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STUDY TITLE

Pregnancy Prevention Program Section of the Risk Management Plan for Soriatane® (acitretin): Survey to Assess Physician and Pharmacist Understanding of the Risk of Teratogenicity Associated with Soriatane

Version 1.0,
DATE: 18 August 2017

Protocol Number:	CMO-EPI-DERM-0527
Serious Adverse Event Reporting Fax Number(s):	+1-714-796-9504 (Back Up Fax No.: +1-714-246-5295)
Serious Adverse Event Reporting e-mail address:	IR-Clinical-SAE@allergan.com
Allergan Medical Safety Physician Contact Information:	Gina Gao, MD Tel (office): +1-908-203-2707 Tel (mobile): +1-908-655-1789 Fax: +1-908-203-2282 or 2285 Email: Gina.Gao@Allergan.com

PASS Information

Title	Pregnancy Prevention Program Section of the Risk Management Plan for Soriatane® (acitretin): Survey to Assess Physician and Pharmacist Understanding of the Risk of Teratogenicity Associated with Soriatane
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Medicinal product	SORIATANE®
Submission eCTD Number	e124355
Submission Control Number	195069
Marketing authorization holder(s) (MAH)	Name: Allergan Inc. Address: 2525 Dupont Drive, Irvine, CA 92612 Phone No.: +1-714-246-4500; +1-800-347-4500
Joint PASS	No
Research question and objectives	The purpose of this survey study, in response to the PPP section of the Risk Management Plan (RMP) (Checklist 3d), is to understand: • How physicians prescribe Soriatane • What teratogenicity risks physicians and pharmacists are aware of and communicate to women of childbearing potential • What strategies they use to minimize the likelihood of pregnancy among women of childbearing potential • Their awareness and use of existing educational materials regarding appropriate prescription and dispensing of Soriatane
Country(-ies) of study	Canada
Author	Mei Sheng Duh, MPH, ScD Managing Principal and Chief Epidemiologist Analysis Group Inc. 111 Huntington Avenue 14th Floor Boston, MA 02199

Marketing Authorization Holder(s)

MAH(s)	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500
MAH contact person	Anupama Patil Telephone: +1-800-668-6424 Ext. 7355 E-mail: Anupama.Patil@Allergan.com

Approval Page, Allergan

Project Title:	Pregnancy Prevention Program Section of the Risk Management Plan for Soriatane® (acitretin): Survey to Assess Physician and Pharmacist Understanding of the Risk of Teratogenicity Associated with Soriatane
Protocol ID Number	Anupama Patil Telephone: +1-800-668-6424 Ext. 7355 E-mail: Anupama.Patil@Allergan.com
Effective Date	18 August 2017
Author	Mei Sheng Duh, MPH, ScD Managing Principal and Chief Epidemiologist Analysis Group Inc. 111 Huntington Avenue 14th Floor Boston, MA 02199
Version	1.0

The following people have reviewed the protocol and give their approval:

Allergan

DocuSigned by:
Cheryl Watton
83BD11B0E7D6490...

August 21, 2017

Cheryl Watton, MD, MBA *Signature* Date
VP, Head of Global Patient Safety & Epidemiology (GPSE)

DocuSigned by:
Anita Verga
31FAC1B62FF448D...

August 21, 2017

Anita Bhagroo Verga, DrPH *Signature* Date
Executive Director, Epidemiology
Global Patient Safety & Epidemiology (GPSE)

DocuSigned by:
Ilse Sjoholm
988B74186A1B4A2...

August 21, 2017

Ilse Sjoholm, MScPharm *Signature* Date
Associate VP, EU QPPV
Global Patient Safety & Epidemiology (GPSE)

1. Table of Contents

2. List of Abbreviations

Term/Abbreviation	Definition
PPP	Pregnancy Prevention Program
RMP	Risk Management Plan
GP	General Practitioners
CI	Confidence Interval
SSL	Secure Socket Layer
ADR	Adverse Drug Reaction
AE	Adverse Event
eCRF	electronic Case Report Form
ICF	Informed Consent Form
IEC	Independent Ethics Committee
MAH	Marketing Authorisation Holder
NIS	Non-interventional Study

3. Responsible Parties

Name	Address	Title & Affiliation
Mei Sheng Duh, MPH, ScD	111 Huntington Avenue 14th Floor Boston, MA 02199	Managing Principal and Chief Epidemiologist, Analysis Group, Inc.
Brian Ellman, MBA	111 Huntington Avenue 14th Floor Boston, MA 02199	Vice President, Analysis Group, Inc.
Lynn Huynh, MPH, MBA, DrPH	111 Huntington Avenue 14th Floor Boston, MA 02199	Manager, Analysis, Group Inc.

4. Abstract

Study Title: Pregnancy Prevention Program Section of the Risk Management Plan for Soriatane® (acitretin): Survey to Assess Physician and Pharmacist Understanding of the Risk of Teratogenicity Associated with Soriatane

Version 1.0 Date: 18 August 2017

Main Protocol Author: Mei Sheng Duh, MPH, ScD, Analysis Group, Inc.

Rationale and background:

To address Health Canada's request, Analysis Group, Inc. (AGI) and BioTrak propose to assist Allergan in developing and conducting a one-time health care provider study which includes two surveys, one for targeted physician specialists and one for pharmacists, to evaluate the extent of their base knowledge of teratogenic risk associated with Soriatane® (acitretin) use among females of childbearing potential, and to further evaluate the necessity of additional educational materials for Canadian physicians and pharmacists regarding appropriate prescription and dispensing of oral retinoid products (Checklist 3d). The results of this research will inform the appropriate next step regarding the Pregnancy Prevention Program (PPP) program for Allergan.

Research question and objectives:

The purpose of this survey study, in response to the PPP section of the Risk Management Plan (RMP) (Checklist 3d), is to understand:

- How physicians prescribe Soriatane
- What teratogenicity risks physicians and pharmacists are aware of and communicate to women of childbearing potential
- What strategies they use to minimize the likelihood of pregnancy among women of childbearing potential
- Their awareness and use of existing educational materials regarding appropriate prescription and dispensing of Soriatane

Study design:

This is a one-time survey study of Canadian physicians and pharmacists. Two separate survey questionnaires will be developed for physicians and pharmacists, respectively. AGI and BioTrak propose to conduct these brief surveys in two phases: pre-test and full launch.

The Pretest Phase

Survey pretesting is used to evaluate the readability and interpretation of each survey comprehension question. This involves pretesting and functionality testing of the internet-hosted survey tool, including the electronic data-capture system. In addition, the pretesting is performed

to determine if any question performance problems are related to clarity of wording versus respondent understanding.

From Allergan's list of physicians and pharmacists for the pretest phase, it is expected that at least 10 physicians and 10 pharmacists (20 in total) will agree to pretest the survey questionnaires. A multimodal approach of email, mail, or fax will be taken to recruit physicians and pharmacists. Physicians and pharmacists will be given the option of completing the survey online (in English or French) or via telephone operator support (in English only). Physicians and pharmacists will log into the internet survey using the unique survey code found on their survey invitation flyer or use the telephone-supported survey option to test for readability and comprehension of the questionnaires. Qualified participants may complete the survey one time only. It is anticipated that it will take approximately 4 weeks to complete the pre-test phase. Based on the results from the pretest phase, revisions to the survey questionnaires will be made as required. Approval from Allergan of the final questionnaire will be obtained before embarking the full launch phase.

After receiving Allergan's approval of the protocol and survey instruments, AGI and BioTrak will first pre-test the survey instruments for understandability.

Respondents will complete the online survey and will then be asked to rate each survey question for clarity on a scale of 1 to 6, with 1 = very clear, very easy to understand, 2 = Clear, easy to understand, 3 = Somewhat clear, somewhat understandable, 4 = Somewhat unclear, somewhat difficult to understand, 5 = Unclear, difficult to understand, and 6 = very unclear, very difficult to understand. Respondents will then be asked to review the correct answer options for each question and respond to open-ended questions evaluating the clarity of comprehension questions.

