.2
Correct identified all potential risks of TROBALT [2]						
Yes	60	42.6 (34.3, 51.2)	90	33.0 (27.4, 38.9)	150	36.2 (31.6, 41.1)

Question	Current TROBALT Prescribers N=141		Current TROBALT Non-prescribers N=273		Complete Respondents N=414	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 12: According to the current product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:						
Liver function tests						
Yes	97	68.8	163	59.7	260	62.8
No [1]	32	22.7	52	19.0	84	20.3
I don't know	12	8.5	58	21.2	70	16.9
A comprehensive ophthalmological examination						
Yes [1]	123	87.2 (80.6, 92.3)	215	78.8 (73.4, 83.5)	338	81.6 (77.6, 85.3)
No	9	6.4	17	6.2	26	6.3
I don't know	9	6.4	41	15.0	50	12.1
Blood pressure assessment						
Yes	35	24.8	49	17.9	84	20.3
No [1]	78	55.3	122	44.7	200	48.3
I don't know	28	19.9	102	37.4	130	31.4
Measurement of plasma creatinine values						
Yes	77	54.6	128	46.9	205	49.5
No [1]	42	29.8	52	19.0	94	22.7
I don't know	22	15.6	93	34.1	115	27.8
Question 13: According to the current product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?						
Immediately stop TROBALT						
Selected	40	28.4	76	27.8	116	28.0
Not selected [1]	101	71.6	197	72.2	298	72.0

Question	Current TROBALT Prescribers N=141		Current TROBALT Non-prescribers N=273		Complete Respondents N=414	
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Discontinue TROBALT if other suitable treatment options are available.						
Selected [1]	72	51.1 (42.5, 59.6)	129	47.3 (41.2, 53.4)	201	48.6 (43.6, 53.5)
Not selected	69	48.9	144	52.7	213	51.4
No action required						
Selected	0	0.0	1	0.4	1	0.2
Not selected [1]	141	100.0	272	99.6	413	99.8
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued						
Selected [1]	73	51.8 (43.2, 60.3)	147	53.8 (47.7, 59.9)	220	53.1 (48.2, 58.0)
Not selected	68	48.2	126	46.2	194	46.9
If TROBALT is continued, the patient should be monitored more closely						
Selected [1]	54	38.3 (30.2, 46.9)	114	41.8 (35.8, 47.9)	168	40.6 (35.8, 45.5)
Not selected	87	61.7	159	58.2	246	59.4

[1] Correct response.
[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' were selected.
Source: Table 3, Appendix A.

10.6 Subgroup Analyses

Planned subgroup analyses of the responses to all questions relating to the understanding of the risks associated with TROBALT were stratified by:

- The primary specialty of the physician respondent:
  - Epilepsy or Epileptology;
  - Neurology with an interest in the treatment of epilepsy;
  - General Neurology;
  - Neuropsychiatry;
  - Neurosurgery.

- The number of patients treated with epilepsy per month:
  - 1 to 10;
  - 11 to 50;
  - 51 to 100;
  - 101 or more.

In addition a *post hoc* subgroup analysis of the responses to all questions relating to the understanding of the risks associated with TROBALT was stratified by the country of the physician respondent. As the number of respondents from Switzerland, Hong Kong, and Norway were ≤ 30 respondents each, these data would not be included in the subgroup analysis. It was decided for this analysis to use a subgroup of at least 20 as to not exclude a non-EU country (Switzerland) that was only one below the group size for the cut-off.

- The country of the physician respondent:
  - Belgium
  - Slovakia
  - Spain
  - Switzerland
  - United Kingdom

10.6.1 Physician Respondent Primary Specialty

The subgroup analysis by primary specialty for physician respondents who completed the survey is shown in Table 8. The primary specialty of the physician respondents is shown below:

- Epilepsy or Epileptology
- Neurology with an interest in the treatment of epilepsy
- General Neurology
- Neuropsychiatry
- Neurosurgery

The primary medical specialty for approximately half of physicians was General Neurology (N=218, 52.7%), followed by physicians reporting a specialty in Neurology with an interest in the treatment of epilepsy (N=158, 38.2%). Additionally, some prescribers self-identified themselves as epilepsy specialists/epileptologists (N=35, 8.5%) (Table 6 and Table 8). The remaining primary medical specialties were each represented by a very small number of physicians: Neuropsychiatry (N=2, 0.5%), and Neurosurgery (N=1, 0.2%).

The subgroup analysis of responses by the primary medical specialties of General Neurology and Neurology with an interest in the treatment of epilepsy paralleled the main analysis results for Complete Respondents. The analyses of the specialities of Epilepsy or Epileptology, Neuropsychiatry, and Neurosurgery showed higher correct response rates, however the numbers of physicians in the latter two medical specialties were so small that any conclusions based on the results for these primary medical specialties would be meaningless.

Table 8 Responses to all Questions Related to Understanding the Risks Associated with TROBALT (Subgroup Analysis by Primary Speciality)

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 10: According to the product labelling for TROBALT(retigabine), TROBALT should now only be used as:										
Monotherapy of partial onset seizures	1	2.9	1	0.6	0	0.0	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	4	11.4	38	24.1	48	22.0	0	0.0	0	0.0
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated [1]	29	82.9 (66.4, 93.4)	118	74.7 (67.2, 81.3)	157	72.0 (65.6, 77.9)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
I don’t know	1	2.9	1	0.6	13	6.0	0	0.0	0	0.0

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no", or "I don't know" for each of the following.										
Pigment changes (discolouration) of ocular tissues, including the retina										
Yes [1]	34	97.1 (85.1, 99.9)	136	86.1 (79.7, 91.1)	166	76.1 (69.9, 81.6)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	0	0.0	9	5.7	18	8.3	0	0.0	0	0.0
I don't know	1	2.9	13	8.2	34	15.6	0	0.0	0	0.0
Pigment changes (discolouration) of the nails, lips and/or skin										
Yes [1]	32	91.4 (76.9, 98.2)	126	79.7 (72.6, 85.7)	135	61.9 (55.1, 68.4)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	3	8.6	19	12.0	25	11.5	0	0.0	0	0.0
I don't know	0	0.0	13	8.2	58	26.6	0	0.0	0	0.0
Respiratory distress										
Yes	3	8.6	8	5.1	10	4.6	0	0.0	0	0.0
No [1]	26	74.3	103	65.2	113	51.8	2	100.0	1	100.0
I don't know	6	17.1	47	29.7	95	43.6	0	0.0	0	0.0

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Urinary retention										
Yes [1]	31	88.6 (73.3, 96.8)	112	70.9 (63.1, 77.8)	133	61.0 (54.2, 67.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	3	8.6	26	16.5	24	11.0	0	0.0	0	0.0
I don't know	1	2.9	20	12.7	61	28.0	0	0.0	0	0.0
Ischaemic colitis										
Yes	2	5.7	3	1.9	3	1.4	0	0.0	0	0.0
No [1]	25	71.4	94	59.5	102	46.8	1	50.0	1	100.0
I don't know	8	22.9	61	38.6	113	51.8	1	50.0	0	0.0
Psychotic disorders (including confusional state and hallucinations)										
Yes [1]	31	88.6 (73.3, 96.8)	120	75.9 (68.5, 82.4)	145	66.5 (59.8, 72.7)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	3	8.6	15	9.5	9	4.1	0	0.0	0	0.0
I don't know	1	2.9	23	14.6	64	29.4	0	0.0	0	0.0

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
QTc prolongation										
Yes [1]	30	85.7 (69.7, 95.2)	108	68.4 (60.5, 75.5)	131	60.1 (53.3, 66.6)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	4	11.4	21	13.3	18	8.3	0	0.0	0	0.0
I don't know	1	2.9	29	18.4	69	31.7	0	0.0	0	0.0
Rhabdomyolysis										
Yes	2	5.7	7	4.4	10	4.6	0	0.0	0	0.0
No [1]	21	60.0	73	46.2	82	37.6	2	100.0	1	100.0
I don't know	12	34.3	78	49.4	126	57.8	0	0.0	0	0.0
Correctly identified all potential risks of TROBALT [2]										
Yes [1]	25	71.4 (53.7, 85.4)	67	42.4 (34.6, 50.5)	55	25.2 (19.6, 31.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
Question 12: According to the current product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:										
Liver function tests										
Yes	10	28.6	116	73.4	134	61.5	0	0.0	0	0.0
No [1]	17	48.6	26	16.5	38	17.4	2	100.0	1	100.0
I don't know	8	22.9	16	10.1	46	21.1	0	0.0	0	0.0

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
A comprehensive ophthalmological examination										
Yes [1]	35	100.0 (90.0, 100.0)	132	83.5 (76.8, 89.0)	168	77.1 (70.9, 82.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	0	0.0	12	7.6	14	6.4	0	0.0	0	0.0
I don't know	0	0.0	14	8.9	36	16.5	0	0.0	0	0.0
Blood pressure assessment										
Yes	5	14.3	36	22.8	43	19.7	0	0.0	0	0.0
No [1]	21	60.0	83	52.5	93	42.7	2	100.0	1	100.0
I don't know	9	25.7	39	24.7	82	37.6	0	0.0	0	0.0
Measurement of plasma creatinine values										
Yes	11	31.4	97	61.4	97	44.5	0	0.0	0	0.0
No [1]	15	42.9	34	21.5	42	19.3	2	100.0	1	100.0
I don't know	9	25.7	27	17.1	79	36.2	0	0.0	0	0.0
Question 13: According to the current product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?										
Immediately stop TROBALT										
Selected	10	28.6	43	27.2	63	28.9	0	0.0	0	0.0
Not Selected [1]	25	71.4	115	72.8	155	71.1	2	100.0	1	100.0

Question	Epilepsy or Epileptology N=35		Neurology with an Interest in Epilepsy Treatment N=158		General Neurology N=218		Neuropsychiatry N=2		Neurosurgery N=1	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Discontinue TROBALT if other suitable treatment options are available										
Selected [1]	23	65.7 (47.8, 80.9)	82	51.9 (43.8, 59.9)	94	43.1 (36.4, 50.0)	1	50.0 (1.3, 98.7)	1	100.0 (2.5, 100.0)
Not Selected	12	34.3	76	48.1	124	56.9	1	50.0	0	0.0
No action required.										
Selected	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0
Not Selected [1]	35	100.0	157	99.4	218	100.0	2	100.0	1	100.0
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued										
Selected [1]	19	54.3 (36.6, 71.2)	79	50.0 (42.0, 58.0)	119	54.6 (47.7, 61.3)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
Not Selected	16	45.7	79	50.0	99	45.4	0	0.0	0	0.0
If TROBALT is continued, the patient should be monitored more closely										
Selected [1]	17	48.6 (31.4, 66.0)	62	39.2 (31.6, 47.3)	87	39.9 (33.4, 46.7)	1	50.0 (1.3, 98.7)	1	100.0 (2.5, 100.0)
Not Selected	18	51.4	96	60.8	131	60.1	1	50.0	0	0.0

[1] Correct response.
[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' were selected.
Source: Table 5, Appendix A.

10.6.2 Number of Patients with Epilepsy Treated per Month

The subgroup analysis by the number of patients with epilepsy treated per month by physician respondents who completed the survey is shown in Table 9. The numbers of patients with epilepsy treated per month are shown with the following designations in the header of the table:

- 1 to 10
- 11 to 50
- 51 to 100
- 101 or more

Approximately half of physicians treated between 11 and 50 patients (N=218, 52.7%) or between 1 and 10 patients (N=100, 24.2%) with epilepsy per month. The remaining physicians treated between 51 and 100 patients (N=73, 17.6%) or 101 or more patients (N=23, 5.6%) with epilepsy per month (Table 5 and Table 9).

The results for the subgroup analysis by the number of patients with epilepsy treated per month showed an increase in the percentage of correct responses for physicians who treated more patients per month. The exception was for Question 13 regarding what should be done if retinal pigmentation or vision changes are detected in a patient taking TROBALT, where the responses were similar between the physicians no matter how many patients with epilepsy they treated per month.

Table 9 Responses to all Questions Related to Understanding the Risks Associated with TROBALT (Subgroup Analysis by Number of Patients with Epilepsy Treated per Month)

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 10: According to the product labelling for TROBALT, TROBALT should now only be used as:								
Monotherapy of partial onset seizures	0	0.0	2	0.9	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	28	28.0	47	21.6	13	17.8	2	8.7
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated [1]	66	66.0 (55.8, 75.2)	163	74.8 (68.5, 80.4)	57	78.1 (66.9, 86.9)	21	91.3 (72.0, 98.9)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0
I don’t know	6	6.0	6	2.8	3	4.1	0	0.0

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no", or "I don't know" for each of the following:								
Pigment changes (discolouration) of ocular tissues, including the retina								
Yes [1]	64	64.0 (53.8, 73.4)	184	84.4 (78.9, 89.0)	68	93.2 (84.7, 97.7)	23	100.0 (85.2, 100.0)
No	15	15.0	11	5.0	1	1.4	0	0.0
I don't know	21	21.0	23	10.6	4	5.5	0	0.0
Pigment changes (discolouration) of the nails, lips and/or skin								
Yes [1]	52	52.0 (41.8, 62.1)	162	74.3 (68.0, 80.0)	61	83.6 (73.0, 91.2)	21	91.3 (72.0, 98.9)
No	17	17.0	22	10.1	6	8.2	2	8.7
I don't know	31	31.0	34	15.6	6	8.2	0	0.0
Respiratory distress								
Yes	4	4.0	11	5.0	5	6.8	1	4.3
No [1]	56	56.0	131	60.1	44	60.3	14	60.9
I don't know	40	40.0	76	34.9	24	32.9	8	34.8

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Urinary retention								
Yes [1]	63	63.0 (52.8, 72.4)	142	65.1 (58.4, 71.4)	54	74.0 (62.4, 83.5)	20	87.0 (66.4, 97.2)
No	12	12.0	32	14.7	7	9.6	2	8.7
I don't know	25	25.0	44	20.2	12	16.4	1	4.3
Ischaemic colitis								
Yes	1	1.0	4	1.8	2	2.7	1	4.3
No [1]	49	49.0	122	56.0	40	54.8	12	52.2
I don't know	50	50.0	92	42.2	31	42.5	10	43.5
Psychotic disorders (including confusional state and hallucinations)								
Yes [1]	69	69.0 (59.0, 77.9)	153	70.2 (63.6, 76.2)	59	80.8 (69.9, 89.1)	18	78.3 (56.3, 92.5)
No	7	7.0	16	7.3	3	4.1	1	4.3
I don't know	24	24.0	49	22.5	11	15.1	4	17.4
QTc prolongation								
Yes [1]	60	60.0 (49.7, 69.7)	136	62.4 (55.6, 68.8)	60	82.2 (71.5, 90.2)	16	69.6 (47.1, 86.8)
No	13	13.0	25	11.5	3	4.1	2	8.7
I don't know	27	27.0	57	26.1	10	13.7	5	21.7

