NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**ALECENSA SURVEY TO PRESCRIBERS: EFFECTIVENESS MEASURE TO INVESTIGATE THE CORRECT IMPLEMENTATION OF ALECENSA LABEL GUIDANCE BY PRESCRIBERS**
PROTOCOL NUMBER:	BO40643
VERSION NUMBER:	1
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
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	Deputy QPPV	16-Nov-2018 17:42:42

CONFIDENTIAL

DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	Study not registered
ACTIVE SUBSTANCE:	ATC code L01XE36: Alectinib
STUDIED MEDICINAL PRODUCT:	Alecensa
PRODUCT REFERENCE NUMBER:	EMEA/H/C/004164
PROCEDURE NUMBER{S}:	EMEA/H/C/004164/MEA/002
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this study is to evaluate the effectiveness of Alecensa's risk minimisation measures (RMM) for the important identified risks (interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia and CPK elevations) as outlined in the risk management plan (RMP) and label, by assessing their correct implementation by Health Care Professionals (HCPs) The primary objective for this study is as follows: • To assess the awareness, knowledge, and clinical practice of HCPs regarding the specific important identified risks related to Alecensa and their related minimization measures The secondary objectives for this study are as follows: • To measure HCP's awareness of the important identified risks and their related minimization measures • To measure HCP's knowledge on the requirement for specific dose modifications for the above mentioned important identified risks • To measure HCPs' knowledge on the requirement for specific monitoring for the above mentioned important identified risks • To measure whether HCPs' follow the Summary of Product Characteristics (SPC) recommendations regarding the specific clinical measures
COUNTRIES OF STUDY POPULATION:	Countries in Europe, final list of countries not determined yet
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	Dr. [redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
EC	Ethics Committee
EEA	European Economic Area
EDC	Electronic data capture
EMEA	European Medicines Agency
GVP	Good Pharmacovigilance Practices
HCP	Health care provider
ILD	Interstitial lung disease
IRB	Institutional Review Board
MAH	Marketing authorization holder
NSCLC	Non–small cell lung cancer
RMM	Risk minimization measures
RMP	Risk management plan
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
W&P	Warnings and precautions

2. RESPONSIBLE PARTIES

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3. SYNOPSIS

TITLE:	**ALECENSA SURVEY TO PRESCRIBERS: EFFECTIVENESS MEASURE TO INVESTIGATE THE CORRECT IMPLEMENTATION OF ALECENSA LABEL GUIDANCE BY PRESCRIBERS**
PROTOCOL NUMBER:	BO40643
VERSION NUMBER:	1
EU PAS REGISTER NUMBER:	Study not registered
STUDIED MEDICINAL PRODUCT:	Alecensa
SCIENTIFIC RESPONSIBLE	[redacted], Roche
MAIN AUTHOR	[redacted], Roche
PHASE:	IV, non-interventional study
INDICATION:	Treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small lung cancer (NSCLC) in the first-line setting or previously treated with crizotinib
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

Rationale and Background

Alecensa is an oral, small molecule tyrosine-kinase inhibitor that targets ALK and c-RET oncogenes. Alecensa has received marketing authorization from the European Medical Agency for the treatment of ALK-positive advanced NSCLC patients. Alecensa as monotherapy is currently indicated for the treatment of adult patients with ALK-positive NSCLC in both the first-line setting, or following treatment with crizotinib.

Treatment with Alecensa is associated with important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia and creatine phosphokinase (CPK) elevations. To facilitate the management of these identified risks, clinical measures have been included in the SPC.

To assess the effectiveness of the clinical measures described in the SPC to mitigate these important identified risks, the MAH (F Hoffmann-La Roche Ltd, hereafter referred to as Roche) plans to conduct a survey with HCPs with the intent to measure the effectiveness of the risk minimization measures (RMM) implemented in the Alecensa label.

Research Question and Objectives

The aim of this study is to evaluate the effectiveness of Alecensa's RMM for the important identified risks (ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity,

severe myalgia, and CPK elevations) as outlined in the RMP and label, by assessing their correct implementation by HCPs.

Objectives

The primary objective for this study is as follows:

- To assess the awareness, knowledge, and clinical practice of HCPs regarding the specific important identified risks related to Alecensa and their related minimization measures

The secondary objectives for this study are as follows:

- To measure HCP's awareness of the important identified risks and their related minimization measures
- To measure HCP's knowledge on the requirement for specific dose modifications for the above mentioned important identified risks
- To measure HCPs' knowledge on the requirement for specific monitoring for the above mentioned important identified risk
- To measure whether HCPs' follow the SPC recommendations regarding the specific clinical measures

Study Design

The study will be an anonymous, cross-sectional, multinational, multi-channel survey conducted among HCPs in European countries using primary data collection in the form of a questionnaire.

Description of Study

The survey will be conducted between 18 and 24 months after the first line approval of Alecensa for ALK+ NSCLC. The survey questionnaire will include multiple-choice, open, and closed questions as appropriate and will be sent to the participating HCPs to collect information on their awareness, knowledge, and clinical practice about the specific guidance included in the label to minimize the risk of ILD/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia, and CPK elevations. The survey will be conducted in a web-based format as a standard and by phone if the participating HCPs prefer it.

Population

A sample size of 200 completed questionnaires from HCPs, who have treated (newly initiated or repeatedly administrated/ prescribed) any ALK-positive NSCLC patients with Alecensa according to local label at least once in the 6 months prior to taking the survey, is envisaged.

To achieve this, the survey questionnaire will be sent to a diverse group of about 2000 potential prescribers of Alecensa (i.e., HCPs specialised in oncology or pulmonology) from geographically dispersed European countries. To minimize selection bias, a comprehensive database of registered HCPs worldwide will be used. Subsamples of the database (oncologists and pulmonologists in the target countries) will be randomly contacted. All HCPs will provide informed consent and data will be anonymised when presented to Roche.

Variables

1) Variables related to HCPs participation: response rate, refusal rate
2) Variables related to HCPs practice information: location (i.e., country), duration of practice (years in practice), primary speciality (oncologist, pulmonologist), type of setting (i.e., office-based, hospital based), past experience with Alecensa
3) Variables related to the HCP awareness about the important identified risks (warnings and precautions [W&P]) in the label of Alecensa and the measures for risk minimization: awareness (yes/no)
4) Variables related to the HCPs knowledge on the requirement for specific monitoring and dose modification: Important identified risks (W&P) for Alecensa, specific monitoring, specific advices to patients, requirements for terminating Alecensa or dose modifications
5) Variables related to the HCPs compliance with the clinical measures for important identified risks (W&P): frequency of AST/ALT, CPK, and heart rate and blood pressure monitoring, instructions for dose reduction
6) Other variables: Source of information for Alecensa safety profile and prescribing information – percentages of HCPs per source of information

Data Sources

The study is a survey using primary data collection conducted through HCP questionnaires administered by web or phone and is planned to be conducted in 6 European countries.