Another pre-testing measure is the level of respondent burden when taking the surveys as determined by the range of the median time for survey completion and the time-to-completion for 80% of the respondents. The number of questions will be considered for its contribution to survey duration. Long surveys may lead to a higher risk of survey incompleteness and a low response rate. The pretesting data will be compiled into report form including suggested reduction of questions and survey language changes if required.

The Full Launch Phase

The study procedure will consist of recruiting prescribers and dispensers of Soriatane in Canada to participate in a voluntary online survey. The expected duration of the survey fielding will be 8-12 weeks. Results of each survey will be analyzed and reported in aggregate.

The survey instrument will be available in electronic format and made accessible via the internet. The survey instrument will be confidential and securely hosted online. The online survey platform will include PharmaTrak™ Viewer, a perpetually updated web statistics feature for internet-hosted surveys that includes summary statistics of enrollment and individual question performance or profiles. This online summary statistics viewer permits continuous assessment of the survey performance for any ad-hoc interval period.

The contact list is projected to contain a combined total of at least 3,000 prescribers ("physicians") and intended dispensing pharmacists. It is anticipated that all physicians and pharmacists on the list will be invited in order to achieve the targeted sample size (N=200 physicians and N=200 pharmacists). To increase the response rate, four physician key opinion leaders will assist in the recruitment effort. Their names will be included in the survey invitation letter. Allergan will provide AGI and BioTrak with the names of the key opinion leaders.

Recruitment will be achieved by sending a unique coded survey invitation to physicians and pharmacists via a multimodal approach consisting of email, mail and/or fax. Physicians and pharmacists will be given the option of completing the survey online (in English or French) or via telephone operator support (in English only). Physicians and pharmacists will log into the internet survey using the unique survey code found on their survey invitation flyer or use the telephone-supported survey option. For participants who use telephone support, a PHIPA (Personal Health Information Protection Act) compliant call operator will be available during business hours (7:30am-4:30pm PST) to support "keying in" participant responses using the online hosted survey. This approach eliminates paper records and keeps survey summary web statistics up-to-date. Participants will be asked to read and accept an informed consent statement if taking the survey online; alternatively, participants will be consented over the phone. Allergan will be blinded to the names of the survey participants.

All respondents will be informed that they may only take the survey one time. After the qualified participants have successfully completed the survey, they will receive a message informing them that they have successfully completed the survey, and that a participant fee will be mailed 2-3 weeks after completion. Physicians will be offered a participation fee of $150 Canadian, and Pharmacists $75 Canadian. Duplicity of name and address will be checked prior to issuing the participation fees. Respondents who procure more than one survey code and complete the survey more than once will have their new survey data removed from the data file (based upon an audit by BioTrak). If feasible, BioTrak will also review the target list prior to survey mailings to minimize the chance of sending out more than one survey code to each physician and pharmacist.

The online survey formats are designed such that questions need to be answered before the respondent can advance to the next question and complete the survey. The survey will not allow physicians or pharmacists to go back to previous questions in the survey once the arrow button is clicked to move on to the next question. The online survey will timeout after 60 minutes of idle time, a message will be displayed informing them that the survey has closed due to inactivity. If they would like to complete the survey they will need to contact BioTrak via email to receive a new code to access and complete the survey. Data from respondents who do not complete the survey (partially completed surveys) will be removed from the data file. The frequency of survey drop-outs will be reported.

For non-responders (i.e., physicians/pharmacists who do not respond to the initial attempt of recruitment), a proposed tiered-sequential approach will be taken to obtain responses. The approach involves sending out follow-up reminders via email or fax approximately 1 week after

the initial survey invitation. Up to four attempts will be made to send out follow-up reminders to non-responders. In the invitation letter, physicians and pharmacists will be able to opt out from additional attempts to obtain responses.

Once the survey questionnaires have been finalized based on pretest findings, AGI and BioTrak will move forward with the full study launch.

Population:

The two surveys are designed to be completed by the physicians which include dermatologists, general practitioners/family physicians with focused practice designation in dermatology (GP derms), and pharmacists in Canada. Specifically, the key group of interest consists of doctors who prescribe Soriatane to the greatest at-risk group (women of childbearing potential) and pharmacists who dispense Soriatane. The target list of all dermatologists and GP derms consists of approximately 1,073 individuals in Canada and the target list for pharmacists consists of approximately 1,822 individuals who are licensed pharmacists.

Allergan will provide a list of physicians and pharmacists with complete contact information (i.e., phone number, email address, fax, and postal address) to AGI and BioTrak for the pretest phase. For the full launch phase, a full list of approximately 3,000 physicians and pharmacists with contact information (i.e., phone number, email address, fax, and postal address) will be used.

Variables:

The Soriatane **physician** survey will incorporate the following key measures:

- Key Measure 1: To determine the knowledge the current prescribing practices of Soriatane in females of childbearing potential
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women.
- Key Measure 3: To determine if Soriatane is appropriately prescribed in females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and distribution of patient informational materials to patients.
- Key Measure 4: Awareness and use of patient educational materials including adherence to the Soriatane PPP.

The Soriatane **pharmacist** survey will incorporate the following key measures:

- Key Measure 1: To determine the current dispensing practices of Soriatane in females of childbearing potential
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women.

- Key Measure 3: To determine if Soriatane is not dispensed to pregnant women and if it is appropriately dispensed to females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and dispensing of patient informational materials to patients.

Data sources:

This is a one-time survey study of Canadian physicians and pharmacists. Two separate survey questionnaires will be administered to physicians and pharmacists, respectively.

Study size:

A source population of approximately 3,000 Canadian physicians and pharmacists on the contact list provided will be invited to participate in the survey.

The target sample size is 200 physicians and 200 pharmacists. Once the survey sample size of N=200 for each survey is achieved, the survey will close and no additional survey respondents will be accepted. Physicians and pharmacists who attempt to access the survey once it is closed, will see a message thanking them for their time and notifying them that the survey has reached its maximum number of responses and is now closed. This sample size will provide a 6% confidence interval bound around the 80% correct response rate based on a binomial distributional assumption. Confidence interval bounds around the 80% correct response rate for a target sample size of 100 and 50 are provided in Appendix 4.

Data analysis:

All completed surveys will be analyzed. Partially completed surveys will not be analyzed, however, the frequency of survey drop-outs will be reported.

The Pretest Phase

There will be a descriptive analysis of the demographic data and other information collected from each respondent. Examples of information collected from the respondent include clinical practice, region, and current use of Soriatane. A summary description on the clarity and comprehension of each question will be summarized.

Based on pretest results, if required, the survey methodologists will revise the draft survey instrument for the full launch phase.

The Full Launch Phase – Survey Fielding

Summary statistics will be provided for physicians and pharmacists. In reporting the summary measures, categorical variables will be summarized using frequency and relative percentage and continuous variables will be described using the mean (standard deviation [SD]) and median (interquartile range [IQR]). For questions involving "All", "Most", "Some", and "None" as response options, the frequency of responses and distributions will be reported. Depending on the correct response rates of the physicians and pharmacists, root cause analysis may be conducted to identify factors associated with low correct scores.