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Rhabdomyolysis								
Yes	6	6.0	9	4.1	2	2.7	2	8.7
No [1]	40	40.0	96	44.0	34	46.6	9	39.1
I don't know	54	54.0	113	51.8	37	50.7	12	52.2
Correctly identified all potential risks of TROBALT [2]								
Yes [1]	27	27.0 (18.6, 36.8)	73	33.5 (27.3, 40.2)	38	52.1 (40.0, 63.9)	12	52.2 (30.6, 73.2)
Question 12: According to the current product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:								
Liver function tests								
Yes	64	64.0	139	63.8	46	63.0	11	47.8
No [1]	14	14.0	45	20.6	19	26.0	6	26.1
I don't know	22	22.0	34	15.6	8	11.0	6	26.1
A comprehensive ophthalmological examination								
Yes [1]	68	68.0 (57.9, 77.0)	182	83.5 (77.9, 88.2)	66	90.4 (81.2, 96.1)	22	95.7 (78.1, 99.9)
No	12	12.0	10	4.6	4	5.5	0	0.0
I don't know	20	20.0	26	11.9	3	4.1	1	4.3

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Blood pressure assessment								
Yes	18	18.0	43	19.7	19	26.0	4	17.4
No [1]	46	46.0	112	51.4	33	45.2	9	39.1
I don't know	36	36.0	63	28.9	21	28.8	10	43.5
Measurement of plasma creatinine values								
Yes	49	49.0	103	47.2	43	58.9	10	43.5
No [1]	18	18.0	53	24.3	18	24.7	5	21.7
I don't know	33	33.0	62	28.4	12	16.4	8	34.8
Question 13: According to the current product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?								
Immediately stop TROBALT								
Selected	23	23.0	65	29.8	21	28.8	7	30.4
Not Selected [1]	77	77.0	153	70.2	52	71.2	16	69.6
Discontinue TROBALT if other suitable treatment options are available								
Selected [1]	50	50.0 (39.8, 60.2)	97	44.5 (37.8, 51.4)	42	57.5 (45.4, 69.0)	12	52.2 (30.6, 73.2)
Not Selected	50	50.0	121	55.5	31	42.5	11	47.8
No action required								
Selected	0	0.0	1	0.5	0	0.0	0	0.0
Not Selected [1]	100	100.0	217	99.5	73	100.0	23	100.0

Question	1 to 10 Patients N=100		11 to 50 Patients N=218		51 to 100 Patients N=73		101 or more Patients N=23	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued								
Selected [1]	58	58.0 (47.7, 67.8)	108	49.5 (42.7, 56.4)	43	58.9 (46.8, 70.3)	11	47.8 (26.8, 69.4)
Not Selected	42	42.0	110	50.5	30	41.1	12	52.2
If TROBALT is continued, the patient should be monitored more closely								
Selected [1]	41	41.0 (31.3, 51.3)	90	41.3 (34.7, 48.1)	32	43.8 (32.2, 55.9)	5	21.7 (7.5, 43.7)
Not Selected	59	59.0	128	58.7	41	56.2	18	78.3

[1] Correct response.
[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' were selected.
Source: Table 6, Appendix A.

10.6.3 Physician Respondent by Country

The *post hoc* subgroup analysis by country of the physician respondents who completed the survey is shown in Table 10. The country of the physician respondents are shown in the header of the table:

- Belgium
- Slovakia
- Spain
- Switzerland
- United Kingdom

The physician respondents who completed the survey were from the countries of Spain (N=186, 44.9%), Slovakia (N=66, 15.9%), United Kingdom (N=63, 15.2%), Belgium (N=51, 12.3%), Switzerland (N=29, 7.0%), Norway (N=17, 4.1%), and the city of Hong Kong (N=2, 0.5%). The higher response by physicians from Spain might possibly be explained by the fact that all invitation letters were sent to these physicians via email, and electronic communication is a preferable method for busy physicians. Invitation letters were sent by regular postal mail to physicians in all other countries and may not have been opened or read. As the number of respondents from Switzerland, Hong Kong, and Norway were ≤ 30 respondents each, these data would not be included in the subgroup analysis. It was decided for this analysis to use a subgroup of at least 20 as to not exclude a non-EU country (Switzerland) that was only one below the group size for the cut-off.

Overall, the *post hoc* subgroup analysis by country paralleled the main analysis results for Complete Respondents. Comparison of the results between countries revealed that overall, respondents from Slovakia had the lowest percentages of correct responses and respondents from Spain had the highest percentages of correct responses.

Table 10 Responses to all Questions Related to Understanding the Risks Associated with TROBALT by Country

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 10: According to the product labelling for TROBALT(retigabine), TROBALT should now only be used as:										
Monotherapy of partial onset seizures	0	0.0	1	1.5	0	0.0	1	3.4	0	0.0
Adjunctive treatment of partial onset seizures	4	7.8	33	50.0	31	16.7	4	13.8	11	17.5
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated [1]	46	90.2 (78.6, 96.7)	32	48.5 (36.0, 61.1)	152	81.7 (75.4, 87.0)	21	72.4 (52.8, 87.3)	46	73.0 (60.3, 83.4)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	2.0	0	0.0	3	1.6	3	10.3	6	9.5
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no", or "I don't know" for each of the following.										
Pigment changes (discolouration) of ocular tissues, including the retina										
Yes [1]	40	78.4 (64.7, 88.7)	38	57.6 (44.8, 69.7)	170	91.4 (86.4, 95.0)	19	65.5 (45.7, 82.1)	55	87.3 (76.5, 94.4)
No	2	3.9	16	24.2	7	3.8	1	3.4	1	1.6
I don't know	9	17.6	12	18.2	9	4.8	9	31.0	7	11.1

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Pigment changes (discolouration) of the nails, lips and/or skin										
Yes [1]	31	60.8 (46.1, 74.2)	29	43.9 (31.7, 56.7)	148	79.6 (73.1, 85.1)	20	69.0 (49.2, 84.7)	51	81.0 (69.1, 89.8)
No	6	11.8	21	31.8	16	8.6	1	3.4	3	4.8
I don't know	14	27.5	16	24.2	22	11.8	8	27.6	9	14.3
Respiratory distress										
Yes	1	2.0	2	3.0	13	7.0	3	10.3	2	3.2
No [1]	26	51.0	44	66.7	113	60.8	16	55.2	32	50.8
I don't know	24	47.1	20	30.3	60	32.3	10	34.5	29	46.0
Urinary retention										
Yes [1]	32	62.7 (48.1, 75.9)	47	71.2 (58.7, 81.7)	127	68.3 (61.1, 74.9)	18	62.1 (42.3, 79.3)	41	65.1 (52.0, 76.7)
No	6	11.8	10	15.2	26	14.0	3	10.3	7	11.1
I don't know	13	25.5	9	13.6	33	17.7	8	27.6	15	23.8
Ischaemic colitis										
Yes	1	2.0	2	3.0	4	2.2	1	3.4	0	0.0
No [1]	27	52.9	38	57.6	106	57.0	11	37.9	29	46.0
I don't know	23	45.1	26	39.4	76	40.9	17	58.6	34	54.0

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Psychotic disorders (including confusional state and hallucinations)										
Yes [1]	32	62.7 (48.1, 75.9)	52	78.8 (67.0, 87.9)	141	75.8 (69.0, 81.8)	21	72.4 (52.8, 87.3)	39	61.9 (48.8, 73.9)
No	4	7.8	5	7.6	11	5.9	1	3.4	4	6.3
I don't know	15	29.4	9	13.6	34	18.3	7	24.1	20	31.7
QTc prolongation										
Yes [1]	28	54.9 (40.3, 68.9)	47	71.2 (58.7, 81.7)	134	72.0 (65.0, 78.4)	15	51.7 (32.5, 70.6)	35	55.6 (42.5, 68.1)
No	4	7.8	7	10.6	15	8.1	5	17.2	9	14.3
I don't know	19	37.3	12	18.2	37	19.9	9	31.0	19	30.2
Rhabdomyolysis										
Yes	0	0.0	7	10.6	8	4.3	1	3.4	3	4.8
No [1]	21	41.2	32	48.5	80	43.0	13	44.8	20	31.7
I don't know	30	58.8	27	40.9	98	52.7	15	51.7	40	63.5
Correctly identified all potential risks of TROBALT [2]										
Yes [1]	13	25.5 (14.3, 39.6)	13	19.7 (10.9, 31.3)	79	42.5 (35.3, 49.9)	12	41.4 (23.5, 61.1)	22	34.9 (23.3, 48.0)

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 12: According to the current product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:										
Liver function tests										
Yes	29	56.9	55	83.3	131	70.4	15	51.7	18	28.6
No [1]	9	17.6	7	10.6	37	19.9	9	31.0	19	30.2
I don't know	13	25.5	4	6.1	18	9.7	5	17.2	26	41.3
A comprehensive ophthalmological examination										
Yes [1]	42	82.4 (69.1, 91.6)	47	71.2 (58.7, 81.7)	168	90.3 (85.1, 94.2)	21	72.4 (52.8, 87.3)	44	69.8 (57.0, 80.8)
No	0	0.0	11	16.7	9	4.8	1	3.4	5	7.9
I don't know	9	17.6	8	12.1	9	4.8	7	24.1	14	22.2
Blood pressure assessment										
Yes	10	19.6	17	25.8	45	24.2	1	3.4	5	7.9
No [1]	26	51.0	36	54.5	88	47.3	14	48.3	27	42.9
I don't know	15	29.4	13	19.7	53	28.5	14	48.3	31	49.2
Measurement of plasma creatinine values										
Yes	15	29.4	42	63.6	107	57.5	11	37.9	19	30.2
No [1]	14	27.5	11	16.7	40	21.5	9	31.0	17	27.0
I don't know	22	43.1	13	19.7	39	21.0	9	31.0	27	42.9

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Question 13: According to the current product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?										
Immediately stop TROBALT										
Selected	21	41.2	13	19.7	49	26.3	11	37.9	14	22.2
Not Selected [1]	30	58.8	53	80.3	137	73.7	18	62.1	49	77.8
Discontinue TROBALT if other suitable treatment options are available										
Selected [1]	15	29.4 (17.5, 43.8)	31	47.0 (34.6, 59.7)	102	54.8 (47.4, 62.1)	12	41.4 (23.5, 61.1)	31	49.2 (36.4, 62.1)
Not Selected	36	70.6	35	53.0	84	45.2	17	58.6	32	50.8
No action required										
Selected	0	0.0	0	0.0	0	0.0	0	0.0	1	1.6
Not Selected [1]	51	100.0	66	100.0	186	100.0	29	100.0	62	98.4
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued										
Selected [1]	23	45.1 (31.1, 59.7)	46	69.7 (57.1, 80.4)	89	47.8 (40.5, 55.3)	12	41.4 (23.5, 61.1)	41	65.1 (52.0, 76.7)
Not Selected	28	54.9	20	30.3	97	52.2	17	58.6	22	34.9

Question	Belgium N=51		Slovakia N=66		Spain N=186		Switzerland N=29		United Kingdom N=63	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
If TROBALT is continued, the patient should be monitored more closely										
Selected [1]	22	43.1 (29.3, 57.8)	27	40.9 (29.0, 53.7)	71	38.2 (31.2, 45.6)	13	44.8 (26.4, 64.3)	27	42.9 (30.5, 56.0)
Not Selected	29	56.9	39	59.1	115	61.8	16	55.2	36	57.1

[1] Correct response.
[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' were selected.
Source: Table 5, Appendix A.

10.6.4 Informational Materials Regarding the Risks Associated with TROBALT

All physician respondents were asked questions about how they learned of the risks associated with TROBALT and how they would like to continue to receive updated information regarding the risks associated with TROBALT. The analysis results for the responses to these questions are shown in Table 11.

Most physician respondents learned about the risks associated with TROBALT directly from GSK (59.9%), mainly via receipt of "Dear Health Care Professional" information letters (42.0%) and through company representatives (37.7%). The second source identified most by respondents as a source of TROBALT risk information was from government health agencies (49.0%). Regarding how physician respondents would like to continue to receive future information regarding the risks associated with TROBALT, 74.4% of respondents want to continue to receive information about the risks associated with TROBALT directly from GSK via receipt of "Dear Health Care Professional" information letters (51.7%) and through company representatives (52.7%).

Table 11 Analysis of Questions Regarding Receiving Informational Materials

	Complete Respondents N=414	
	n	%
Question 14: From which of the following sources have you learned about the risks associated with use of TROBALT (retigabine)? Please select ALL that apply		
Directly from GlaxoSmithKline	248	59.9
Dear Health Care Professional information letter	174	42.0
Representative	156	37.7
Product labelling	106	25.6
Medical information	74	17.9
Via medical symposia at scientific meetings	56	13.5
Other printed information	28	6.8
Product website	21	5.1
Government Health Agency	203	49.0
National Formulary	144	34.8
Professional Neurology Association	129	31.2
Journal articles	108	26.1
Other healthcare professionals	96	23.2
Independent medical websites	84	20.3

	Complete Respondents N=414	
	n	%
Question 15: How do you prefer to receive information concerning new safety information for GlaxoSmithKline medicines? Please select ALL that apply.		
Directly from GlaxoSmithKline	308	74.4
Representative	218	52.7
Dear Health Care Professional information letter	214	51.7
Product labelling	133	32.1
Via medical symposia at scientific meetings	127	30.7
Medical information	96	23.2
Product website	46	11.1
Other printed information	38	9.2
Government Health Agency	224	54.1
Professional Neurology Association	172	41.5
Journal articles	131	31.6
National Formulary	129	31.2
Independent medical websites	80	19.3
Other healthcare professionals	64	15.5

Source: Table 4, Appendix A.

10.7 Adverse Events/Adverse Reactions

No AEs were reported by physician respondents who completed the survey.

11 DISCUSSION

11.1 Key Results

A total of 467 physicians responded and were screened for participation (meeting the target sample size), and 426 (91.2%) of these were considered eligible (not an employee of GSK, UBC, or a GO) for participation into the survey. Of all respondents who accessed the survey, 414 (88.7%) completed the survey and were eligible for analysis (141 TROBALT Prescribers and 273 TROBALT Non-prescribers). About three-quarters of Complete Respondents (74.2%; TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 72.5%) understood that the current labelling indication for TROBALT is approved for use in adjunctive treatment of drug-resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.

Physician Understanding of Specific Risks and the Appropriate Patient Population Related to TROBALT

Pigment changes (discolouration) of ocular tissues, including the retina: Overall, 81.9% of Complete Respondents (TROBALT Prescribers: 86.5% and TROBALT Non-prescribers: 79.5%) identified that the specific risks associated with TROBALT included pigment changes (discolouration) of ocular tissues, including the retina. Additionally, 81.6% of Complete Respondents (TROBALT Prescribers: 87.2% and TROBALT Non-prescribers: 78.8%) identified that according to the safety monitoring measures in current product labelling, a comprehensive ophthalmological examination is required.

Pigment changes (discolouration) of the nails, lips, and/or skin: 71.5% of Complete Respondents (TROBALT Prescribers: 77.3% and TROBALT Non-prescribers: 68.5%) identified that the specific risks associated with TROBALT included pigment changes (discolouration) of the nails, lips and/or skin.

Urinary retention: 67.4% of Complete Respondents (TROBALT Prescribers: 75.9% and TROBALT Non-prescribers: 63.0%) identified that the specific risks associated with TROBALT included urinary retention.

