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.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *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 Clincal 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 Study Report
Control: Not applicable

Title:	**European Survey of Prescriber Understanding of Risks Associated with TROBALT™**
Phase:	IV
Compound Number:	GW582892
Effective Date:	31-JAN-2014
Description:	Cross-sectional survey results of prescribers on the effectiveness of the physician guide on physician understanding of the significant risks associated with TROBALT™ (retigabine) as part of the European Risk Management Plan requirements.

Subject: European neurologists' survey, prescriber understanding of key risks associated with antiepileptic medication TROBALT

Author: [redacted], PhD

Indication Studied: Antiepileptic

The survey concentrated on the risks described in the Physician's Guide for TROBALT, although it is recognised that the Physician's Guide is not the only source of information concerning risks associated with medication use.

The goal of the survey was to evaluate the effectiveness of the educational plan as specified in the European Risk Management Plan (RMP).

POST-AUTHORISATION SAFETY STUDIES (PASS) INFORMATION

Title	**European Survey of Prescriber Understanding of Risks Associated with TROBALT™**
Version identifier of the final study report	1.0
Date of last version of the final study report	31-JAN-2014
European Union (EU) PAS registration number	ENCEPP/SDPP/4851
Active substance	Antiepileptic, ATC code: N03AX21, retigabine
Medicinal product	TROBALT™ (retigabine)
Product reference	EU/1/11/681/001-013
Procedure number	Not applicable
Marketing authorisation (MAH) holder	Glaxo Group Limited
Joint PASS	No
Research question and objectives	The objective of this study is to assess prescribers' understanding and knowledge of the significant risks associated with TROBALT use as evaluated by a survey instrument.
Countries of study	United Kingdom (UK), Germany, Denmark, Sweden, Switzerland, Spain, Slovakia, and Norway
Author	[redacted]

MARKETING AUTHORISATION HOLDER

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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
TROBALT™

Trademarks not owned by the GlaxoSmithKline group of companies
None

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 WEUKBRE5744.

Name of Project Officer: [redacted]

Title of Project Officer: Director Therapeutic Area, Epidemiology

Signature: [redacted]

Date: 31/1/2014

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: Safety Physici[redacted]

Signature: [redacted]

Date: 30/1[redacted]

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1. ABSTRACT

Title

European Survey of Patient and Prescriber Understanding of Risks Associated with TROBALT™

Keywords

TROBALT, antiepileptic, risk, understanding

Rationale and background

The patient and physician respondent survey was undertaken to evaluate the understanding of the significant 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 objectives of this study are to assess patients' and prescribers' understanding and knowledge of the significant risks associated with TROBALT use as evaluated by a survey instrument.

Study design

This was a cross sectional survey of:

1) 250 patients recruited from across the United Kingdom, Sweden, Denmark, Switzerland, Spain, Slovakia and Norway and up to 100 patients from Germany who were currently using or had filled a prescription for TROBALT at least once in the last 3 months.

   Although the protocol objectives included conducting a patient survey, data collection was not completed due to the lack of participation by TROBALT prescribers in recruiting their patients (only 3 patients completed the survey). Recruitment of patients was particularly challenging due to the inability to contact patients directly given the patient confidentiality regulations. Therefore, no results from the patient survey are presented in this report.

2) 200 neurologists who had prescribed an an antiepileptic drug (AED) at least once in the last 3 months, and who were on the list to which a letter containing the Physician's Guide for TROBALT was distributed across the United Kingdom, Sweden, Denmark, Switzerland, Spain, Slovakia and Norway. At least 75 of the neurologists were to have prescribed TROBALT. The survey also aimed to include 100 neurologists from Germany, of which approximately 50 of whom were to have prescribed TROBALT.

Protocol Update

GSK will submit the study final report along with a request for protocol variation to the European Medicines Agency (EMA) consisting of:

1) Removal of the patient survey from the protocol due to the lack of participation by physicians in recruiting patients, the relatively low uptake of retigabine in Europe, and the inability to contact patients directly due to patient confidentiality regulations.

2) Removal of Sweden from the survey as the physician survey was near completion prior to the launch of the survey in Sweden, and there is representation from two other Scandinavian countries, Denmark and Norway. This would allow the physician survey results to be available sooner.

For the reasons cited above, the patient survey was not completed. Therefore, this report contains no patient survey data analyses.

Setting

A physician respondent survey was conducted across 7 European countries (the UK, Germany, Spain, Denmark, Switzerland, Slovakia, and Norway). The rationale for surveying these particular countries is because they were first to launch TROBALT so any issues identified from these countries regarding the effectiveness of the Physician's Guide and Patient Information Leaflet (PIL) in communicating the risks of TROBALT can be addressed as soon as possible, and the key messages can be revised in a timely manner.

Subjects and study size, including dropouts

The majority of physicians were neurologists. A total of 8430 invitations were sent to physicians to complete the online surveys. A total of 301 surveys were completed.

Variables and data sources

The questions and statements comprising the knowledge survey were constructed to test the understanding of the significant risks associated with TROBALT. Each survey was composed of multiple choice and close-ended questions. There were no open-ended questions included. For statements or questions that use "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.

Results

A total of 301 prescribers responded and were screened for participation (meeting the target sample size), and 294 of these (97.7%) were considered eligible for analysis. Of those, 96 prescribers were German physicians. All eligible respondents completed the survey online.

Indication for use: Almost all (91.5%) physicians surveyed recalled that TROBALT is approved for use in partial-onset seizures, but only three-quarters (78.2%) recalled that it can only be prescribed to patients who are at least 18 years of age. Most (88.1%) understood that TROBALT is not indicated for monotherapy.

Dose-related questions: Approximately three-quarters (74.1%) of physicians surveyed from all countries recalled that TROBALT should be taken three times/day. Almost three-quarters (72.8%) recalled that TROBALT can only be increased by 150 mg/day every 7 days. Slightly more than half (56.5%) of physicians recalled that a patient can reach the minimum maintenance dose of 600 mg/day by 3 weeks using the Treatment Initiation Pack. Slightly more than two-thirds (68.3%) of physicians surveyed from all countries recalled that the maximum recommended dose of TROBALT is 1200 mg.

Central Nervous System (CNS) side effects-related questions: Two-thirds (66.3%) of physicians surveyed from all countries recalled that patients taking TROBALT in clinical studies had a higher risk of experiencing a confusional state. However, only slightly more than half recalled patients had a higher risk of experiencing hallucinations (55.8%) and psychotic disorders (54.1%). A small percentage (39.8%) recalled that these symptoms were reported within the first 8 weeks after starting treatment with TROBALT. Fewer (20.4%) recalled that appropriate dose titration may minimise the risk of CNS side effects.

Urinary symptom-related questions: Slightly less than two-thirds of physicians surveyed from all countries recalled that patients taking TROBALT in clinical studies had a higher risk of experiencing urinary retention (64.6%). About half (55.4%) of these physicians recalled that they should specifically advise their patients taking TROBALT about all of the urinary symptoms (including pain when urinating, difficulty starting urination, slow stream, and inability to pass urine). Approximately the same percentage (55.1%) recalled that AEs related to voiding dysfunction were reported within the first 8 weeks after starting treatment with TROBALT.

Cardiac-related questions: Overall, physicians had a less recall of information regarding the cardiac risks compared to urinary risks associated with TROBALT. Less than half (44.6%) recalled that TROBALT has been shown to produce a possible QT prolongation at 1200 mg. Few physicians recalled that it is recommended to perform an electrocardiogram (ECG) on patients with congestive heart failure (CHF) (25.9%), ventricular hypertrophy (26.2%), and hypokalemia (24.1%). Almost half (44.9%) recalled that the ECG should be rechecked after reaching the maintenance dose in patients who had a QTc interval of > 400 milliseconds (ms) before starting TROBALT. However, more (76.5%) physicians recalled that they should warn patients to whom they prescribed TROBALT about new cardiac effects of syncope, palpitations, and any other symptoms of arrhythmia.

In addition to analyses of all physicians from all countries surveyed and analyses of those physicians specifically from Germany, several subgroup analyses were conducted to see if there was a difference in understanding the risks above by evaluating the following subgroups:

1) physicians who prescribed TROBALT,

2) whether or not they read the TROBALT information letter

In general, sub-group analyses showed that physicians who had prescribed TROBALT and/or read the TROBALT information letter had better recall of the information regarding the use of TROBALT in patients with partial-onset seizures and the risks associated with its use.

Discussion

Overall, there is awareness, to varying degrees, of the risks associated with the use of TROBALT. GlaxoSmithKline needs to build on this and strengthen risk minimisation activities to improve the understanding of these risks. This is further discussed in the Conclusion section.

Statistical Methods

All statistical analyses were descriptive, i.e., no formal hypotheses were tested. Confidence intervals (CI) were calculated at the 95% level, and no adjustments were performed for multiplicity. Counts and percentages were calculated for each question/item in the questionnaire. Questions 19 and 20 were not presented to respondents from Switzerland due to labelling variation in that country. Percentages were based on the population to whom a specific question was presented.

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 to the survey questions section in the protocol. “I don’t know” was generally categorised as an incorrect response.

The primary outcome was 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 confidence intervals, were 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 were provided.

Populations and Subgroup Analysis

Primary Population

The analysis of the entire survey included only completed surveys. The primary population for the analysis was 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.

The outcomes (physician responses to the questions about the risks of TROBALT) and the respondent characteristics were summarised for all seven specified countries combined, and separately for Germany, and for the six countries combined excluding

Germany. All other analyses were performed for the respondents combined from all seven countries.