Milestones:

Milestone	Planned date
Start of data collection	24 July 2017
End of data collection	31 October 2017
Final report of study results	29 December 2017

Results of the survey based on the key measures will assist in determining the effectiveness of the current PPP and determine if modification of existing educational materials or development of new materials are required for physicians and/or pharmacists to better achieve risk minimization.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection	24 July 2017
End of data collection	31 October 2017
Final report of study results	29 December 2017

7. Rationale and Background

Soriatane® (acitretin) was approved in 1994 by Health Canada for the treatment of severe psoriasis (including erythrodermic and pustular types) and other disorders of keratinization. It is the only antipsoriatic retinoid drug available for systemic use in Canada. Some known common and rare side effects include cheilitis, skin dryness and peeling, pruritus, nose bleeds, dry eyes, headache, alopecia, nail dystrophy, nausea, mood changes, including depression, hyperlipidemia, diffuse idiopathic skeletal hyperostosis, pancreatitis, leukopenia, toxic hepatitis, myopathy, pseudotumor cerebri, reduced night vision and retinoic acid syndrome. As a class, retinoids are teratogenic and strictly contraindicated in pregnancy. They are not to be administered to women of childbearing potential unless they are able and willing to use contraception one month before, during Soriatane therapy and for 3 years after discontinuation of Soriatane.

In August 2012, Health Canada requested the development of a Pregnancy Prevention Program (PPP) for Soriatane. The PPP for Soriatane was reviewed and approved by Health Canada on March 14, 2013. The objective of the PPP is to ensure safe use of acitretin and to prevent to pregnancy and foetal exposure. The objective was to be met by communicating currently available information to healthcare professionals and patients, in order to minimize cases of teratogenicity via:

- Ensuring correct prescribing practices in females of childbearing potential and adherence to the contraindication of use in pregnant women;
- Informing healthcare providers and their patients to avoid concomitant administration of acitretin with alcohol, including food/drinks/medication containing alcohol.

On July 13, 2015, Actavis Group PTC EHF (hereafter, Allergan or Sponsor) received a letter from Health Canada requesting that Allergan submit a Risk Management Plan (RMP) for Soriatane containing a pharmacovigilance plan and risk mitigation strategies for known and potential risks associated with the use of Soriatane. Health Canada provided a "checklist" and requested that

Allergan address the components of the checklist in the preparation of the RMP. On October 9, 2015, a RMP for Soriatane was submitted to Health Canada.

In its checklist, Health Canada requested that Allergan collect from healthcare professionals information on Canadian trends and additional pharmacovigilance activities. In response to this request, as one of the initial steps, the current study was developed. In this study, two distinct one-time online surveys of (1) healthcare providers who most commonly treat psoriasis (i.e., dermatologists and general practitioners/family physicians with focused practice designation in dermatology) and (2) pharmacists who dispense Soriatane to determine their base knowledge of teratogenic risk associated with Soriatane use among females of childbearing potential, and to further evaluate the necessity of additional educational materials regarding appropriate prescription and dispensing of oral retinoid products (Checklist 3d).

8. Research Question and Objectives

The objective of this survey study is to assess current practices when prescribing and dispensing Soriatane to females of childbearing potential and to measure the knowledge of Soriatane teratogenic risk to the fetus among physicians and pharmacists. The objective will be met by conducting online surveys of physicians who represent intended prescribers of Soriatane (i.e., dermatologists and general practitioner dermatologists) and licensed pharmacists. The results of this research will guide Allergan and Health Canada regarding appropriate next steps for the PPP program.

9. Research Methods

9.1 Study Design

Physician Study

Overview of Study Design

This section includes a description and rationale for sample selection, methods of recruitment, and confidentiality for physician stakeholders. The physician study methodology will consist of two phases; a pre-testing phase followed by the full study sample launch. Physicians will be invited to participate in a voluntary online survey. Aggregate results will be reported.

The Soriatane physician survey is shown in Appendix 1 of this protocol. The survey will be administered online through the use of an exclusive secure internet site. Physicians may select to complete the survey in either English or French via the internet and, if requested, with computer-assisted telephone support (in English only).

The survey will be conducted with physicians in Canada who are considered intended prescribers of Soriatane: dermatologists and general practitioners/family physicians with focused practice

designation in dermatology, collectively referred to as "Physicians." Physicians who participate in the survey pretesting phase of the study will be excluded from the full launch study to avoid duplicates and response bias.

Pretesting

Once the survey programming and quality-control testing has been successfully completed using the quality-control measures stated in section 4.2.1, the survey will be pretested in English with 10 physicians. The goal of pretesting is to assess readability, usability, and comprehension of the survey questions. Using a list of physicians provided by Allergan, the research vendor will invite physicians to participate in the survey pretesting.

Pretest respondents will be asked to rate the survey questions for clarity on a scale of 1 to 6 – with 1 = very clear, very easy to understand, 2 = Clear, easy to understand, 3 = Somewhat clear, somewhat understandable, 4 = Somewhat unclear, somewhat difficult to understand, 5 = Unclear, difficult to understand, and 6 = very unclear, very difficult to understand – and to respond to open-ended questions to further evaluate the clarity of each question as written. Analysis of these responses and review of open-ended comments will be used to base subjective analysis recommendations for any desired language or question content revisions to the survey instrument. A survey pretest and validation report incorporating the pretesting results and any recommendations will be provided to Allergan prior to survey fielding. Original documents, including revision history of the survey instrument, will be maintained on file by the research vendor. Once the survey is approved by Allergan, a second version in French will be created for review by the key opinion leaders.

Eligible participants who complete the survey pretesting will be offered an appropriate and commensurate participant fee upon completion of survey ($150 Canadian Visa card). Respondents who participate in the pretesting will be excluded from participating in the Soriatane study survey to avoid the potential of bias.

Study Materials

Study materials shall consist of the survey questionnaire presented in English and French (Appendix 1). Recruitment announcements in English and French in the form of printed letters/invitations, emails, and fax messages are shown in Appendix 3.

Pharmacist Study

Overview of Study Design

This section includes a description and rationale for sample selection, methods of recruitment, and confidentiality for pharmacist stakeholders. The pharmacist study methodology will consist of two phases: a pretesting phase followed by the full study sample launch. Pharmacists will be invited to participate in a voluntary survey, and data analysis and reporting will be subsequently conducted.

The Soriatane pharmacist survey is shown in Appendix 2 of this protocol. The survey will be available in both English and French. Pharmacists may select to complete the survey in either English or French via the internet and, if requested, with computer-assisted telephone support (in English only). The survey will be administered online through the use of an exclusive secure internet site.

The survey will be conducted among pharmacists in Canada who are licensed and actively practicing and dispensing Soriatane in a retail or outpatient pharmacy setting ("Pharmacists"). Pharmacists who participate in the survey pretesting phase of the study will be excluded from the full launch study to avoid response bias.

Pretesting

Once the survey programming and quality-control testing has successfully completed using the quality control measures stated in section 5.3.1, the survey will be pretested in English with 10 pharmacists. The goal of pretesting is to assess readability, usability, and comprehension of the survey questions. Using a list of pharmacists provided by Allergan, the research vendor will invite pharmacists to participate in the survey pretesting.

Pretest respondents will be asked to rate survey questions for clarity on a scale of 1 to 6, as in the physician questionnaires. Analysis of these responses and review of open-ended comments will be used to base subjective analysis recommendations for any desired language or question content revisions to the survey instrument. A survey pretest and validation report incorporating the pretesting results and any recommendations will be provided to Allergan prior to survey fielding. Original documents, including revision history of the survey instrument, will be maintained on file by the research vendor.

Eligible participants who complete the survey will be offered an appropriate and commensurate participant fee upon completion of survey ($75 Canadian Visa card). Respondents who participate in the pretesting phase will be excluded from participating in the Soriatane study survey to avoid the potential of bias.

Study Materials

Study materials shall consist of survey questionnaires (Appendix 2). Recruitment announcements in the form of printed letters/invitations, emails, and fax messages are shown in Appendix 3 in English and French.

9.2 Setting

Physician Study

Sample Selection and Recruitment

Analysis Group, Inc. (AGI) and BioTrak will manage survey recruitment by inviting target physicians in the pretesting and full study phases to participate in the physician survey using an

available list provided. All physicians on the target list will be invited via multi-modal recruitment involving mail, email, fax communications as available, and follow-up telephone calls as needed to fill sample. To increase the response rate, physician key opinion leaders will assist in the recruitment effort. The physician key opinion leader's names will be included in the survey invitation letter. Allergan will provide AGI and BioTrak with the name of the physician key opinion leaders, as well as the target list of physicians for the pre-testing phase. Physicians may participate by invitation only (see Appendix 3 for invitation).

