EPIDEMIOLOGY STUDY REPORT

An assessment of physician knowledge and understanding of the risks of vandetanib (Caprelsa®) within the European Union

Vandetanib

Study type:	Cross-sectional study
Company:	Genzyme Europe B.V.
Version Number/Status:	2.0
Study Number	VANDEC08518

This study was conducted in accordance with Sanofi standard operating procedures for epidemiologic studies

---

Date: 22-June-2018 Total number of pages: 38

PASS information:

Title:

An assessment of physician knowledge and understanding of the risks of vandetanib (Caprelsa®) within the European Union

Vandetanib

Version identifier of the final study report	*2.0*

Date of last version of the final study report	*May 25, 2017*
EU PAS register number	*ENCEPP/SDPP/4242*
Active substance	*CAPRELSA® (vandetanib)*
Medicinal product	CAPRELSA® (*vandetanib*)
Product reference	*Vandetanib*
Procedure number	*N/A*
Marketing authorisation holder(s)	*Genzyme Europe B.V.; Gooimeer 10, 1411 DD, Naarden, Netherlands,*
Joint PASS	*No*
Research questions and objective(s):	*The primary objective was to assess the knowledge and understanding of physicians in relation to key elements in Caprelsa educational materials*
Country(-ies) of study	*United Kingdom, Germany, France, Spain, Italy, Belgium, Austria, Luxembourg, Netherlands, Sweden, Finland, Denmark, Norway, Ireland, Bulgaria, Slovakia, Greece, Poland*
Author	*William A. Blumentals, Ph.D.* *Epidemiology and Benefit-Risk* *Sanofi Genzyme* *50 Binney Street* *Cambridge, MA 02142* *USA* *William.Blumentals@sanofi.com*

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	*Genzyme Europe B.V.; Gooimeer 10, 1411 DD, Naarden, Netherlands,*
MAH contact person	*Paolo Caferra* *Global Regulatory Affairs – Region Europe* *Naarden, The Netherlands*

TABLE OF CONTENTS

1 ABSTRACT

Title

An assessment of physician knowledge and understanding of the risks of vandetanib (Caprelsa®) within the European Union

Keywords

- Medullary thyroid cancer
- Vandetanib
- Physician survey study

Rationale and background

Caprelsa (vandetanib) is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. Caprelsa was approved for use in the European Union on 17 February 2012. The Marketing Authorization of Caprelsa was transferred to Genzyme Europe B.V. on 8 September 2016, and Genzyme Europe B.V. maintains responsibility for conducting the physician survey study.

For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before an individual treatment decision (see important information in sections 4.4 and 5.1 of the EU Summary of Product Characteristics[1]).

At the time of approval it was agreed that the Sponsor would distribute an educational pack to potential prescribers of Caprelsa to support understanding of the benefit-risk profile of the product. The educational pack contains:

- The Summary of the Product Characteristics and Package leaflet
- Educational material for physicians
- Patient Alert Cards for patients (with text approved by the CHMP)

The educational material for physicians was required to contain the following elements as stated in the European Public Assessment report[1]:

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de pointes and sudden death
- Vandetanib treatment must not be started in patients:
  - Whose ECG QTc interval is greater than 480 msec
  - Who have congenital long QTc syndrome
  - Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take
- The role and use of the Patient Alert Card

However, prior to launch in each Member State, the Sponsor was required to agree with each national competent authority regarding:

- The final content and format of the educational materials

- The physician distribution list for the educational pack (to be used at the time of launch and thereafter).

To assess the effectiveness of the educational materials, the Sponsor also committed to implement a survey of prescribers and potential prescribers of Caprelsa.

Therefore, a yearly survey was performed in each country in the European Union twelve months after Caprelsa was launched in that country for three consecutive years. The first countries were initially fielded in November 2013 and the last countries were fielded in March 2018 (Table 1).

If the survey indicated that physicians did not understand or comply with the educational material, a plan was implemented to further educate physicians and maximise understanding of the risk-benefit profile of the product.

Research question and objectives

The primary objective was:

- To assess the knowledge and understanding of physicians in relation to the key elements in the Caprelsa educational materials.

Study design

A cross-sectional study was conducted to assess knowledge and understanding of physicians in relation to the key elements in the Caprelsa educational materials.