Subgroup Analysis

An analysis of the responses to the questions about the risks of TROBALT and the respondent characteristics was performed for the subgroup of prescribers who ever prescribed TROBALT and for the prescribers who did not prescribe TROBALT. The analysis was stratified by the countries as described above (all seven countries, Germany alone, and for the six countries excluding Germany).

The subgroup analysis comparing the respondents who reported reading the TROBALT information letter (yes vs. no) was only performed for the questions about the risks of TROBALT. For the subgroup analysis, the physicians from all seven countries were combined.

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
EDC	electronic data capture
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
GSK	GlaxoSmithKline
MAH	Marketing authorisation holder
ms	milliseconds
PASS	Post-Authorisation Safety Studies
PIL	Patient Information Leaflet
REMS	Risk Evaluation and Mitigation Strategies
RMP	Risk Management Plan
UBC	United BioSource Corporation
UK	United Kingdom

2. INVESTIGATORS

This was a cross sectional survey of 200 neurologists across United Kingdom, Sweden, Denmark, Switzerland, Spain, Slovakia, Norway, and Germany. The survey was never launched in Sweden due to reasons outlined above.

3. MILESTONES

Initiation Date:	30 November 2012
Completion Date:	04 October 2013

4. RATIONALE AND BACKGROUND

As part of a European post-marketing commitment, GlaxoSmithKline (GSK) conducted a survey of physicians' and patients' understanding of the significant risks associated with TROBALT™ (retigabine). The surveys concentrated on the risks described in the approved European Union (EU) Patient Information Leaflet (PIL) and Physician's Guide for TROBALT. The goal of the surveys was to evaluate the effectiveness of the educational plan as specified in the European Risk Management Plan (RMP).

4.1. Rationale

The population targeted for this survey was the subgroup of neurologists commonly referred to as 'epileptologists' who were known from past experience to be the specialists who first initiated prescriptions of a new antiepileptic drug (AED) and who had been specifically targeted by GSK for educational activities regarding TROBALT.

The design for this study was based on GSK's previous experience designing RMPs for GSK products, and on the prior experience of United BioSource Corporation (UBC) in conducting similar surveys in the EU.

The prescriber survey concentrated on the risks described in the Physician's Guide for TROBALT, though it is recognised that the Physician's Guide is not the only source of information concerning risks associated with medication use.

The goal of the surveys was to evaluate the effectiveness of the educational plan as specified in the European RMP.

5. RESEARCH QUESTION AND OBJECTIVES

The main objectives of the study were:

- To conduct a survey of patients' understanding of the significant risks with TROBALT (retigabine).

- To conduct a survey of neurologists who are prescribing AEDs on their understanding of the significant risks associated with TROBALT.

Although the protocol objectives covered both patient and prescriber surveys, the full patient survey was not conducted as represented in the Protocol Amendment submitted to the European Medicines Agency (EMA) along with this study report. The rationale for removing the patient survey from the protocol was due to the lack of participation by TROBALT prescribers in recruiting their patients, the relatively low uptake of retigabine in Europe, and the inability to contact patients directly due to patient confidentiality regulations. Therefore, only the results of the prescriber survey are presented and summarised in this report.

6. AMENDMENTS AND UPDATES

The original protocol (dated 18 May 2012) for this European survey of patient and prescriber understanding of the risks associated with TROBALT was amended three times as shown in Table 1. The complete protocol as amended is included in Annex 1.

Table 1 Protocol Amendments

Number	Date	Section of Study Protocol	Amendment	Reason
1	*11 Jun 2012*	*Study Design*	*To add 3 countries to the survey (Norway, Spain, and Slovakia)* *To analyse Germany separately (due to a change in reimbursement for TROBALT)*	*- Gain wider access to prescribers' understanding of risk information* *- Due to a reimbursement decision*
2	*12 Sep 2012*	*Study Design*	*To provide predicted timelines for study completion,* *To remove the patient gift,* *To specify physician payment for study participation,* *To add a question regarding the titration pack (with a note that this does not apply to Switzerland).*	*At the request of the EMA*
3	*09 Dec 2013*	*Study Design*	*To remove the patient survey from the protocol due to no recruitment.* *Remove Sweden from survey due to delays in ethics committee submission, and proposal to conduct HCP analysis earlier with 197 responses from 6 other countries, and 96 HCPs separately from Germany.*	*Based on recruitment issues*

7. RESEARCH METHODS

7.1. Study Design

The aim of this survey was to recruit a random sample of 300 neurologists who had prescribed an AED at least once in the last 3 months and who were on the list to which an educational letter containing the Physician's Guide for TROBALT. The goal was to include 100 neurologists from Germany, of whom 50 were to have prescribed TROBALT. The remaining 200 neurologists were to be from the United Kingdom, Denmark, Sweden, Switzerland, Spain, Slovakia, and Norway; at least 75 of whom were to have prescribed TROBALT. The survey was never launched in Sweden due to a delay in ethics submission, as described in the protocol amendment.

These numbers reflected a trade-off between what was 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), and also to allow analysis of the sub-sample of neurologists who had prescribed TROBALT.

Neurologists were targeted for the educational letter on the basis that they constituted the broadest group of physicians who were reasonably likely to initiate a prescription of TROBALT. Furthermore, a subgroup of neurologists commonly referred to as 'epileptologists' who were known from past experience to be the specialists who first initiated prescriptions of a new AED and who were therefore specifically targeted for promotional activity by GSK were the primary target of this survey. The survey concentrated on the risks described in the Physician's Guide for TROBALT, although it was recognised that the Physician's Guide was not the only source of information concerning risks associated with medication use.

This study design was based on experience from risk management evaluation studies previously completed by GSK and UBC. UBC has designed and conducted assessment surveys in over 20 European countries to evaluate prescribers' understanding of risk messages. Recruitment and analytic strategies included in the proposal were similar to those programs. Further, both UBC and GSK conducted similar knowledge, attitude and behaviour surveys in the United States to evaluate Risk Evaluation and Mitigation Strategies (REMS).

7.2. Setting (Survey Design)

This survey was conducted in the first countries to launch TROBALT (the United Kingdom, Denmark, Germany, Norway, Slovakia, Spain, and Switzerland). The rationale for selecting these countries was that they were the first to launch TROBALT. Therefore, any issues identified from these countries regarding the effectiveness of the Physician's Guide and PIL in communicating the risks of TROBALT could be addressed as soon as possible, and the key messages could be revised in a timely manner. Although Switzerland is not part of the European Union, the key messages regarding the risks with TROBALT were in alignment with the key risk messages for the other countries, and therefore Switzerland was included in the countries surveyed. In addition, these countries were likely to provide the greatest number of neurologists with experience in prescribing TROBALT.

The survey was conducted from 30 November 2012 to 04 October 2013.

Physicians were recruited by selecting a random sample of neurologists from lists of all potential TROBALT prescribers in each country provided by GSK. The neurologists were recruited through an invitation to participate in the survey. Invitations (that included an introductory educational letter, an invitation to complete the survey, and the survey instrument) were sent by e-mail to those neurologists for whom an e-mail address were available or by mail for those neurologists without e-mail addresses (Annex 1). The invitation directed the neurologist how to access the survey on-line on the website to complete the survey. Physicians were provided a unique code in the survey invitation letter and were asked to provide the 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 1).

7.3. Subjects

A total of 301 prescribers responded and were screened for participation (meeting the target sample size), and 294 of these (97.7%) were considered eligible for analysis. Of those eligible, 96 prescribers were German physicians. All eligible respondents completed the survey.

7.4. Variables (Questionnaire Structure)

The questions and statements comprising the knowledge survey were constructed to test the understanding of the significant risks associated with TROBALT. Each survey was composed of multiple choice and close-ended questions. There were no open-ended questions 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 contained in (Annex 1).

7.5. Data Sources and Measurement (Questionnaire Questions and Statements)

The questionnaire (survey instrument) that was utilised for neurologists who prescribe AEDs and to whom the TROBALT Letter containing the Physician’s Guide was sent is shown in the protocol (Annex 1).

7.6. 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:

- The Internet survey questionnaires were programmed to ensure that questions were asked in the appropriate sequence.
- All lists of response options were randomised to minimise the potential for positional bias.
- All questions were presented in a standard order.
- Respondents could not go back to a question once the question was answered and could not skip ahead. All questions had to be answered in order for a survey to be considered complete.
- Computer programming was reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7.7. Study Size

7.7.1. Sample Size

Table 2 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 250 physicians will provide a margin of error of ± 6.0 percentage points of this estimate with a 95% confidence interval. Subgroups of the total sample will have smaller numbers of physicians, resulting in larger margins of error and therefore provide estimates with lower precision.

Table 2 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

This survey recruited a random sample of 300 neurologists prescribing AEDs and who had been sent the TROBALT Physician's Guide. A sample of 200 neurologists were recruited from across the United Kingdom, Denmark, Switzerland, Spain, Slovakia and Norway, and 100 neurologists were recruited from Germany.

The recruitment was from among those who have prescribed an AED at least once in the last 3 months, and who were on the list to which an educational letter including the Physician's Guide TROBALT was distributed. The survey recruited 75 physicians (from the seven specified countries) and 50 physicians from Germany with experience of prescribing TROBALT for sub-analyses, as these individuals were expected to be more aware of the risks of TROBALT. The subgroup of neurologists commonly referred to as 'epileptologists' who were known from past experience to be the specialists who first initiated prescriptions of a new AED and were therefore specifically targeted for promotional activity by GSK, were the primary target of this survey.