Psychotic disorders (including confusional state and hallucinations: 72.2% of Complete Respondents (TROBALT Prescribers: 78.7% and TROBALT Non-prescribers: 68.9%) identified that the specific risks associated with TROBALT included psychotic disorders (including confusional state and hallucinations).

QTc prolongation: 65.7% of Complete Respondents identified that the specific risks associated with TROBALT included QTc prolongation (TROBALT Prescribers: 75.2% vs. TROBALT Non-prescribers: 60.8%).

Action taken in the event of retinal pigmentation or vision changes: 99.8% of Complete Respondents (TROBALT Prescribers: 100.0% and TROBALT Non-prescribers: 99.6%) correctly identified that action was required if retinal pigmentation or vision changes were detected in a patient taking TROBALT. Approximately half of Complete Respondents (53.1%; TROBALT Prescribers: 51.8% and TROBALT Non-prescribers: 53.8%) identified that patients who are currently on TROBALT require careful reassessment of the balance of benefits and risks before deciding whether TROBALT should be continued. Slightly less than half of Complete Respondents (48.6%; TROBALT Prescribers: 51.1% and TROBALT Non-prescribers: 47.3%) selected that TROBALT should be discontinued if other suitable treatment options are available, and 40.6% of Complete Respondents (TROBALT Prescribers: 38.3% and TROBALT Non-prescribers: 41.8%) selected that if TROBALT is continued, the patient should be monitored more closely.

Subgroup Analyses:

Primary specialty of the physician: The subgroup analysis of responses by the primary medical specialties of Epilepsy or Epileptology (N=35), Neuropsychiatry (N=2), and Neurosurgery (N=1) showed higher correct response rates than the main analysis results for Complete Respondents. However, the numbers of physicians in the medical

specialties Neuropsychiatry and Neurosurgery were so small that any conclusions based on the results for these primary medical specialties are meaningless.

Number of patients treated with epilepsy per month: An analysis was conducted comparing the knowledge of physicians by the numbers of patients with epilepsy per month they treated (1 to 10, 11 to 50, 51 to 100 and 101 or more). The results for the subgroup analysis by the number of patients with epilepsy treated per month showed an increase in the percentages of correct responses for physicians who treated more patients per month. The exception was for Question 13 regarding what should be done if retinal pigmentation or vision changes are detected in a patient taking TROBALT where the responses were similar between the physicians no matter how many patients with epilepsy they treated per month.

Country of the physician respondents: A *post hoc* subgroup analysis by country of the physician respondents paralleled the main analysis results for Complete Respondents. Comparison of the results between countries revealed that overall, respondents from Slovakia had the lowest percentages of correct responses and respondents from Spain had the highest percentages of correct responses.

11.2 Limitations

Although the survey recruitment strategies were intended to recruit a heterogeneous sample of prescribers for participation and the survey was sent to over 7000 physicians, participation was voluntary and participants were self-selected. Additionally, the country with highest response was Spain, where the invitation letters were all sent via email; all other physicians were sent invitation letters via regular postal mail. Therefore, the sample may not be representative of all physician respondents who prescribe TROBALT and treat patients with epilepsy. As an analysis of non-responders was not possible, it will remain unknown if there are TROBALT Prescribers who did not complete the survey and what their understanding is of the risks associated with TROBALT.

The inclusion of a subpopulation of TROBALT Prescribers potentially biased the findings of the Complete Responders, through enrichment, since those physicians might reasonably be assumed to have a better understanding of the risks associated with TROBALT. Due to an initial low response of current TROBALT Prescribers, additional reminder letters were sent to physicians who did not respond asking current TROBALT Prescribers to complete the survey to try and meet the target sample size. However, this type of enrichment of the sample was not anticipated to bias the outcome, as these physicians also received the DHCP information.

The possibility also exists that TROBALT was prescribed by physicians who were not included on the mailing list for the DHCP. However, this was considered unlikely, due to the indication per the approved labelling for TROBALT to be restricted to a patient population normally treated by physicians who are specialists in treating epilepsy. Therefore, the results should be generalizable to the population of TROBALT Prescribers and those who could use the product.

It is possible that a prescriber could have researched the answers to the questions while taking the test. There is no way to control this type of behaviour in an unmonitored, self-administered survey.

11.3 Interpretation

Broadly this survey has demonstrated a satisfactory awareness of the most important safety issues associated with TROBALT, including the risk of pigmentation events. Understanding was stronger for TROBALT Prescribers than TROBALT Non-prescribers, stronger for physicians with a greater speciality in the management of epilepsy than general neurologists and stronger for those HCPs who tend to treat a higher number of epilepsy patients per month. There was some evidence that HCP understanding was less satisfactory among physicians in Slovakia than for the other countries, although no clear rationale for this finding has yet been identified.

Approximately three quarters of all respondents identified that the current licensed indication for TROBALT now limits the adjunctive usage of this medicine to patients with partial onset seizures where other appropriate combinations have proven inadequate, or poorly tolerated. Over 80% of all respondents recognised the risk of ocular pigmentation events with TROBALT (including retinal) and understood that comprehensive ophthalmologic safety assessments were required. In the event of detecting either retinal pigmentation, or visual changes virtually all respondents understood that action was required. However, there was a high level of variability in the choice of action identified, potentially driven by a range of different hypothetical patient considerations and the way the question was presented.

11.4 Generalisability

This was a voluntary survey and therefore the sample, while selected, may not be representative of all physicians who prescribe TROBALT.

12 OTHER INFORMATION

None.

13 CONCLUSIONS

This survey of HCPs was conducted across 7 counties and has recorded the complete responses of 414 physicians who regularly treat patients with epilepsy. A total of 141 physicians were self-identified as current TROBALT Prescribers and 273 physicians as TROBALT Non-prescribers. Recruiting TROBALT Prescribers proved to be significantly more difficult than finding physicians who do not prescribe the medicine, reflecting the relatively modest current usage of the product internationally.

The findings from this HCP survey indicate there is a satisfactory understanding of the most important safety issues associated with the use of TROBALT. The majority of respondents recognised the appropriate population for treatment with TROBALT and the requirement to monitor for a number of potential effects, including retinal pigmentation

and changes in vision. The understanding appeared to be stronger among current HCP TROBALT Prescribers but remained satisfactory in those physicians that do not manage epilepsy patients with this medicine.

14 REFERENCES

Clopper, C, Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404–13.

APPENDICES

Appendix A Prescriber Survey Tables

Table 1.1 Survey Administration Statistics

Question	N	%
The number of invitations issued to physicians	7335	
The number of reminder letters issued to physicians	13085	
The number of respondents screened for participation	467	100.0
The number of all respondents	459	98.3
The number of respondents eligible for participation	426	91.2
The number of respondents who completed the survey	414	88.7

Note: percentages are calculated based on the number of screened respondents. Screened respondents are all respondents who assessed the online survey with the unique code and answered at least the first question with any response.
All respondents are the respondents who answered all inclusion / exclusion questions.

Table 1.2 Survey Participant Screening Results

Question	All Respondents N=459		Complete Respondents N=414	
	n/N	%	n	%
Question 1: Are you an employee of GlaxoSmithKline or UBC or an Government Official?				
Yes[1]	6/459	1.3		
No	453/459	98.7	414	100.0
Question 2: This survey is voluntary. Do you agree to participate in this survey?				
Yes	453/453	100.0	414	100.0
Question not asked[2]	6			
Question 5: On a monthly basis, how many patients with epilepsy do you treat in your practice?				
I do not treat patients with epilepsy[1]	20/453	4.4		
1 - 10	109/453	24.1	100	24.2
11 - 50	224/453	49.4	218	52.7
51 - 100	76/453	16.8	73	17.6
101 or more	24/453	5.3	23	5.6
Question not asked[2]	6			
Question 6: When was the last time you prescribed an anti-epileptic drug for a patient with epilepsy?				
In the last week	357/433	82.4	348	84.1
In the last month	54/433	12.5	52	12.6
In the last 3 months	8/433	1.8	8	1.9
In the last 6 months	7/433	1.6	6	1.4

Table 1.2 Survey Participant Screening Results

Question	All Respondents N=459		Complete Respondents N=414	
	n/N	%	n	%
More than 6 months ago[1]	7/433	1.6		
Question not asked[2]	26			

[1] Ineligible to participate in the survey.
[2] Question not asked due to a previous question elimination.

Table 1.3 Time To Complete Survey (Completers, Only)

Summary Statistic	**Time (min)**
N	414
Mean (SD)	11.1 (21.83)
Minimum	2
Median	7.2
Maximum	375
Category	**n (%)**
0 to <5 Minutes	87 (21.0)
5 to <10 Minutes	199 (48.1)
10 to <15 Minutes	76 (18.4)
15 to <20 Minutes	27 (6.5)
20 to <25 Minutes	7 (1.7)
25 to <30 Minutes	4 (1.0)
30 Minutes or more	14 (3.4)

Table 2 Description of Survey Participants

Question	Current TROBALT prescribers N=141		Current TROBALT non-prescribers N=273		Complete respondents N=414	
	n	%	n	%	n	%
Question 3: How would you classify your primary medical specialty?						
Epilepsy or Epileptology	27	19.1	8	2.9	35	8.5
Neurology with an interest in the treatment of epilepsy	56	39.7	102	37.4	158	38.2
General Neurology	57	40.4	161	59.0	218	52.7
Neuropsychiatry	0	0.0	2	0.7	2	0.5
Neurosurgery	1	0.7	0	0.0	1	0.2
Question 4: In what country is your primary medical practice?						
UK	13	9.2	50	18.3	63	15.2
Spain	56	39.7	130	47.6	186	44.9
Belgium	23	16.3	28	10.3	51	12.3
Hong Kong	2	1.4	0	0.0	2	0.5
Norway	7	5.0	10	3.7	17	4.1
Slovakia	28	19.9	38	13.9	66	15.9
Switzerland	12	8.5	17	6.2	29	7.0
Question 9: When was the last time you initiated a patient on TROBALT (retigabine)?						
In the last month	13	9.2	0	0.0	13	3.1
In the last 3 months	27	19.1	5	1.8	32	7.7

Table 2 Description of Survey Participants

Question	Current TROBALT prescribers N=141		Current TROBALT non-prescribers N=273		Complete respondents N=414	
	n	%	n	%	n	%
Between 3 to 6 months	29	20.6	6	2.2	35	8.5
Between 6 to 12 months	39	27.7	32	11.7	71	17.1
More than 12 months ago	33	23.4	61	22.3	94	22.7
Question not asked (Answered No or I don't know to Question 7)			169	61.9	169	40.8

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 10: According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:						
Monotherapy of partial onset seizures	1	0.7	1	0.4	2	0.5
Adjunctive treatment of partial onset seizures	30	21.3	60	22.0	90	21.7
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.[1]	109	77.3 (69.5, 83.9)	198	72.5 (66.8, 77.7)	307	74.2 (69.7, 78.3)
Status epilepticus	0	0.0	0	0.0	0	0.0
I don't know	1	0.7	14	5.1	15	3.6
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:						
Pigment changes (discolouration) of ocular tissues, including the retina						
Yes[1]	122	86.5 (79.8, 91.7)	217	79.5 (74.2, 84.1)	339	81.9 (77.8, 85.5)

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
No	7	5.0	20	7.3	27	6.5
I don't know	12	8.5	36	13.2	48	11.6
Pigment changes (discolouration) of the nails, lips and/or skin						
Yes[1]	109	77.3 (69.5, 83.9)	187	68.5 (62.6, 74.0)	296	71.5 (66.9, 75.8)
No	14	9.9	33	12.1	47	11.4
I don't know	18	12.8	53	19.4	71	17.1
Respiratory distress						
Yes	9	6.4	12	4.4	21	5.1
No	90	63.8	155	56.8	245	59.2
I don't know	42	29.8	106	38.8	148	35.7
Urinary retention						
Yes[1]	107	75.9 (68.0, 82.7)	172	63.0 (57.0, 68.7)	279	67.4 (62.6, 71.9)
No	20	14.2	33	12.1	53	12.8
I don't know	14	9.9	68	24.9	82	19.8
Ischaemic colitis						

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Yes	6	4.3	2	0.7	8	1.9
No	82	58.2	141	51.6	223	53.9
I don't know	53	37.6	130	47.6	183	44.2
Psychotic disorders (including confusional state and hallucinations)						
Yes[1]	111	78.7 (71.0, 85.2)	188	68.9 (63.0, 74.3)	299	72.2 (67.6, 76.5)
No	11	7.8	16	5.9	27	6.5
I don't know	19	13.5	69	25.3	88	21.3
QTc prolongation						
Yes[1]	106	75.2 (67.2, 82.1)	166	60.8 (54.7, 66.6)	272	65.7 (60.9, 70.3)
No	12	8.5	31	11.4	43	10.4
I don't know	23	16.3	76	27.8	99	23.9
Rhabdomyolysis						
Yes	6	4.3	13	4.8	19	4.6
No	69	48.9	110	40.3	179	43.2
I don't know	66	46.8	150	54.9	216	52.2

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Correctly identified all potential risks of TROBALT [2]						
Yes	60	42.6 (34.3, 51.2)	90	33.0 (27.4, 38.9)	150	36.2 (31.6, 41.1)
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:						
Liver function tests						
Yes	97	68.8	163	59.7	260	62.8
No	32	22.7	52	19.0	84	20.3
I don't know	12	8.5	58	21.2	70	16.9
A comprehensive ophthalmological examination						
Yes[1]	123	87.2 (80.6, 92.3)	215	78.8 (73.4, 83.5)	338	81.6 (77.6, 85.3)
No	9	6.4	17	6.2	26	6.3
I don't know	9	6.4	41	15.0	50	12.1
Blood pressure assessment						
Yes	35	24.8	49	17.9	84	20.3
No	78	55.3	122	44.7	200	48.3

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
I don't know	28	19.9	102	37.4	130	31.4
Measurement of plasma creatinine values						
Yes	77	54.6	128	46.9	205	49.5
No	42	29.8	52	19.0	94	22.7
I don't know	22	15.6	93	34.1	115	27.8
Question 13: According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?						
Immediately stop TROBALT						
Selected	40	28.4	76	27.8	116	28.0
Not Selected	101	71.6	197	72.2	298	72.0
Discontinue TROBALT if other suitable treatment options are available						
Selected[1]	72	51.1 (42.5, 59.6)	129	47.3 (41.2, 53.4)	201	48.6 (43.6, 53.5)
Not Selected	69	48.9	144	52.7	213	51.4
No action required						
Selected	0	0.0	1	0.4	1	0.2
Not Selected	141	100.0	272	99.6	413	99.8

Table 3 Responses to all Questions Related to the Understanding the Risks associated with TROBALT

	Current TROBALT prescribers (N=141)		Current TROBALT non-prescribers (N=273)		Complete respondents (N=414)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued						
Selected[1]	73	51.8 (43.2, 60.3)	147	53.8 (47.7, 59.9)	220	53.1 (48.2, 58.0)
Not Selected	68	48.2	126	46.2	194	46.9
If TROBALT is continued, the patient should be monitored more closely						
Selected[1]	54	38.3 (30.2, 46.9)	114	41.8 (35.8, 47.9)	168	40.6 (35.8, 45.5)
Not Selected	87	61.7	159	58.2	246	59.4

[1] Correct response

[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' has been selected.

