TITLE PAGE

STUDY REPORT NO 1101047

PASS INFORMATION

TITLE:	**ALECENSA SURVEY TO PRESCRIBERS: EFFECTIVENESS MEASURE TO INVESTIGATE THE CORRECT IMPLEMENTATION OF ALECENSA LABEL GUIDANCE BY PRESCRIBERS.**
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STUDY REPORT APPROVAL

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ACTIVE SUBSTANCE	ATC code L01XE36: Alectinib
PRODUCT REFERENCE NUMBER{S}:	EMEA/H/C/004164
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JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this study is to evaluate the effectiveness of Alecensa's risk minimisation measures (RMMs) for the important identified risks (interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia and creatine phosphokinase [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 the HCPs' awareness of the important identified risks and their related minimization measures • To measure the HCPs' knowledge on the requirement for specific dose modifications for the above mentioned important identified risks • To measure the HCPs' knowledge on the requirement for specific monitoring for the above mentioned important identified risks • To measure whether the HCPs follow the Summary of Product Characteristics (SmPC) recommendations regarding the specific clinical measures
COUNTRIES OF STUDY POPULATION:	Germany, the United Kingdom, Italy, Austria, Belgium, Hungary and Sweden.

MARKETING AUTORISATION HOLDER(S)

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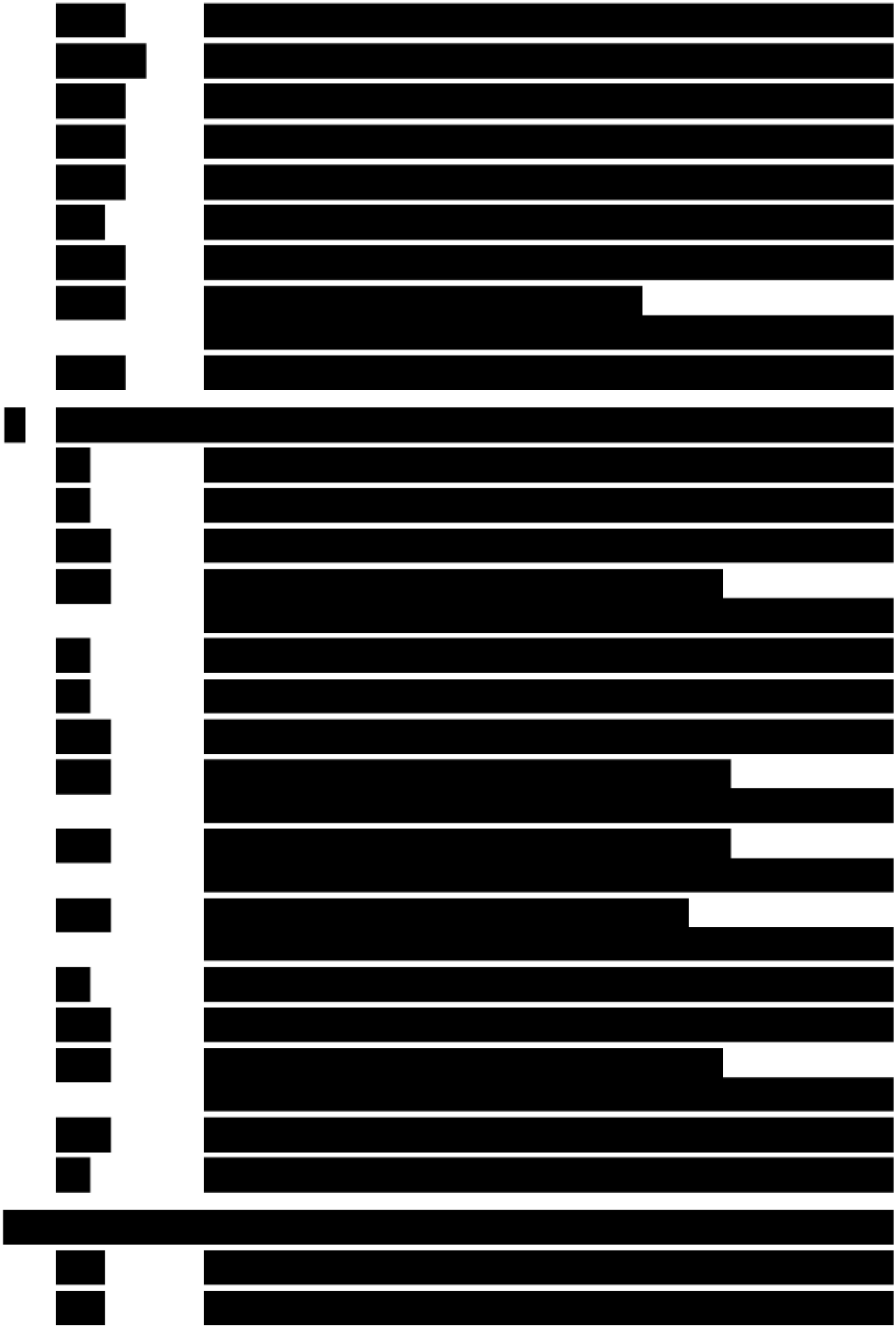