BioTrak will field and manage all associated physician communications. Recruited physicians will be provided with a unique survey code. The first screen will ask for the unique survey code and will validate that the code is correct and has not been previously used. If a survey code has been previously used, a message will be displayed informing respondent that the survey code has been used and to contact BioTrak for further support via email. By entering the code, physicians will arrive at the survey and first be asked the language in which they prefer to complete the survey in (English or French), followed by further screening to ensure that they are a qualified respondent. Any physicians terminated during the screening as a result of disqualification will be shown a message thanking them for their time and will be provided contact information of the research vendor if they have any questions.

To comply with research standards and encourage participation, physicians will be informed that their responses will be anonymous and will only be tabulated with others in the aggregate. Eligible participants who complete the survey will be offered an appropriate and commensurate participant fee upon completion of the survey ($150 Canadian Visa card).

The identities of the survey participants who complete any portion of the survey will not be shared with the Sponsor, or Health Canada. Participants are kept anonymous. Participants will be informed that their answers to the survey questions will not affect their ability to prescribe Soriatane.

Sample Inclusion and Control for Bias

Physicians may only complete the survey one time during the period of the Soriatane study (including the pretesting phase). The rationale is that once a respondent has taken the survey, future participation in the survey could result in duplicated responses and introducing acquiescence bias that may affect the validity of the survey. Respondents who procure more than one survey code because of duplicates in the contact list and complete the survey more than once will have their new survey data removed completely from the data file. The contact data (e.g., name, address) will be verified for duplicates once every two weeks to identify a respondent who intentionally or unintentionally completed the survey twice. If feasible, BioTrak will also review the target list prior to survey mailings to minimize the chance of sending out more than one survey code to each physician. BioTrak will review the target list to minimize the chance of sending out more than one survey code to physicians. The original survey data will be retained for analysis.

The online survey formats are designed such that questions need to be answered before the respondent can advance to the next question and complete the survey. The survey will not allow physicians to go back to previous questions in the survey once the arrow button is clicked to move on to the next question. The online survey will timeout after 60 minutes of idle time, a message will be displayed informing them that the survey has closed due to inactivity. If they would like to complete, the survey respondent will need to contact BioTrak via email to receive a new code to access and complete the survey. Data from respondents who do not complete the survey (partially completed surveys) will be removed from the data file. These respondents will not qualify for collection of the participant fee. Frequency of survey dropouts will be reported. These incomplete respondents will not qualify for collection of the participant fee.

An internet-hosted survey is expected to result in minimal bias as it provides easy, private and confidential survey participation to all healthcare professionals and avoids subjectivity or bias associated with written or in-person interview processes. In addition, response options are randomized to minimize response bias from order effects. The research vendor will offer telephone and email support for prescribers needing support with online survey participation.

Pharmacist Study

Sample Selection and Recruitment

AGI and BioTrak will manage survey recruitment invitations by inviting target pharmacists in the pretesting and full study phases to participate in the pharmacist survey using an available list provided. Allergan will provide AGI and BioTrak with the target list of pharmacists for the pre-testing phase. All pharmacists on the target list will be invited via multi-modal recruitment involving mail, email, fax communications as available, and follow-up telephone calls as needed to fill sample (see Appendix 3 for invitation).

BioTrak will field and manage all associated pharmacist communications. Recruited pharmacists will be provided with a unique survey code. The first screen will ask for the unique survey code and will validate that the code is correct and has not been previously used. By entering the code, pharmacists will arrive at the survey and first be asked the language in which they prefer to complete the survey (English or French), followed by further screening to ensure that they are a qualified respondent. Any pharmacists terminated during the screening as a result of disqualification will be shown a message thanking them for their time and will be provided contact information of the research vendor if they have any questions. To comply with research standards and encourage participation, pharmacists will be informed that their responses will be anonymous and will only be tabulated with others in the aggregate. Eligible participants who complete the survey will be offered an appropriate and commensurate participant fee upon completion of the survey ($75 Canadian Visa card).

The identities of the survey participants who complete any portion of the survey will not be shared with Allergan.

Sample Inclusion and Control for Bias

Pharmacists may only complete the survey one time during the period of the Soriatane study which also includes the pretesting. The rationale is that once a respondent has taken the survey, future participation in the survey could result in duplicated responses and introducing acquiescence bias that may affect the validity of the survey. Respondents who procure more than one survey code and complete the survey more than once will have their new survey data removed completely from the data file; the original survey data will be retained for analysis. If feasible, BioTrak will also review the target list prior to survey mailings to minimize the chance of sending out more than one survey code to each pharmacist.

The online survey formats are designed such that questions need to be answered before the respondent can advance to the next question and complete the survey. The survey will not allow pharmacists to go back to previous questions in the survey once the arrow button is clicked to move on to the next question. The online survey will timeout after 60 minutes of idle time, a message will be displayed informing them that the survey has closed due to inactivity. If they would like to complete the survey, respondents will need to contact BioTrak via email to receive a new code to access and complete the survey. Data from respondents who do not complete the survey (partially completed surveys) will be removed from the data file. These respondents will not qualify for collection of the participant fee. Frequency of survey dropouts will be reported.

An internet-hosted survey is expected to result in minimal bias of the sample because it avoids subjectivity or bias associated with written or in-person interview processes. In addition, response options are randomized to minimize response bias from order effects. The research vendor will offer telephone and email support for prescribers needing support with online survey participation.

9.3 Variables

The Soriatane **physician** survey will incorporate the following key measures:

- Key Measure 1: To determine the knowledge the current prescribing practices of Soriatane in females of childbearing potential
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women.
- Key Measure 3: To determine if Soriatane is appropriately prescribed in females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and distribution of patient informational materials to patients.
- Key Measure 4: Awareness and use of patient educational materials including adherence to the Soriatane PPP.

The Soriatane **pharmacist** survey will incorporate the following key measures:

- Key Measure 1: To determine the current dispensing practices of Soriatane in females of childbearing potential
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women.
- Key Measure 3: To determine if Soriatane is not dispensed to pregnant women and if it is appropriately dispensed to females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and dispensing of patient informational materials to patients.

9.4 Data Sources

This is a one-time survey study of Canadian physicians and pharmacists. Two separate survey questionnaires will be administered to physicians and pharmacists, respectively. Invititations to participate in the one-time survey study will be sent to dermatologists and pharmacists using a target list of all dermatologists and GP derms which consists of approximately 1,073 individuals in Canada and the target list for pharmacists which consists of approximately 1,822 individuals who are licensed pharmacists.

9.5 Study Size

Physician Study

The proposed Soriatane physician survey of the key measures supports descriptive and possibly inferential statistical analysis depending on the final sample sizes. The proposed sample size of N=200 survey respondents has a 95% confidence interval of ±6% surrounding the targeted observed rate of correct response of 80% (see Table 1 in Appendix 4). Confidence interval bounds around the 80% correct response rate for a sample size of 100 and 50 are provided in Appendix 4.

Many individual question item results are binomial, scored as either correct or incorrect (refer to Section 6). Therefore, a binomial statistic is utilized to estimate the confidence boundaries. This binomial test calculates the lower and upper boundaries of the two-sided 95% confidence interval (CI) as it relates to stakeholder's understanding and recognition of the Soriatane study key measures. The lower boundary of the CI is of particular interest in order to be confident that the sample size is sufficient to detect the lower boundary of the 95% CI of the correct response rate, and that this lower boundary is acceptable to Health Canada.