Table 4 Analysis of Questions Regarding Receiving Informational Materials

	Complete Respondents N=414	
	n	**%**
Question 14: From which of the following sources have you learned about the risks associated with use of TROBALT (retigabine)? Please select ALL that apply.		
a.Directly from GlaxoSmithKline	248	59.9
i. Dear Health Care Professional information letter	174	42.0
ii. Medical information	74	17.9
iii. Product labelling	106	25.6
iv. Other printed information	28	6.8
v. Product website	21	5.1
vi. Representative	156	37.7
vii. Via medical symposia at scientific meetings	56	13.5
b.Government Health Agency	203	49.0
c.National Formulary	144	34.8
d.Professional Neurology Association	129	31.2
e.Independent medical websites	84	20.3
f.Journal articles	108	26.1
g.Other health care professionals	96	23.2
Question 15: How do you prefer to receive information concerning new safety information for GlaxoSmithKline medicines? Please select ALL that apply.		
a.Directly from GlaxoSmithKline	308	74.4

Table 4 Analysis of Questions Regarding Receiving Informational Materials

	Complete Respondents N=414	
	n	**%**
i. Dear Health Care Professional information letter	214	51.7
ii. Medical information	96	23.2
iii. Product labelling	133	32.1
iv. Other printed information	38	9.2
v. Product website	46	11.1
vi. Representative	218	52.7
vii. Via medical symposia at scientific meetings	127	30.7
b.Government Health Agency	224	54.1
c.National Formulary	129	31.2
d.Professional Neurology Association	172	41.5
e.Independent medical websites	80	19.3
f.Journal articles	131	31.6
g.Other health care professionals	64	15.5

Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:										
Monotherapy of partial onset seizures	1	2.9	1	0.6	0	0.0	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	4	11.4	38	24.1	48	22.0	0	0.0	0	0.0
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.[1]	29	82.9 (66.4, 93.4)	118	74.7 (67.2, 81.3)	157	72.0 (65.6, 77.9)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	2.9	1	0.6	13	6.0	0	0.0	0	0.0

Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:										
Pigment changes (discolouration) of ocular tissues, including the retina										
Yes[1]	34	97.1 (85.1, 99.9)	136	86.1 (79.7, 91.1)	166	76.1 (69.9, 81.6)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	0	0.0	9	5.7	18	8.3	0	0.0	0	0.0
I don't know	1	2.9	13	8.2	34	15.6	0	0.0	0	0.0
Pigment changes (discolouration) of the nails, lips and/or skin										
Yes[1]	32	91.4 (76.9, 98.2)	126	79.7 (72.6, 85.7)	135	61.9 (55.1, 68.4)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	3	8.6	19	12.0	25	11.5	0	0.0	0	0.0
I don't know	0	0.0	13	8.2	58	26.6	0	0.0	0	0.0
Respiratory distress										
Yes	3	8.6	8	5.1	10	4.6	0	0.0	0	0.0

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Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
No	26	74.3	103	65.2	113	51.8	2	100.0	1	100.0
I don't know	6	17.1	47	29.7	95	43.6	0	0.0	0	0.0
Urinary retention										
Yes[1]	31	88.6 (73.3, 96.8)	112	70.9 (63.1, 77.8)	133	61.0 (54.2, 67.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	3	8.6	26	16.5	24	11.0	0	0.0	0	0.0
I don't know	1	2.9	20	12.7	61	28.0	0	0.0	0	0.0
Ischaemic colitis										
Yes	2	5.7	3	1.9	3	1.4	0	0.0	0	0.0
No	25	71.4	94	59.5	102	46.8	1	50.0	1	100.0
I don't know	8	22.9	61	38.6	113	51.8	1	50.0	0	0.0
Psychotic disorders (including confusional state and hallucinations)										
Yes[1]	31	88.6 (73.3, 96.8)	120	75.9 (68.5, 82.4)	145	66.5 (59.8, 72.7)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)

Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
No	3	8.6	15	9.5	9	4.1	0	0.0	0	0.0
I don't know	1	2.9	23	14.6	64	29.4	0	0.0	0	0.0
QTc prolongation										
Yes[1]	30	85.7 (69.7, 95.2)	108	68.4 (60.5, 75.5)	131	60.1 (53.3, 66.6)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	4	11.4	21	13.3	18	8.3	0	0.0	0	0.0
I don't know	1	2.9	29	18.4	69	31.7	0	0.0	0	0.0
Rhabdomyolysis										
Yes	2	5.7	7	4.4	10	4.6	0	0.0	0	0.0
No	21	60.0	73	46.2	82	37.6	2	100.0	1	100.0
I don't know	12	34.3	78	49.4	126	57.8	0	0.0	0	0.0
Correctly identified all potential risks of TROBALT [2]										
Yes	25	71.4 (53.7, 85.4)	67	42.4 (34.6, 50.5)	55	25.2 (19.6, 31.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)

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Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:										
Liver function tests										
Yes	10	28.6	116	73.4	134	61.5	0	0.0	0	0.0
No	17	48.6	26	16.5	38	17.4	2	100.0	1	100.0
I don't know	8	22.9	16	10.1	46	21.1	0	0.0	0	0.0
A comprehensive ophthalmological examination										
Yes[1]	35	100.0 (90.0, 100.0)	132	83.5 (76.8, 89.0)	168	77.1 (70.9, 82.5)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
No	0	0.0	12	7.6	14	6.4	0	0.0	0	0.0
I don't know	0	0.0	14	8.9	36	16.5	0	0.0	0	0.0
Blood pressure assessment										
Yes	5	14.3	36	22.8	43	19.7	0	0.0	0	0.0
No	21	60.0	83	52.5	93	42.7	2	100.0	1	100.0

Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
I don't know	9	25.7	39	24.7	82	37.6	0	0.0	0	0.0
Measurement of plasma creatinine values										
Yes	11	31.4	97	61.4	97	44.5	0	0.0	0	0.0
No	15	42.9	34	21.5	42	19.3	2	100.0	1	100.0
I don't know	9	25.7	27	17.1	79	36.2	0	0.0	0	0.0
Question 13: According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?										
Immediately stop TROBALT										
Selected	10	28.6	43	27.2	63	28.9	0	0.0	0	0.0
Not Selected	25	71.4	115	72.8	155	71.1	2	100.0	1	100.0
Discontinue TROBALT if other suitable treatment options are available										
Selected[1]	23	65.7 (47.8, 80.9)	82	51.9 (43.8, 59.9)	94	43.1 (36.4, 50.0)	1	50.0 (1.3, 98.7)	1	100.0 (2.5, 100.0)
Not Selected	12	34.3	76	48.1	124	56.9	1	50.0	0	0.0
No action required										

Table 5 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 1: Primary specialty

	S1a: Epilepsy or Epileptology (N=35)		S1b: Neurology with an interest in the treatment of epilepsy (N=158)		S1c: General Neurology (N=218)		S1d: Neuropsychiatry (N=2)		S1e: Neurosurgery (N=1)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Selected	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0
Not Selected	35	100.0	157	99.4	218	100.0	2	100.0	1	100.0
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued										
Selected[1]	19	54.3 (36.6, 71.2)	79	50.0 (42.0, 58.0)	119	54.6 (47.7, 61.3)	2	100.0 (15.8, 100.0)	1	100.0 (2.5, 100.0)
Not Selected	16	45.7	79	50.0	99	45.4	0	0.0	0	0.0
If TROBALT is continued, the patient should be monitored more closely										
Selected[1]	17	48.6 (31.4, 66.0)	62	39.2 (31.6, 47.3)	87	39.9 (33.4, 46.7)	1	50.0 (1.3, 98.7)	1	100.0 (2.5, 100.0)
Not Selected	18	51.4	96	60.8	131	60.1	1	50.0	0	0.0

[1] Correct response

[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' has been selected.

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:								
Monotherapy of partial onset seizures	0	0.0	2	0.9	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	28	28.0	47	21.6	13	17.8	2	8.7
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.[1]	66	66.0 (55.8, 75.2)	163	74.8 (68.5, 80.4)	57	78.1 (66.9, 86.9)	21	91.3 (72.0, 98.9)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	6	6.0	6	2.8	3	4.1	0	0.0
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Pigment changes (discolouration) of ocular tissues, including the retina								
Yes[1]	64	64.0 (53.8, 73.4)	184	84.4 (78.9, 89.0)	68	93.2 (84.7, 97.7)	23	100.0 (85.2, 100.0)
No	15	15.0	11	5.0	1	1.4	0	0.0
I don't know	21	21.0	23	10.6	4	5.5	0	0.0

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Pigment changes (discolouration) of the nails, lips and/or skin								
Yes[1]	52	52.0 (41.8, 62.1)	162	74.3 (68.0, 80.0)	61	83.6 (73.0, 91.2)	21	91.3 (72.0, 98.9)
No	17	17.0	22	10.1	6	8.2	2	8.7
I don't know	31	31.0	34	15.6	6	8.2	0	0.0
Respiratory distress								
Yes	4	4.0	11	5.0	5	6.8	1	4.3
No	56	56.0	131	60.1	44	60.3	14	60.9
I don't know	40	40.0	76	34.9	24	32.9	8	34.8
Urinary retention								
Yes[1]	63	63.0 (52.8, 72.4)	142	65.1 (58.4, 71.4)	54	74.0 (62.4, 83.5)	20	87.0 (66.4, 97.2)
No	12	12.0	32	14.7	7	9.6	2	8.7
I don't know	25	25.0	44	20.2	12	16.4	1	4.3
Ischaemic colitis								
Yes	1	1.0	4	1.8	2	2.7	1	4.3
No	49	49.0	122	56.0	40	54.8	12	52.2

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
I don't know	50	50.0	92	42.2	31	42.5	10	43.5
Psychotic disorders (including confusional state and hallucinations)								
Yes[1]	69	69.0 (59.0, 77.9)	153	70.2 (63.6, 76.2)	59	80.8 (69.9, 89.1)	18	78.3 (56.3, 92.5)
No	7	7.0	16	7.3	3	4.1	1	4.3
I don't know	24	24.0	49	22.5	11	15.1	4	17.4
QTc prolongation								
Yes[1]	60	60.0 (49.7, 69.7)	136	62.4 (55.6, 68.8)	60	82.2 (71.5, 90.2)	16	69.6 (47.1, 86.8)
No	13	13.0	25	11.5	3	4.1	2	8.7
I don't know	27	27.0	57	26.1	10	13.7	5	21.7
Rhabdomyolysis								
Yes	6	6.0	9	4.1	2	2.7	2	8.7
No	40	40.0	96	44.0	34	46.6	9	39.1
I don't know	54	54.0	113	51.8	37	50.7	12	52.2
Correctly identified all potential risks of TROBALT [2]								
Yes	27	27.0 (18.6, 36.8)	73	33.5 (27.3, 40.2)	38	52.1 (40.0, 63.9)	12	52.2 (30.6, 73.2)

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Liver function tests								
Yes	64	64.0	139	63.8	46	63.0	11	47.8
No	14	14.0	45	20.6	19	26.0	6	26.1
I don't know	22	22.0	34	15.6	8	11.0	6	26.1
A comprehensive ophthalmological examination								
Yes[1]	68	68.0 (57.9, 77.0)	182	83.5 (77.9, 88.2)	66	90.4 (81.2, 96.1)	22	95.7 (78.1, 99.9)
No	12	12.0	10	4.6	4	5.5	0	0.0
I don't know	20	20.0	26	11.9	3	4.1	1	4.3
Blood pressure assessment								
Yes	18	18.0	43	19.7	19	26.0	4	17.4
No	46	46.0	112	51.4	33	45.2	9	39.1
I don't know	36	36.0	63	28.9	21	28.8	10	43.5
Measurement of plasma creatinine values								
Yes	49	49.0	103	47.2	43	58.9	10	43.5

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 13: According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?								
No	18	18.0	53	24.3	18	24.7	5	21.7
I don't know	33	33.0	62	28.4	12	16.4	8	34.8
Immediately stop TROBALT								
Selected	23	23.0	65	29.8	21	28.8	7	30.4
Not Selected	77	77.0	153	70.2	52	71.2	16	69.6
Discontinue TROBALT if other suitable treatment options are available								
Selected[1]	50	50.0 (39.8, 60.2)	97	44.5 (37.8, 51.4)	42	57.5 (45.4, 69.0)	12	52.2 (30.6, 73.2)
Not Selected	50	50.0	121	55.5	31	42.5	11	47.8
No action required								
Selected	0	0.0	1	0.5	0	0.0	0	0.0
Not Selected	100	100.0	217	99.5	73	100.0	23	100.0
Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued								
Selected[1]	58	58.0 (47.7, 67.8)	108	49.5 (42.7, 56.4)	43	58.9 (46.8, 70.3)	11	47.8 (26.8, 69.4)
Not Selected	42	42.0	110	50.5	30	41.1	12	52.2

Table 6 Responses to all Questions Related to the Understanding the Risks associated with TROBALT Sub-group analysis 2: Number of patients treated with epilepsy per month

	1 - 10 (N=100)		11 - 50 (N=218)		51 - 100 (N=73)		101 or more (N=23)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
If TROBALT is continued, the patient should be monitored more closely								
Selected[1]	41	41.0 (31.3, 51.3)	90	41.3 (34.7, 48.1)	32	43.8 (32.2, 55.9)	5	21.7 (7.5, 43.7)
Not Selected	59	59.0	128	58.7	41	56.2	18	78.3

[1] Correct response

[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' has been selected.