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1. SYNOPSIS/ABSTRACT

Title

Alecensa survey to prescribers: Effectiveness measure to investigate the correct implementation of Alecensa label guidance by prescribers.

Keywords

Post-authorization safety study, non-interventional study, survey, HCP, physician, questionnaire, NSCLC, alectinib

Rationale and Background

Alecensa® (alectinib) is an oral, small molecule tyrosine-kinase inhibitor targeting anaplastic lymphoma kinase (ALK) and c-RET oncogenes. It received marketing authorization from the European Medicines Agency (EMA) as a monotherapy for treatment of ALK-positive advanced non-small cell lung cancer (NSCLC) adult patients in the crizotinib-failed setting on February 16th, 2017 and in the first-line setting on December 18th, 2017.

Treatment with Alecensa (alectinib) is associated with the important identified risks of interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and creatine phosphokinase (CPK) elevations, as outlined in the risk management plan (RMP). To facilitate the management of these identified risks, clinical measures have been included in the Summary of Product Characteristics (SmPC).

Research Question and Objectives

The aim of this study was to evaluate the effectiveness of the risk minimization measures (RMMs) for Alecensa, as described in the SmPC, by assessing their correct implementation by the prescribing health care providers (HCPs) for the important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and CPK elevation.

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

Secondary objectives: 1) To measure the HCPs' awareness of the important identified risks and their related minimization measures; 2) To measure the HCPs' knowledge on the requirement for specific dose modifications for the important identified risks; 3) To measure the HCPs' knowledge on the requirement for specific monitoring for the important identified risks; 4) To measure whether the HCPs follow the SmPC recommendations regarding the specific clinical measures.

Amendment and Updates to Protocol

None

Study Design

The study was an anonymous, cross-sectional, multinational, multi-channel survey with HCPs in European countries in form of a web-based questionnaire. The survey included HCPs that had treated ALK-positive NSCLC patients with Alecensa according to the local label at least once in the six months prior to taking the survey.
The study start date (i.e., begin of data collection) was May 22nd, 2019, which was approximately 18 months after receipt of approval for first-line treatment of adult patients with ALK-positive advanced NSCLC in the European Economic Area (EEA). The end of the study was the date of the last completed HCP questionnaire, which was October 21st, 2019.

Setting

The survey was conducted targeting office and hospital-based Alecensa prescribers in seven European countries (Austria, Belgium, Germany, Hungary, Italy, Sweden and the United Kingdom [UK]), which were selected to ensure representation based on different country sizes, cultures, and healthcare systems within Europe.

Subjects and study size

The study was an HCP-only survey and no patients were involved.

HCPs in the IQVIA [redacted] database were identified as potential prescribers of Alecensa (i.e., oncologists and pulmonologists) and had not provided their general opt-out to participating in survey studies were considered as the target population.

Inclusion criterion:

- HCPs must have treated patients with ALK-positive NSCLC with Alecensa according to the local label at least once in the six months prior to taking the survey.

Exclusion criteria:

- 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.

The target study size was set at 200 questionnaires completed by 200 distinct HCPs from all the study countries. The HCPs were randomly selected on an ongoing basis from the IQVIA [redacted] database, keeping a representative regional spread, until the target number of HCPs for each country was reached.

Variables and Data Sources

The following variables were recorded or derived:

1) Variables related to the HCPs' participation:

The following different rates were calculated:

- Response rate (total, complete response, and partial response);
- Refusal rate.

2) Variables related to the HCPs' practice information:

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

3) Variables related to the HCPs' awareness about the important identified risks in the label of Alecensa as well as the HCPs' awareness of the clinical measures with respect to the identified risks (Warnings and Precautions [W&P]) - percentages of the HCPs with the answer "yes":

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

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

- The important identified risks (W&P) for Alecensa (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);
- 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).

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

- Frequency of monitoring (tick boxes with correct and false answers) – including:
    - AST/ALT monitoring;
    - 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 the HCPs per source of information.