Physicians were initially recruited from the distribution list for the educational material. Screening criteria for physicians included:

- Primary medical specialty of Oncologist, Endocrinologist, or Surgeon
    - Note: Other specialties were permitted if the physician was included in a distribution list
- Have seen a medullary thyroid cancer (MTC) patient in the past 3 years or might see one in the next year
- Not employed (or have an immediate family member employed) by the MAH or a European Regulatory Agency

A sample of physicians who were targeted to receive the Caprelsa educational pack at the time of launch (and in subsequent months) were selected to receive an invitation to participate in the survey on an annual basis for three years, the first survey being conducted approximately one year after launch in each market. Additionally, if sample quota (n=10-40 depending on country) was not achieved using the lists of doctors who received educational packs, invitations were sent to other physicians in the same country who could potentially prescribe Caprelsa if these physicians had registered in national databases to take surveys.

Additional screening criteria may have been used to determine appropriate participants. Such screening criteria may include but are not limited to:

1. Number of years in practice
2. Treatment of specific number of patients with medullary thyroid cancer
3. Physician specialty

Setting

The survey was conducted in each market in the European Union where Caprelsa was launched.

The number of prescribers (or potential prescribers) receiving the material in any one market may be small; therefore a physician may be invited to participate in the survey more than once. Each annual survey was treated as an independent sample. Physicians could only complete the survey once per year, but may have been surveyed in other years.

The survey was a self-administered, internet-based questionnaire accessed through a secure website, instructing the participant to enter a unique code provided in the invitation.

The survey was written to reflect the wording and screen-by-screen presentation of questions for the internet-based survey administration. Completion of the entire survey was expected to take less than 10 minutes.

Study country

Educational packs were distributed in accordance with the list of potential Caprelsa prescribers agreed with each national competent authority.

The EU countries where Caprelsa launched include:

United Kingdom, Germany, France, Spain, Italy, Belgium, Austria, Luxembourg, Netherlands, Sweden, Finland, Denmark, Norway, Ireland, Bulgaria, Slovakia, Greece, Poland

Sample size

The survey aimed to recruit between 10 and 40 physicians from each country included in the project in each year that the fieldwork was being completed. However, there was no fixed sample size for the survey due to two factors:

- The distribution lists for the educational material were targeted to appropriate physicians in each market. In some markets the resultant distribution list was small.

- Considering the targeted nature of the distribution lists, the likelihood of finding respondents for the survey may have been reduced.

Taking these practical considerations into account, the distribution lists for the materials were utilized to initiate physician recruitment and then it was supplemented with national databases as needed.

Survey administration

Study participants were directed to a secure website where they were instructed to enter a unique code to access the survey. Respondents provided their consent to participate in a study that was designed for market research purposes and not intended to be promotional in any way. Respondents were asked not to share the content of the survey.

In countries where it was the cultural norm, physicians were also reached by telephone and directed to the questionnaire on the computer.

The data entry system used for the survey was secure for receiving and storing survey data. Prescriber-identifying information was stored separately from survey data.

Recruitment details

The following describes the steps that were taken for the recruitment:

1. The distribution lists for the educational materials were matched to national physician databases held by Adelphi Research (the market research provider administering the survey on behalf of the Sponsor /Sanofi Genzyme)

2. Physicians in the Adelphi Research databases that matched the distribution lists were then targeted to complete the questionnaire
3. In the event that additional physician samples were required, international databases held by field partners of Adelphi were used to reach additional physicians
4. Screener information were developed to use for all physicians in the event sample supplementation was necessary

Statistical analysis

The responses to each survey question were reported as descriptive statistics. The frequency distribution of correct responses to each question (the number and percentage of respondents who gave correct answers to each response option) was presented.

Each question was evaluated individually. Each year of survey was analyzed as an individual sample.

The following were reported, as appropriate, as part of this analysis:

- The number of invitations issued to healthcare providers
- The number and percentage of healthcare providers eligible for participation
- The number and percentage of healthcare providers who completed the survey
- Frequency distribution of responses to each survey question (the number of and percentage of respondents who responded to each question)

Results

Results were aggregated across the 18 EU countries where the survey was fielded (Tables 1-4 show countries fielded and respective sample sizes), with a total sample size of n=1,028 respondents over three years. A summary of the data is below with analyses conducted primarily by years after the materials were distributed, as well as prescribers who received the materials (sample sizes by groups provided in Table 5). Year 1 data was collected for each country after first distribution of materials (n=341), Year 2 after the second annual distribution (n=347), and Year 3 after the third annual distribution (n=340).