The sample of neurologists who were invited to participate was a random sample of all neurologists who received the Physician's Guide for TROBALT. The sample of participating neurologists was self-selected since respondents voluntarily responded to the invitation to participate. However, the survey recruitment strategies were intended to recruit a heterogeneous sample of prescribers for participation. For Germany, TROBALT was no longer available for new patients, so only neurologists who had patients being treated with TROBALT in November 2012 were targeted.

These numbers reflected a trade-off between what is practical in terms of recruitment, given the relatively low predicted prescribing of TROBALT, and sufficient precision around outcome estimates (proportion giving correct responses per question), and also allowed analysis of the sub-sample of neurologists who had prescribed TROBALT.

7.8. Privacy Protection and Confidentiality

All data collected during the survey were held confidentially. The electronic data capture (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, answers to the key messages regarding the risks with TROBALT, and an honorarium after the survey was completed. Respondent contact information was also needed in the event that an adverse event (AE) was reported.

7.9. Statistical Methods

7.9.1. Main Summary Measures

All statistical analyses were descriptive, i.e., no formal hypothesis was tested. All confidence intervals were computed at the 95% level, and no adjustment was performed for multiplicity. Counts and percentages were calculated for each question/item in the questionnaire. Questions 19 and 20 were not presented to respondents from Switzerland due to labelling variation in that geography. Percentages were based on the population to whom a specific question was presented.

Responses to the questions related to knowledge, attitudes and behaviours were categorised as "Correct response" or "Incorrect response" as detailed in the correct answers to the survey questions section in the protocol. "I don't know" was generally categorised as an incorrect response.

7.9.2. Main Statistical Methods

7.10. Analysis of the Safe Use Messages

The primary outcome was 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 confidence intervals, were 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 were provided.

7.11. Populations and Subgroup Analysis

7.11.1. Primary Population

The analysis of the entire survey included only completed surveys. The primary population for the analysis was 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.

The outcomes (physician responses to the questions about the risks of TROBALT) and the respondent characteristics were summarised for all seven specified countries combined, and separately for Germany and for the six countries combined excluding Germany. All other analyses were performed for the respondents combined from all seven countries.

7.11.2. Subgroup Analysis

An analysis of the responses to the questions about the risks of TROBALT and the respondent characteristics were performed for the subgroup of prescribers who ever prescribed TROBALT and for the prescribers who did not prescribe TROBALT. The analysis was stratified by the countries as described above (all seven countries, Germany alone, and for the six countries excluding Germany).

The subgroup analysis comparing the respondents who reported reading the TROBALT information letter (yes vs. no) was only performed for the questions about the risks of TROBALT. For the subgroup analysis, the physicians from all seven countries were combined.

7.11.3. Missing values

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

7.11.4. Sensitivity analyses

Not applicable.

7.11.5. Amendments to the Statistical Analysis Plan

The Statistical Analysis Plan was not amended.

7.12. Quality control

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

8. RESULTS

8.1. Survey Administration Results

A total of 8430 invitation letters were issued (Table 3); 1380 reminder letters were sent only to physicians in the UK. Although the survey was planned to include physicians from Sweden, due to the accompanying protocol amendment, no invitation letters were sent to physicians in Sweden. A total of 301 prescribers responded and were screened for participation (meeting the target sample size), and 294 of these (97.7%) were considered eligible for analysis. Of those, 96 prescribers were German physicians. All eligible respondents completed the survey. All respondents completed the survey online.

Table 3 Survey Administration Statistics

Survey Invitee Results	All Respondents	
	N	%
Number of invitation letters issued	8430 [1]	
Number of reminder letters issued	1380 [2]	
Number of respondents	301	
Number of prescribers who did not complete the survey	1	0.3
Number of prescribers who did not live in a targeted survey country	1	0.3
Number of prescribers who did not prescribe TROBALT within the last 3 months	5	1.7
Number of prescribers eligible for analysis	294	97.7

[1] Invitation letters were sent to physicians in Denmark, Germany, Norway, Slovakia, Spain, Switzerland, and the United Kingdom (UK). No invitation letters were sent to physicians in Sweden.
[2] Reminder letters were only sent to physicians in the UK.

The 294 prescribers completed the online survey in a mean time of 13.6 ± 7.29 minutes (Table 4). Most prescribers took between 5 and 15 minutes to complete the survey (Table 5).

Table 4 Time to Complete Survey (Minutes) for Completed Surveys

Summary Statistic	Time (min)
N	294
Mean (SD)	13.6 (7.29)
Minimum	4
Median	11.8
Maximum	48

Table 5 Number of Responders Who Completed Surveys per Category of Time

Category	N (%)
0 - <5 Minutes	6
5 - <10 Minutes	102
10 - <15 Minutes	93
15 - <20 Minutes	50
20 - <25 Minutes	22
25 - <30 Minutes	11
30 Minutes or More	10

8.2. Participants

Description of Survey Participants

Table 6 displays the survey screening results of the physicians who received the invitation letters to participate in the survey. Of the 294 eligible physicians who completed the survey, 94.9% prescri bed antiepileptic drugs within the last month. Almost half (49.0%) of them reported that they had prescribed TROBALT. The geographical distribution of eligible physicians was: Germany 32.7%, Spain 20.4%, United Kingdom 18.0%, Slovakia 9.5%, Switzerland 7.8%, Norway 6.5%, and Denmark 5.1%.

Table 6 Survey Participant Screening Results

Question	All Respondents N=301		Eligible and Complete Respondents N=294	
	N	%	N	%
Question 1: Do you agree to take part in this survey?				
Yes	300	99.7	294	100.0
No [1]	1	0.3		
Question 2: When was the last time you prescribed an anti-epileptic drug for a patient?				
Less than a month ago	280	93.0	279	94.9
Between 1 and 2 months ago	10	3.3	10	3.4
Between 2 and 3 months ago	5	1.7	5	1.7
More than 3 months ago [1]	5	1.7		
Question not asked [2]	1	0.3		
Question 3: Have you ever prescribed TROBALT?				
Yes	144	47.8	144	49.0
No	143	47.5	142	48.3
I don't know	8	2.7	8	2.7
Question not asked [2]	6	2.0		
Question 4: In which country is your primary medical practice?				
Germany	96	31.9	96	32.7
Denmark	15	5.0	15	5.1
United Kingdom	53	17.6	53	18.0
Switzerland	23	7.6	23	7.8
Sweden [3]	0	0.0	0	0.0
Spain	60	19.9	60	20.4
Slovakia	28	9.3	28	9.5
Norway	19	6.3	19	6.5
Other [1]	1	0.3		
Question not asked [2]	6	2.0		
Question 5: Are you an employee of GlaxoSmithKline or United BioSource Corporation?				
Yes[1]	0	0.0		
No	294	97.7	294	100.0
Question not asked [2]	7	2.3		

[1] Ineligible to participate in the survey.
[2] Question not asked due to a previous question elimination.
[3] Although Sweden was an option for this question, the survey was never launched in Sweden due to Protocol revision.

Table 7 summarises the background of the physicians who completed the survey. Of the eligible physicians from all countries, most (91.8%) reported neurology as their primary medical specialty, with an additional 4.8% who specialised in epileptology. Approximately two-thirds (64.3%) of them read the TROBALT information letter that was sent to them, and half (50.7%) learned about the risks of TROBALT via the launch letter. Approximately three-quarters (72.8%) were male, and slightly less (70.0%) had been practicing medicine for at least 11 years.

The physicians from Germany reported a similar primary medical specialty distribution to all physicians who completed the survey. However, only about half (52.1%) read the TROBALT information letter that was sent at the launch, but they learned about the risks of TROBALT via a journal article (54.2%). There was a slightly higher percentage of male physicians from Germany (81.3%). Only slightly more than half (56.3%) had been practicing medicine for at least 11 years.

Table 7 Responses to Physician Questions

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	%	N	%	N	%
Question 24: How would you classify your primary medical specialty?						
Neurology	270	91.8	91	94.8	179	90.4
Neurosurgery	3	1.0	0	0.0	3	1.5
Epileptology	14	4.8	4	4.2	10	5.1
Other (specify) [1]	7	2.4	1	1.0	6	3.0
Question 25: Have you read the TROBALT information letter that was sent at the launch of TROBALT?						
Yes	189	64.3	50	52.1	139	70.2
No	63	21.4	25	26.0	38	19.2
I don't know	42	14.3	21	21.9	21	10.6
Question 26: From which of the following sources have you learned about the risks associated with use of TROBALT? (Please select all that apply.)						
TROBALT launch letter	149	50.7	34	35.4	115	58.1
GlaxoSmithKline medical information	104	35.4	29	30.2	75	37.9
Other health care professionals	59	20.1	25	26.0	34	17.2
GlaxoSmithKline promotional materials	77	26.2	15	15.6	62	31.3
GlaxoSmithKline sales representatives	102	34.7	14	14.6	88	44.4
Journal article	105	35.7	52	54.2	53	26.8
GlaxoSmithKline-sponsored educational meeting	29	9.9	4	4.2	25	12.6
None of the above	39	13.3	13	13.5	26	13.1
Question 27: What is your gender?						
Male	214	72.8	78	81.3	136	68.7
Female	80	27.2	18	18.8	62	31.3

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	%	N	%	N	%
Question 28: For how many years have you been in medical practice?						
Less than 3 years	4	1.4	1	1.0	3	1.5
3–5 years	26	8.8	18	18.8	8	4.0
6–10 years	55	18.7	23	24.0	32	16.2
11–15 years	71	24.1	26	27.1	45	22.7
16–20 years	51	17.3	12	12.5	39	19.7
More than 20 years	84	28.6	16	16.7	68	34.3
Prefer not to answer	3	1.0	0	0.0	3	1.5

[1] Other medical specialties are listed in Appendix 1.