Data collection

The survey data collection methods used were (at the preference of the HCPs):

- The HCPs' completion of the questionnaire via a web portal;

The HCPs' completion of the questionnaire over the phone, guided with an IQVIA team member.

Statistical Methods

The overall questionnaire response rates and the response rates for the different groups (countries and speciality) were calculated in order to detect any participation bias. Analysable questionnaires were those completed and submitted by the participants on the web or over the phone.

The scoring was performed based on the percentage of correctly answered items per question or domain. A weight variable was then applied to each statistical unit (i.e., the analysable HCP questionnaire) during calculation of the results in order to correct overall scores for any over- or under-sampling of a stratum. The unweighted and the weighted results are presented in this report. However, for the purpose of generalizing the results to the target population, only the weighted results are discussed.

For each HCP, an individual success outcome on the effectiveness of the RMMs was calculated based on the criteria for success on three domains as follows:

- awareness = 100%
- knowledge ≥ 60%
- clinical practice ≥ 75%
- average correct responses to the questions of each domain, respectively.

The percentage of the HCPs meeting the success criteria in all three domains was used as the overall success factor for the implementation of RMMs for the important identified risks for Alecensa (alectinib). Furthermore, as defined in the study's statistical analysis plan (SAP), overall success of the effectiveness of the RMMs for Alecensa was considered to be achieved when the overall weighted percentage of the HCPs who achieved individual successful effectiveness in at least two domains is equal to or higher than 60%. The profile of the HCPs with incorrect answers was also described including all available relevant background variables collected in the survey (e.g., country, duration of practice, type of setting, and speciality), past experience with Alecensa

(number of patients treated) as well as the source of information on the safety profile and prescribing information of Alecensa.

A post-hoc analysis was conducted using a less stringent definition for individual success on the "clinical practice" domain with the threshold set at 66.7%.

Results

A total of 4,346 HCPs from seven countries (Austria, Belgium, Germany, Hungary, Italy, Sweden, and the UK) were selected to be invited to participate in the survey, of whom 4,150 HCPs were reachable. Of the reachable HCPs:

- 2,514 HCPs did not respond to the invitation;
- 393 HCPs were not eligible to participate;
- 939 HCPs refused to participate (refusal rate: 22.6%);
- 304 HCPs agreed to participate in the survey (response rate: 7.3%). Of this group,
    - 203 HCPs completed the questionnaire (complete response rate: 4.9%)
    - 101 HCPs partially responded to the questionnaire (partial response rate: 2.4%).

Only completed questionnaires (203 in total) were used in the analysis and presentation of results. The majority of the respondents who completed the questionnaires were oncologists (71.9%). Pulmonologists in Italy and the UK are not usually involved in treating lung cancer patients and thus all respondents from these two countries were oncologists. Most HCPs (81.8%) were hospital-based, 7.9% were office-based, and 10.3% were both office and hospital-based in equal amounts. The majority of the HCPs had more than 10 years of experience as practicing physicians (77.3%).

The overall weighted percentage of the HCPs who achieved individual successful effectiveness in at least two of the three domains assessed in the study was 85.2%, which exceeded the predefined 60%-threshold set for the primary outcome of this study in the SAP. Additionally, the weighted percentage of the HCPs who achieved individual successful effectiveness on all three domains of the questionnaire was 23.0% (95% CI: 16.6%-29.4%).

At the domain level, the following results were achieved for the secondary outcomes:

- 94.7% (95% CI: 91.2%-98.2%) of the HCPs were fully aware of the identified risks related to Alecensa and their minimization measures (i.e., correctly answered 100% of the questions of the awareness domain).

- 86.1% (95% CI: 80.7%-91.6%) of the HCPs were knowledgeable about the W&P related to treatment with Alecensa as well as the required minimisation measures for the important identified risks (i.e., received at least a 60% average score for the questions of the knowledge domain).

- 27.1% (95% CI: 20.2%-33.9%) of the HCPs followed the recommendations for the monitoring measures and dose levels in their clinical practice (i.e., received at least a 75% average score for the questions of the clinical practice domain)

The complete response rates were similar in all study countries. The highest response rate was observed in Austria (6.8%), whereas the lowest response rate was seen in Sweden (3.3%).

Overall, the relative speciality distribution of the HCPs who completed the questionnaire was consistent with the one observed among the reachable HCPs (approximately 1:2.6, pulmonologists to oncologists). However, in Belgium and Sweden, pulmonologists were more likely to complete the questionnaire than oncologists.

Germany had the highest percentage (34.4%) of reachable HCPs who refused to participate in the survey, followed by the UK (24%), Italy (23.7%), Sweden (23.4%), Belgium (13%) and Austria (11.5%). Only 3% of the reachable HCPs in Hungary refused to participate in the survey.