From the survey population, across Europe 68% of HCPs (Year 1: 68%, Year 2: 70%; Year 3: 66%) who had prescribed Caprelsa confirmed they had received the educational materials (Table 5). Individual country range: 25-100%. Countries with <40% materials received had extremely small sample sizes of prescribers (Slovakia: n=3; Bulgaria: n=4; Poland: n=6) and thus may not be representative of the total population. A further 14% of prescribers (Year 1: 14%, Year 2: 12%; Year 3: 16%) did not know if they had received the educational materials (country range: 0-50%) and 18% of prescribers (Year 1: 19%, Year 2: 17%; Year 3: 18%) stated they had not received the educational materials (country range: 0-38%). This suggests that the materials were distributed to an appropriate HCP population in each market.

Across markets, the results suggested that educational materials have been effective in informing HCPs as to the appropriate use of Caprelsa. Of the physicians who received the educational materials, the rate of the correct responses was 78% (76% in Year 1, 78% in Year 2 and 80% in Year 3) (Table 6); there was an incremental increase in correct responses received over time, improving from Year 1 to Year 3. For physicians who did not receive the educational pack, the rate of correct responses was 58% (52% in Year 1, 59% in Year 2 and 65% in Year 3), suggesting that knowledge of Caprelsa improved over time, even among those who did not recall receiving materials.

As an example of improvement at the question level, physicians improved incrementally by year in their understanding that a patient should receive an alert card with each prescription regardless of whether they received educational materials or not. (Total: Year 1: 28%, Year 2: 35%, Year 3: 39%; Received materials: Year 1: 34%, Year 2: 44%, Year 3: 42%; Did not receive materials: Year 1: 27%, Year 2: 29%, Year 3: 35%).

Conclusion

The results indicate that the educational materials were distributed to an appropriate HCP population in each of the selected European markets and the educational materials have been effective in informing HCPs as to the risk of Caprelsa. Based on the correct responses captured, the data showed consistency and improvement over the 3-year period.

Marketing Authorization Holder(s)

Genzyme Europe B.V

Names and affiliations of principal investigators

William A. Blumentals, Ph.D.

Epidemiology and Benefit-Risk

Sr. Director, Pharmacoepidemiology Team Lead at Sanofi Genzyme

50 Binney Street, 2nd Floor

Cambridge, MA 02142

2 LIST OF ABBREVIATIONS

Abbreviation	Description
A&E	Accident and Emergency
AT	Austria
BG	Bulgaria
BL	Belgium
CHMP	Committee for Medicinal Products for Human Use
DE	Germany
DK	Denmark
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FI	Finland
FR	France
GR	Greece
IE	Ireland
IT	Italy
LU	Luxembourg
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
NIGB	National Information Governance Board
NHS	National Health Service
NL	Netherlands
NO	Norway
PL	Poland
SE	Sweden
SK	Slovakia
SP	Spain
SMPC	Summary of Product Characteristics
UK	United Kingdom

3 INVESTIGATORS

William A. Blumentals, Ph.D.
Epidemiology and Benefit-Risk
Sanofi Genzyme
50 Binney Street
Cambridge, MA 02142
USA

4 OTHER RESPONSIBLE PARTIES

Not applicable.

5 MILESTONES

The planned dates for the study milestones are presented below:

Milestone	Planned date
Start of study	*May 1, 2013*
Interim study report 1	*2014*
Interim study report 2	*2015*
Interim study report 3	*August 4, 2016*
Interim study report 4	*July 2017*
Final report of study results	*June 22, 2018*

6 RATIONALE AND BACKGROUND

Caprelsa (vandetanib) is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1 of the EU Summary of Product Characteristics[1]).

Caprelsa was approved for use in the European Union on 17 February 2012. At the time of approval it was agreed that the Sponsor would distribute an educational pack to potential prescribers of Caprelsa to support understanding of the benefit: risk profile of the product.