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:												
Monotherapy of partial onset seizures	0	0.0	0	0.0	0	0.0	1	2.6	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	2	8.7	2	7.1	10	35.7	23	60.5	11	19.6	20	15.4
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.[1]	21	91.3 (72.0, 98.9)	25	89.3 (71.8, 97.7)	18	64.3 (44.1, 81.4)	14	36.8 (21.8, 54.0)	45	80.4 (67.6, 89.8)	107	82.3 (74.6, 88.4)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
I don’t know	0	0.0	1	3.6	0	0.0	0	0.0	0	0.0	3	2.3

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:								
Monotherapy of partial onset seizures	1	8.3	0	0.0	0	0.0	0	0.0
Adjunctive treatment of partial onset seizures	1	8.3	3	17.6	1	7.7	10	20.0
Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.[1]	9	75.0 (42.8, 94.5)	12	70.6 (44.0, 89.7)	12	92.3 (64.0, 99.8)	34	68.0 (53.3, 80.5)
Status epilepticus	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	8.3	2	11.8	0	0.0	6	12.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Pigment changes (discolouration) of ocular tissues, including the retina												
Yes[1]	19	82.6 (61.2, 95.0)	21	75.0 (55.1, 89.3)	18	64.3 (44.1, 81.4)	20	52.6 (35.8, 69.0)	53	94.6 (85.1, 98.9)	117	90.0 (83.5, 94.6)
No	1	4.3	1	3.6	4	14.3	12	31.6	2	3.6	5	3.8
I don't know	3	13.0	6	21.4	6	21.4	6	15.8	1	1.8	8	6.2
Pigment changes (discolouration) of the nails, lips and/or skin												
Yes[1]	16	69.6 (47.1, 86.8)	15	53.6 (33.9, 72.5)	12	42.9 (24.5, 62.8)	17	44.7 (28.6, 61.7)	49	87.5 (75.9, 94.8)	99	76.2 (67.9, 83.2)
No	2	8.7	4	14.3	8	28.6	13	34.2	4	7.1	12	9.2
I don't know	5	21.7	9	32.1	8	28.6	8	21.1	3	5.4	19	14.6

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Pigment changes (discolouration) of ocular tissues, including the retina								
Yes[1]	11	91.7 (61.5, 99.8)	8	47.1 (23.0, 72.2)	12	92.3 (64.0, 99.8)	43	86.0 (73.3, 94.2)
No	0	0.0	1	5.9	0	0.0	1	2.0
I don't know	1	8.3	8	47.1	1	7.7	6	12.0
Pigment changes (discolouration) of the nails, lips and/or skin								
Yes[1]	11	91.7 (61.5, 99.8)	9	52.9 (27.8, 77.0)	12	92.3 (64.0, 99.8)	39	78.0 (64.0, 88.5)
No	0	0.0	1	5.9	0	0.0	3	6.0
I don't know	1	8.3	7	41.2	1	7.7	8	16.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Respiratory distress												
Yes	1	4.3	0	0.0	0	0.0	2	5.3	7	12.5	6	4.6
No	14	60.9	12	42.9	21	75.0	23	60.5	31	55.4	82	63.1
I don't know	8	34.8	16	57.1	7	25.0	13	34.2	18	32.1	42	32.3
Urinary retention												
Yes[1]	17	73.9 (51.6, 89.8)	15	53.6 (33.9, 72.5)	20	71.4 (51.3, 86.8)	27	71.1 (54.1, 84.6)	42	75.0 (61.6, 85.6)	85	65.4 (56.5, 73.5)
No	4	17.4	2	7.1	6	21.4	4	10.5	7	12.5	19	14.6
I don't know	2	8.7	11	39.3	2	7.1	7	18.4	7	12.5	26	20.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Respiratory distress								
Yes	1	8.3	2	11.8	0	0.0	2	4.0
No	8	66.7	8	47.1	7	53.8	25	50.0
I don't know	3	25.0	7	41.2	6	46.2	23	46.0
Urinary retention								
Yes[1]	11	91.7 (61.5, 99.8)	7	41.2 (18.4, 67.1)	9	69.2 (38.6, 90.9)	32	64.0 (49.2, 77.1)
No	0	0.0	3	17.6	2	15.4	5	10.0
I don't know	1	8.3	7	41.2	2	15.4	13	26.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Ischaemic colitis												
Yes	0	0.0	1	3.6	1	3.6	1	2.6	4	7.1	0	0.0
No	14	60.9	13	46.4	20	71.4	18	47.4	28	50.0	78	60.0
I don't know	9	39.1	14	50.0	7	25.0	19	50.0	24	42.9	52	40.0
Psychotic disorders (including confusional state and hallucinations)												
Yes[1]	17	73.9 (51.6, 89.8)	15	53.6 (33.9, 72.5)	23	82.1 (63.1, 93.9)	29	76.3 (59.8, 88.6)	43	76.8 (63.6, 87.0)	98	75.4 (67.1, 82.5)
No	2	8.7	2	7.1	2	7.1	3	7.9	4	7.1	7	5.4
I don't know	4	17.4	11	39.3	3	10.7	6	15.8	9	16.1	25	19.2

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Ischaemic colitis								
Yes	1	8.3	0	0.0	0	0.0	0	0.0
No	6	50.0	5	29.4	6	46.2	23	46.0
I don't know	5	41.7	12	70.6	7	53.8	27	54.0
Psychotic disorders (including confusional state and hallucinations)								
Yes[1]	12	100.0 (73.5, 100.0)	9	52.9 (27.8, 77.0)	9	69.2 (38.6, 90.9)	30	60.0 (45.2, 73.6)
No	0	0.0	1	5.9	1	7.7	3	6.0
I don't know	0	0.0	7	41.2	3	23.1	17	34.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:												
QTc prolongation												
Yes[1]	13	56.5 (34.5, 76.8)	15	53.6 (33.9, 72.5)	21	75.0 (55.1, 89.3)	26	68.4 (51.3, 82.5)	44	78.6 (65.6, 88.4)	90	69.2 (60.5, 77.0)
No	2	8.7	2	7.1	3	10.7	4	10.5	4	7.1	11	8.5
I don't know	8	34.8	11	39.3	4	14.3	8	21.1	8	14.3	29	22.3
Rhabdomyolysis												
Yes	0	0.0	0	0.0	3	10.7	4	10.5	1	1.8	7	5.4
No	10	43.5	11	39.3	14	50.0	18	47.4	24	42.9	56	43.1
I don't know	13	56.5	17	60.7	11	39.3	16	42.1	31	55.4	67	51.5

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
QTc prolongation								
Yes[1]	11	91.7 (61.5, 99.8)	4	23.5 (6.8, 49.9)	9	69.2 (38.6, 90.9)	26	52.0 (37.4, 66.3)
No	1	8.3	4	23.5	1	7.7	8	16.0
I don't know	0	0.0	9	52.9	3	23.1	16	32.0
Rhabdomyolysis								
Yes	1	8.3	0	0.0	1	7.7	2	4.0
No	8	66.7	5	29.4	4	30.8	16	32.0
I don't know	3	25.0	12	70.6	8	61.5	32	64.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Correctly identified all potential risks of TROBALT [2]												
Yes	7	30.4 (13.2, 52.9)	6	21.4 (8.3, 41.0)	8	28.6 (13.2, 48.7)	5	13.2 (4.4, 28.1)	26	46.4 (33.0, 60.3)	53	40.8 (32.2, 49.7)
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Liver function tests												
Yes	15	65.2	14	50.0	24	85.7	31	81.6	44	78.6	87	66.9
No	6	26.1	3	10.7	3	10.7	4	10.5	10	17.9	27	20.8
I don't know	2	8.7	11	39.3	1	3.6	3	7.9	2	3.6	16	12.3

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 11: According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Correctly identified all potential risks of TROBALT [2]								
Yes	9	75.0 (42.8, 94.5)	3	17.6 (3.8, 43.4)	4	30.8 (9.1, 61.4)	18	36.0 (22.9, 50.8)
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Liver function tests								
Yes	4	33.3	11	64.7	2	15.4	16	32.0
No	7	58.3	2	11.8	5	38.5	14	28.0
I don't know	1	8.3	4	23.5	6	46.2	20	40.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:												
A comprehensive ophthalmological examination												
Yes[1]	20	87.0 (66.4, 97.2)	22	78.6 (59.0, 91.7)	22	78.6 (59.0, 91.7)	25	65.8 (48.6, 80.4)	50	89.3 (78.1, 96.0)	118	90.8 (84.4, 95.1)
No	0	0.0	0	0.0	4	14.3	7	18.4	4	7.1	5	3.8
I don't know	3	13.0	6	21.4	2	7.1	6	15.8	2	3.6	7	5.4
Blood pressure assessment												
Yes	6	26.1	4	14.3	9	32.1	8	21.1	16	28.6	29	22.3
No	15	65.2	11	39.3	15	53.6	21	55.3	26	46.4	62	47.7
I don't know	2	8.7	13	46.4	4	14.3	9	23.7	14	25.0	39	30.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:								
A comprehensive ophthalmological examination								
Yes[1]	11	91.7 (61.5, 99.8)	10	58.8 (32.9, 81.6)	11	84.6 (54.6, 98.1)	33	66.0 (51.2, 78.8)
No	0	0.0	1	5.9	1	7.7	4	8.0
I don't know	1	8.3	6	35.3	1	7.7	13	26.0
Blood pressure assessment								
Yes	0	0.0	1	5.9	1	7.7	4	8.0
No	9	75.0	5	29.4	8	61.5	19	38.0
I don't know	3	25.0	11	64.7	4	30.8	27	54.0

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Belgium				Slovakia				Spain			
	Current TROBALT Prescribers (N=23)		Current TROBALT Non-Prescribers (N=28)		Current TROBALT Prescribers (N=28)		Current TROBALT Non-Prescribers (N=38)		Current TROBALT Prescribers (N=56)		Current TROBALT Non-Prescribers (N=130)	
Question	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:												
Measurement of plasma creatinine values												
Yes	7	30.4	8	28.6	17	60.7	25	65.8	37	66.1	70	53.8
No	9	39.1	5	17.9	6	21.4	5	13.2	15	26.8	25	19.2
I don't know	7	30.4	15	53.6	5	17.9	8	21.1	4	7.1	35	26.9
Question 13: According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?												
Immediately stop TROBALT												
Selected	8	34.8	13	46.4	3	10.7	10	26.3	16	28.6	33	25.4
Not Selected	15	65.2	15	53.6	25	89.3	28	73.7	40	71.4	97	74.6

Table 7 Responses to all Questions Related to the Understanding the Risks associated with TROBALT by Country and Prescriber Status

	Switzerland				UK			
	Current TROBALT Prescribers (N=12)		Current TROBALT Non-Prescribers (N=17)		Current TROBALT Prescribers (N=13)		Current TROBALT Non-Prescribers (N=50)	
Question	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer 'yes', 'no' or 'I dont know' for each of the following:								
Measurement of plasma creatinine values								
Yes	4	33.3	7	41.2	5	38.5	14	28.0
No	7	58.3	2	11.8	4	30.8	13	26.0
I don't know	1	8.3	8	47.1	4	30.8	23	46.0
Question 13: According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?								
Immediately stop TROBALT								
Selected	4	33.3	7	41.2	5	38.5	9	18.0
Not Selected	8	66.7	10	58.8	8	61.5	41	82.0

[1] Correct response.

[2] All potential risks of TROBALT are counted as correctly identified if 'Pigment changes (discolouration) of ocular tissues, including the retina', 'Pigment changes (discolouration) of the nails, lips and/or skin', 'Urinary retention', 'Psychotic disorders (including confusional state and hallucinations)', and 'QTc prolongation' has been selected.

Appendix B Prescriber Survey Listings

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

List of Modular Appendices for this Report are:

- **Protocol**
- **Statistical Analysis Plan**
- **Correct Answers Document (Version 2, 01 Jul 2014)**

TITLE PAGE

Division: Worldwide Development
Retention Category: GRS019
Information Type: Worldwide Epidemiology Study Protocol Amendment

Title: Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™

Compound Number: GW582892

Development Phase IV

Effective Date: 19-MAY-2014

Protocol Amendment Number: 01

Description: GlaxoSmithKline (GSK) will launch a study to evaluate the impact of risk management communication activities, outside the United States. This relates to the information added to the TROBALT Prescribing Information related to retinal pigmentation in June 2013 to fulfil the prescriber comprehension assessment.

Subject: Prescriber survey of the understanding of specific risks associated with TROBALT, communicated in the Healthcare Provider letter and TROBALT Prescribing Information.

Author(s): [redacted] MD, PhD (GlaxoSmithKline)

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Revision Chronology:

2014N191555_00	2014-APR-28	Original
2014N191555_01	2014-MAY-19	Amendment No. 01:

- Revising the sub-populations for the analysis plan, which will be:

1) Physicians who currently have patients taking TROBALT (consideration will be given to the time since last initiation of treatment)
2) Physicians who currently do not have patients taking TROBALT (consideration will be given to the sub-populations who have never prescribed Trobalt and those who previously have done so)

- Change the Help Desk email address to: [redacted]
- Revision of the Appendix 3: Questionnaire for physicians who prescribe AEDs and were sent a DHCP Letter in June 2013 based on Comprehension Testing conclusions

SPONSOR SIGNATORY:

STUDY TITLE: Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™

Study: 201426

Development Phase: IV

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Safety Physician

Signature: [redacted]

Date: 19 May 2014

SPONSOR INFORMATION PAGE

Worldwide Epidemiology
Study Identifier: 201426

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Telephone: [redacted]

VENDOR SIGNATORY

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Vendor Name: United BioSource Corporation

Name of signatory:

[redacted]

Vendor Signature

15 May 2014

Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
AED	Anti-epileptic drug
DHCP	Dear Healthcare Professional
EU	European Union
EDC	Electronic Data Capture
GSK	GlaxoSmithKline
HCP	Healthcare Professional
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UBC	United BioSource Corporation
UK	United Kingdom
US	United States of America

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
TROBALT

Trademarks not owned by the GlaxoSmithKline group of companies
None

PROTOCOL SUMMARY

Rationale

The European Risk Management Plan (RMP) describes the measures taken by GlaxoSmithKline (GSK), the maker of TROBALT™ (retigabine) – later referred to TROBALT, to communicate the identified risks associated with TROBALT. As part of this RMP, GSK will conduct a survey of physicians' understanding of specific risks associated with TROBALT (retigabine), as described in the Prescribing Information (PI) and communicated to health care professionals. The goal of the survey is to assess prescriber awareness of label changes for retigabine and evaluate the effectiveness of the communication of recognised risks related to use of TROBALT in 11 European markets and Hong Kong.

The results of this survey will be used to inform GSK as to whether any additional measures are needed to help ensure appropriate use of the product.

Objective(s)

The objective of this study is to assess prescribers' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey instrument.

Study Design

This is a cross sectional survey of a targeted sample of 1000 physicians:

- who have prescribed an anti-epileptic drug (AED) at least once in the last 6 months, and
- who were sent a Dear Healthcare Professional (DHCP) letter in June 2013, and
- who practice in one of the following 12 countries (Austria, Belgium, Bulgaria, France, Hong Kong, Italy, Norway, Poland, Slovakia, Spain, Switzerland and the United Kingdom).

The study will consist of two parts:

(1) Comprehension Testing (sample in UK only) to determine if the survey instrument is clear and questions are understood, and

(2) the online Physician Survey.

The Comprehension Testing will be conducted among a group of 16 physicians in the UK to evaluate the draft survey instrument and study procedures prior to rolling out the Physician Survey in12 countries. A full description of the Comprehension Testing has been detailed in a separate qualitative research plan including a description of the research methodology and the physician sample to be recruited. The findings from the

Comprehension Testing will serve as the basis for whether or not any modifications need to be made to the survey instrument.

The Physician Survey will be conducted in two phases: Screening Phase and Assessment Phase.

A target sample of 200 prescribers and 200 non-prescribers will be sought. The Screening Phase of the survey will include potential prescribers of TROBALT (i.e. those who have prescribed any AED within the past 6 months).

The respondents will be asked several questions to obtain information on their medical specialty, country in which they practice, AED prescribing history, and whether they have prescribed TROBALT. Respondents, who have prescribed TROBALT, and a sample of those who have not prescribed TROBALT, will be asked to take part in the Assessment Phase of the survey.

The purpose of the Assessment Phase of the survey is to evaluate respondents' understanding of the risks associated with TROBALT. There will be approximately 200 prescribing physicians who have prescribed TROBALT included in the study across the following countries: Austria, Belgium, Bulgaria, France, Hong Kong, Italy, Norway, Poland, Slovakia, Spain, Switzerland and the United Kingdom. Additionally, there will be up to 200 prescribing physicians who have never or not recently prescribed TROBALT selected from all countries.