Study Size

A sample of 200 HCPs will be surveyed. Given the average 10% response rate obtained in previous similar surveys, it is expected that approximately 2000 HCPs from approximately 6 European countries combined will be invited to participate. This estimate is in line with the low response rate reported for similar surveys in the literature (Agyemang et al. 2017).

Data Analysis

The statistical analysis will be conducted using SAS (Version 9.4 or above).

Results will be presented in total, by country, and by speciality (i.e., oncologist and pulmonologist), if applicable in the target country.

Continuous variables will be presented by the number of valid cases, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Categorical variables will be presented as the total number and relative percentage per category. Confidence intervals of 95% will be calculated as appropriate.

Individual awareness scores will be descriptively analysed and reported as percentages. Awareness level will be calculated as the mean of the individual scores.

Individual knowledge scores and individual HCP clinical practice scores will be calculated as the percentage of correctly answered survey questions; scores will range from 0 to 100% with 100% representing the percentage of all knowledge questions and

clinical practice questions being answered correctly, respectively. Knowledge level and clinical practice level will be calculated as the mean of individual scores.

Calculations will firstly be performed on raw data in total, by speciality, and by country; subsequently results will be weighted according to the real proportion of HCPs in each country to accurately reflect the population the survey seeks to measure.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g., country, type of setting, and speciality, if applicable and feasible) between respondent and non-respondent HCPs.

A successful outcome on the effectiveness of risk minimisation measures is defined a priori by the following target levels:

1. Proportion of HCPs being aware of the important identified risk and related minimisation measures for Alecensa (Question Q2 and Q3 of HCP questionnaire) – Success: ≥75%
2. Proportion of HCPs knowledgeable about the important risks, specific monitoring, dose modification (Questions Q5 to Q8 of HCP questionnaire) – Success ≥60%
3. Proportion of HCPs answering the clinical practice questions in compliance to the SPC (Questions Q9-Q10 of HCP questionnaire) – Success ≥75%

The proportion of HCPs meeting the success criteria in all three categories is the overall success factor for the implementation of RMM for the important identified risks for Alecensa. The thresholds used are in accordance with success rates applied in other studies approved by PRAC and provide a balance between the ideal scenario of achieving a 100% rate of awareness, knowledge and compliance and what can be realistically expected from routine RMMs in the clinical practice.

The proportion of HCPs meeting the success criteria in all three categories is the overall success factor for the implementation of RMM for the important identified risks for Alecensa.

Milestones

Start Date of Study

The study start date will be the date of the first data collection, i.e., the date from which information from the HCP questionnaire is recorded in the study database. The planned start date is June 2019, which is approximately 18 months after receipt of first line approval for Alecensa in the European Economic Area (EEA).

End of Study

The end of the study will be the date from which the last data collected from the last HCP questionnaire is recorded in the study database. The planned end of study date is December 2019, which corresponds to approximately 24 months after receipt of first line approval for Alecensa in the EEA.

Length of Study

The fieldwork for this study will last approximately 6 months. The final study report is planned for submission in December 2020.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of protocol in the EU PAS register	After approval of the protocol and before start of data collection
Start of data collection	June 2019
End of data collection	December 2019
Final report of study results	December 2020
Registration of the results in the EU PAS register	After approval of the final study report

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

Alecensa (alectinib) is an oral, small molecule tyrosine-kinase inhibitor targeting anaplastic lymphoma kinase and c-RET oncogenes. Alecensa has received marketing authorization from the European Medical Agency for the treatment of ALK-positive advanced NSCLC patients. Alecensa was approved as monotherapy for the treatment of adult patients with ALK-positive NSCLC in the crizotinib-failed setting on 16 February 2017 and in the first-line setting on 18 December 2017.

Treatment with Alecensa is associated with the important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and CPK elevations. To facilitate the management of these identified risks, clinical measures have been included in the SPC. These risk mitigation measures include:

- Specific dose modification guidance for ILD/pneumonitis, for increased ALT, AST, and bilirubin, for symptomatic bradycardia, and for CPK increases

- Recommendations for monitoring of pulmonary symptoms indicative of ILD/pneumonitis, as well as for monitoring of liver function, including frequency, and for monitoring of CPK levels, including frequency
- Specific patient advice for sun protection to avoid phototoxicity and for reporting of certain symptoms of myalgia

To assess the effectiveness of these clinical measures described in the SPC to mitigate these important identified risks, Roche plans to conduct a survey with HCPs with the intent to measure the effectiveness of the risk minimization measures implemented in the Alecensa label.

For information on the condition under observation, please refer to the most recent version of the SPC.

For information on Alecensa please refer to the most recent version of the SPC.

6.2 STUDY BACKGROUND

Treatment with Alecensa is associated with the important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and CPK elevations. To facilitate the management of these identified risks, clinical measures have been included in the SPC.

According to the guidelines on good pharmacovigilance practices (GVP) Module V, VIII, and XVI, effectiveness of risk minimization activities should be assessed (European Medicines Agency 2012a, 2012b, 2014). Therefore, Roche propose to conduct a Non-Interventional Post-Authorisation Safety Study in the form of a survey that will evaluate the effectiveness of the risk minimization measures implemented in the label for the above mentioned important identified risks.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The aim of this study is to evaluate the effectiveness of Alecensa's risk minimisation measures described in the SPC by assessing their correct implementation by prescribing HCPs for the important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and CPK elevations.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- To assess the awareness, knowledge, and clinical practice of HCPs regarding the specific important identified risks related to Alecensa and their related minimization measures

The secondary objectives for this study are as follows:

- To measure HCP's awareness of the important identified risks and their related minimization measures
- To measure HCP's knowledge on the requirement for specific dose modifications for the above mentioned important identified risks

- To measure HCPs' knowledge on the requirement for specific monitoring for the above mentioned important identified risk
- To measure whether HCPs' follow the SPC recommendations regarding the specific clinical measures

8. RESEARCH METHODS

8.1 STUDY DESIGN

This study will be an anonymous, cross-sectional, multinational, multi-channel survey conducted among HCPs in European countries in the form of a questionnaire.

The HCPs will initially be contacted by email. The survey will be conducted in a web-based format as a standard and by phone if the participating HCPs prefer it.

Start Date of Study

The anticipated study start date will be in June 2019 which is approximately 18 months after receipt of first line approval in the EEA.