The educational pack contains:

- The Summary of the Product Characteristics and Package leaflet
- Educational material for physicians
- Patient Alert Cards for patients (with text approved by CHMP)

The educational material for physicians was required to contain the following elements as stated in the European Public Assessment report[1]:

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de pointes and sudden death
- Vandetanib treatment must not be started in patients:
  - Whose ECG QTc interval is greater than 480 msec
  - Who have congenital long QTc syndrome
  - Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take
- The role and use of the Patient Alert Card

However, prior to launch in each Member State, The Sponsor was required to agree with each national competent authority:

- The final content and format of the educational material

- The physician distribution list for the educational pack (to be used at the time of launch and thereafter).

To assess the effectiveness of the educational material, The Sponsor also committed to implement a survey of prescribers and potential prescribers of Caprelsa.

Therefore, a yearly survey was performed in each country in the European Union twelve months after Caprelsa was launched for three consecutive years.

The Marketing Authorization of Caprelsa was transferred to Genzyme Europe B.V. on 8 September 2016. Genzyme Europe B.V. resumes the responsibility to conduct the physician survey study.

If the survey indicated that physicians did not understand or comply with the educational materials, a plan was implemented to further educate physicians and maximise understanding of the risk-benefit profile of the product.

7 RESEARCH QUESTIONS AND STUDY OBJECTIVES

The primary objective was:

- To assess the knowledge and understanding of physicians in relation to the key elements in the Caprelsa educational material.

8 AMENDMENTS AND UPDATES

No amendments or updates were made to the original study protocol.

9 RESEARCH METHODS

9.1 STUDY DESIGN

Across-sectional study was conducted in order to assess the knowledge and understanding of physicians in relation to the key elements in the Caprelsa educational material

Physicians were initially recruited from the distribution list for the educational material. This section of the sample would therefore reflect the list of prescribers targeted in each market. The initial distribution lists were selected based upon a criteria of "*any oncologist or endocrinologist working at a referral centre for medullary thyroid cancer and who may prescribe*". However, in some markets this list was supplemented by additional prescribers who The Sponsor /Sanofi Genzyme identified as prescribers/potential prescribers post launch or by the national competent authority (for example, the national authority may have specified that all oncologists should receive the materials irrespective of whether they worked at a referral centre).

Any supplementary recruitment required through the international databases held by field partners of Adelphi Research was made according to the agreed screening criteria. Screening criteria for physicians included:

- Primary medical specialty of Oncologist, Endocrinologist, or Surgeon
    - Note: Other specialties were permitted if the physician was included in a distribution list
- Have seen a medullary thyroid cancer (MTC) patient in the past 3 years or might see one in the next year
- Not employed (or have an immediate family member employed) by the MAH or a European Regulatory Agency

A sample of physicians who were targeted to receive the Caprelsa educational pack at the time of launch (and in subsequent months) was selected to receive an invitation to participate in the survey on an annual basis for three years, the first survey being conducted approximately one year after launch in each market.

Additional screening criteria may be used to determine appropriate participants. Such screening criteria may include but is not limited to:

1. Number of years in practice
2. Treatment of specific number of patients with medullary thyroid cancer
3. Physician specialty

Basic demographic questions included in the survey were analysed after the fieldwork was complete, and details of the sample structure were made available alongside with the survey results.

Physicians who might have access to confidential information about this survey were excluded (i.e. physicians or their immediate family members who ever worked for the Sponsor /Sanofi Genzyme or a European Regulatory Agency were not be eligible to participate).

An Internet survey was provided to respondents given the relative ease of completing the questionnaire at a convenient time and location. Physicians were provided with a unique code during the recruitment process and were then asked to provide the unique code in order to gain access to the online survey. All respondents who are eligible to participate answer the same questions. The code was inactivated after use to prevent fraud and minimize the chance of a respondent participating in the survey more than once. A reminder notice was sent to invited participants who have not responded within two to three days of the initial invitation and subsequent contacts may continue to be made to reach the physician.

Physicians were targeted up to four times, depending on the cultural norm. No response was regarded as a lack of interest in the research.

9.2 SETTING

The survey was conducted in each market in the European Union where Caprelsa was launched. The number of prescribers (or potential prescribers) receiving the material in any one market may have been small given that medullary thyroid cancer is rare. Therefore, a physician could have been invited to participate in the survey more than once. The survey was a self-administered,

internet-based questionnaire accessed through a secure website, instructing the participant to enter a unique code provided in the invitation.