Appendix 4 provides the exact 95% two-sided confidence boundaries for a sample size of 200, 100 and 50 and Appendix 5 describes the Clopper-Pearson method used for the calculation of the exact confidence boundaries. Once the survey sample size of N=200 is achieved, the survey will close and no additional survey respondents will be accepted. Physicians who attempt to access the survey once it is closed, will see a message thanking them for their time and notifying them that the survey has reached its maximum number of responses and is now closed.

Pharmacist Study

The proposed Soriatane pharmacist survey of the key measures supports descriptive and possibly inferential statistical analysis depending on the final sample sizes. The proposed sample size of N=200 survey respondents has a 95% confidence interval of ±6% surrounding the targeted observed rate of correct response of 80% (refer to Section 4.6 and Table 1 in Appendix 4). Once the survey sample size of N=200 is achieved, the survey will close and no additional survey respondents will be accepted. Pharmacists who attempt to access the survey once it is closed, will see a message thanking them for their time and notifying them that the survey has reached its maximum number of responses and is now closed.

9.6 Data Management

Survey data and physician/pharmacist information will be kept on a secure server. Electronic files with individual survey responses will be retained and held confidential by the research vendor. Security measures include use of a secure socket layer (SSL) security certificate for the online survey website, server intrusion detection, disaster recovery via daily remote offsite back-up, and physical and personnel controls of server access. Data files will be securely archived for up to 7 years after the date of receipt.

Information collected during the study may only be utilized for this Allergan project and will be kept confidential and access will be restricted to the surveyors, survey methodologists, and AGI. The data will be securely retained and held confidential by BioTrak. Hard copies of all returned study materials, if applicable, and any electronic files with respondent identity and indivudal survey responses will be securely retained and held confidential by BoiTrak.

BioTrak's web server is perpectually backed up every 15 minutes. Data downloaded from the web server to BioTrak's cloud server is continuously backed up through synchronized servers in secure global positions.

Our team adheres to the operating principles set forth in the HIPAA "Security Rule" when working with electronic personal health information (EPHI) and Council of American Survey Research Organizations (CASRO) compliant. These principles will be followed when handling data from the study, regardless of recruitment method.

9.7 Data Analysis

Statistical Analyses and Interpretation of Individual Survey Questions

Responses for all questions of each survey will be tabulated and reported descriptively, including frequencies with percentages for categorical variables as appropriate. All results will be reported in the aggregate for each survey sample. Please see sample reporting table below (Table 1).

Table 1. Sample [Cohort] Responses to all Survey Questions

Question QX.				
(Question stated here)				
Sub-question		Correct Response n (%)	Incorrect Response n (%)	Don't Know/ Not Sure n (%)
QX-1				
QX-2				
QX-3				
QX-4				

Statistical Analyses and Interpretation of Key Measures

The survey questions for each stakeholder are intended to assess the efficacy of the current Soriatane safety materials by measuring knowledge, awareness, and practice behavior with respect to using Soriatane in females of childbearing potential or in women who are pregnant. The percentage of respondents selecting the correct item to each question linked to the key measure and its two-sided 95% CI will be reported. The surveys are provided in Appendix 1.

The reported measures from the **physician** survey will incorporate the following:

- Key Measure 1: To determine the current prescribing practices of Soriatane in females of childbearing potential. The linked questions are: Q6, Q7, Q8.
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women. The linked questions are: Q11-1, Q11-2, Q11-4, 11-5, Q11-6, and Q11-7.
- Key Measure 3: To determine if Soriatane is not prescribed to pregnant women and if it is appropriately prescribed to females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and distributing patient informational materials to patients. The linked questions are: Q9 and Q10.
- Key Measure 4: Awareness and use of patient educational materials including adherence to the Soriatane PPP. The linked questions are: Q4, Q5, Q9, Q10, and Q12.

The reported measures from the **pharmacist** survey will incorporate the following:

- Key Measure 1: To determine the current dispensing practices of Soriatane in females of childbearing potential. The linked questions are: Q3, Q4, Q5.
- Key Measure 2: To determine the participant(s)' knowledge of the risk of teratogenicity when using Soriatane in females of childbearing potential and pregnant women. The linked questions are: Q6-1, Q6-2 and Q6-4.

- Key Measure 3: To determine if Soriatane is not dispensed to pregnant women and if it is appropriately dispensed to females of childbearing potential including patient counseling, assurance that proper contraception measures are taken, and dispensing of patient informational materials to patients. The linked questions are: Q7, Q8, Q9.

Tables with the mean, median, and 95% confidence boundary will be reported for the aggregated linked questions for each measure as well as each individual question.

Statistical Analyses and Interpretation of [Cohort] Overall Knowledge Rates

The overall knowledge rate for each stakeholder survey will be determined from the aggregate score of all survey comprehension question items. Comprehension scores (Physician survey Q11 items and Pharmacist survey Q6 items) will be examined using simple descriptive statistics by calculating the mean, median, and the 95% confidence interval of the mean. Please see sample reporting table below (Table 2).

Table 2. Sample [Cohort] Respondent Comprehension Scores for Respondent Overall Performance in Three Key Messages

Descriptive Statistics	Mean	Median	Standard Deviation	Lower 95% Confidence Boundary	Upper 95% Confidence Boundary
Overall (N=200)					

Sub-analyses

Sub-analyses will be completed and reported for each stakeholder group (i.e., physicians and pharmacists) as necessary to investigate root causes associated with performance if the correct response rates are lower than expected. For example, sub-analyses may examine demographic characteristics, receipt and extent of reading of the Soriatane safety materials as it relates to the rate of correct scoring.

9.8 Quality Control

The survey will be web programmed then undergo quality-control testing in two steps. The first step involves programming the internet-hosted survey from an approved paper draft into a web-based survey protocol. Once programmed, each question is tested to ensure correct functionality and performance, and then put through test simulations to ensure accurate and reliable electronic data collection.

The online survey formats are designed such that questions need to be answered before the respondent can advance and complete the survey. Data from respondents who do not complete the survey (partially completed surveys) will be removed from the data file. Therefore, there will be no missing values.

9.9 Limitations of the Research Methods

The Soriatane study for physicians and pharmacists applies several reasonable measures to minimize sample bias with the surveys. The surveys rely upon voluntary actions of physicians and pharmacists to participate. Key strengths of this survey methodology include:

- Pretesting of the survey instruments in both stakeholder groups to verify readability and usability.
- Survey fielding via online hosted questionnaire avoiding subjectivity or bias associated with written or in-person interview processes.
- Multiple recruitment strategies to ensure sampling mix and goals are achieved.
- Safeguards to ensure personally identifiable information and survey results remain secure and confidential.
- Real-time data reporting to assess survey trends and results at any time.
- Evaluation of respondents terminated from the survey via survey qualifying questions to assess potential exclusion bias for any stakeholder demographics.

It is recognized that no one survey methodology is perfect and that there are some limitations to the study design. These may include:

- Inability to control respondent accessing the Soriatane educational materials while completing the survey, potentially leading to improved survey comprehension scores.
- Potential for overly optimistic responses to Soriatane PPP participation questions.
- Self-selection as a basis of survey participation.

9.10 Other Aspects

Not applicable

9.10.1 Source Documents

Not applicable

9.10.2 File Retention and Archiving

Survey data and physician/pharmacist information will be kept on a secure server. Electronic files with individual survey responses will be retained and held confidential by the research vendor. Security measures include use of a secure socket layer (SSL) security certificate for the online survey website, server intrusion detection, disaster recovery via daily remote offsite back-up, and physical and personnel controls of server access. Data files will be securely archived for up to 7 years after the date of receipt.

10. Protection of Human Subjects

Study conduct will be in accordance with the Belmont Report on Ethical Principles and Guidelines for the Protection of Human Subjects of Research, US Code of Federal Regulations Title 45 Section 46 Subpart A, and privacy regulations.