End of Study

The end of the study will be the date from which the last data collected from the last HCP questionnaire is recorded in the study database. Anticipated study completion is December 2019, estimated for 24 months after receipt of first line approval in the EEA.

The questionnaire for data collection overview is provided in Appendix 1.

8.1.1 Rationale for Study Design

According to the guidelines on GVP Module V, VIII, and XVI, effectiveness of risk minimisation measures should be assessed (European Medicines Agency 2012a,2012b, 2014). This will be achieved using a survey to HCPs to evaluate both their awareness and knowledge of these risk minimization measures described in the label. To ensure that only relevant HCPs are targeted, the survey will only include HCPs that have treated (newly or repeatedly) ALK-positive NSCLC patients with Alecensa according to local label at least once in the 6 months prior to taking the survey. To minimize selection bias, a comprehensive database of registered HCPs [redacted] will be used to randomly enrol HCPs meeting the above criteria.

8.2 SETTING

The survey will be conducted among office and hospital-based Alecensa prescribers in a selected number of European countries.

Target countries will be selected for the conduct of the survey due to their representative nature of the European population. These countries from different parts of Europe will be chosen in such a way that countries with different sizes, cultures, and healthcare systems are represented.

The selection of countries to be involved in the survey will also consider the following criteria:

- Where Alecensa has been registered, marketed, and available to prescribers for at least 6 months prior to the start of the survey
- Where Alecensa availability and market penetration is sufficiently high to allow HCPs participation

To preselect the countries the predicted market uptake will be taken into account and will ensure that the study will be performed in countries where Alecensa is available and accessible to patients.

8.2.1 Countries

It is planned to conduct the study in 6 European countries.

The countries recommended for the survey are based on approval timelines and expected number of treated patients while balancing geographical spread. According to the current status of market launch sequence in European countries the following countries are planned: Austria, Belgium, Germany, Spain, Sweden, and the United Kingdom. The aforementioned countries represent a country market share in Europe of more than 90% in the second quarter 2018 (see Table 1). However, the list of countries is subject to change and will be finalized, based on the criteria above, before the start of the study.

Table 1. Market share of European countries for Alecensa in Q2 2018

Country	Market share of European countries for Alecensa in Q2 2018 (in %)[1]
Germany	61
Austria	9
UK	8
Spain	7
Sweden	5
Belgium	2
Hungary	2
Ireland	2
Portugal	1
Croatia	1
Norway	1
Italy	1

[1]Only European countries with Alecensa sales equivalent to at least 1% of the total European sales volume of Alecensa are recorded

8.2.2 Study Population

In each country, HCPs will be identified according to their speciality as specified in the proprietary [redacted] lists. The [redacted] lists are representative of the relevant HCP population in the selected countries and aim to provide coverage above 90% across the countries currently suggested for inclusion in the survey.

For this study, physicians in oncology and pulmonology will be considered. Due to the indication treatment of adult patients with ALK-positive NSCLC, they are the main prescriber group of Alecensa and, therefore, the target audience of the RMM.

All HCPs (i.e., oncologists and pulmonologists) in the study countries who can be identified as potential prescribers of Alecensa and have not provided their general opt out will be considered as the target population. The HCPs will be randomly selected from the [redacted] database, on an ongoing basis keeping a representative regional

spread, to participate in the survey until the target number of HCPs for that country is reached or the list is exhausted.

Inclusion criteria:

HCPs (i.e., either oncologists or pulmonologists) must meet the following criteria for study entry:

- HCPs must have treated patients (newly initiated or repeated administration/prescription) with ALK-positive NSCLC with Alecensa according to local label at least once in the 6 months prior to taking the survey

Exclusion criteria:

Inactive and retired HCPs (when documented information is available to identify them) will be deleted from the contact lists before randomization. HCPs who meet any of the following criteria will be excluded from study entry:

- HCPs who are not involved in patient treatment
- HCPs who may have conflicts of interest with the survey (i.e., HCPs employed by regulatory bodies, pharmaceutical industries)
- Employment by Roche, or any research organization/vendor contracted by Roche to administer the survey

8.2.3 Concomitant Medication and Treatment

Not applicable

8.2.4 Dosage, Administration, and Compliance

Not applicable

8.3 VARIABLES

The following variables will be considered:

1) Variables related to HCPs participation:

The following different cases will be distinguished (for details see definition in 8.7 Data Analysis):

- Response rate
- Refusal rate

2) Variables related to HCPs practice information:

- Location (country)
- Duration of practice (years of practice as a physician)
- HCP primary speciality (oncologist, pulmonologist)
- Type of setting (office-based, hospital based or both)
- Past experience with Alecensa (number of patients treated)

3) Variables related to the HCP awareness about the important identified risks in the label of Alecensa as well as the HCP awareness of clinical measures with respect to the identified risks (W&P) - percentages of HCPs with the answer “yes”:

   - Awareness of important identified risks (yes/no)
   - Awareness of clinical measures for risk minimization (yes/no)

4) Variables related to the HCPs knowledge on the requirement for specific monitoring and dose modification - percentages of HCPs with correct answers:

   - Important identified risks (W&P) for Alecensa (tick boxes with correct and false answers)
   - Specific monitoring with respect to the important identified risks (W&P) (tick boxes with correct and false answers)
   - Specific advice to patients with respect to the important identified risks (W&P) (tick boxes with correct and false answers)
   - Requirements for terminating Alecensa or specific dose modifications for the important identified risks (W&P) (tick boxes with different instructions for the management of patients, one correct answer possible per scenario)

5) Variables related to the HCPs clinical practice with respect to compliance with the clinical measures for important identified risks (W&P) – percentages of HCPs with correct answers:

   - Frequency of monitoring measures (tick boxes with correct and false answers) including:
     - AST/ALT monitoring
     - Creatine Phosphokinase (CPK) monitoring
     - Heart rate and blood pressure monitoring
   - Dose reduction scheme (to be filled in by the HCP)

6) Other variables: Source of information for Alecensa safety profile and prescribing information – percentages of HCPs per source of information

8.4 DATA SOURCES

The study is a survey using primary data collection conducted through a HCP questionnaire and collected by web or phone. Both methods will be proposed to HCPs and they will be given the choice to select one or the other.

8.4.1 Identification of HCPs

In each country, HCPs will be identified according to their speciality as specified in using the proprietary [redacted] lists, which is representative of the relevant HCP population and has a coverage of above 90%.

[redacted] is a comprehensive worldwide database of healthcare professionals. It is constructed according to ISO 9001: 2015 Quality Management Systems Requirements. The lists are representative of the HCP population in the selected countries.