The survey was written to reflect the wording and screen-by-screen presentation of questions for the internet-based survey administration. Completion of the entire survey was expected to take less than 10 minutes.

9.3 STUDY COUNTRY

Educational packs were distributed in accordance with the list of potential Caprelsa prescribers agreed with each national competent authority.

The EU countries where Caprelsa has launched includes:

United Kingdom, Germany, France, Spain, Italy, Belgium, Austria, Luxembourg, Netherlands, Sweden, Finland, Denmark, Norway, Ireland, Bulgaria, Slovakia, Greece, Poland

9.4 VARIABLES

Exposure

NA

Outcomes

NA

9.5 DATA SOURCES AND MEASUREMENT

Survey administration

Study participants were directed to a secure website where they were instructed to enter a unique code to access the survey. Respondents provided their consent to participate in a study that was designed for market research purposes and not intended to be promotional in any way. Respondents were asked not to share the content of the survey.

In countries where it was the cultural norm, physicians were also reached by telephone and directed to the questionnaire on the computer.

The data entry system used for receiving and storing survey data was secure. Prescriber-identifying information was stored separately from survey data.

Recruitment details

The following describes the steps that were taken for physician recruitment:

1. The distribution lists for the educational materials were matched to national physician databases held by Adelphi Research (the market research provider administering the survey on behalf of The Sponsor /Sanofi Genzyme)
2. Physicians on the Adelphi Research databases that matched the distribution lists were then targeted to complete the questionnaire
3. In the event that a higher survey sample size required, national databases held by Adelphi Research were used to reach additional physicians
4. Screener information were developed to use for all physicians in the event that a greater survey sample size was necessary

Additional efforts to support recruitment were considered throughout the study. Efforts may have included but were not limited to the following

- Raising the honoraria to increase interest in participation
- Utilizing a custom recruit method to individually research physician contact information

9.6 BIAS

To minimize bias in the sample:

- Physicians were recruited from the Sponsor lists or national databases in each country containing email contact information for potential respondents.
- Strategies implemented were intended to recruit a heterogeneous sample of physicians for participation.
- Respondents who work for, or have immediate family members who work for, Sanofi Genzyme (Sponsor) or a European Regulatory Agency were excluded.
- Respondents were provided a unique link to gain access to the online survey. After a full sample was achieved, links were deactivated.

To minimize bias in the survey:

- All questions were programmed to ensure that questions were asked in the appropriate sequence. Skip patterns were clearly indicated in the survey documentation and the computer system automatically directed the respondent to the next appropriate question based on their previous response. Respondents could not go back to a question once the question had been answered and could not skip ahead. All questions were answered in sequence to complete the survey.
- Response options presented in a list were randomized to minimize positional bias, where appropriate.
- Programming was reviewed by quality control and pretests were conducted among a small number of physicians in each country prior to implementing the survey, to ensure questionnaire comprehension and clarity.

9.7 STUDY SIZE

The survey aimed to recruit between 10 and 40 physicians from each country included in the project in each year that the fieldwork is being completed. However, there was no fixed sample size for the survey due to two factors:

- The distribution lists for the educational material were targeted to appropriate physicians in each market. In some markets the resultant distribution list was small.

- Considering the targeted nature of the distribution lists, the likelihood of finding respondents for the survey may have been reduced.

Taking these practical considerations into account, the distribution lists for the materials were utilized to initiate physician recruitment and then supplemented with national databases as needed.

Final sample sizes for each country are presented in Table 1 in the appendix.

9.8 DATA MANAGEMENT AND TRANSFORMATION

NA

9.9 STATISTICAL METHODS

9.9.1 Main summary measures

The responses to each survey question were reported as descriptive statistics. The frequency distribution of correct responses to each question (the number and percentage of respondents who give correct answers to each response option) were presented.

Each question was evaluated individually. Each year of survey was analyzed as an individual sample.

The following was reported, as appropriate, as part of this analysis:

- The number of invitations issued to healthcare providers (Tables 2-4)
- The number and percentage of healthcare providers eligible for participation (Tables 2-4)
- The number and percentage of healthcare providers who completed the survey (Tables 2-4)
- The specific survey questions that were used to assess knowledge and the proportion of respondents who correctly and incorrectly answered each question (Tables 6 and 7)

9.9.2 Main statistical methods

This was a descriptive study, and only univariate analyses were conducted, stratified by country of origin, prescribers of Caprelsa, and physicians who received materials.