8.3. Descriptive Data

The descriptive data regarding the physicians who completed the survey are discussed in Section 8.2 above.

8.4. Outcome Data

Not applicable.

8.5. Main Results

8.5.1. Results from All Seven Countries

Table 8 displays the responses by all eligible physicians (defined as those who completed the survey) to all questions related to the understanding of the risks associated with TROBALT. The majority (91.5%) of physicians from all seven countries understood that TROBALT is approved for use in partial-onset seizures, and three-quarters (78.2%) recalled that it can only be prescribed to patients who are at least 18 years of age. Most (88.1%) recalled that TROBALT is not indicated for monotherapy. However, only about two-thirds (68.3%) of the respondents recalled the maximum recommended dose (1200 mg); approximately three-quarters (74.1%) recalled that TROBALT should be taken three times/day. Almost three-quarters (72.8%) recalled that TROBALT can only be increased by 150 mg/day every 7 days. Slightly more than half (56.5%) of the physicians recalled that a patient can reach the minimum maintenance dose of 600 mg/day by 3 weeks using the Treatment Initiation Pack.

About two-thirds of physicians from all countries recalled that patients taking TROBALT in clinical studies had a higher risk of experiencing a confusional state (66.3%) and

urinary retention (64.6%), while only slightly more than half of physicians recalled those patients had a higher risk of experiencing hallucinations (55.8%) and psychotic disorders (54.1%).

Only slightly more than half (55.1%) of these physicians recalled that patients in clinical studies experienced AEs related to voiding dysfunction within the first 8 weeks after starting treatment with TROBALT; but only slightly more than one-third (39.8%) recalled that the confusional state, hallucinations, and/or psychotic disorders were generally reported within the same time period. Few (20.4%) recalled that appropriate dose titration may minimise the risk of central nervous system (CNS) side effects. Only slightly more than half (55.4%) of these physicians recalled that they should specifically advise their patients taking TROBALT about all of the urinary symptoms (including pain when urinating, difficulty starting urination, slow stream, and inability to pass urine).

Less than half (44.6%) recalled that TROBALT has been shown to produce a possible QT prolongation at 1200 mg. Approximately one-quarter of physicians recalled that it is recommended to perform an electrocardiogram (ECG) on patients with congestive heart failure (CHF) (25.9%), ventricular hypertrophy (26.2%), and hypokalemia (24.1%). Almost half (44.9%) did recall that the ECG should be rechecked after reaching the maintenance dose in patients who had a QTc interval of > 400 ms before starting TROBALT. Three-quarters (76.5%) of physicians recalled that they should warn patients to whom they prescribed TROBALT about new cardiac effects of syncope, palpitations, and any other symptoms of arrhythmia.

Table 8 Responses to all Questions Related to Understanding the Risks Associated with TROBALT (All eligible physicians)

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: For which of the following conditions is TROBALT approved for use?						
Migraine	2	0.7	1	1.0	1	0.5
Partial-onset seizures [1]	269	91.5 (87.7, 94.4)	89	92.7 (85.6, 97.0)	180	90.9 (86.0, 94.5)
All types of seizures	11	3.7	3	3.1	8	4.0
All of the above	3	1.0	0	0.0	3	1.5
None of the above	3	1.0	0	0.0	3	1.5
I don't know	6	2.0	3	3.1	3	1.5
Question 7: Is TROBALT indicated for use as monotherapy?						
Yes	16	5.4	10	10.4	6	3.0
No [1]	259	88.1 (83.8, 91.6)	80	83.3 (74.4, 90.2)	179	90.4 (85.4, 94.1)
I don't know	19	6.5	6	6.3	13	6.6
Question 8: What is the maximum recommended daily maintenance dose of TROBALT for most patients? (Please select the best response.)						
600 mg	16	5.5	6	6.3	10	5.1
900 mg	28	9.6	8	8.3	20	10.2
1200 mg [1]	200	68.3 (62.6, 73.6)	61	63.5 (53.1, 73.1)	139	70.6 (63.7, 76.8)
2000 mg	1	0.3	1	1.0	0	0.0
None of the above	3	1.0	2	2.1	1	0.5
I don't know	45	15.4	18	18.8	27	13.7

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Which one of the following statements is true? (Please select the best response.)						
TROBALT should be taken once a day.	16	5.4	6	6.3	10	5.1
TROBALT should be taken twice a day.	33	11.2	14	14.6	19	9.6
TROBALT should be taken three times a day [1]	218	74.1 (68.7, 79.1)	66	68.8 (58.5, 77.8)	152	76.8 (70.3, 82.5)
TROBALT should be taken four times a day.	0	0.0	0	0	0	0.0
None of the above	0	0.0	0	0	0	0.0
I don’t know	27	9.2	10	10.4	17	8.6
Question 10: When increasing the dose, what is the maximum total daily dose at which TROBALT can be increased once every 7 days? (Please select the best response.)						
50 mg	30	10.2	11	11.5	19	9.6
150 mg [1]	214	72.8 (67.3, 77.8)	58	60.4 (49.9, 70.3)	156	78.8 (72.4, 84.3)
300 mg	35	11.9	22	22.9	13	6.6
600 mg	7	2.4	1	1.0	6	3.0
None of the above	8	2.7	4	4.2	4	2.0
Question 11: Which one of the following statements is true? (Please select the best response.)						
There are no lower age limits for TROBALT usage.	10	3.4	3	3.1	7	3.5
The youngest age at which TROBALT can be used is 12.	18	6.1	5	5.2	13	6.6
The youngest age at which TROBALT can be used is 18. [1]	230	78.2 (73.1, 82.8)	76	79.2 (69.7, 86.8)	154	77.8 (71.3, 83.4)
I don’t know	36	12.2	12	12.5	24	12.1

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: The quickest time by which the minimum maintenance dose of 600 mg should be reached is the third week.						
True [1]	197	67.0 (61.3, 72.4)	51	53.1 (42.7, 63.4)	146	73.7 (67.0, 79.7)
False	62	21.1	29	30.2	33	16.7
I don't know	35	11.9	16	16.7	19	9.6
Question 13: For the general population, the recommended total initial dosage should be 150 mg per day for one week.						
True	89	30.3	39	40.6	50	25.3
False [1]	178	60.5 (54.7, 66.2)	47	49.0 (38.6, 59.4)	131	66.2 (59.1, 72.7)
I don't know	27	9.2	10	10.4	17	8.6
Question 14: People taking TROBALT had a higher chance of experiencing which of the following risks in clinical studies. (Please select all that apply.)						
Urinary retention [1]	190	64.6 (58.9, 70.1)	66	68.8 (58.5, 77.8)	124	62.6 (55.5, 69.4)
Confusional state [1]	195	66.3 (60.6, 71.7)	66	68.8 (58.5, 77.8)	129	65.2 (58.1, 71.8)
Hallucinations [1]	164	55.8 (49.9, 61.5)	64	66.7 (56.3, 76.0)	100	50.5 (43.3, 57.7)
Psychotic disorders [1]	159	54.1 (48.2, 59.9)	65	67.7 (57.4, 76.9)	94	47.5 (40.4, 54.7)
Myocardial infarction	8	2.7	4	4.2	4	2.0
Renal carcinoma	0	0.0	0	0	0	0.0
All of the above	11	3.7	2	2.1	9	4.5
None of the above	12	4.1	4	4.2	8	4.0
I don't know	37	12.6	12	12.5	25	12.6

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 15: It is known from controlled studies that adverse events related to voiding dysfunction generally tend to be reported how soon after starting TROBALT?						
Within the first week	32	10.9	17	17.7	15	7.6
Within the first 8 weeks [1]	162	55.1 (49.2, 60.9)	44	45.8 (35.6, 56.3)	118	59.6 (52.4, 66.5)
After 4 months	3	1.0	1	1.0	2	1.0
After 12 months	0	0.0	0	0	0	0.0
I don't know	97	33.0	34	35.4	63	31.8
Question 16: It is known from controlled studies that confusional state, hallucinations, and/or psychotic disorders generally tend to be reported how soon after starting TROBALT?						
4 weeks	76	25.9	34	35.4	42	21.2
8 weeks [1]	117	39.8 (34.2, 45.6)	26	27.1 (18.5, 37.1)	91	46.0 (38.9, 53.2)
12 weeks	13	4.4	2	2.1	11	5.6
16 weeks	2	0.7	0	0.0	2	1.0
I don't know	86	29.3	34	35.4	52	26.3
Question 17: Which of the following urinary symptoms, if any, should you specifically advise patients taking TROBALT to watch out for? (Please select the best response.)						
Pain when urinating	4	1.4	1	1.0	3	1.5
Difficulty starting urination	51	17.3	19	19.8	32	16.2
Slow stream	1	0.3	1	1.0	0	0.0
Inability to pass urine	46	15.6	15	15.6	31	15.7
All of the above [1]	163	55.4 (49.6, 61.2)	48	50.0 (39.6, 60.4)	115	58.1 (50.9, 65.0)
None of the above	1	0.3	0	0.0	1	0.5
I don't know	28	9.5	12	12.5	16	8.1