11. Management and Reporting of Adverse Events/Adverse Reactions

Survey participants will be informed that the intent of the survey is not to collect information regarding individual patient adverse experiences on any particular drug. Any adverse events or technical product complaints associated with the use of Soriatane should be reported to the product manufacturer(s). Safety reporting training materials provided by the product manufacturer(s) will be reviewed by research vendor.

In the event that adverse event or technical product complaint information is received during the conduct of the survey, the adverse event information will be documented on an Adverse Event Form and sent to the product manufacturer(s) within one business day of receipt for serious adverse event and/or according to procedures outlined by the product manufacturers. The call operator will inform the survey participant that the information will be forwarded to the Soriatane drug safety office for regulatory authority reporting. The respondent will be asked if they want to share their personal contact information so that he/she may be contacted by the Soriatane drug safety office for additional information or would prefer to remain anonymous.

11.1 Definitions

Not applicable

12. Plans for Disseminating and Communicating Study Results

Respondent information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by a survey code number. The information developed in this research study will be used by Allergan to meet the Soriatane Health Canada RMP survey requirement and may be disclosed by Allergan to authorized parties excluding respondent personally identifiable information. The results of this study may be published in aggregate form under the direction of Allergan.

The study protocol and final study report will be included in regulatory communications in line with the RMP, Periodic Safety Update Reports, and other regulatory reporting requirements. The study report will be prepared using a template following the GVP Module VIII Section B.6.3 (EMA, 2016) and will be posted in the EU PAS Register (ENCePP, 2016b).

In its Guidelines for Good Pharmacoepidemiology Practices, the International Society for Pharmacoepidemiology contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. "…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2016). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al., 2008).

Communication via appropriate scientific venues, e.g., International Society for Pharmacoepidemiology, will be considered.

The MAH and the investigator will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2016).

13. References

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ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; December 2016. Available at: http://www.icmje.org/urm_main.html. Accessed 11 January 2017.

ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. International Society for Pharmacoepidemiology; June 2015. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 19 April 2017.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9.

Annex 1. List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	Appendix 1	August 18, 2017	Physician Survey
2	Appendix 2	August 18, 2017	Pharmacist Survey
3	Appendix 3	August 18, 2017	Survey Recruitment Materials
4	Appendix 4	August 18, 2017	Exact Two-Sided 95% Confidence Intervals Using Binomial Distribution
5	Appendix 5	August 18, 2017	Clopper-Pearson for the Exact Confidence Interval

APPENDIX 1
Physician Survey

(English and French versions)

Version: English

Welcome. We appreciate your interest in this survey.

To begin, please re-enter your 9-character survey code below.

Character position	1	2	3	4	5	6	7	8	9
Value req.	<S>	<H>	<1>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>

You may contact us by email at support@biotrak.com or call 1-760-448-4820 if you have any questions

This brief survey is conducted by an independent research company, BioTrak Research. The purpose of this survey is to understand your prescribing practices related to the use of SORIATANE® (acitretin). Your participation in this survey is voluntary. Your responses will be confidential and only tabulated in aggregate with other participants. Your identity will be kept private and only used to mail you your survey compensation. Your responses to the survey questions will not affect your ability to prescribe SORIATANE®. If you qualify to participate in the survey and complete the entire survey, you will receive a $150 Canadian visa card. There is no compensation for individuals who do not qualify or who do not complete the entire survey. This survey works best when you are open and honest with your answers. Please do not guess when responding to the questions; instead, select "Don't know" or a similar option. You will not have the opportunity to go back to previous questions in the survey once you click the arrow button that takes you to the next question. This study is not designed to collect adverse event (AE) information.

[Survey Screening Questions]

S1: Have you ever prescribed SORIATANE® (acitretin)?

1	Yes
2	No

Programming note: If option 2 is selected, terminate and display: "We regret that you do not qualify for this survey. If you feel that you have received this message in error, please contact BioTrak by email at support@biotrak.com or call 1-760-448-4820."

S2: The information developed in this study is the sole property of the study Sponsor and may be used by the study Sponsor for any purpose; the collection of which shall exclude respondent "personal information" or "personal health information" as those terms are defined in the *Personal Information Protection and Electronic Documents Act* and/or applicable Provincial Legislation. The study Sponsor will use the aggregate results to meet regulatory reporting requirements and will disclose the aggregate results to authorized parties. The results of this research study may be

published in aggregate form under the study Sponsor's direction. You acknowledge that you will not receive the results of the research study and disclaim any right(s) you may have in the study results. Please confirm below if you understand and agree to the terms set forth above and if you wish to continue.

1	Yes
2	No

Programming note: If option 2 is selected, terminate and display: "We regret that you do not qualify for this survey. If you feel that you have received this message in error, please contact BioTrak by email at support@biotrak.com or call 1-760-448-4820."

Please note you may only take this survey one time. Only survey participants completing the entire survey will be compensated. In the following screens, you will be asked a number of questions about SORIATANE® (acitretin). Please do not guess at the answers; instead, if you do not recognize the answer select "Don't know".

[Survey Questions]

Q1: Which best describes your medical specialty?

Please select one answer.

1	Dermatology
2	General practitioners/family physicians with focused practice designation in dermatology
3	Other _____

Q2: How many years have you been prescribing SORIATANE® (acitretin)?

Please enter one answer.

Open numerical text box

Q3: Approximately how many prescriptions of SORIATANE® (acitretin) do you write in an average year?

Please enter one answer.

Open numerical text box

Programming note: Range bound 1-500

Q4. What is your level of familiarity with the SORIATANE® (acitretin) Pregnancy Prevention Program (PPP)?

Please select one answer.

1	I am AWARE of the PPP materials but have NOT obtained them.
2	I am AWARE of the PPP materials and I HAVE obtained them.
3	I am UNAWARE of the PPP materials.

Programming note: If Q4 =1 or 3 skip Q5

Programming note: Randomize order of presentation.

Q5. How did you obtain or receive the SORIATANE® (acitretin) **Pregnancy Prevention Program (PPP)** materials?

Please select all that apply.

1	Mail (direct mail from company or by request)
2	Online download
3	Company representative
4	Other

Q6: Have you ever prescribed SORIATANE® (acitretin) to a **female patient of childbearing potential**?

Please select one answer.

1	Yes
2	No

Programming note: If Q6=No, skip Q7 & Q8 & Q9 & Q10

Q7: What percentage of the [enter value from Q3] SORIATANE® (acitretin) prescriptions are for each of the following patient populations?

Please complete the table below.

	Percentage of prescriptions per year for:	**%**
1	Patients other than females of childbearing potential	
2	Female patients of childbearing potential	
	Total must equal 100%	**100%**

Programming note: Rotate order presentation

Q8: When prescribing SORIATANE® (acitretin) to **female patients of childbearing potential**, what are the disorders intended to be treated?

Please complete the table below using percent distributions.

	Distribution of your SORIATANE prescriptions for female patients of childbearing potential	**%**
1	Severe psoriasis (includes erythrodermic and pustular types)	
2	Other disorders of keratinization	
3	Other medical conditions not listed above	

	Total must equal 100%	**100%**

Q9: When prescribing SORIATANE® (acitretin), approximately what proportion of your **female patients of childbearing potential** receive the following patient materials?

Please select "All," "Most", "Some," or "None," for each item.

		All	Most	Some	None
1	SORIATANE® General Guidelines booklet/ patient brochure				
2	Informed Consent form for SORIATANE® Patients				
3	Checklist to assess patients' understanding of risks (*Patient Self-Evaluation form*)				
4	SORIATANE® Pregnancy Prevention Program booklet				
5	My *own or other pregnancy prevention materials.* Please specify *own or other pregnancy prevention materials* e.g., informed consent, brochure (optional). _____				

Programming note: randomize order for items Q9-1 through Q9-4

Q10: When considering SORIATANE® (acitretin) for **female patients of childbearing potential**, for what proportion of patients do you complete the Pregnancy Prevention Program's Physician Checklist? Please select the one best choice.