In any case, all HCPs in the study countries who are potential prescribers (i.e., oncologists or pulmonologists) of Alecensa will be considered as the target population and will be randomly enrolled, on an ongoing basis keeping a representative regional spread until the study size is reached or the list is exhausted (see 8.4.2 Data Collection) (Kish 1995).

8.4.2 Data Collection

Questionnaire

The questionnaire will include multiple-choice, open, and closed questions as appropriate and will be sent to the participating HCPs to collect information on their awareness, knowledge, and clinical practice about the specific guidance included in the label to minimize the risk of ILD/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia, and CPK elevations.

The questionnaire will be translated into the relevant local languages. Translation will be done using the back and forth method of translation (i.e., from English into local language and then from local language into English). Physicians selected randomly from a panel of active physicians (i.e., physicians who regularly complete questionnaires of this nature) of the relevant specialities in the [redacted] database will ensure the meaning of the questions is retained in the translations (2-3 physicians per country). Before deployment, the questionnaire will be field tested to ensure accuracy.

The HCP questionnaire completion is estimated to take about 15 minutes.

Conduct of survey

For data collection a period of up to 6 months is planned. Data collection will be conducted between 18 and 24 months after the first line treatment approval by the European Medicines Agency (EMEA). In this 6-month time frame the fieldwork start date may vary by country based on the date of local market launch.

To ensure comprehension of the invitation and the survey, the entire HCP outreach will be conducted in the respective country's local language. The survey and invitation as well as any reminders will be translated by native speakers of the respective language at [redacted].

HCPs will be randomly contacted by emails or phone calls, when needed, according to their strata (country and if applicable speciality) by the [redacted] team. Their recruitment will be done as follows:

- HCPs will be invited to participate in the survey (via emails or phone calls). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the HCPs at this step. [redacted] will ensure that the compensation is in line with relevant guidelines of each country and that it only constitutes a compensation for the actual effort and time that is needed to fill-in the questionnaire
- If they agree to participate in the survey, they will click on the link included in the email to access the survey and the instructions for the web questionnaire completion
- HCPs can also choose to participate in the survey by phone in the local language. In this case, an appointment for a phone interview will be scheduled with them

- HCPs who self-report having treated patients with Alecensa at least once in the 6 months prior to the study and are not employed by a pharmaceutical company, [redacted], or by regulatory bodies will be eligible to complete the survey. Both parameters are included as screening questions in the questionnaire
- Once HCPs have passed the screening questions of the questionnaire, they are moved through the questions one question at a time. HCPs can only progress to the next question when the previous question was answered. Only wholly completed questionnaires can be submitted
- If the questionnaire is not completed within one week, the HCPs will be sent a reminder by email one week after the link was sent to them
- If the study sample size is not achieved in the stratum (speciality/country), a second reminder by phone will be conducted 1.5 weeks after the link has been sent
- If the questionnaire is still not fully completed, a third and final reminder will be sent to the HCPs by email approximately three weeks after the start of the survey

If necessary, i.e., if the minimum number of needed responders is still not reached, the recruitment will be continued to achieve the study sample size in a specific stratum.

A HCP will be considered as unreachable if he/she has been contacted between 3 and 5 times without any answer being received.

For each HCP of the sample, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each stratum (HCP speciality/country) will be stopped when the target is reached. If the files have been exhausted in any particular stratum, the recruitments in this stratum will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

The number of HCPs passing the screening questions, incidence rate, and the survey response rate will be monitored regularly by [redacted]. If the survey response rate or incidence rate is too low, the recruitment may be undertaken in additional countries.

8.4.3 Data Collected at Study Completion

Not applicable

8.4.4 Safety Data Collection

Not applicable

8.5 STUDY SIZE

8.5.1 Study size calculation

The sample size formula based on the normal approximation to the binomial is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half the desired width of the confidence interval, and Z1–α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = .05 then Z = 1.96).

The proportions of interest (p) here are the proportions mentioned under specific objectives above. As p is not known in advance, we consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative i.e., the largest sample size. For example, the required sample size would be 100 for precision levels of 10%. Table 2 below provides precision of the estimate (width of 95% CI around the estimate) for a range of sample sizes.

Table 2 Precision of the Estimate for a Range of Sample Sizes

Sample Size	Statistical Precision (%)
100	±9.8
150	±8.0
200	±6.9
250	±6.2
300	±5.7
350	±5.2
400	±4.9

For this survey, a sample size of approximately 200 completed questionnaires aggregated across the target countries is being considered, which is based on both statistical and practical considerations. With a sample size of 200, the statistical precision around the estimate will be ±6.9%; the precision will increase with larger sample sizes. It is to be noted that the final survey sample size will depend on HCPs' willingness to participate in the survey. While the target is 200 respondents, all completed responses received by the cut-off date will be included in the analysis.

Assuming that the survey response could be as low as 10%, about 2,000 HCPs will be invited to participate in this survey in order to increase the number of HCPs passing the screening questions and the likelihood that at least 200 HCPs fill out the questionnaire This estimate is in line with the low response rate reported for similar surveys in the literature (Agyemang et al. 2017).

Ideally, the sample of 200 HCPs should be proportionally split between the selected countries based on the number of HCPs in each country and then further split among HCP specialties based on their real proportion. However, due to large variance in the number of HCPs in targeted countries such a distribution would yield to a number of interviews in smaller countries (such as Sweden) or/and in specialties too small to allow the applicability of common statistical methods. A pragmatic split will therefore be implemented to allocate a sufficient sub-sample size to the less represented countries. An example of potential split among countries is given in Table 3.

We will then weight back the results according to the real proportion of HCPs from [redacted] lists to avoid the skewness of the overall sample.

8.5.2 Sampling Plan

For each selected country, the sample survey will include HCPs identified and recruited from the [redacted] list. The [redacted] database covers above 90% of the specialities of

interest (i.e., oncologists and pulmonologists) in the target countries (i.e., Austria, Belgium, Germany, Spain, Sweden, and the UK).

A screening question will check whether the physician did ever treat patients with Alecensa in the last 6 months prior to the survey and can therefore be considered for the survey.

With respect to the indication for Alecensa the survey will be deployed amongst oncologists and pulmonologists. The split between the two will depend on who provides care for NSCLC patients in each respective country.

As per sample size defined above and the number of selected countries, the following potential split of sample into strata of the HCPs by country is planned thereby taking into account the size of the country and the HCP universe size (see Table 3)

This table is indicative and will be adjusted according to the final list of countries included and the responsive HCP per strata. It is aimed to have at least 20 completed questionnaires per country.