Study Assessments

The outcome of the survey is the proportion of physicians providing correct responses to a series of questions concerning specific risks associated with TROBALT. Additional analyses will compare the level of understanding between physicians who have prescribed TROBALT and those who have never or not recently prescribed the product. The specific risks evaluated will be from those listed in Section 4.2.

1. INTRODUCTION

GlaxoSmithKline (GSK) will conduct a survey of physicians who are prescribing anti-epileptic drugs (AEDs) to determine their understanding of specific risks associated with TROBALT. The target physicians to be surveyed in each country will be based on those who have received a Dear Healthcare Professional (DHCP) letter (Appendix 1) sent in June 2013. The survey will concentrate on risks described in the product label for TROBALT, as revised on 31st May 2013. It is recognised that the DHCP letter and TROBALT Prescribing Information (PI) are not the only source of information concerning risks associated with medication use available to the prescriber.

The design for this study is based on GSK's previous experience designing risk management programs for GSK products, and on the prior experience of United BioSource Corporation (UBC) in conducting similar surveys in the European Union (EU).

The results of this survey will be used to inform GSK as to whether any additional measures are required to optimise the benefit/risk profile for retigabine.

2. OBJECTIVE

The objective of this study is to assess prescribers' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey instrument.

3. INVESTIGATION PLAN

3.1. Study Design

This study is sponsored by GSK, and will be conducted by United BioSource Corporation (UBC), an international research consultancy.

Physicians will be recruited by selecting a random sample from lists provided by GSK or its local vendor in each country. The list includes names of all potential AED prescribers who were mailed a DHCP letter (Appendix 1). Following recruitment, physicians' understanding of the potential risks associated with TROBALT will be evaluated using an online survey. Each invitation will include information on how to access the survey on-line, and will include a unique code to ensure that the invitation is used only once.

To ensure comprehension of the survey invitation and the survey questions, all of the physician outreach will be conducted in the local country language. Specifically, the surveys and invitation letters will all be translated by a certified translation company.

The study will consist of two parts: Comprehension Testing of the draft survey with a small group of physicians to be sure the questions and response options are understood and the Physician Survey which is a cross-sectional survey of physicians across 12 countries.

3.2. Comprehension Testing

The purpose of the Comprehension Testing is to evaluate draft questions to be used in the Physician Survey instrument in approximately 16 subjects. Survey questions will be designed to assess physician understanding of specific risks associated with TROBALT.

Structured physician one-to-one in-depth telephone interviews will yield qualitative findings and will help provide the basis for the development of the survey. Revisions to the questionnaire or to study procedures will be made before administration of the main survey.

The survey instrument used for the Comprehension Testing will be revised based on physician responses before being fielded for the main study. The survey instrument will be developed in English and then later translated into relevant languages for the other participating countries.

3.3. Physician Survey

The physician survey will be conducted in two phases: Screening Phase and the Assessment Phase. This cross-sectional study has been designed to assess prescribers' understanding of the appropriate patient population to treat with TROBALT and the new safety monitoring activities that have been instituted.

The selected countries are the eight largest markets in the EU based on estimated number of patients receiving TROBALT (the United Kingdom, Spain, France, Italy, Belgium, Slovakia, Poland and Austria). One additional EU country (Bulgaria) was selected upon the potential uncertainty related to reimbursement of an ophthalmology exam mandated by the TROBALT PI. Three non-EU countries (Switzerland, Hong Kong and Norway) were selected to represent markets where TROBALT is available outside the EU.

3.3.1. Screening Phase

The Screening Phase seeks to survey physicians to identify the proportion of physicians who have prescribed TROBALT and to summarize the type of medical specialty of those physicians with experience in prescribing TROBALT.

A target sample of 200 prescribers and 200 non-prescribers will be sought. The Screening Phase of the survey will include potential prescribers of TROBALT (i.e. those who have prescribed any AED within the past 6 months).

The survey will be composed of multiple choice and close-ended questions. There will be no open-ended questions included.

The electronic data capture (EDC) system will be configured to allow those physicians identified by their responses to the survey in the Screening Phase (Part 1) to transition into the Assessment Phase (Part 2). The EDC system will allow the first 200 physicians who indicate they have prescribed TROBALT since July 2013 to continue to Part 2 and will also limit to 200 the number of non-prescribers who are asked to complete the additional questions in Part 2.

3.3.2. Assessment Phase

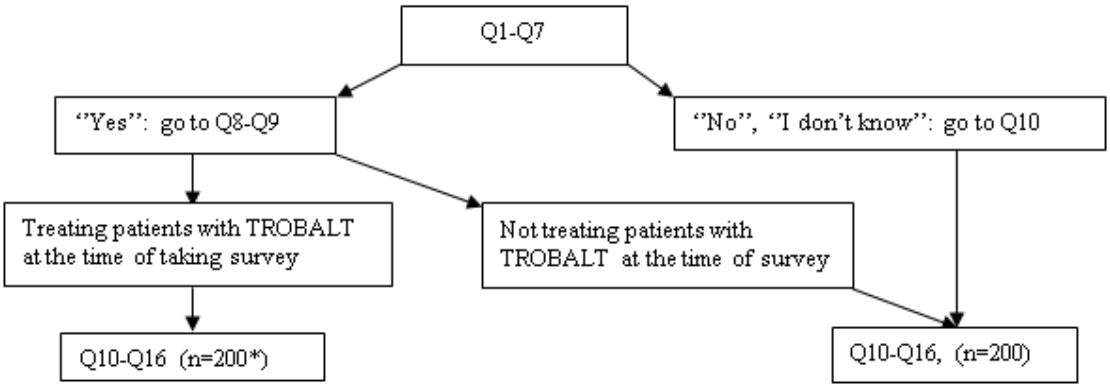
The Assessment Phase is the main part of the Physician Survey. In addition to the TROBALT prescribers, the Assessment Phase will include up to 200 respondents from the Screening Phase who have not prescribed TROBALT in order to evaluate the general awareness to the risks associated with TROBALT. The Assessment Phase will evaluate each physician's understanding of specific risks associated with TROBALT use.

The outcome of this study is the proportion of the physicians/epilepsy specialists that correctly respond to individual survey questions. The proportion responding correctly will be tabulated separately for each item.

Physician information will be collected in order to further characterise the respondent population. This will include country, type of medical practice, and number of patients with epilepsy treated. The country in which practice occurs will be collected at the beginning of the survey in order to ensure a sample of respondents from each included country.

At the conclusion of the online survey, the final computer screen will display a summary of the relevant sections from the country-specific Prescribing Information to allow the physician access to the full TROBALT label, to ensure they have a reminder and full understanding of the safety revisions that were implemented in 2013.

Figure 1 Schematic of respondent enrolment into each phase of the study, based on responses to specific questions



* In case of a very low response, known prescribers will be specifically invited to participate. Such enrichment of the sample is not anticipated to bias the outcomes as the targeted physicians will also be DHCP recipients and will need to fulfil inclusion criteria.

3.4. Study Population

3.4.1. Physicians Prescribing Anti-Epileptic Drugs

This survey aims to invite a random sample of physicians prescribing AEDs and who have been sent a DHCP letter in Austria, Belgium, Bulgaria, France, Hong Kong, Italy, Norway, Poland, Slovakia, Spain, Switzerland and the United Kingdom.

The selected countries are the eight largest markets in the EU for TROBALT use based on estimated number of patients receiving TROBALT (the United Kingdom, Spain, France, Italy, Belgium, Slovakia, Poland and Austria). One additional EU country (Bulgaria) was selected upon the potential uncertainty related to reimbursement of an ophthalmology exam mandated by the TROBALT PI. Three non-EU countries (Hong Kong, Norway and Switzerland) were selected to represent markets where TROBALT is available, outside the EU.

If required, additional countries may be included in the survey to reach the minimum recruitment target. The recruitment will be from among those who have prescribed an anti-epileptic drug at least once in the last 6 months, and who were on the list to which a DHCP letter was distributed in June 2013. The survey will aim to recruit at least 200 physicians (from the 12 specified countries) prescribing TROBALT for sub-analyses, as these individuals would be expected to be more aware of the risks of TROBALT, and up to 200 physicians not prescribing TROBALT as a comparison.

3.4.2. Inclusion criteria for Physician Survey

Physicians will be required to meet all the following inclusion criteria:

1. Must manage patients with epilepsy.
2. Must have prescribed an AED at least once in the last 6 months.
3. Must be on the list to which a DHCP letter was distributed in June 2013.

3.4.3. Exclusion criteria for Physician Survey

Physicians meeting any of the following criteria will not be eligible to take the survey:

1. Currently an employee of GSK or UBC.

3.4.4. Methods of Recruitment

The physicians will be recruited through an invitation to participate in the survey. The invitation will direct the physicians to the survey website to complete the survey. Invitations will be sent by mail to those physicians for whom a mail address is available. If there is no response after the first invitation, then subsequent reminders will be sent until the target of completed surveys is met. During this time, the response rates for each country will be monitored to ensure that the outreach is sufficient to meet target goals.

Physicians will be provided a unique code in the survey invitation letter and will be asked to provide the unique code to gain access to the online survey. The code will be deactivated after use to minimize the possibility for fraud.

Physicians will be paid the equivalent of £60 for their participation, which is fair market value for a survey estimated to take 20 minutes to complete.

3.5. Survey Design

The final study design is based on experience from risk management studies previously completed by GSK and UBC. GSK conducted a similar survey of TROBALT prescribers in 2012 and 2013. Both UBC and GSK have conducted similar knowledge, attitude and behaviour surveys in the US to evaluate Risk Evaluation and Mitigation Strategies (REMS).

3.5.1. Questionnaire Structure

Survey will be composed of multiple choice and close-ended questions. There will be no open-ended questions included. For statements or questions that use “yes” vs. “I don’t know” or “no” response options, the desired response for key risk messages is generally “yes” indicating knowledge of, or behaviour in accordance with, the objectives of the program.

3.5.2. Measures to Minimise Bias in the Surveys

The following are measures to minimise bias in the surveys:

1. All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey.

2. Response options presented in a list will be randomized to minimize positional bias.

3. Comprehension Testing will be conducted among 16 physicians in the UK to evaluate the draft survey questions and to assess the questions understanding and whether proper wording has been used prior to the survey being implemented to the full sample.

4. STUDY ASSESSMENTS AND PROCEDURES

4.1. Physicians Screening and Assessment

The physicians' introduction information is outlined in Appendix 2, and the survey instrument for the prescribers' assessment is in Appendix 3. The prescribers' questionnaire will begin with a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The screening questions included in the prescriber survey cover the following general areas:

1. Exclusion of employees at GSK or UBC
2. Agreement to take the survey
3. Time since the last prescription written for any AED
4. Ever prescribed TROBALT*
5. Currently have patients who are taking TROBALT*
6. The last time a patient was initiated on TROBALT*

*Used to ensure that the sample includes at least 200 TROBALT prescribers

4.2. Physicians Outcomes

Physicians understanding of specific risks and the appropriate patient population related to TROBALT will be assessed using a standardised questionnaire.

The outcome of this study is the proportion of physicians that correctly respond to individual survey questions concerning risks associated with TROBALT. The proportion responding correctly will be tabulated separately for each item in the physician understanding survey instrument. The risks that will be evaluated in the survey are listed below:

1. Pigment changes (discolouration) of ocular tissues, including the retina
2. Pigment changes (discolouration) of the nails, lips and/or skin
3. Urinary retention
4. Psychotic disorders (including confusional state and hallucinations)
5. QTc prolongation.

Physician demographic information will be collected in order to further characterise the respondent population. This will include country, type of medical practice, and number of patients with epilepsy treated.

At the conclusion of the online survey, the final computer screen will display a summary of the relevant information from the country-specific Prescribing Information, which can be printed for reference to allow the physician access to the full TROBALT label to ensure they have a reminder and full understanding of the safety revisions that were implemented in 2013.

5. DATA COLLECTION AND MANAGEMENT

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

6. DATA ANALYSIS

6.1. Analysis Population

The population for analysis will comprise all physicians recruited into the study, meeting eligibility criteria as assessed in the survey screener, and completing the survey.

The outcomes will be summarised for all 12 specified countries combined.

The following sub-populations for analyses will be:

1) Physicians who currently have patients taking TROBALT (consideration will be given to the time since last initiation of treatment)

2) Physicians who currently do not have patients taking TROBALT (consideration will be given to the sub-populations who have never prescribed Trobalt and those who previously have done so)

6.2. Analyses

The primary outcome is the proportion of physicians answering each question of the understanding of the risks associated with TROBALT correctly. Point estimates for the proportion with correct responses, and associated confidence intervals, will be calculated for each question about the risks of TROBALT. In the case of multiple choice questions, the number and proportion of physicians reporting each response will also be provided.

The proportion of correct answers to survey questions will be summarised overall, and separately for those physicians who have prescribed TROBALT.

7. PRECISION BY SAMPLE SIZE

Table 1 summarises the margin of error at the 95% confidence level provided by varying sample sizes and estimates of percentage of physicians indicating a correct response. For example, if the estimate of the percentage of physicians indicating a correct response to an individual survey question is 60%, then a sample of 200 physicians will provide a margin of error of ± 7.0 percentage points of this estimate with a 95% confidence interval.

Table 1 Sample size and precision estimates

Sample Size	Proportion of Correct Responses to Each Question						
	50	60	70	75	80	85	90
	Precision/ Margin of Error (±%) with 95% Confidence Interval						
50	14	14	12	11	10	9.0	8.0
100	10	10	9.0	8.0	8.0	7.0	6.0
150	8.0	8.0	7.3	7.0	6.7	5.7	4.7
200	7.0	7.0	6.5	6.0	5.5	5.0	4.0
250	6.0	6.0	5.6	5.4	4.8	4.6	3.6
300	5.7	5.7	5.3	5.0	4.7	4.0	3.3
350	5.1	5.1	4.9	4.4	4.3	3.9	3.1
400	5.0	4.8	4.5	4.3	4.0	3.5	3.0
450	4.7	4.4	4.2	3.9	3.8	3.2	2.7
500	4.4	4.2	4.0	3.8	3.6	3.2	2.6

8. STUDY LIMITATIONS

There are some limitations inherent in the study design.

The sample of the physicians who are invited to participate will be a random sample of all physicians who received a DHCP letter. The sample of participating physicians will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

A non-responder analysis will not be possible, so it will remain unknown, if there are TROBALT prescribers among the non-responders and what their understanding is of the risks.

In case of a very low response, known prescribers will be specifically invited to participate. Such enrichment of the sample is not anticipated to bias the outcomes as the targeted physicians will also be DHCP recipients and will need to fulfil inclusion criteria.

There is a possibility that TROBALT is prescribed by physicians who were not included on the mailing list for a DHCP, however this is unlikely since the indication for TROBALT is restricted to a specific patient population that is normally treated by physicians who are epilepsy specialists.

Due to the low numbers of TROBALT prescribers per country, the main analysis will combine all countries. It is acknowledged that there may be differences between countries. However, the safety information in each country specifies the risks with TROBALT.