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 18: According to the TROBALT Physician's Guide, appropriate dose titration may minimize the risk of which of the following adverse events? (Please select the best response.)						
QT prolongation	35	11.9	11	11.5	24	12.1
CNS side effects such as hallucinations [1]	60	20.4 (16.0, 25.5)	21	21.9 (14.1, 31.5)	39	19.7 (14.4, 25.9)
Urinary retention	21	7.1	7	7.3	14	7.1
All of the above	128	43.5	34	35.4	94	47.5
None of the above	10	3.4	5	5.2	5	2.5
I don't know	40	13.6	18	18.8	22	11.1
Question 19: Using the Treatment Initiation Pack, by which week can the patient reach a dose of 600 mg/day? [2]						
2 weeks	34	12.5	14	14.6	20	11.4
3 weeks [1]	153	56.5 (50.3, 62.4)	48	50.0 (39.6, 60.4)	105	60.0 (52.3, 67.3)
4 weeks	60	22.1	24	25.0	36	20.6
5 weeks	7	2.6	4	4.2	3	1.7
None of the above	17	6.3	6	6.3	11	6.3
Switzerland	23		23		23	
Question 20: At what dose has TROBALT been shown to produce a possible QT prolonging effect? [2]						
600 mg	18	6.6	5	5.2	13	7.4
900 mg	16	5.9	9	9.4	7	4.0
1200 mg [1]	121	44.6 (38.6, 50.8)	35	36.5 (26.9, 46.9)	86	49.1 (41.5, 56.8)
1800 mg	14	5.2	6	6.3	8	4.6
I don't know	102	37.6	41	42.7	61	34.9
Switzerland	23		0		23	

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 21: For which patients is it recommended that an ECG is recorded before initiating TROBALT? (Please select all that apply.)						
Patients with hypertension	5	1.7	2	2.1	3	1.5
Patients with congestive heart failure [1]	76	25.9 (20.9, 31.3)	22	22.9 (15.0, 32.6)	54	27.3 (21.2, 34.0)
Patients with ventricular hypertrophy [1]	77	26.2 (21.3, 31.6)	20	20.8 (13.2, 30.3)	57	28.8 (22.6, 35.6)
Patients with hypokalemia [1]	71	24.1 (19.4, 29.5)	19	19.8 (12.4, 29.2)	52	26.3 (20.3, 33.0)
All of the above	178	60.5	61	63.5	117	59.1
None of the above	2	0.7	1	1.0	1	0.5
I don’t know	24	8.2	7	7.3	17	8.6
Question 22: What should you do in a patient with a QTc of more than 440 ms before starting TROBALT? (Please select the best response.)						
Recheck the ECG 1 week after the first dose	105	35.7	49	51.0	56	28.3
Recheck the ECG at monthly intervals	18	6.1	9	9.4	9	4.5
Recheck the ECG after reaching the maintenance dose [1]	132	44.9 (39.1, 50.8)	27	28.1 (19.4, 38.2)	105	53.0 (45.8, 60.1)
I don’t know	39	13.3	11	11.5	28	14.1

Question	All 7 Countries N=294		Germany N=96		6 Countries Excluding Germany N=198	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 23: Which new cardiac effects in particular should you warn your patients about after prescribing TROBALT?(Please select all that apply.)						
Syncope	20	6.8	7	7.3	13	6.6
Palpitations	16	5.4	9	9.4	7	3.5
Any other symptoms of arrhythmia	23	7.8	10	10.4	13	6.6
All of the above [1]	225	76.5 (71.3, 81.3)	71	74.0 (64.0, 82.4)	154	77.8 (71.3, 83.4)
None of the above	25	8.5	8	8.3	17	8.6

[1] Correct response.
[2] Question not presented to respondents with main residence in Switzerland.

8.5.2. Results from Germany

Table 8 above displays the responses by all eligible physicians to all questions related to the understanding of the risks associated with TROBALT for 96 physicians from Germany and responses by all eligible physicians from the 6 countries excluding Germany. The responses from German physicians mostly paralleled that for the physicians from the 6 countries excluding Germany. Responses to questions where the percentages for physicians from Germany were > 10% difference from that of physicians from the 6 countries excluding Germany are described below.

Fewer physicians from Germany understood that the recommended total initial dosage is not 150 mg/day for one week compared to physicians from the 6 countries excluding Germany (49.0% vs 66.2%, respectively), or understood that the maximum total daily dose at which TROBALT can be increased once every 7 days is 150 mg/day (60.4% vs. 78.8%, respectively). Fewer physicians from Germany understood that the quickest time by which the minimum maintenance dose of 600 mg should be reached is the third week compared to physicians from the 6 countries excluding Germany (53.1% vs. 73.7%, respectively).

Similar percentages of physicians from Germany compared to physicians from the 6 countries excluding Germany understood that patients taking TROBALT in clinical studies had a higher risk of experiencing confusional state and urinary retention. However, more physicians from Germany recalled those patients had a higher risk of experiencing hallucinations (66.7% vs. 50.5%, respectively) and psychotic disorders (67.7% vs. 47.5%, respectively). Fewer physicians from Germany understood that confusional state, hallucinations, and/or psychotic disorders from clinical studies

generally tended to be reported within the first 8 weeks after starting TROBALT (27.1% vs. 46.0%, respectively), as did voiding dysfunction (45.8% vs. 59.6%, respectively).

Fewer physicians from Germany compared to physicians from the 6 countries excluding Germany understood that TROBALT has been shown to produce a possible QT prolonging effect at 1200 mg (36.5% vs. 49.1%, respectively), or that they should recheck the ECG after reaching the maintenance dose for a patient who had a QTc > 440 ms prior to dosing (28.1% vs. 53.0%, respectively).

8.6. Other Analyses

Subgroup analyses were stratified by the countries as for the main analyses.

A subgroup analysis of the responses to the questions about the risks of TROBALT and the respondent characteristics were performed for the subgroup of prescribers who ever prescribed TROBALT.

Subgroups of interest were analysed only for the questions about the risks of TROBALT for the subgroups shown below with the physicians from all seven countries were combined.

- Gender (male vs. female)
- Length of time practicing medicine (< 3 years, 3-10 years, 11-20 years, > 20 years)
- Reading the TROBALT information letter (yes vs. no)
- Primary specialty (Neurology, Neurosurgery, Epileptology, Other)

8.6.1. Physicians Who Prescribed TROBALT

The respondent characteristics for the subgroup of prescribers (N = 144) who ever prescribed TROBALT and completed the survey are shown in Table 9. The percentage of prescribers who reported Neurology practice as their primary medical specialty paralleled that of all physicians who completed the survey (90.3 vs. 91.8%, respectively) (see Table 7). However, the percentage of physicians who ever prescribed TROBALT and specialised in Epileptology was double that for all physicians who completed the survey (9.7% vs. 4.8%, respectively). Most (80.6%) of the physicians who prescribed TROBALT read the TROBALT information letter that was sent to them and almost two-thirds (63.9%) learned about the risks of TROBALT via the launch letter compared to for all physicians who completed the survey (64.3% and 50.7%, respectively).

Table 9 Description of Survey Participants (Physicians who Prescribed TROBALT, only)

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	%	N	%	N	%
Question 24: How would you classify your primary medical specialty?						
Neurology	130	90.3	44	91.7	86	89.6
Neurosurgery	0	0.0	0	0.0	0	0.0
Epileptology	14	9.7	4	8.3	10	10.4
Other (specify) [1]	0	0.0	0	0.0	0	0.0
Question 25: Have you read the TROBALT information letter that was sent at the launch of TROBALT?						
Yes	116	80.6	30	62.5	86	89.6
No	18	12.5	12	25.0	6	6.3
I don't know	10	6.9	6	12.5	4	4.2
Question 26: From which of the following sources have you learned about the risks associated with use of TROBALT? (Please select all that apply.)						
TROBALT launch letter	92	63.9	19	39.6	73	76.0
GlaxoSmithKline medical information	69	47.9	19	39.6	50	52.1
Other health care professionals	29	20.1	12	25.0	17	17.7
GlaxoSmithKline promotional materials	55	38.2	12	25.0	43	44.8
GlaxoSmithKline sales representatives	72	50.0	11	22.9	61	63.5
Journal article	60	41.7	27	56.3	33	34.4
GlaxoSmithKline-sponsored educational meeting	22	15.3	4	8.3	18	18.8
None of the above	6	4.2	2	4.2	4	4.2
Question 27: What is your gender?						
Male	102	70.8	40	83.3	62	64.6
Female	42	29.2	8	16.7	34	35.4

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	%	N	%	N	%
Question 28: For how many years have you been in medical practice?						
Less than 3 years	2	1.4	0	0.0	2	2.1
3–5 years	9	6.3	5	10.4	4	4.2
6–10 years	30	20.8	12	25.0	18	18.8
11–15 years	33	22.9	12	25.0	21	21.9
16–20 years	25	17.4	10	20.8	15	15.6
More than 20 years	43	29.9	9	18.8	34	35.4
Prefer not to answer	2	1.4	0	0.0	2	2.1

[1] Other medical specialties are listed in Listing 1.

Results of the analysis of the responses by physicians who prescribed TROBALT to the questions related to the understanding of the risks associated with TROBALT are shown in Table 10.