Table 3 Split of Sample by Country According to a Sample of 200 HCP Questionnaires

Planned Country	Overall Number of Completed Questionnaires[a]	Universe Oncologists[b]	Universe Pulmonologists[b]
Germany	50	2900	2400
United Kingdom	45	2700	2500
Spain	45	2300	N/A[c]
Austria	20	300	600
Belgium	20	500	700
Sweden	20	600	300
Total	**200**	**N/A**	**N/A**

[a]The split between specialties depends on the involvement of specialties in the management of advanced lung cancer patients in the different target countries and may be subject to change.

[b]Universe: Numbers of oncologists/pulmonologists in the country according to [redacted] (version June 2018)

[c]Only oncologists are relevant in the treatment of NSCLC in Spain

8.5.3 Sample adjustment

Since the relative weight of each country and each category of HCPs in the final sample may be different from its real proportion, the extrapolation of the raw survey results to the overall target population would not be relevant without adjustment. The survey results will be weighted to reflect the real proportion of the countries and the real proportion of each speciality in order to allow the extension of the survey results to the

overall target population. Both unweighted and weighted results will be presented in the report.

A weight variable will be applied to each statistical unit (i.e., the HCPs) during the results calculation to correct any over-or under-sampling that may have occurred for a country or speciality. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country and per speciality. The weights will be normalized to obtain their sum equal to the sample size.

8.6 DATA MANAGEMENT

[redacted] will be responsible for data management of this study, including quality checking of the data.

The survey will be conducted according to the Standard Operating Procedures (SOPs) of [redacted] and [redacted].

Collected data will be entered and stored in a central database specific to the survey.

A study database will be created by merging the databases of each country together. The study database will be locked once validated.

8.6.1 Data Quality Assurance

[redacted] QC team will be responsible for the data management of this study, including quality checking of the data. [redacted] will produce a Data Quality Review Plan that describes the quality checking to be performed on the data.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values (implausible answers, e.g., an answer of 999mg)

Automatic checks for plausibility and consistency will be programmed into the questionnaire tool, which will prevent contradicting values from being entered. [redacted] will not query HCPs' answers to questions in the questionnaire.

Non-admissible values will be avoided by implementation of the appropriate controls in the questionnaire at the time of its completion by the HCPs. Any non-admissible values identified after database lock (if any) will be excluded from the analysis.

The marketing authorization holder will perform oversight of the data management of this study, including approval of [redacted] data management plans and specifications.

The QC team will comply with the Roche's procedures regarding archiving and record management.

8.6.2 Source Data Documentation

Not applicable

8.7 DATA ANALYSIS

General considerations

The statistical analysis will be conducted using the SAS software (Version 9.4 or above).

The statistical results of the HCP data will be presented in the same report, by country, by speciality, and in total (see Table 4 as example).

Continuous variables will be presented by their number (of valid cases), mean, standard deviation, and median, Q1, Q3, minimum, and maximum.

Categorical variables will be presented as the total number and relative percentage per category. These will be the percentage per category.

In case of multiple choice questions, the frequency of each option provided by the physicians will be reported in the statistical results. Different combinations of the answers provided will not be considered.

Confidence intervals of 95% will be estimated, as appropriate.

Table 4 Mock Tables to Implement in the Statistical and Study Reports

Country	Speciality (Pulmo)	Speciality (Onco)	All (unweighted)	All (weighted)
Country 1	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				
Country 2	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				
Country 3	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				
Country x	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

….				
Overall - unweighted results	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				
Overall - weighted results	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				

Note: the table structure may be adjusted for the final study report.

Handling of missing data

All questions in the questionnaire will be mandatory and cannot be skipped. Questionnaires can only be submitted when fully completed. Therefore, missing data are not expected to occur.

Entering erroneous information is only possible for open questions. These non-admissible values (if any) identified after database lock will be excluded from analysis.

Analysis of HCP Participation Rate

The following different cases will be distinguished:

- HCPs who refused to participate (R): HCPs explicitly mentioned their refusal to participate
- HCPs with partial questionnaires (P): HCPs who clicked on the link provided in the invitation email, who began the questionnaire but never submitted it
- HCPs with completed questionnaire (C): HCPs who completed the entire questionnaire
- Contacted HCPs: HCPs who was reached by phone or who received a web link to the online survey via email. For survey invitations issued via postal mail the assumption will be made that if mail is not returned, HCP will be considered "contacted" = C+P+R
- HCPs who agreed to participate: HCPs willing to participate in the survey (e.g., by phone or by clicking on the link provided in the invitation email) = P+C

The HCPs' participation in the survey will be examined as follows (adapted from: *American Association for Public Opinion Research 2016*) :

- Response rate $= \frac{C}{C+P+R}$
- Refusal rate $= \frac{R}{C+P+R}$

The participation rates will be presented by country and by speciality.

Questionnaire analysis

Analysable questionnaires are those completed and submitted by the participants on the web or by phone. If the questionnaire is just filled on the web but not submitted, or if the name and surname of the participant is disclosed, the questionnaire will not be analysed and will be discarded.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among HCPs who provided answers to those questions.

Awareness questions (Questions Q2 to Q3 of HCP questionnaire:
Individual HCP awareness scores will be descriptively analysed and reported as percentages. HCP awareness level will be calculated as the mean of the individual scores.

Knowledge questions (Questions Q5 to Q8 of HCP questionnaire):
For each question, the number and percentage of HCPs answering correctly each sub-question will be presented. Subsequently, individual HCP knowledge scores will be calculated as the percentage of correctly answered knowledge questions; scores will range from 0 to 100% with 100% representing the percentage of all knowledge questions being answered correctly. HCP knowledge level will be calculated as the mean of individual scores.

Clinical practice questions (Questions Q9 and Q10 of HCP questionnaire):
For each question, HCPs answering correctly each sub-question will be presented. Subsequently, individual HCP clinical practice scores will be calculated as the percentage of correctly answered survey questions; scores will range from 0 to 100% with 100% representing the percentage of all clinical practice questions being answered correctly. HCP clinical practice level will be calculated as the mean of individual scores.

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, the line "Overall - unweighted results" will show only the results observed on the overall sample and will not reflect the countries' universe since this sample is not proportional to the size of the lists in each country.

In a second step, the results will be weighted according to the real proportion of HCPs in each country in order to accurately reflect the population that the survey seeks to measure.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g., country, type of setting (hospital or office-based), and speciality, if applicable and feasible) between respondent and non-respondent HCPs.

Moreover, the profile of HCPs with incorrect answers could be identified and described with all available relevant covariates collected in the survey (e.g., country, duration of practice, type of setting, and speciality) and past experience with Alecensa (number of patients treated).