1.	All
2.	Most
3.	Some
4.	None

Note: "X" marks the correct response and will not be displayed to survey respondent.

Q11a: According to the following statements about SORIATANE® (acitretin), which of the following are true?

Please select "True", "False", or "Don't Know/ Not Sure" for each question item.

		True	**False**	**Don't Know/ Not Sure**
Q11a-1	SORIATANE® (acitretin) is highly teratogenic and must not be used by females who are pregnant or intend to become pregnant.	X		
Q11a-2	SORIATANE® (acitretin) may be used by females who are pregnant or intend to become pregnant as long as they sign an Informed Consent form.		X	
Q11a-3	The patient is capable of complying with mandatory contraceptive measures reliably and without fail (complete abstinence or simultaneous use of two effective and complementary forms of birth control) starting 1 month before, during, and for at least 3 years after stopping SORIATANE® therapy.	X		
Q11a-4	The physician should assess whether the patient is reliable in understanding and following instructions in the SORIATANE® (acitretin) Pregnancy Prevention Program (PPP).	X		
Q11a-5	The patient has had two negative serum or urine pregnancy tests before starting with SORIATANE® therapy: The first test (with a negative result) done at the time of the initial assessment when the patient was qualified for SORIATANE® therapy; the second (confirmatory) test (with a negative result) performed within 3 days prior to the first dose.	X		

Programming note: Randomize order presentation

Q11b: Now please review the question items below. According to the following statements about SORIATANE® (acitretin), which of the following are true?

Please select "True", "False", or "Don't Know/ Not Sure" for each question item.

		True	**False**	**Don't Know/ Not Sure**
Q11b-1	Alcohol must not be ingested by female patients either during treatment with SORIATANE® (acitretin) or for 2 months after treatment cessation.	X		
Q11b-2	St. John's Wort may be taken concomitantly with hormonal contraceptives in females of childbearing potential treated with SORIATANE® (acitretin).		X	
Q11b-3	Patients should be informed not to donate blood when using SORIATANE® (acitretin) and for 3 years after stopping its use.	X		

Q12: Approximately what proportion of your patients are informed to *not* donate blood when using SORIATANE® (acitretin) and for 3 years after stopping its use? Please select the one best choice.

1.	All
2.	Most
3.	Some
4.	None

R1. Please re-enter your survey code to proceed.

Character position	1	2	3	4	5	6	7	8	9
Value req.	< S>	<H>	<1>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>

On the next page, please provide your contact information for mailing your $150 Visa card. Your contact information will be stored separately from your survey responses to ensure that your responses are confidential and anonymous. It is important that you complete all contact information fields. You will see a message confirming that you have completed all fields at the end. Please allow 2-3 weeks to receive your Visa card.

Information that would allow you to be identified will be known only to the research vendor (BioTrak), and will be used only by the research vendor to mail you a Visa card. This information will remain electronically on a secure data server. Your responses to this survey will be kept confidential and anonymous.

First Name	
Last Name	
Address 1	
Address 2	[optional]
City	
Province	
Postal	
Telephone	
Email	[optional]

Thank you for your input today! You have successfully completed the survey.

Version: French [To be developed once the English version is finalized]

APPENDIX 2
Pharmacist Survey

(English and French versions)

Version: English

Welcome. We appreciate your interest in this survey.

To begin, please re-enter your 9-character survey code below.

Character position	1	2	3	4	5	6	7	8	9
Value req.	<S>	<S>	<1>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>

You may contact us at 1-760-448-4820 or email us at support@biotrak.com if you have any questions or if you would like to complete the survey by telephone. Call center hours are Mon. – Fri. 7:30am to 4:00pm PST.

This brief survey is conducted by an independent research company, BioTrak Research. The purpose of this survey is to understand your practices related to the dispensing of SORIATANE® (acitretin). Participation in this survey is voluntary. Your responses will be confidential and only tabulated in aggregate with other participants. Your identity will be kept private and only used to mail you your survey compensation. Your answers to the survey questions will not affect your ability to dispense SORIATANE®. If you qualify to participate in the survey and complete the entire survey, you will receive a $75 Canadian visa card. There is no compensation for individuals who do not qualify or who do not complete the entire survey. This survey works best when you are open and honest with your answers. Please do not guess when responding to the questions; instead, select "Don't know" or a similar option. You will not have the opportunity to go back to previous questions in the survey once you click the arrow button that takes you to the next question. This study is not designed to collect adverse event (AE) information.

[Survey Screening Questions]

S1: Which title best describes you?

1	Licensed pharmacist
2	Pharmacy technician
3	Non-licensed pharmacy personnel
4	Other (pharmacy assistant, etc.)

Programming Note: If option 1 is not selected, terminate and display "We regret that you do not qualify for this survey. If you feel that you have received this message in error, please contact BioTrak by email at support@biotrak.com or call 1 760-448-4820."

S2: Have you ever dispensed a prescription for SORIATANE® (acitretin)?

1	Yes
2	No

Programming note: If option 2 is selected, terminate and display: "We regret that you do not qualify for this survey. If you feel that you have received this message in error, please contact BioTrak by email at support@biotrak.com or call 1-760-448-4820."

S3: The information developed in this study is the sole property of the study Sponsor and may be used by the study Sponsor for any purpose; the collection of which shall exclude respondent "personal information" or "personal health information" as those terms are defined in the *Personal Information Protection and Electronic Documents Act* and/or applicable Provincial Legislation. The study Sponsor will use the results to meet regulatory reporting requirements and may disclose aggregate results to authorized parties. The results of this research study may be published in aggregate form under the Sponsor's direction. You acknowledge that you will not receive the results of the research study and disclaim any right(s) you may have in the study results. Please confirm below if you understand and agree to the terms set forth above and if you wish to continue.

1	Yes
2	No

Programming note: If option 2 is selected, terminate and display: "We regret that you do not qualify for this survey. If you feel that you have received this message in error, please contact BioTrak by email at support@biotrak.com or call 1-760-448-4820."

Please note you may only take this survey one time. Only survey participants completing the entire survey will be compensated. In the following screens, you will be asked a number of questions about SORIATANE® (acitretin). Please do not guess at the answers; instead, if you do not recognize the answer select "Don't know". In responding to the survey questions, we request that you provide responses based on your own experience in dispensing of the prescription. Dispensing of the prescription includes both "new" and "refills".

[Survey Questions]

Q1: How many years have you been dispensing SORIATANE® (acitretin)?

Please enter one answer.

Open numerical text box

Q2: Approximately how many prescriptions (new and refill) of SORIATANE® (acitretin) have you personally dispensed in the last 12 months?

Please enter one answer.

Open numerical text box

Programming note: Range bound 0-500

Q3: Have you ever dispensed SORIATANE® (acitretin) to a **female patient of childbearing potential**?

Please select one answer.

1	Yes
2	No

Programming note: If Q3=No then skip Q4 & Q5 & Q9

Q4: What percentage of the [enter value from Q2] SORIATANE® (acitretin) prescriptions (new and refill) that you dispensed in the last 12 months are for **female patients of childbearing potential** versus other patients?

Please complete the table below

	Percentage of prescriptions dispensed per year for:	**%**
1	Female patients of childbearing potential	

2	All other patients (including females of non-childbearing potential and males)	
	Total must equal 100%	**100%**

Q5: When was the last time you dispensed a prescription (new and refill) for SORIATANE® (acitretin) to a **female patients of childbearing potential**?

Please select one answer.

1	< 3 months
2	3-6 months ago
3	6-12 months ago
4	13-24 months ago
5	>24 months ago
6	I do not know since I do not inquire about childbearing potential

Note: "X" marks the correct response and will not be displayed to survey respondent.

Q6: According to the following statements about SORIATANE® (acitretin), which of the following is true?

Please select "True", "False", or "Don't Know/Not Sure" for each question item.