9. STUDY MANAGEMENT

9.1. Ethical Committee Approval and Consent

Survey participation is voluntary. The survey will begin with a question indicating the physician's agreement to participate in the survey. If the individual does not agree, the survey will be ended.

Ethics approval will be sought as required by individual countries.

9.2. Reporting of Adverse Events

The reporting of Adverse Event (AE) is not expected or requested during the survey, because answers are closed-ended i.e., there are no free text fields into which the respondent could enter AE information. However, as reporting suspected adverse reactions after authorisation of the medicinal product is important to allow continued monitoring of the benefit/risk balance of the medicinal product, physicians will be asked to report any suspected AEs via the national reporting system.

9.3. Study Reporting and Publications

The recruitment period is estimated to be 6 months from May 2014, though this could be earlier if the target number of participants is reached sooner than October 2014. A final report will be written by Q4 2014 and uploaded in the EU PAS Register (www.encepp.eu).

10. APPENDICES

10.1. Appendix 1: Template for the letter to prescribers including the restrictions for use of TROBALT

Restrictions for use of Trobalt™ (retigabine) - treatment may lead to pigment changes of ocular tissues, including retina, and skin, lips and/or nails

Dear Healthcare Professional

GlaxoSmithKline (GSK) would like to inform you of a restriction of the indication for Trobalt™ (retigabine) following reports of pigment changes and provide you with recommendations for monitoring.

Summary

Trobalt™ should now only be used as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.
Pigment changes (discolouration) of ocular tissue, including the retina, have been reported in long-term clinical studies with retigabine.

Blue-grey discolouration of the nails, lips and/or skin have also been observed in these studies.

Patients currently receiving treatment should be reviewed at a routine (non-urgent) appointment. The balance of benefits and risks should be re-evaluated, and patients should be informed of the risk of pigmentation with long term treatment.

A comprehensive ophthalmological examination (including visual acuity test, slit-lamp examination, and dilated fundoscopy) should be performed at treatment start and at least every 6 months thereafter while treatment is ongoing. Patients already treated with retigabine should have an appointment scheduled for an ophthalmological examination.

If retinal pigment or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. Also in patients who develop discolouration of the nails, lips or skin, treatment with Trobalt™ should only be continued after a careful re-assessment of the balance of benefits and risks.

Further information on the safety concern

Trobalt™ (retigabine) is now indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.
Among the patients treated with retigabine in two long-term clinical studies and the associated compassionate use programme, eye examinations in 55 patients were completed up to 2 May 2013. Baseline eye assessments were not performed in these studies. Twenty-one cases of pigment changes (discolouration) of ocular tissue, including

15 involving the retina have been reported. Five patients had worse than 20/20 visual acuity. One of these patients had visual acuity of 20/160 in one eye, while the remaining four had visual acuity of 20/25 to 20/40 in one or both eyes. Mild abnormalities on retinal electrophysiology tests have been reported in two further subjects, both of whom had visual acuity reported to be normal. In one of those subjects, a generalised reduction in the visual fields of both eyes on Humphrey Visual Testing was also noted.
Up to 2 May 2013, 51 cases with events relating to discolouration/ pigmentation of the nails, lips and/or skin after treatment with retigabine were received from the two long-term clinical studies and the compassionate use programme. The events generally presented after long-term exposure to retigabine, with a median time to onset of 4.4 years (range 4 months to 6.7 years) (time to onset refers to date discolouration events were first reported; in some cases the patient is described as having the event(s) before mentioning them to the investigator). There appeared to be no relation with age or gender. Events tended to occur at higher doses, usually 900 mg/day or higher.
The changes described above have been observed in a high proportion of patients who were still ongoing in the long-term studies. About one third of the patients examined so far have presented with retinal pigment changes. The cause, natural history and long-term prognosis of the changes are currently unknown, and further investigative work is ongoing.

Reports of pigmentation/discolouration are considered to be very common adverse events (1/10) following prolonged treatment with retigabine.
The Summary of Product Characteristics and Package Leaflet are being revised to include information on the amended indication and these safety risks.

Call for reporting

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.
Healthcare professionals should continue to report suspected adverse reactions to the <national competent authority contact details> in accordance with the national spontaneous reporting system rules < enter details as relevant>.

Communication Information

Should you have any questions or require additional information please contact <GSK Local Operating companies to include details>
The information contained in this letter has been endorsed by the European Medicines Agency and national Competent Authorities.
Annexes
Yours sincerely

10.2. Appendix 2: Health Care Professional Introduction to the Online Survey Regarding TROBALT

Introduction

GlaxoSmithKline (GSK), the maker of TROBALT™ (retigabine), is surveying health care professionals to assess awareness of a safety issue reflected in recent label changes for TROBALT. This survey is part of an effort by the European Medicines Agency (EMA) and GSK to ensure that TROBALT is being used appropriately. It is also aiming to recognize preferences for sources of specialist information which may be used in future for effective communication /education. The questionnaire will take no more than 20 minutes to complete.

Disclaimer

This research is sponsored by GSK, a pharmaceutical company. The aim of this research is to assess knowledge about the prescribing information for TROBALT. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

How We Use Your Information

Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to GSK. Your name will not be used in any report. Your name and address will be used to send you the honorarium after you complete the survey. Honorarium

If you are eligible to take the questionnaire, complete all the questions, and provide your contact information, you will receive [letter will be customized per country up to £60.00].

This compensation represents the fair value for your services in connection with completion of the Survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

How We Protect Your Privacy

Maintaining the privacy of your personal information is important to us. All the information you provide will be kept strictly confidential. This survey is not a promotional effort and you will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the EMA or local country Ethics Committees.

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at: [redacted] and your questions will be answered.

10.3. Appendix 3: Questionnaire for physicians who prescribe AEDs and were sent a DHCP Letter in June 2013

Screening Phase

1. Are you an employee of GlaxoSmithKline or UBC?
    a. Yes (EXCLUDE)
    b. No

2. This survey is voluntary. Do you agree to take part in this survey?
    a. Yes
    b. No (EXCLUDE)

3. How would you classify your primary medical specialty?
    a. Epilepsy or Epileptology
    b. Neurology with an interest in the treatment of epilepsy
    c. General Neurology
    d. Neuropsychiatry
    e. Neurosurgery

4. In what country is your primary medical practice [EXPAND THE LIST OF COUNTRIES]?

5. On a monthly basis, how many patients with epilepsy do you treat in your practice?
    a. I do not treat patients with epilepsy (EXCLUDE)
    b. 1-10
    c. 11-50
    d. 51-100
    e. 101 or more

6. When was the last time you prescribed an anti-epileptic drug for a patient with epilepsy?
    a. In the last week
    b. In the last month
    c. In the last 3 months
    d. In the last 6 months
    e. More than 6 months ago (EXCLUDE)

7. Have you ever prescribed TROBALT (retigabine)? (USED TO ENSURE THAT THE SAMPLE INCLUDES THE MINIMAL NUMBER OF TROBALT PRESCRIBERS)
    a. Yes
    b. No (GO TO Q10)

8. Do you currently have patients who are taking TROBALT (retigabine)? (ONLY IF RESPONSE TO Q7 IS Yes)
    a. Yes
    b. No
    c. I don't know

9. When was the last time you initiated a patient on TROBALT (retigabine)? (ONLY IF RESPONSE TO Q7 IS Yes)
    a. In the last month
    b. In the last 3 months
    c. Between 3 to 6 months
    d. Between 6 to 12 months
    e. More than 12 months ago

Assessment Phase

10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as: <Please select the best response>
    a. Monotherapy of partial onset seizures
    b. Adjunctive treatment of partial onset seizures
    c. Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.
    d. Status epilepticus
    e. I don't know

11. According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no" or "I don't know" for each of the following:
    a. Pigment changes (discolouration) of ocular tissues, including the retina
    b. Pigment changes (discolouration) of the nails, lips and/or skin
    c. Respiratory distress
    d. Urinary retention
    e. Ischaemic colitis
    f. Psychotic disorders (including confusional state and hallucinations)
    g. QTc prolongation
    h. Rhabdomyolysis

12. According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:
    a. Liver function tests
    b. A comprehensive ophthalmological examination
    c. Blood pressure assessment
    d. Measurement of plasma creatinine values

13. According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT? Please select ALL that apply:
    a. Immediately stop TROBALT
    b. Discontinue TROBALT if other suitable treatment options are available
    c. No action required
    d. Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued
    e. If TROBALT is continued, the patient should be monitored more closely

14. From which of the following sources have you learned about the risks associated with use of TROBALT (retigabine)? < Please select ALL that apply >
    a. Directly from GlaxoSmithKline
        i. Dear Health Care Professional information letter
        ii. Medical information
        iii. Product labelling
        iv. Other printed information
        v. Product website
        vi. Representative
        vii. Via medical symposia at scientific meetings
    b. Government Health Agency
    c. National Formulary
    d. Professional Neurology Association
    e. Independent medical websites
    f. Journal articles
    g. Other health care professionals

15. How do you prefer to receive information concerning new safety information for GlaxoSmithKline medicines? < Please select ALL that apply >
    a. Directly from GlaxoSmithKline
        i. Dear Health Care Professional information letter
        ii. Medical information
        iii. Product labelling
        iv. Other printed information
        v. Product website
        vi. Representative

vii. Via medical symposia at scientific meetings
b. Government Health Agency
c. National Formulary
d. Professional Neurology Association
e. Independent medical websites
f. Journal articles
g. Other health care professionals

16. Do you agree to provide your name and address to the third party conducting this survey on behalf of GSK so that we can issue a payment for your time in completing this survey? Your name and address will not be provided to GSK.
    a. Yes (RECORD NAME AND ADDRESS)
    b. No

Name _____

Address _____

[CLOSING] That ends the survey. Thank you again for your help. The correct answers to the questions about TROBALT follow.

Links to a DHCP, PI, and AE's national reporting system in correct language.

The following are the correct answers to the survey questions about TROBALT.

Please refer to the TROBALT Prescribing Information for further details.

THANK YOU

10.4. Appendix 4: Protocol Changes

Protocol Summary

Objective(s)

PREVIOUS TEXT

The objective of this study is to assess prescribers' awareness of recent label changes, including the appropriate patient population related to TROBALT as evaluated by a survey instrument.

REVISED TEXT

The objective of this study is to assess prescribers' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey instrument.

Study Design

PREVIOUS TEXT:

The Screening Phase of the survey will include up to 1000 potential prescribers of TROBALT (i.e. those who have prescribed any AED within the past 6 months) in order to reach a target sample of 200 prescribers and 200 non-prescribers assuming a recruitment failure of 60%.

REVISED TEXT

A target sample of 200 prescribers and 200 non-prescribers will be sought. The Screening Phase of the survey will include potential prescribers of TROBALT (i.e. those who have prescribed any AED within the past 6 months).

3.3.1 Screening Phase

PREVIOUS TEXT

Up to 1000 physicians will be invited to take part, by selecting a random sample of prescribers of AEDs from those who were sent a DHCP letter. Assuming a recruitment failure of 60%, this will permit a target sample of 200 prescribers and 200 non-prescribers to be achieved.

REVISED TEXT

A target sample of 200 prescribers and 200 non-prescribers will be sought. The Screening Phase of the survey will include potential prescribers of TROBALT (i.e. those who have prescribed any AED within the past 6 months).

6.1. Analysis Population

PREVIOUS TEXT

The outcomes will be summarised for all 12 specified countries combined.

The two sub-populations for analyses will be 1) the physicians who have prescribed TROBALT after receiving a DHCP letter in June 2013, and 2) the physicians who have prescribed TROBALT in the past, but before receipt of the DHCP letter or the physicians who have never prescribed TROBALT.

REVISED TEXT

The outcomes will be summarised for all 12 specified countries combined.

The following sub-populations for analyses will be:

1) Physicians who currently have patients taking TROBALT (consideration will be given to the time since last initiation of treatment)

2) Physicians who currently do not have patients taking TROBALT (consideration will be given to the sub-populations who have never prescribed Trobalt and those who previously have done so)

Appendix 2:

PREVIOUS TEXT

If you have questions about or problems with the survey, please contact the Help Desk at: [redacted] and your questions will be answered.

REVISED TEXT

If you have questions about or problems with the survey, please contact the Help Desk at: [redacted] and your questions will be answered.

Appendix 3:

PREVIOUS TEXT

Appendix 3 Questionnaire for physicians who prescribe AEDs and were sent a DHCP Letter in June 2013

SCREENING PHASE

1. Are you an employee of GlaxoSmithKline or UBC?
    a. Yes (EXCLUDE)
    b. No

2. This survey is voluntary. Do you agree to take part in this survey?
    a. Yes
    b. No (EXCLUDE)

3. How would you classify your primary medical specialty?
    a. General Neurology
    b. Neurology with an interest in the treatment of epilepsy
    c. Neurosurgery
    d. Epilepsy or Epileptology
    e. Other [EXPAND THE LIST OF SPECIALIZATIONS]

4. In what country is your primary medical practice [EXPAND THE LIST OF COUNTRIES]?

5. On a monthly basis, how many patients with epilepsy do you manage in your practice?
    a. <10
    b. 10-50
    c. 51-100
    d. >100
    e. I do not treat patients with epilepsy (EXCLUDE)

6. When was the last time you prescribed an anti-epileptic drug for a patient with epilepsy?
    a. In the last week
    b. In the last month
    c. In the last 3 months
    d. In the last 6 months
    e. More than 6 months ago (EXCLUDE)

7. Have you ever prescribed TROBALT (retigabine)? (USED TO ENSURE THAT THE SAMPLE INCLUDES THE MINIMAL NUMBER OF TROBALT PRESCRIBERS)
    a. Yes
    b. No (GO TO Q10)
    c. I don't know (GO TO Q 10)

8. Do you currently have patients who are taking TROBALT? (ONLY IF RESPONSE TO Q7 IS Yes)
    a. Yes
    b. No
    c. I don't know

9. When was the last time you initiated a patient on TROBALT (ONLY IF RESPONSE TO Q7 IS Yes)
    a. In the last month
    b. In the last 3 months
    c. In the last 9 months
    d. Over 9 months ago

ASSESSMENT PHASE

10. According to the product labelling for TROBALT, TROBALT should now only be used as: <Please select the best response>
    a. First line treatment of drug resistant partial onset seizures
    b. Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.
    c. Status epilepticus
    d. I don't know

11. Which of the following are potential risks associated with TROBALT? Answer "yes", "no" or "I don't know" for each of the following:
    a. Pigment changes (discolouration) of ocular tissues, including the retina
    b. Pigment changes (discolouration) of the nails, lips and/or skin
    c. Respiratory distress
    d. Urinary retention (generally within the first 8 weeks of treatment)
    e. Ulcerative colitis
    f. Psychotic disorders (including confusional state and hallucinations)
    g. QTc prolongation
    h. Rhabdomyolysis

12. According to the current product labelling for TROBALT, patients who are currently on TROBALT require which of these safety monitoring measures? Answer “yes”, “no” or “I don’t know” for each of the following:
    a. Liver function tests (any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours).
    b. A comprehensive ophthalmological examination (including visual acuity, slit-lamp examination, and dilated fundoscopy)
    c. Blood pressure assessment (consideration should be given to discontinuation of treatment if a clinically significant increase in blood pressure is observed).
    d. Measurement of plasma creatinine values (if serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment).