Assessment of success

A successful outcome on the effectiveness of risk minimisation measures is defined a priori by the following target levels:

1. Proportion of HCPs being aware of the important identified risk and related minimisation measures for Alecensa (Question Q2 and Q3 of HCP questionnaire) – Success: ≥75%
2. Proportion of HCPs knowledgeable about the important risks, specific monitoring, dose modification (Questions Q5 to Q8 of HCP questionnaire) – Success ≥60%
3. Proportion of HCPs answering the clinical practice questions in compliance to the SPC (Questions Q9 andQ10 of HCP questionnaire) – Success ≥75%

The proportion of HCPs meeting the success criteria in all three categories is the overall success factor for the implementation of RMM for the important identified risks for Alecensa. The thresholds used are in accordance with success rates applied in other studies approved by PRAC and provide a balance between the ideal scenario of achieving a 100% rate of awareness, knowledge and compliance and what can be realistically expected from routine RMMs in the clinical practice.

8.8 QUALITY CONTOL

8.8.1 Study Documentation

Validation of questionnaire

The questionnaire will be tested by targeted HCPs (at least one per speciality) in each country for their comprehensibility, consistency, and the appropriateness of medical terms used. The questionnaires will be translated from English into local language using the back and forth method to ensure an accurate translation of the local versions of the questionnaire. Translation and back translation will be performed by [redacted] personnel.

Approaches for validating the results

The quality control for validating the results will be conducted at five levels:

1. At data collection level, the survey data will be collected using a secure online electronic data capture (EDC) survey system. The proposed data entry system has been tested and is secure for receiving and storing survey data. A web-based data repository will be used to warehouse survey data and other relevant program information. This EDC system is an EU Annex 11 and 21 Code of Federal Regulations Part 11 compliant platform for the entry, storage, manipulation, analysis, and transmission of electronic information. This platform ensures compliance with all relevant regulatory guidelines and is already used in several PRAC-approved surveys (European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance study register).[1] All data entered will be single data entry directly done by the respondent or the interviewer in the case of phone interviews. Verification of the reliability and security of the web questionnaire interface will be done by [redacted] QC team. A qualified data manager will perform the monitoring of the quality and datasets definition.

2. At the study database level, final data quality checks will be applied (beyond data management process):
    - Identification and count of non-analysable questionnaires: estimation of the percentage of HCPs without complete analysable questionnaire
    - Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. Once data is validated and quality checked, the database will be locked
3. At the statistical analysis level: all data management and statistical analyses programs developed and used in the analyses will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4. At the results level, a data review will be done to ensure data integrity.
5. At the study level, all aspects of the study will be conducted according to the SOPs of [redacted] and [redacted] divisions. According to the SOPs, an independent review of the survey results and report will be conducted by a person who was not in charge of their preparation.

8.8.2 Site Audits and Inspections

Not applicable.

8.8.3 Safeguards, security and traceability of contacts

Operators of the call centre specialised in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts will be traced using the management software.

8.8.4 Retention of Records

The study documentation will be stored in the study master file.

The data from the web questionnaires and the phone interviews will be stored on the survey database for 5 years.

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[1] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). http://www.encepp.eu/encepp/studySearch.htm: EUPAS11379, EUPAS11765, EUPAS6355, EUPAS9871

Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All documentation pertaining to the study, including paper and electronic records will be retained for a minimum of 5 years after the end of the study, in accordance with [redacted] Standards.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Bias

The potential for selection bias of HCPs participating in a survey is an inherent bias/limitation to any study based on volunteer participation.

Among non-response bias, targeted HCPs may also have activated filters in their mail box to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the HCPs do not check their email box frequently they will not receive the invitation during the recruitment period. This is one of the reasons why the HCPs will also be contacted by phone.

Moreover, web surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or clinical practice, e.g., physicians can copy-paste information gathered online instead of giving their own opinions (Wyatt 2000). Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (Nederhof 1985).

The access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once and a traceability system. Thus, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

Limits inherent to surveys

In such surveys, the generalisation and external validity of the results is restricted to HCPs who have an active email address or phone number and are willing (and able) to answer a questionnaire. These HCPs may not be fully representative of the whole targeted HCP population (Wyatt 2000).

Generalisation of the survey results

The raw survey results cannot be generalized to the overall HCP target population, except if a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e., raw data) and weighted results will be presented in the report.

8.10 OTHER ASPECTS

Strengths of the research methods:

1. The information contained in the [redacted] file of each country is updated constantly with proactive updates. Quality controls are implemented on a regular basis.
2. The sampling of HCPs follows a stratified randomized method which guarantees the representativeness of the contacted population to limit selection bias due to voluntary participation. HCPs will be contacted up to five times before moving forward to other HCPs in the lists.

3. The questionnaire includes general questions followed by specific ones to limit a learning process during the survey. As the HCPs may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.
4. The questionnaire is tested for its clarity. It is also checked whether there are questions which would suggest a specific answer for any reason for example social desirability. The translation of the questionnaire is tested before implementation.
5. The study is conducted by an experienced team specialised in the design and conduct of such surveys in the area of safety. It follows [redacted] SOPs as well as the methodological guidelines on European Network of Centres for Pharmacoepidemiology and Pharmacovigilance and EMEA GVP.

9. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential and only aggregated data will be analysed and communicated in a report.

9.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.1.1 Informed Consent

HCPs participating in the study have to consent for data collection and need to be informed about the purpose of the survey and their storage of data. [redacted] will ensure that the national and European data protection and ethical requirements are met for the HCPs. This will be done electronically.

9.1.2 Institutional Review Board or Ethics Committee

Each participating country should locally ensure all necessary regulatory submissions (e.g., IRB/Independent Ethics Committee) are performed in accordance with local regulations including local data protection regulations.

9.1.3 Financial Disclosure

HCPs will be offered a compensation for the time spent participating in this survey (that they may refuse). For HCPs involved in the HCP survey, the estimated time to complete the questionnaire is 15 minutes. The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, which states:

“When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the

time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws."

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of material implemented as RMM. This survey does not involve data collection on clinical endpoints on individual patients. Although adverse event information is not being actively solicited via this protocol, any safety information for an individual patient that is volunteered by a study physician during the course of this research must be reported as described below.

In the event that a study participant reports a safety event associated with a Roche product, [redacted] will forward any information on adverse events (AE; serious and non-serious) that involve Roche products to the Roche Pharmacovigilance department using the AE report form available via the national spontaneous reporting system. This will be done within the timeline of 24h for serious AE or within 30 days for non-serious AE.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, Roche is dedicated to openly providing information on the study to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the marketing authorization holder prior to submission for publication or presentation. This allows the marketing authorization holder to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of marketing authorization holder personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate marketing authorization holder personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the marketing authorization holder, except where agreed otherwise.