		True	False	Don't Know/ Not Sure
Q6-1	SORIATANE® (acitretin) is highly teratogenic and must not be used by females who are pregnant or intend to become pregnant.	X		
Q6-2	Ethanol must not be ingested by female patients either during treatment with SORIATANE® (acitretin) or for 2 months after treatment cessation.	X		
Q6-3	SORIATANE® (acitretin) may be used by females who are pregnant or intend to become pregnant as long as they sign an Informed Consent form.		X	
Q6-4	Patients should be informed not to donate blood when using SORIATANE® (acitretin) and for 3 years after stopping its use.	X		

Programming note: Randomize order presentation

Q7: When dispensing SORIATANE® (acitretin), for approximately what proportion of patients do you provide a **patient information sheet**?

1.	All
2.	Most
3.	Some
4.	None

Programming note: If Q7=None then skip Q8

Q8: When dispensing SORIATANE® (acitretin), does the information sheet contain an explanation of the risks such as teratogenicity and recommendations for the use of contraceptive methods?

Please select one answer.

1	Yes
2	No

Q9: Approximately what proportion of female patients of childbearing potential do you ask if they received instructions regarding the SORIATANE® (acitretin) **Pregnancy Prevention Program (PPP)** from their prescribing physician?

1.	All
2.	Most
3.	Some
4.	None

Q10: In approximately what proportion of the prescriptions (new and refill) that you fill for SORIATANE® (acitretin) do you inform the patient to *not* donate blood when using SORIATANE® (acitretin) and for 3 years after stopping its use?

1.	All
2.	Most
3.	Some
4.	None

R1: Please re-enter your survey code to proceed.

Character position	1	2	3	4	5	6	7	8	9
Value req.	< S>	<S>	<1>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>	<0-9>

On the next page, please provide your contact information for mailing your $75 Canadian Visa card. Your contact information will be stored separately from your survey responses to ensure that your responses are confidential and anonymous. It is important that you complete all contact information fields. You will see a message confirming that you have completed all fields at the end. Please allow 2-3 weeks to receive your gift card.

Information that would allow you to be identified will be known only to the research vendor (BioTrak), and will be used only by the research vendor to mail you a Visa card. This information will remain electronically on a secure data server. Your responses to this survey will be kept confidential and anonymous.

First Name	
Last Name	
Address 1	
Address 2	[optional]
City	
Province	
Postal	
Telephone	
Email	[optional]

Thank you for your input today! You have successfully completed the survey.

Version: French [To be developed once the English version is finalized]

APPENDIX 3
Survey Recruitment Materials

(English and French versions will be available)

Physicians Recruitment Example
(French version will be developed once English version is finalized)
To be used for mail, fax, and email

Dear <<First Name>> <<Last Name>>, <<Suffix>>:

In response to a Health Canada request, you are being asked to participate in a survey regarding SORIATANE® (acitretin). This important voluntary survey is for prescribers of SORIATANE. The survey is sponsored by the manufacturer of SORIATANE and administered by BioTrak Research Inc.

Physicians who complete this brief survey will be mailed a $150 Canadian Visa card.

To access the online survey:

- **Please go to: www.Soriatane.TreatmentSurvey.com**
- **Enter the following survey code: <<Survey code>>**

Individual results from the survey will be kept confidential and are aggregated with those from other participants for analysis and reporting purposes. This study is not designed to collect adverse event (AE) information.

You can receive assistance by phone at 1-760-448-4820 Mon.-Fri. 10:30am-7:00pm EST (7:30am-4:00pm PST) or by email to support@biotrak.com. Please complete this important voluntary survey to help comply with Health Canada's request.

Warm regards,

[Insert Key Opinion Leaders Name, signature, and Contact Information]
Alias email: xxxxxxxx@xxx.com
Direct: (xxx) 448-xxxx

Pharmacists Recruitment Example
(French version will be developed once English version is finalized)
To be used for mail, fax, and email

Dear <<First Name>> <<Last Name>>, <<Suffix>>:

In response to a Health Canada request you are being asked to participate in a survey regarding SORIATANE® (acitretin). This important voluntary survey is for pharmacists who dispense SORIATANE. The survey is sponsored by the manufacturer of SORIATANE and administered by BioTrak Research Inc.

Pharmacists who complete this brief survey will be mailed a $75 Canadian Visa card.

To access the online survey:

- **Please go to: www.SoriataneRx.TreatmentSurvey.com**
- **Enter the following survey code: <<Survey code>>**

Individual results from the survey will be kept confidential and are aggregated with those from other participants for analysis and reporting purposes. This study is not designed to collect adverse event (AE) information.

You can receive assistance by phone at 1-760-448-4820 Mon.-Fri. 10:30am-7:00pm EST (7:30am-4:00pm PST) or by email to support@biotrak.com. Please complete this important voluntary survey to help comply with Health Canada's request.

Warm regards,

Larry Risen
President and Senior Director of Research
support@biotrak.com
Direct: (760) 448-4820

APPENDIX 4
Exact Two-sided 95% Confidence Intervals Using Binomial Distribution

Appendix-Table 1. Exact Two-Sided 95% Confidence Boundaries for a Sample size of 200 Using Binomial Distribution

Rate of Correct Response	Lower Boundary of 95% Exact Confidence Interval	Upper Boundary of 95% Exact Confidence Interval
50%	43%	57%
55%	48%	62%
60%	53%	67%
65%	58%	72%
70%	63%	76%
75%	68%	81%
80%	74%	85%
85%	79%	90%
90%	85%	94%
95%	91%	98%
100%	98%	100%

Appendix-Table 2. Exact Two-Sided 95% Confidence Boundaries for a Sample size of 100 Using Binomial Distribution

Rate of Correct Response	Lower Boundary of 95% Exact Confidence Interval	Upper Boundary of 95% Exact Confidence Interval
50%	40%	60%
55%	45%	65%
60%	50%	70%
65%	55%	74%
70%	60%	79%
75%	65%	83%
80%	71%	87%
85%	76%	91%
90%	82%	95%
95%	89%	98%
100%	96%	100%

Appendix-Table 3. Exact Two-Sided 95% Confidence Boundaries for a Sample Size of 50 Using Binomial Distribution

Rate of Correct Response	Lower Boundary of 95% Exact Confidence Interval	Upper Boundary of 95% Exact Confidence Interval
50%	36%	65%
55%	41%	70%
60%	45%	74%
65%	51%	79%
70%	55%	82%
75%	62%	87%
80%	66%	90%
85%	73%	94%
90%	78%	97%
95%	86%	100%
100%	89%	100%

APPENDIX 5
Clopper-Pearson for the Exact Confidence Interval

Clopper-Pearson for the Exact Confidence Interval:

Given Y positive responses in a sample of n questions, the upper and lower boundary of an exact 95% confidence interval for the percentage of positive responses is given by Clopper and Pearson:

$$P_U = \left[1 + \frac{n-Y}{Y+1} F(0.025; 2n-2Y, 2Y+2)\right]^{-1}$$

$$P_L = \left[1 + \frac{n-Y+1}{Y} F(0.975; 2n-2Y+2, 2Y)\right]^{-1}$$

Annex 2. ENCePP checklist for Study Protocols

Study title:
Pregnancy Prevention Program Section of the Risk Management Plan for Soriatane® (acitretin): Survey to Assess Physician and Pharmacist Understanding of the Risk of Teratogenicity Associated with Soriatane

Study reference number:
CMO-EPI-DERM-0527

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☐	☒	
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	9.1
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.2
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6; 9.10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2; 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

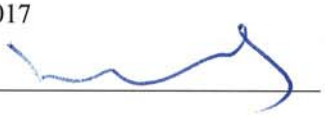
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Mei Sheng Duh, MPH, ScD, Analysis Group, Inc.

Date: 08/18/2017

Signature: 

Annex 3. Additional Information

Not applicable