Slightly higher, but similar, percentages of physicians who prescribed TROBALT understood the prescribing information compared to all physicians who completed the survey (Table 8 , Table 10).

Slightly higher, but similar, percentages of physicians who prescribed TROBALT compared to all physicians who completed the survey recalled about the risks reported in patients taking TROBALT in clinical studies. There were also slightly higher, but similar, percentages of physicians in both analyses who understood the risks for the CNS, urinary symptoms, and cardiac effects associated with TROBALT and appropriate dose titration may minimise the risk of CNS side effects. Similar percentages also understood the related ECG testing recommendations and warnings about new cardiac effects for patients to whom they prescribed TROBALT (Table 8 , Table 10).

Table 10 Responses to all Questions Related to Understanding Risks Associated with TROBALT (Physicians who Prescribed TROBALT, only)

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 6: For which of the following conditions is TROBALT approved for use?						
Migraine	0	0.0	0	0.0	0	0.0
Partial-onset seizures [1]	139	96.5 (92.1, 98.9)	46	95.8 (85.7, 99.5)	93	96.9 (91.1, 99.4)
All types of seizures	5	3.5	2	4.2	3	3.1
All of the above	0	0.0	0	0.0	0	0.0
None of the above	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 7: Is TROBALT indicated for use as monotherapy?						
Yes	6	4.2	3	6.3	3	3.1
No [1]	136	94.4 (89.3, 97.6)	45	93.8 (82.8, 98.7)	91	94.8 (88.3, 98.3)
I don't know	2	1.4	0	0.0	2	2.1
Question 8: What is the maximum recommended daily maintenance dose of TROBALT for most patients? (Please select the best response.)						
600 mg	12	8.4	4	8.3	8	8.4
900 mg	20	14.0	6	12.5	14	14.7
1200 mg [1]	104	72.7 (64.7, 79.8)	35	72.9 (58.2, 84.7)	69	72.6 (62.5, 81.3)
2000 mg	0	0.0	0	0.0	0	0.0
None of the above	1	0.7	0	0.0	1	1.1
I don't know	6	4.2	3	6.3	3	3.2
Question 9: Which one of the following statements is true? (Please select the best response.)						
TROBALT should be taken once a day.	4	2.8	1	2.1	3	3.1
TROBALT should be taken twice a day.	18	12.5	7	14.6	11	11.5
TROBALT should be taken three times a day [1]	121	84.0 (77.0, 89.6)	39	81.3 (67.4, 91.1)	82	85.4 (76.7, 91.8)
TROBALT should be taken four times a day.	0	0.0	0	0.0	0	0.0
None of the above	0	0.0	0	0.0	0	0.0
I don't know	1	0.7	1	2.1	0	0.0

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: When increasing the dose, what is the maximum total daily dose at which TROBALT can be increased once every 7 days? (Please select the best response.)						
50 mg	9	6.3	3	6.3	6	6.3
150 mg [1]	114	79.2 (71.6, 85.5)	29	60.4 (45.3, 74.2)	85	88.5 (80.4, 94.1)
300 mg	17	11.8	16	33.3	1	1.0
600 mg	4	2.8	0	0.0	4	4.2
None of the above	0	0.0	0	0.0	0	0.0
Question 11: Which one of the following statements is true? (Please select the best response.)						
There are no lower age limits for TROBALT usage.	3	2.1	1	2.1	2	2.1
The youngest age at which TROBALT can be used is 12.	12	8.3	4	8.3	8	8.3
The youngest age at which TROBALT can be used is 18. [1]	120	83.3 (76.2, 89.0)	42	87.5 (74.8, 95.3)	78	81.3 (72.0, 88.5)
I don't know	9	6.3	1	2.1	8	8.3
Question 12: The quickest time by which the minimum maintenance dose of 600 mg should be reached is the third week.						
True [1]	98	68.1 (59.8, 75.6)	26	54.2 (39.2, 68.6)	72	75.0 (65.1, 83.3)
False	39	27.1	18	37.5	21	21.9
I don't know	7	4.9	4	8.3	3	3.1
Question 13: For the general population, the recommended total initial dosage should be 150 mg per day for one week.						
True	49	34.0	22	45.8	27	28.1
False [1]	93	64.6 (56.2, 72.4)	25	52.1 (37.2, 66.7)	68	70.8 (60.7, 79.7)
I don't know	2	1.4	1	2.1	1	1.0

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: People taking TROBALT had a higher chance of experiencing which of the following risks in clinical studies? (Please select all that apply)						
Urinary retention [1]	107	74.3 (66.4, 81.2)	35	72.9 (58.2, 84.7)	72	75.0 (65.1, 83.3)
Confusional state [1]	102	70.8 (62.7, 78.1)	36	75.0 (60.4, 86.4)	66	68.8 (58.5, 77.8)
Hallucinations [1]	86	59.7 (51.2, 67.8)	36	75.0 (60.4, 86.4)	50	52.1 (41.6, 62.4)
Psychotic disorders [1]	80	55.6 (47.1, 63.8)	35	72.9 (58.2, 84.7)	45	46.9 (36.6, 57.3)
Myocardial infarction	2	1.4	1	2.1	1	1.0
Renal carcinoma	0	0.0	0	0.0	0	0.0
All of the above	6	4.2	1	2.1	5	5.2
None of the above	8	5.6	3	6.3	5	5.2
I don't know	3	2.1	1	2.1	2	2.1
Question 15: It is known from controlled studies that adverse events related to voiding dysfunction generally tend to be reported how soon after starting TROBALT?						
Within the first week	16	11.1	8	16.7	8	8.3
Within the first 8 weeks [1]	96	66.7 (58.3, 74.3)	24	50.0 (35.2, 64.8)	72	75.0 (65.1, 83.3)
After 4 months	1	0.7	1	2.1	0	0.0
After 12 months	0	0.0	0	0.0	0	0.0
I don't know	31	21.5	15	31.3	16	16.7
Question 16: It is known from controlled studies that confusional state, hallucinations, and/or psychotic disorders generally tend to be reported how soon after starting TROBALT?						
4 weeks	47	32.6	20	41.7	27	28.1
8 weeks [1]	60	41.7 (33.5, 50.2)	13	27.1 (15.3, 41.8)	47	49.0 (38.6, 59.4)
12 weeks	9	6.3	2	4.2	7	7.3
16 weeks	0	0.0	0	0.0	0	0.0
I don't know	28	19.4	13	27.1	15	15.6

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Which of the following urinary symptoms, if any, should you specifically advise patients taking TROBALT to watch out for? (Please select the best response.)						
Pain when urinating	1	0.7	1	2.1	0	0.0
Difficulty starting urination	22	15.3	12	25.0	10	10.4
Slow stream	1	0.7	1	2.1	0	0.0
Inability to pass urine	24	16.7	7	14.6	17	17.7
All of the above [1]	90	62.5 (54.1, 70.4)	24	50.0 (35.2, 64.8)	66	68.8 (58.5, 77.8)
None of the above	0	0.0	0	0.0	0	0.0
I don't know	6	4.2	3	6.3	3	3.1
Question 18: According to the TROBALT Physician's Guide, appropriate dose titration may minimize the risk of which of the following adverse events? (Please select the best response.)						
QT prolongation	17	11.8	7	14.6	10	10.4
CNS side effects such as hallucinations [1]	29	20.1 (13.9, 27.6)	10	20.8 (10.5, 35.0)	19	19.8 (12.4, 29.2)
Urinary retention	11	7.6	5	10.4	6	6.3
All of the above	70	48.6	18	37.5	52	54.2
None of the above	7	4.9	3	6.3	4	4.2
I don't know	10	6.9	5	10.4	5	5.2
Question 19: Using the Treatment Initiation Pack, by which week can the patient reach a dose of 600 mg/day? [2]						
2 weeks	16	11.6	8	16.7	8	8.9
3 weeks [1]	85	61.6 (52.9, 69.7)	26	54.2 (39.2, 68.6)	59	65.6 (54.8, 75.3)
4 weeks	30	21.7	12	25.0	18	20.0
5 weeks	1	0.7	0	0.0	1	1.1
None of the above	6	4.3	2	4.2	4	4.4
Question 20: At what dose has TROBALT been shown to produce a possible QT prolonging effect? [2]						
600 mg	10	7.2	0	0.0	10	11.1
900 mg	9	6.5	7	14.6	2	2.2
1200 mg [1]	70	50.7 (42.1, 59.3)	17	35.4 (22.2, 50.5)	53	58.9 (48.0, 69.2)
1800 mg	9	6.5	5	10.4	4	4.4
I don't know	40	29.0	19	39.6	21	23.3

Question	All 7 Countries N=144		Germany N=48		6 Countries Excluding Germany N=96	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 21: For which patients is it recommended that an ECG is recorded before initiating TROBALT? (Please select all that apply.)						
Patients with hypertension	4	2.8	2	4.2	2	2.1
Patients with congestive heart failure [1]	36	25.0 (18.2, 32.9)	8	16.7 (7.5, 30.2)	28	29.2 (20.3, 39.3)
Patients with ventricular hypertrophy [1]	39	27.1 (20.0, 35.1)	9	18.8 (8.9, 32.6)	30	31.3 (22.2, 41.5)
Patients with hypokalemia [1]	34	23.6 (16.9, 31.4)	9	18.8 (8.9, 32.6)	25	26.0 (17.6, 36.0)
All of the above	95	66.0	34	70.8	61	63.5
None of the above	1	0.7	1	2.1	0	0.0
I don't know	4	2.8	1	2.1	3	3.1
Question 22: What should you do in a patient with a QTc of more than 440 ms before starting TROBALT? (Please select the best response.)						
Recheck the ECG 1 week after the first dose	56	38.9	28	58.3	28	29.2
Recheck the ECG at monthly intervals	8	5.6	4	8.3	4	4.2
Recheck the ECG after reaching the maintenance dose [1]	67	46.5 (38.2, 55.0)	11	22.9 (12.0, 37.3)	56	58.3 (47.8, 68.3)
I don't know	13	9.0	5	10.4	8	8.3
Question 23: Which new cardiac effects in particular should you warn your patients about after prescribing TROBALT? (Please select all that apply)						
Syncope	10	6.9	5	10.4	5	5.2
Palpitations	11	7.6	7	14.6	4	4.2
Any other symptoms of arrhythmia	12	8.3	6	12.5	6	6.3
All of the above [1]	111	77.1 (69.3, 83.7)	35	72.9 (58.2, 84.7)	76	79.2 (69.7, 86.8)
None of the above	8	5.6	2	4.2	6	6.3

[1] Correct response.
[2] Question not presented to respondents with main residence in Switzerland.