9.9.3 Missing values

NA

9.9.4 Sensitivity analyses

No sensitivity analyses were performed for this study.

9.9.5 Amendments to the statistical analysis plan

No amendments to the statistical analysis plan were made.

9.10 QUALITY CONTROL

Programming to produce all result data tables was thoroughly reviewed by a second programmer/analyst at each step of the analysis to validate coding rules and order of operations as well as statistical methodology, as appropriate.

10 RESULTS

10.1 OVERVIEW OF COUNTRIES INCLUDED IN THE ANALYSIS

Results are presented according to year, with all countries having completed 3 years. Year 1 data was collected for each country after first distribution of materials (n=341), Year 2 after the second annual distribution (n=347), and Year 3 after the third annual distribution (n=340).

Table 1 shows the field month and year of each country included in each year of analysis. Tables 2-4 describe the number of physicians contacted, those who were screened, and those who completed the survey for Years 1-3 respectively.

Countries covered in this analysis included:

- UK
- Germany
- Norway
- Denmark
- Luxembourg
- Sweden
- Finland
- Austria
- Netherlands

- France
- Belgium
- Italy
- Spain
- Ireland
- Bulgaria
- Slovakia
- Greece
- Poland

10.2 YEAR 1, YEAR 2 AND YEAR 3 SUMMARY

From the survey population, across Europe 68% of HCPs (Year 1: 68%, Year 2: 70%; Year 3: 66%) who had prescribed Caprelsa confirmed they had received the educational materials (Table 5). Individual country range: 25-100%. Countries with <40% materials received had extremely small sample sizes of prescribers (Slovakia: n=3; Bulgaria: n=4; Poland: n=6) and thus may not be representative of the total population. A further 14% of prescribers (Year 1: 14%, Year 2: 12%; Year 3: 16%) did not know if they had received the educational materials (country range: 0-50%) and 18% of prescribers (Year 1: 19%, Year 2: 17%; Year 3: 18%) stated they had not received the educational materials (country range: 0-38%).

Across markets, the results suggest that the educational materials have been effective in informing HCPs as to the appropriate use of Caprelsa. Of the physicians who received the educational materials, the rate of the correct responses was 78% (76% in Year 1, 78% in Year 2 and 80% in Year 3) (Table 6); there was an incremental increase in correct responses received over time, improving from Year 1 to Year 3. For physicians who did not receive the educational pack, the rate of correct responses was 58% (52% in Year 1, 59% in Year 2 and 65% in Year 3).

As an example of improvement at the question level, physicians improved incrementally by year in their understanding that that a patient should receive an alert card with each prescription regardless of whether they received educational materials or not. (Total: Year 1: 28%, Year 2: 35%, Year 3: 39%; Received materials: Year 1: 34%, Year 2: 44%, Year 3: 42%; Did not receive materials: Year 1: 27%, Year 2: 29%, Year 3: 35%).

10.3 DATA FOR INDIVIDUAL QUESTION

Across markets the results were broadly consistent. The results indicated that in all markets the HCPs who received a pack (Year 1: n=106 HCPs, Year 2: n=124 HCPs, Year 3: n=135 HCPs) answered most of the questions correctly as indicated by the proportion of correct responses below:

For example,

- Q2. Please indicate whether you believe each of the following statements to be true or false.
    - Torsade de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered Caprelsa (vandetanib) – True (Overall: 84%, Year 1: 80%, Year 2: 85%, Year 3: 87%); directionally higher in Year 2 and Year 3 compared to Year 1
    - Caprelsa (vandetanib) can prolong the QT interval in a dose-dependent manner – True (Overall: 94%, Year 1: 91%, Year 2: 97%, Year 3: 95%); directionally higher in Years 2 and 3 compared to Year 1
    - Caprelsa (vandetanib) can be administered to patients with hypokalaemia under certain circumstances: True (Overall: 47%, Year 1: 45%, Year 2: 48%, Year 3: 47%); directionally higher in Years 2 and 3 compared to Year 1
        - Please note: After the first year of fielding, this question wording was changed from: Caprelsa (vandetanib) should not be administered to patients with hypokalaemia under any circumstances: False
    - Monitoring of serum electrolytes is not required for Caprelsa (vandetanib) patients – False (Overall: 79%, Year 1: 80%, Year 2: 77%, Year 3: 81%); consistent over the 3 years
    - Monitoring for QT prolongation should occur after any reduction of Caprelsa (vandetanib) dose due to QT prolongation, or for any dose interruption greater than 2 weeks – True (Overall: 87%, Year 1: 85%, Year 2: 85%, Year 3: 90%); directionally higher in Year 3 compared to Years 1 and 2

Please refer to tables 7 and 8 for the detailed responses to all questions by physicians who received the educational pack.