The final survey report validated by Roche will be communicated to EMEA. An abstract of the results will be uploaded to the EU-PAS registry.

12. REFERENCES

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Appendix 1- ENCePP Checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

ALECENSA SURVEY TO PRESCRIBERS: EFFECTIVENESS MEASURE TO INVESTIGATE THE CORRECT IMPLEMENTATION OF ALECTINIB LABEL GUIDANCE BY PRESCRIBERS

Study reference number: BO40643

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	3 and 5
1.1.2 End of data collection[3]	☒	☐	☐	3 and 5

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	3 and 5

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)	☒	☐	☐	3, 6.1, 7.1, and 8.1.1
2.1.2 The objective(s) of the study?	☒	☐	☐	3 and 7.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3 and 8.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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)	☒	☐	☐	3 and 8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	3 and 8.4
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)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	3 and 8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	3
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	8.2
4.2.4 Disease/indication?	☐	☐	☒	8.2
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)	☒	☐	☐	8.2

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)	☐	☐	☒	
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?	☒	☐	☐	3 and 7.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3 and 8.7
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)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
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)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	3 and 8.4.2
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 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?	☒	☐	☐	3 and 8.7
10.2 Are descriptive analyses included?	☒	☐	☐	3 and 8.7
10.3 Are stratified analyses included?	☒	☐	☐	3 and 8.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5.1

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)	☒	☐	☐	8.8.4
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8.1

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?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
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)	☒	☐	☐	8.5.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	8.8.4

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?	☒	☐	☐	4

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)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Appendix 2 – HCP Questionnaire

Evaluation of the effectiveness of risk minimization measures for Alectinib in the European Union

HCP questionnaire

SURVEY FOR THE EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION MEASURES FOR ALECTINIB IN THE EUROPEAN UNION

Invitation Letter

Dear Dr…….

We, [redacted], are contacting you to request your participation in a post-authorization non-interventional survey on behalf of F. Hoffmann-La Roche (Roche), who is the marketing authorization holder of Alecensa® (alectinib) in your country.

The objective of this survey is to evaluate the effectiveness of risk minimisation measures for alectinib and, in particular, to assess physicians' awareness and knowledge of important identified risks (warning and precautions) and the specific clinical measures to address them as described in the Summary of Product Characteristics (SPC) and the local label. The survey is sponsored and funded by Roche, and has been agreed with the European Medicines Agency (EMA).

This survey concerns general questions on the use of Alecensa® and the awareness of routine risk minimisation measures implemented.

The questionnaire will be conducted anonymously. Your identity will remain confidential and the results obtained will be presented in aggregated form to Roche and Regulatory Agencies. No connections will be made between your identity and your answers to the questionnaire.

The questionnaire does not involve any promotional material and there will be no further contact for marketing purposes based on your answers to the survey.

The overall questionnaire will take approximately 15 minutes and can be completed web-based or by phone.

You will be compensated for the time you have invested to complete the survey *[to be adapted to the speciality and country].*

We would greatly appreciate your participation in this questionnaire and thank you very much in advance for your time. Please click on the link below to access the questionnaire:

http://URLxxx *[to be inserted for each country].*

You may at all times request a copy of your personal information, have it corrected and object to its processing by contacting [redacted] Team at [redacted] *contact details*].

Kind regards,

[redacted] Team

SURVEY FOR THE EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION MEASURES FOR ALECTINIB IN THE EUROPEAN UNION

Web questionnaire

Introduction and disclaimer

This survey is a non-interventional post-authorization safety study that has been designed in order to comply with Article 21a.(b) of Directive 2001/83/EC and evaluate the effectiveness of risk minimization measures for Alecensa® (alectinib) in the EU. In particular, to assess physicians' awareness and knowledge of important identified risks (warnings and precautions) and specific clinical measures to address them as described in the Summary of Product Characteristics (SPC).

The survey has been agreed with the European Medicines Agency (EMA) and it is sponsored by F.Hoffmann-La Roche (Roche), the Marketing Authorisation Holder (MAH) of Alecensa®. [redacted], is in charge of the implementation of this survey and the analysis of the results on Roche's behalf.

Your identity will always remain confidential. The results obtained from the survey will be disclosed in aggregated form to Roche and regulatory agencies, thus protecting your identity.

We greatly appreciate your participation in this research survey.

The questionnaire will take approximately 15 minutes to complete.

As appreciation for the time you will dedicate to complete the questionnaire you will be compensated with *[to be adapted to the specialty and country]*.

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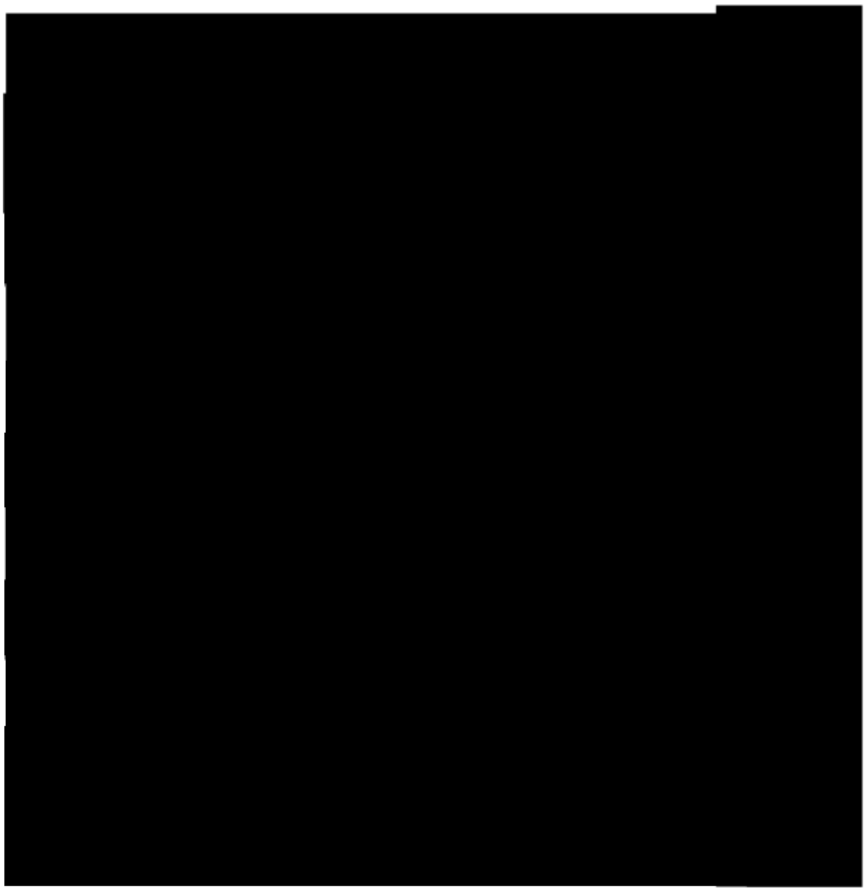