8.6.2. Reading the TROBALT Information Letter

The subgroup analysis of physicians who read the TROBALT information letter (N = 189) compared to those who did not read the TROBALT information letter (or did not know if they read it) (N = 105) was performed on the subgroup of all prescribers who

ever prescribed TROBALT. The results of the analysis of responses to all questions related to the understanding the risks associated with TROBALT for this subgroup analysis are shown in Table 11.

Overall, physicians who read the TROBALT information letter recalled more correct information regarding the use of TROBALT and its associated risks. Similar percentages of physicians in both groups understood that TROBALT is indicated for partial-onset seizures (within 7%), that dose titration may result in decreased hallucinations (within 8%), and that they should advise their patients about possible new cardiac side effects (within 5%).

The largest percentage differences in the ability to recall information between the physicians who read the TROBALT information letter and those that did not (or did not know if they read it) were: that TROBALT should be taken three times a day (85.2% vs. 54.3%, respectively), that AEs related to voiding dysfunction generally were reported within the first 8 weeks after starting TROBALT (67.2% vs. 33.3%, respectively), and that they should recheck the ECG after reaching the maintenance dose for a patient who had a QTc >440 ms prior to dosing (56.1% vs. 24.8%, respectively).

Table 11 Responses to all Questions Related to the Understanding Risks Associated with TROBALT (Subgroup Analysis 3: Reading the TROBALT Information Letter)

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 6: For which of the following conditions is TROBALT approved for use?				
Migraine	1	0.5	1	1.0
Partial-onset seizures [1]	178	94.2 (89.8, 97.1)	91	86.7 (78.6, 92.5)
All types of seizures	7	3.7	4	3.8
All of the above	2	1.1	1	1.0
None of the above	1	0.5	2	1.9
I don't know	0	0.0	6	5.7
Question 7: Is TROBALT indicated for use as monotherapy?				
Yes	6	3.2	10	9.5
No [1]	178	94.2 (89.8, 97.1)	81	77.1 (67.9, 84.8)
I don't know	5	2.6	14	13.3

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 8: What is the maximum recommended daily maintenance dose of TROBALT for most patients? (Please select the best response.)				
600 mg	12	6.4	4	3.8
900 mg	19	10.1	9	8.6
1200 mg [1]	146	77.7 (71.0, 83.4)	54	51.4 (41.5, 61.3)
2000 mg	0	0.0	1	1.0
None of the above	2	1.1	1	1.0
I don't know	9	4.8	36	34.3
Question 9: Which one of the following statements is true? (Please select the best response.)				
TROBALT should be taken once a day.	7	3.7	9	8.6
TROBALT should be taken twice a day.	19	10.1	14	13.3
TROBALT should be taken three times a day [1]	161	85.2 (79.3, 89.9)	57	54.3 (44.3, 64.0)
TROBALT should be taken four times a day.	0	0.0	0	0.0
None of the above	0	0.0	0	0.0
I don't know	2	1.1	25	23.8
Question 10: When increasing the dose, what is the maximum total daily dose at which TROBALT can be increased once every 7 days? (Please select the best response.)				
50 mg	17	9.0	13	12.4
150 mg [1]	152	80.4 (74.0, 85.8)	62	59.0 (49.0, 68.5)
300 mg	15	7.9	20	19.0
600 mg	4	2.1	3	2.9
None of the above	1	0.5	7	6.7

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 11: Which one of the following statements is true? (Please select the best response.)				
There are no lower age limits for TROBALT usage.	5	2.6	5	4.8
The youngest age at which TROBALT can be used is 12.	11	5.8	7	6.7
The youngest age at which TROBALT can be used is 18. [1]	165	87.3 (81.7, 91.7)	65	61.9 (51.9, 71.2)
I don't know	8	4.2	28	26.7
Question 12: The quickest time by which the minimum maintenance dose of 600 mg should be reached is the third week?				
True [1]	141	74.6 (67.8, 80.6)	56	53.3 (43.3, 63.1)
False	38	20.1	24	22.9
I don't know	10	5.3	25	23.8
Question 13: For the general population, the recommended total initial dosage should be 150 mg per day for one week.				
True	62	32.8	27	25.7
False [1]	121	64.0 (56.7, 70.9)	57	54.3 (44.3, 64.0)
I don't know	6	3.2	21	20.0

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 14: People taking TROBALT had a higher chance of experiencing which of the following risks in clinical studies? (Please select all that apply.)				
Urinary retention [1]	140	74.1 (67.2, 80.2)	50	47.6 (37.8, 57.6)
Confusional state [1]	140	74.1 (67.2, 80.2)	55	52.4 (42.4, 62.2)
Hallucinations [1]	116	61.4 (54.0, 68.4)	48	45.7 (36.0, 55.7)
Psychotic disorders [1]	112	59.3 (51.9, 66.3)	47	44.8 (35.0, 54.8)
Myocardial infarction	5	2.6	3	2.9
Renal carcinoma	0	0.0	0	0.0
All of the above	7	3.7	4	3.8
None of the above	6	3.2	6	5.7
I don't know	7	3.7	30	28.6
Question 15: It is known from controlled studies that adverse events related to voiding dysfunction generally tend to be reported how soon after starting TROBALT?				
Within the first week	16	8.5	16	15.2
Within the first 8 weeks [1]	127	67.2 (60.0, 73.8)	35	33.3 (24.4, 43.2)
After 4 months	1	0.5	2	1.9
After 12 months	0	0.0	0	0.0
I don't know	45	23.8	52	49.5
Question 16: It is known from controlled studies that confusional state, hallucinations, and/or psychotic disorders generally tend to be reported how soon after starting TROBALT?				
4 weeks	54	28.6	22	21.0
8 weeks [1]	92	48.7 (41.4, 56.0)	25	23.8 (16.0, 33.1)
12 weeks	10	5.3	3	2.9
16 weeks	0	0.0	2	1.9
I don't know	33	17.5	53	50.5

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 17: Which of the following urinary symptoms, if any, should you specifically advise patients taking TROBALT to watch out for? (Please select the best response.)				
Pain when urinating	1	0.5	3	2.9
Difficulty starting urination	33	17.5	18	17.1
Slow stream	1	0.5	0	0.0
Inability to pass urine	32	16.9	14	13.3
All of the above [1]	118	62.4 (55.1, 69.4)	45	42.9 (33.2, 52.9)
None of the above	0	0.0	1	1.0
I don't know	4	2.1	24	22.9
Question 18: According to the TROBALT Physician's Guide, appropriate dose titration may minimize the risk of which of the following adverse events? (Please select the best response.)				
QT prolongation	20	10.6	15	14.3
CNS side effects such as hallucinations [1]	44	23.3 (17.5, 30.0)	16	15.2 (9.0, 23.6)
Urinary retention	11	5.8	10	9.5
All of the above	94	49.7	34	32.4
None of the above	9	4.8	1	1.0
I don't know	11	5.8	29	27.6
Question 19: Using the Treatment Initiation Pack, by which week can the patient reach a dose of 600 mg/day? [2]				
2 weeks	23	13.0	11	11.7
3 weeks [1]	111	62.7 (55.1, 69.9)	42	44.7 (34.4, 55.3)
4 weeks	33	18.6	27	28.7
5 weeks	3	1.7	4	4.3
None of the above	7	4.0	10	10.6

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 20: At what dose has TROBALT been shown to produce a possible QT prolonging effect? [2]				
600 mg	17	9.6	1	1.1
900 mg	8	4.5	8	8.5
1200 mg [1]	96	54.2 (46.6, 61.7)	25	26.6 (18.0, 36.7)
1800 mg	10	5.6	4	4.3
I don't know	46	26.0	56	59.6
Question 21: For which patients is it recommended that an ECG is recorded before initiating TROBALT? (Please select all that apply.)				
Patients with hypertension	3	1.6	2	1.9
Patients with congestive heart failure [1]	55	29.1 (22.7, 36.1)	21	20.0 (12.8, 28.9)
Patients with ventricular hypertrophy [1]	61	32.3 (25.7, 39.4)	16	15.2 (9.0, 23.6)
Patients with hypokalemia [1]	57	30.2 (23.7, 37.2)	14	13.3 (7.5, 21.4)
All of the above	118	62.4	60	57.1
None of the above	0	0.0	2	1.9
I don't know	3	1.6	21	20.0
Question 22: What should you do in a patient with a QTc of more than 440 ms before starting TROBALT? (Please select the best response.)				
Recheck the ECG 1 week after the first dose	62	32.8	43	41.0
Recheck the ECG at monthly intervals	11	5.8	7	6.7
Recheck the ECG after reaching the maintenance dose [1]	106	56.1 (48.7, 63.3)	26	24.8 (16.9, 34.1)
I don't know	10	5.3	29	27.6

Question	S3-a Read N=189		S3-b Not Read/I don't know N=105	
	N	% (95% CI)	N	% (95% CI)
Question 23: Which new cardiac effects in particular should you warn your patients about after prescribing TROBALT? (Please select all that apply.)				
Syncope	11	5.8	9	8.6
Palpitations	8	4.2	8	7.6
Any other symptoms of arrhythmia	15	7.9	8	7.6
All of the above [1]	148	78.3 (71.7, 84.0)	77	73.3 (63.8, 81.5)
None of the above	15	7.9	10	9.5

[1] Correct response.
[2] Question not presented to respondents with main residence in Switzerland.