13. According to the current product labelling for TROBALT, what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT? Answer “yes”, “no” or “I don’t know” for each of the following:
    a. Immediately stop TROBALT
    b. Discontinue TROBALT if other suitable treatment options are available.
    c. No action required
    d. Carefully re-asses the balance of benefits and risks before deciding whether TROBALT should be continued.
    e. If TROBALT is continued, the patient should be monitored more closely.

14. From which of the following sources have you learned about the risks associated with use of TROBALT? <Please select all that apply>
    1. GlaxoSmithKline Dear Health Care Professional information letter
    a. Internet
    2. Product website
    3. Professional Neurology Association
    4. Other health care professionals
    b. Other GlaxoSmithKline company information (e.g., physician guide,)
    c. Product label
    d. National Formulary
    e. Government Health Agency
    f. Journal article
    g. GlaxoSmithKline representative
    h. Other, please select (EXPAND THE LIST OF POSSIBLE SOURCE OF INFORMATIONS)

15. How do you prefer to receive information concerning new safety information for GlaxoSmithKline medicines?
    5. Contact from a GlaxoSmithKline representative
    6. GlaxoSmithKline Dear Health Care Professional information letter
    a. Internet
    7. Product or GlaxoSmithKline website
    b. GlaxoSmithKline physician's guide
    c. GlaxoSmithKline product label
    8. National Formulary
    9. Professional Association
    d. Other, please select (EXPAND THE LIST OF POSSIBLE SOURCE OF INFORMATIONS)

16. Do you agree to provide your name and address to the third party conducting this survey on behalf of GSK so that we can issue a payment for your time in completing this survey? Your name and address will not be provided to GSK.
    a. Yes (RECORD NAME AND ADDRESS)
    b. No

Name _____

Address _____

[CLOSING] That ends the survey. Thank you again for your help. The correct answers to the questions about TROBALT follow.

Links to a DHCP, PI, and AE's national reporting system in correct language.

The following are the correct answers to the survey questions about TROBALT.

Please refer to the TROBALT Prescribing Information for further details.

THANK YOU

REVISED TEXT:

Appendix 3: Questionnaire for physicians who prescribe AEDs and were sent a DHCP Letter in June 2013

Screening Phase

1. Are you an employee of GlaxoSmithKline or UBC?
    a. Yes (EXCLUDE)
    b. No

2. This survey is voluntary. Do you agree to take part in this survey?
    a. Yes
    b. No (EXCLUDE)

3. How would you classify your primary medical specialty?
    a. Epilepsy or Epileptology
    b. Neurology with an interest in the treatment of epilepsy
    c. General Neurology
    d. Neuropsychiatry
    e. Neurosurgery

4. In what country is your primary medical practice [EXPAND THE LIST OF COUNTRIES]?

5. On a monthly basis, how many patients with epilepsy do you treat in your practice?
    a. I do not treat patients with epilepsy (EXCLUDE)
    b. 1-10
    c. 11-50
    d. 51-100
    e. 101 or more

6. When was the last time you prescribed an anti-epileptic drug for a patient with epilepsy?
    a. In the last week
    b. In the last month
    c. In the last 3 months
    d. In the last 6 months
    e. More than 6 months ago (EXCLUDE)

7. Have you ever prescribed TROBALT (retigabine)? (USED TO ENSURE THAT THE SAMPLE INCLUDES THE MINIMAL NUMBER OF TROBALT PRESCRIBERS)
    a. Yes
    b. No (GO TO Q10)

8. Do you currently have patients who are taking TROBALT (retigabine)? (ONLY IF RESPONSE TO Q7 IS Yes)
    a. Yes
    b. No
    c. I don't know

9. When was the last time you initiated a patient on TROBALT (retigabine)? (ONLY IF RESPONSE TO Q7 IS Yes)
    a. In the last month
    b. In the last 3 months
    c. Between 3 to 6 months
    d. Between 6 to 12 months
    e. More than 12 months ago

Assessment Phase

10. According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as: <Please select the best response>
    a. Monotherapy of partial onset seizures
    b. Adjunctive treatment of partial onset seizures
    c. Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.
    d. Status epilepticus
    e. I don't know

11. According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT? Answer "yes", "no" or "I don't know" for each of the following:
    a. Pigment changes (discolouration) of ocular tissues, including the retina
    b. Pigment changes (discolouration) of the nails, lips and/or skin
    c. Respiratory distress
    d. Urinary retention
    e. Ischaemic colitis
    f. Psychotic disorders (including confusional state and hallucinations)
    g. QTc prolongation
    h. Rhabdomyolysis

12. According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures? Answer "yes", "no" or "I don't know" for each of the following:
    a. Liver function tests
    b. A comprehensive ophthalmological examination
    c. Blood pressure assessment
    d. Measurement of plasma creatinine values

13. According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT? Please select ALL that apply:
    a. Immediately stop TROBALT
    b. Discontinue TROBALT if other suitable treatment options are available
    c. No action required
    d. Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued
    e. If TROBALT is continued, the patient should be monitored more closely

14. From which of the following sources have you learned about the risks associated with use of TROBALT (retigabine)? < Please select ALL that apply >
    a. Directly from GlaxoSmithKline
        i. Dear Health Care Professional information letter
        ii. Medical information
        iii. Product labelling
        iv. Other printed information
        v. Product website
        vi. Representative
        vii. Via medical symposia at scientific meetings
    b. Government Health Agency
    c. National Formulary
    d. Professional Neurology Association
    e. Independent medical websites
    f. Journal articles
    g. Other health care professionals

15. How do you prefer to receive information concerning new safety information for GlaxoSmithKline medicines? < Please select ALL that apply >
    a. Directly from GlaxoSmithKline
        i. Dear Health Care Professional information letter
        ii. Medical information
        iii. Product labelling
        iv. Other printed information
        v. Product website
        vi. Representative

vii. Via medical symposia at scientific meetings
b. Government Health Agency
c. National Formulary
d. Professional Neurology Association
e. Independent medical websites
f. Journal articles
g. Other health care professionals

16. Do you agree to provide your name and address to the third party conducting this survey on behalf of GSK so that we can issue a payment for your time in completing this survey? Your name and address will not be provided to GSK.
    a. Yes (RECORD NAME AND ADDRESS)
    b. No

Name _____

Address _____

[CLOSING] That ends the survey. Thank you again for your help. The correct answers to the questions about TROBALT follow.

Links to a DHCP, PI, and AE's national reporting system in correct language.

The following are the correct answers to the survey questions about TROBALT.

Please refer to the TROBALT Prescribing Information for further details.

THANK YOU

Survey Analysis Plan

Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™

Version: 2.0

Sponsor: GlaxoSmithKline
1-3 Iron Bridge Road
Stockley Park West
Uxbridge, Middlesex UB11 1BT, UK

Date: 14Aug2015

Status: Final

SAP based on Protocol 2014N191555_01 dated 19-May-2014

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Table of Contents

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LIST OF ABBREVIATIONS/ DEFINITION OF TERMS

Abbreviation	Definition
AED	Antiepileptic drug
SAP	Survey analysis plan
TLF	Tables, listings and figures

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1. INTRODUCTION

This Survey Analysis Plan (SAP) describes the proposed analyses for the results of the neurologist survey conducted under protocol: Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™.

The SAP will be accompanied by a mock tables/ listings document that indicates the format-structure for each of the tables, listings and figures (TLFs) that are to be generated.

2. OBJECTIVE(S)

The objective of this study is to assess prescribers' awareness and knowledge of the management of specific risks associated with TROBALT and the appropriate patient population as evaluated by a survey instrument.

3. METHODOLOGY

3.1 Sample Size

A target sample of 400 (200 prescribers and 200 non-prescribers) will be sought. Precision of estimated comprehension rates for various sample sizes and proportion of correct responses can be found in Table 1, in protocol section 7. The screening phase of the survey will select potential prescribers of TROBALT (i.e. those who have prescribed any antiepileptic drug (AED) within the past 6 months).

These targeted numbers of physicians reflect a trade-off between what is practical in terms of recruitment, given the relatively low predicted prescribing of TROBALT, and providing sufficient precision around outcome estimates (proportion giving correct responses per question).

3.2 Questions and Statements in the Physician Survey

The respondents will be asked several questions to obtain information on their medical specialty, country in which they practice, AED prescribing history, and whether they are current prescribers of TROBALT.
The questions and statements comprising the knowledge survey are constructed to test the understanding of the significant risks associated with TROBALT. The survey is composed of multiple choice and close-ended questions. There are no open-ended questions included. The full questionnaire for the physicians can be found in the protocol in Appendix 3.

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4. STATISTICAL ANALYSIS

The statistical analysis will be mainly descriptive, i.e. no formal hypothesis will be tested. All confidence intervals are exact two-sided 95% confidence intervals and no adjustment will be performed for multiplicity. Exact binomial two sided 95% confidence intervals will be calculated by the method of Clopper and Pearson (Clopper and Pearson, 1934). Counts and percentages will be calculated for each question/item in the questionnaire. Unless otherwise indicated, the percentages will be based on the population to whom a specific question was presented.

All survey questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Therefore, with the exception of missing data from the skip pattern, no missing data are expected.

Responses to the questions related to the knowledge, attitudes and behaviors will be categorized as "Correct response" and "Incorrect response" as detailed in the Correct Answers Document (Version 2, dated 01July2014). "I don't know" is categorized as an incorrect response.

All tables will be produced using SAS Software Version 9.1 or higher.

4.1 Analysis Populations

4.1.1 Primary Population (Complete respondents)

The primary population for the analysis is all eligible respondents who completed the survey. This population will be used for the entire analysis with exception of the participant screening results and the survey administration statistics.

Sub-populations of the complete respondents are the current TROBALT prescribers and the current TROBALT non-prescribers.

A current TROBALT prescriber in the meaning of this SAP is defined as a physicians who currently have patients taking TROBALT; a current TROBALT non-prescriber is defined as a the physicians who do not have currently patients taking TROBALT. Current TROBALT prescribers will be identified from the survey as defined in Table 1 below. All other physicians will be counted as current TROBALT non-prescribers.

Table1: Identification of current TROBALT prescribers

Question	**Possible Response**
Q7: Have you ever prescribed TROBALT'	Yes

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Q8: Do you currently have patients taking TROBALT	Yes

4.1.2 All Respondents

All respondents are the respondents who assessed the online survey with the unique code and answered at least all inclusion/exclusion questions. Respondents who discontinued the survey during the screening questions without being identified as ineligible to participate, will be excluded from the population of all respondents. The participant screening results will be analyzed in the population of all respondents and in the population of the complete respondents.

4.2 Planned Analyses and Summaries

4.2.1 Results of the Survey Administration Statistics

The following measures will be presented for the survey administration statistics:

- The number of invitations issued to physicians
- The number of reminder letters issued to physicians
- The number of respondents screened for participation
- The number of all respondents
- The number of respondents eligible for participation
- The number of respondents who completed the survey

After the survey was going live, there was an update in the Inclusion/Exclusion criteria. In addition to employees of UBC and GSK, also Government Officials will be excluded from the participation in the survey. Follow-up letters were sent to each physician who completed the survey before the EDC update to ask if the physician identify himself as a Government Official. Physicians that completed the survey prior to the inclusion/exclusion update and subsequently identified themselves as government officials will be included in the analyses but not paid. The number of eligible respondents will be based on the modified eligibility criterion.

4.2.2 Survey Participant Screening Results

The survey participants screening results will be presented for the population of all respondents as well as for the population of the Complete respondents. It consists of Question 1, 2, 5 and 6.

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4.2.3 Description of Survey Participant Characteristics

The description of the survey participant characteristics will be performed by means of descriptive statistics in the population of the Complete respondents.

The description of the survey participant characteristics will be analyzed for the current TROBALT prescribers and the current TROBALT non-prescriber, and overall (for the definition of current TROBALT prescribers and current TROBALT non-prescribers, see section 4.1.1.

4.2.4 Analysis of the Safe Use Messages

The Safe Use messages will be analyzed in the population of the Complete respondents and will be analyzed for the current TROBALT prescribers and current TROBALT non-prescribers, and overall.
The primary outcome is the proportion of neurologists answering each question of the understanding of the risks associated with TROBALT correctly. Point estimates for the proportion with correct responses, and associated 95% confidence intervals, will be calculated for each question about the risks of TROBALT. In the case of multiple choice questions, the number and proportion of neurologists reporting each response will also be provided.

4.2.5 Analysis of the Questions Regarding Receiving Informational Materials

The questions regarding receiving informational materials will be analyzed in a descriptive manner in the population of the Complete respondents. No confidence intervals will be calculated for the results of the questions regarding receiving informational materials.

4.3 Subgroup Analysis

The questions about the risks associated with the use of TROBALT will additionally be analyzed by the primary specialty of the prescribers (Epilepsy or Epileptology, Neurology with an interest in the treatment of epilepsy, General Neurology, Neuropsychiatry, Neurosurgery), by the number of patients treated with epilepsy per month (1 to10, 11 to 50, 51 to 100, 101 or more), and by country of residence. In these sub-group analyses, the current TROBALT prescribers and current TROBALT non-prescribers will be combined. The subgroup analysis will only be performed if at least two of the subgroups have a sample size of 30 or more respondents. If two subgroups have a sample size of 30 or more respondents, all subgroups will be presented including the subgroups with less than 30 respondents. Confidence intervals will be calculated for the correct response rate for each question and sub-group.

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REFERENCES

Clopper, C., Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika 26: 404–413.

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Correct Answers Document (Version 2, 01 Jul 2014)

The following are the correct answers to the survey questions about TROBALT.

Please refer to the TROBALT Summary of Product Characteristics for further details.

According to the product labelling for TROBALT (retigabine), TROBALT should now only be used as:

- Adjunctive treatment of drug resistant partial onset seizures where other appropriate drug combinations have proved inadequate or have not been tolerated.

According to the product labelling for TROBALT (retigabine), which of the following are potential risks associated with TROBALT?

- Pigment changes (discolouration) of ocular tissues, including the retina
- Pigment changes (discolouration) of the nails, lips and/or skin
- Urinary retention
- Psychotic disorders (including confusional state and hallucinations)
- QTc prolongation

According to the product labelling for TROBALT (retigabine), patients who are currently on TROBALT require which of these safety monitoring measures?

- A comprehensive ophthalmological examination

According to the product labelling for TROBALT (retigabine), what should you do if retinal pigmentation or vision changes are detected in a patient taking TROBALT?

- Discontinue TROBALT if other suitable treatment options are available
- Carefully re-assess the balance of benefits and risks before deciding whether TROBALT should be continued
- If TROBALT is continued, the patient should be monitored more closely

THANK YOU

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study PRJ2250/201426.

Name of Project Officer: [redacted] MD, PhD

Title of Project Officer: Scientific Affairs Manager
Classic & Established Products

Signature: [redacted]

Date: 26 Aug 2015

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: Director Cl[redacted] & Established Products

Signature: [redacted]

Date: 26 August 2015

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: Senior Director Epidemiology

Signature: [redacted]

Date: 26 August 2015