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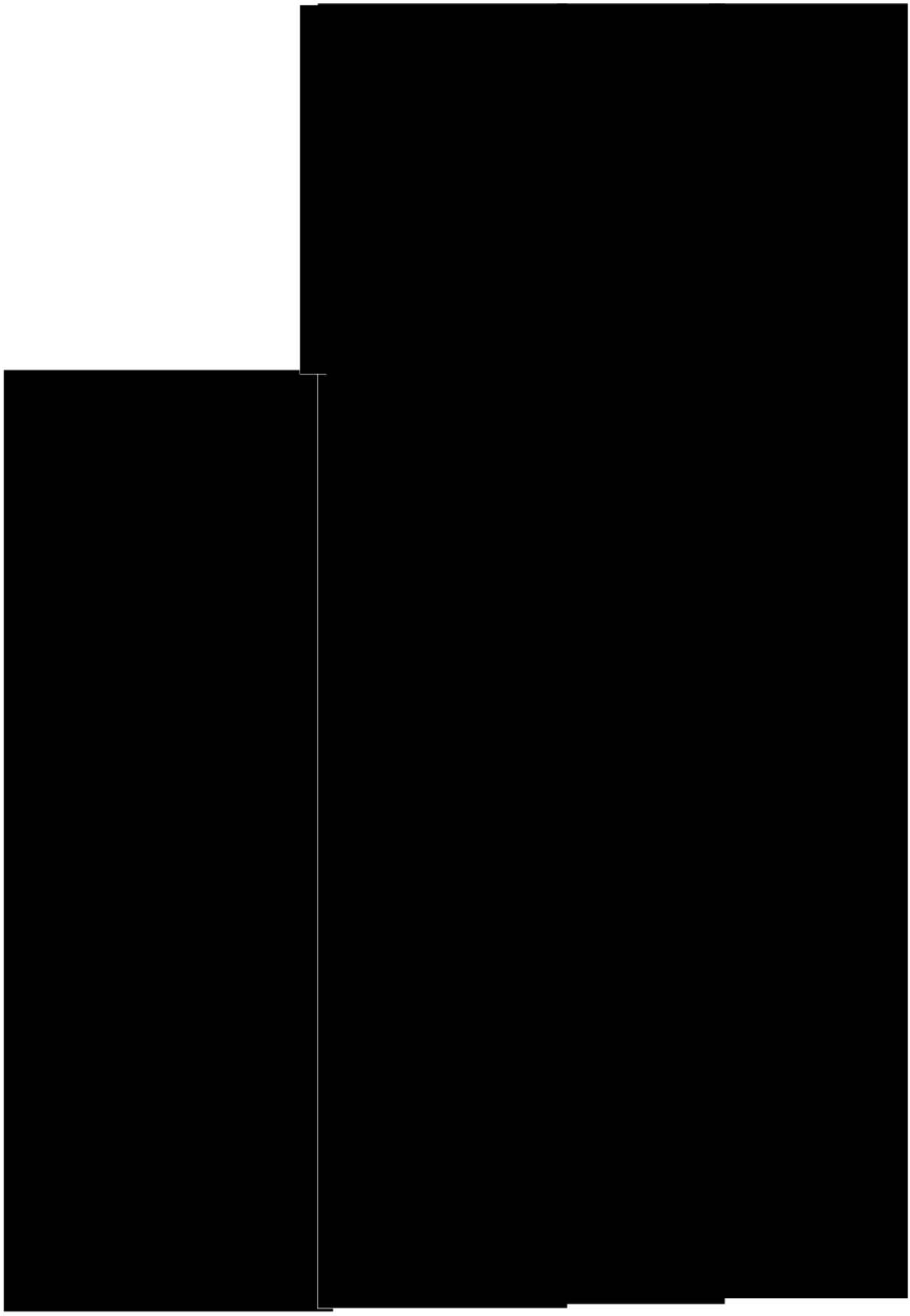

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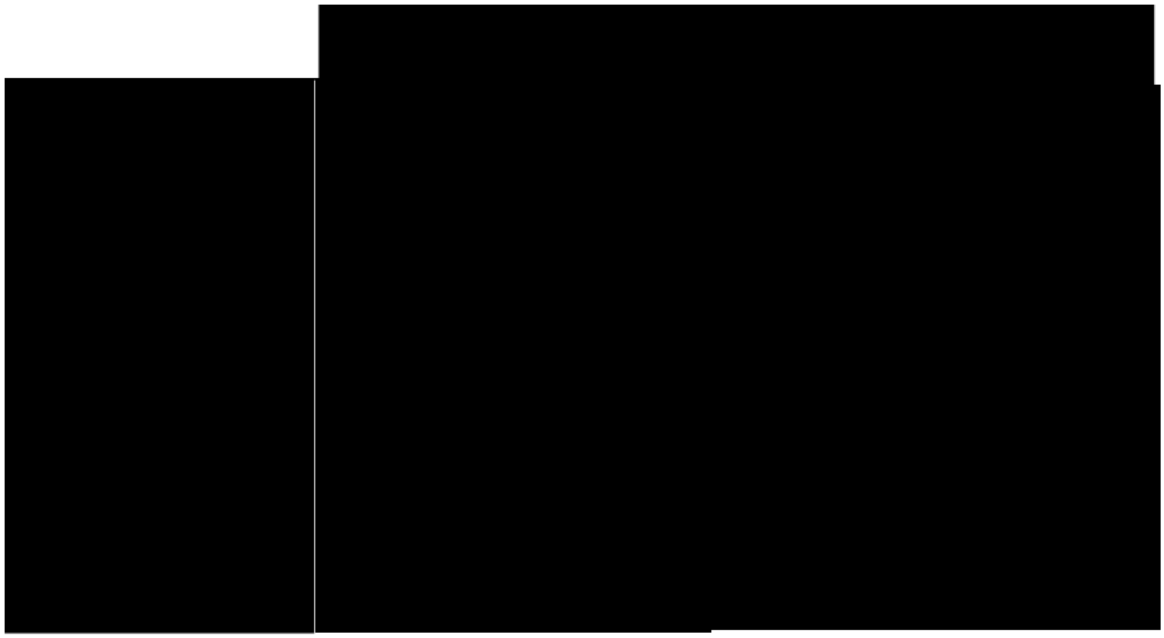

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