8.7. Adverse Events/Adverse Reactions

No AEs were reported by eligible physicians who completed the survey.

9. DISCUSSION

9.1. Key results

The physician survey was undertaken to evaluate the understanding of the significant risks associated with TROBALT and to evaluate the effectiveness of the educational plan as specified in the European RMP. The physician respondent survey was conducted across 7 European countries. A higher response rate was received from Germany, Spain, and the UK than from Denmark, Switzerland, Slovakia, and Norway. Of the 301 prescribers who completed the survey, 294 (97.7%) were considered eligible for analysis. The majority of physicians were neurologists (91.8%).

Indication for use: Almost all (91.5%) physicians surveyed recalled that TROBALT is approved for use in partial-onset seizures, but only three-quarters (78.2%) recalled that it can only be prescribed to patients who are at least 18 years of age. Most (88.1%) understood that TROBALT is not indicated for monotherapy.

Dose-related questions: Approximately three-quarters (74.1%) of physicians surveyed from all countries recalled that TROBALT should be taken three times per day. Almost three-quarters (72.8%) recalled that TROBALT can only be increased by 150 mg/day every 7 days. Slightly more than half (56.5%) of physicians recalled that a patient can reach dose the minimum maintenance of 600 mg/day by 3 weeks using the Treatment Initiation Pack. A modest percentage (68.3%) of physicians surveyed from all countries recalled that the maximum recommended dose of TROBALT is 1200 mg.

CNS side effects related questions: Two thirds (66.3%) of physicians surveyed from all countries recalled that patients taking TROBALT in clinical studies had a higher risk of experiencing confusional state. However, only slightly more than half recalled patients had a higher risk of experiencing hallucinations (55.8%) and psychotic disorders (54.1%). A small percentage (39.8%) recalled that these symptoms were reported within the first 8 weeks after starting treatment with TROBALT. Fewer (20.4%) recalled that appropriate dose titration may minimise the risk of CNS side effects.

Urinary symptom related questions: Slightly less than two-thirds of physicians surveyed from all countries recalled that patients taking TROBALT in clinical studies had a higher risk of experiencing urinary retention (64.6%). About half (55.4%) of these physicians recalled that they should specifically advise their patients taking TROBALT about all of the (including pain when urinating, difficulty starting urination, slow stream, and inability to pass urine). Approximately the same percentage (55.1%) recalled that AEs related to voiding dysfunction were reported within the first 8 weeks after starting treatment with TROBALT.

Cardiac-related questions: Overall, physicians had a lower recall of information regarding the cardiac risks associated with TROBALT. Less than half (44.6%) recalled that TROBALT has been shown to produce a possible QT prolongation at 1200 mg. Few physicians recalled that it is recommended to perform an ECG on patients with CHF (25.9%), ventricular hypertrophy (26.2%), and hypokalemia (24.1%). Almost half (44.9%) recalled that the ECG should be rechecked after reaching the maintenance dose in patients who had a QTc interval of > 400 ms before starting TROBALT. However, more (76.5%) physicians recalled that they should warn patients to whom they prescribed TROBALT about new cardiac effects of syncope, palpitations, and any other symptoms of arrhythmia.

In addition to all physicians from all countries and those specifically from Germany, two subgroup analyses were conducted to see if there was a difference in understanding these risks in subgroups of only physicians who prescribed TROBALT and whether or not they read the TROBALT information letter. In general, sub-group analyses showed that physicians who read the TROBALT information letter and those who had prescribed TROBALT both had better recall of the information regarding the use of TROBALT in patients with partial-onset seizures and the risks associated with its use that those that did not read the TROBALT information letter or prescribe TROBALT.

9.2. Limitations

This was a voluntary survey and therefore, the sample while selected randomly, may not be representative of all physicians who prescribe TROBALT. In addition, the survey was conducted concurrently with the educational materials being sent, and therefore could represent a possible bias to the physicians previous understanding of the risks associated with TROBALT.

9.3. Interpretation

The survey showed that overall physicians (both prescribers and those who had never prescribed TROBALT) had an adequate knowledge of indication for use of TROBALT. The majority (91.5%) of eligible physicians from all seven countries understood that TROBALT is approved for use in partial-onset seizures, and three-quarters (78.2%) recalled that it can only be prescribed to patients who are at least 18 years of age. Most (88.1%) recalled that TROBALT is not indicated for monotherapy.

Specific dose related knowledge was not the primary objective of this survey, but it was noted that this was less well recalled.

Approximately one half to two thirds of eligible physicians recalled that patients taking TROBALT had a higher risk of experiencing specific Central Nervous System (CNS) adverse events and urinary retention.

Less than half of eligible physicians recalled an association between TROBALT and possible QT prolongation, although 76.5% of eligible physicians recalled that they should warn patients to whom they prescribed TROBALT about new cardiac effects of syncope, palpitations, and any other symptoms of arrhythmia.

There was a low level of awareness of much of the detail of specific management of individual risks, e.g.20.4% of eligible physicians recalled that appropriate dose titration may minimise the risk of CNS side effects; 25.9% of eligible physicians recalled that it is recommended to perform an ECG on patients with congestive heart failure.

Despite Germany accounting for approximately one third of physicians, results were reasonably comparable to the other 6 countries.

In general, physicians who had prescribed TROBALT and/or read the TROBALT information letter had better recall of the information regarding the use of TROBALT.

Overall, there is awareness, to varying degrees, of the risks associated with the use of TROBALT. GlaxoSmithKline needs to build on this and strengthen risk minimisation activities to improve the understanding of these risks.

9.4. Generalisability

This was a voluntary survey and therefore, the sample while selected randomly, may not be representative of all physicians who prescribe TROBALT. Since the survey was conducted concurrently with the educational materials being sent, it may not be representative of all physicians who prescribe TROBALT and did not receive the educational materials.

10. OTHER INFORMATION

None.

11. CONCLUSIONS

The survey showed that overall physicians (both prescribers and those who had never prescribed TROBALT) had an adequate knowledge of indication for use of TROBALT, although specific dose related knowledge, which was not a primary survey objective, was much less well recalled.

Fewer eligible physicians recalled that patients taking TROBALT had a higher risk of experiencing specific CNS adverse events and urinary retention and less again recalled an association between TROBALT and possible QT prolongation.

Knowledge was limited on much of the detail of specific management of the individual risks.

The survey targeted neurologists and a subgroup of neurologists commonly referred to as 'epileptologists' who were known from past experience to be the specialists who first initiated prescriptions of a new AEDs. 94.9% of these eligible physicians had prescribed an AED less than a month ago, but approximately half had ever prescribed TROBALT. Within this prescriber subgroup it is unknown how recent their prescribing experience was with retigabine. It would be expected that prescribers with recent experience would have better recall of risks.

Although the response rate between Germany and the rest of the sampled countries were similar, subsequent to survey data collection, TROBALT was withdrawn in Germany. Therefore, these results may not best reflect the current situation as approximately a third of physician respondents came from Germany.

After reviewing the data, GSK believes the survey met the goal of assessing effectiveness of the risk minimisation measures.

The survey results indicate a mixed physician recall of the main known risks associated with TROBALT ranging from adequate to limited recall. The conclusion is that the risk minimisation activities for retigabine should be strengthened.

GlaxoSmithKline have since commenced another EU (including other countries outside the EU and USA) Survey to assess the effectiveness of the communication of specific risks associated with the use of retigabine. This will address a different selection of countries and include stratification by last prescription time period. Once the results from this second survey are available, GlaxoSmithKline will interrogate the data both in aggregate and at an individual question level to examine the effectiveness of the risk minimisation measures and propose the most suitable enhancements to the risk minimisation activities for the use of retigabine outside the USA REMS programme.

12. REFERENCES

None.

13. APPENDICES

13.1. Appendix 1: LISTING OF VERBATIM RESPONSES AND THEIR CORRESPONDING COUNTS OF PRESCRIBERS TO QUESTION 24 (OTHER MEDICAL SPECIALTIES)

Verbatim Response	Count of Prescribers
Neurorehabilitation	2
Paediatrics (epilepsy)	1
Neurology/rehabilitation	1
Psychiatrie	1
Neurologia Infantil	1
Neuropediatria	1

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	*2011N121226_03*	*09-Dec-2013*	*European Survey of Patient and Prescriber Understanding of Risks Associated with* *TROBALT™*