In addition, the overall ratio of the HCPs who refused to participate from each speciality was approximately 1:3.8, pulmonologists to oncologists. The specialty ratio of the HCPs who were reachable was approximately 1:2.6 (pulmonologists to oncologists), meaning that oncologists were generally more likely to refuse participation in the survey than pulmonologists. Countries where relatively more pulmonologists than oncologists refused to participate in the survey included Austria, Hungary and Sweden.

Of the HCPs who answered the three items of the safety monitoring measures question incorrectly (the clinical practice question which had the lowest score, Q9), 69%-71.6% used congresses, conferences or symposia, and 63.5%-65.6% used medical or pharmaceutical representatives as their source of information on Alecensa, compared to 63%-66.2% and 61.7%-64.9% of the HCPs who answered this question correctly, respectively. Furthermore, they also tended to refer to the SmPC less: 58.2%-63.8% of the HCPs who answered this question incorrectly vs. 66.7%-75.3% of the HCPs who answered this question correctly.

Discussion

The overall weighted percentage of the HCPs who achieved individual successful effectiveness in at least two of the three assessed domains in the study was 85.2%, indicating effectiveness of the RMMs according to the predefined threshold of 60%.

Success in all three domains of awareness, knowledge, and clinical practice was achieved by 23% of the HCPs. The majority of the HCPs were aware (94.7%) of the identified risks related to Alecensa and their minimization measures, and knowledgeable (86.1%) about the W&P related to treatment with Alecensa as well as the required minimization measures for the important identified risks. This result (23% success in all three domains) was mostly influenced by the percentage of the HCPs who met the criterion of success in the clinical practice domain (27.1%), which was due to two main factors:

- HCPs were being overcautious in some scenarios and chose (by the virtue of the responses given) to observe stricter safety measures beyond what is indicated in the SmPC leading to incorrect responses;

- the predefined threshold for success in the clinical practice domain, set at 75%, allowed for only one incorrect answer out of the six items of the clinical practice domain questions (Q9 and Q10), which practically corresponded to an 83.3% threshold – an HCP was considered unsuccessful in the clinical practice domain if more than one item was answered incorrectly

Looking at the level of the individual questions of the knowledge domain, the responses to Q6 (knowledge on dose modifications recommendations) suggest that some HCPs may choose to observe stricter dose modifications than what is recommended per Alecensa's label (see Q6d, Q6e, Q6g, Q6i and Q6j for detail). While there are no direct safety risks to patients from this practice, being overcautious in terms of dose modification could prevent patients from receiving adequate exposure to Alecensa. Of note, however, 60.2% of the HCPs chose a less strict answer (resuming Alecensa after temporary withholding instead of permanent discontinuation) to the question related to dose modification in case of hepatotoxicity, meeting Hy's law criteria (Q6b).

The overall scores for Q7 and Q8 (knowledge of the parameters to be monitored and advice to be given to patients taking Alecensa, respectively) were 80.6% and 81.7%, respectively. Responses to Q7 suggest that some HCPs choose to observe additional measures that are not required as per the Alecensa label, (e.g., monitoring bone marrow function (50.7%). A possible reason for this could be that these clinicians believed that they needed to monitor for the adverse reaction of anaemia associated with Alecensa, which is not required by the SmPC. Neutropenia and lymphopenia are laboratory abnormalities known to be associated with ALK inhibitors other than Alecensa, which may have led the HCPs to opt for bone marrow monitoring in their answer.

Looking at the level of the individual questions of the clinical practice domain, Q10 (dose levels prescribing practice) was answered correctly by the majority of the HCPs while the relatively low score for Q9 (monitoring measures practice) reveals the following themes, which align with aforementioned observations. First, in line with the observation from Hy's law dose modification requirement Q6b, the recommended frequency of liver

function monitoring stipulated by the SmPC was not followed by the HCPs. A total of 46.2% of the HCPs chose a shorter period of bi-weekly monitoring (Q9a). Furthermore, the HCPs tended to be overcautious (as with Q6d, Q6e, Q6g, Q6i and Q6j) and monitor CPK levels, heart rate and blood pressure for longer periods or more often than required by the SmPC (Q9b and Q9c).

Conclusion

Based on the results of this survey, 85.2% of the HCPs succeeded in at least two of the three assessed domains. Hence, the 60% predefined criterion for success of the RMMs set in the SAP has been met and the overall results suggest that the RMMs outlined in the SmPC are adequate according to this criterion.

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