11 DISCUSSION

From the survey population, across Europe 68% of HCPs (Year 1: 68%, Year 2: 70%; Year 3: 66%) who had prescribed Caprelsa confirmed they had received the educational materials or had been sent a copy according to the distribution list (individual country range: 25-100%). Since two thirds of prescribers received materials, this suggests that the materials were distributed to an adequate percentage of HCPs in each market.

Across markets, these results demonstrate that the educational materials have been effective in informing HCPs as to the risk of Caprelsa. Overall, there was an increasing trend over time in correct responses.

Limitations inherent in the study design included that the sample of physicians who were invited to participate were self-selected from the materials distribution lists and national databases of doctors who voluntarily responded to the invitation and agreed to participate in market research.

The target response rates per market were unknown based on the rarity of the disease. Every effort was made to maximize response both from the distribution lists and national databases.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The results indicate that the educational materials were distributed to a large percentage of health care providers in each of the selected European markets. The educational materials have been effective in informing HCPs as to the risk of Caprelsa. Based on the level of the data/ responses captured and given the high level of knowledge and understanding of the physicians, the data showed consistency or improvement over the 3-year period.

14 REFERENCES

1. EPAR summary for the public, Caprelsa (vandetanib). EMEA/H/C/002315, 2 March 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002315/WC500123555.pdf

15 APPENDICES

Table 1 - Field Date of Country Included in Each Year of Analysis

	UK	DE	NO	DK	LU	SE	FI	AT	NL	FR	BL	IT	SP	IE	BG	SK	GR	PL
Year 1	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Nov 2013	Jun 2014	May 2014	July 2014	Dec 2014	Sep 2015	Mar 2016	Mar 2016	Dec 2015	Mar 2016
Year 2	April 2014	April 2014	April 2014	April 2014	Sep 2014	April 2014	April 2014	April 2014	Dec 2014	June 2015	May 2015	July 2015	Dec 2015	Sep 2016	Mar 2017	May 2017	April 2017	Mar 2017
Year 3	May 2015	May 2015	April 2015	April 2015	Nov 2015	April 2015	April 2015	April 2015	Nov 2015	June 2016	May 2016	July 2016	Feb 2017	Oct 2017	Mar 2018	Mar 2018	Feb 2018	Mar 2018

Table 2: Summary of Contacts by Country: Year 1

	UK	DE	NO	DK	LU	SE	FI	AT	NL	FR	BL	IT	SP	IE	BG	SK	GR	PL
# of Physicians Contacted	491	2,677	16	300	49	398	223	175	129	85	86	68	92	122	79	288	27	737
# of Physicians Screened	160	195	0	29	23	22	21	33	23	59	44	40	59	10	17	18	12	25
# of Physicians Completed Survey	40	40	0	15	3	13	15	15	15	40	10	40	40	10	10	10	10	15
% of Physicians Contacted Who Completed Survey	8%	1%	0%	5%	6%	3%	7%	9%	12 %	47 %	12 %	59 %	43 %	8%	13 %	3%	37 %	2%

Table 3: Summary of Contacts by Country: Year 2

	UK	DE	NO	DK	LU	SE	FI	AT	NL	FR	BL	IT	SP	IE	BG	SK	GR	PL
# of Physicians Contacted	127	196	17	186	87	677	235	68	248	85	43	76	47	41	247	362	27	913
# of Physicians Screened	77	123	0	15	54	15	15	33	19	60	13	40	40	41	1	6	2	5
# of Physicians Completed Survey	40	40	0	15	5	15	15	15	15	42	10	40	40	10	10	10	10	15
% of Physicians Contacted Who Completed Survey	31 %	20 %	0%	8%	6%	2%	6%	22 %	6%	49 %	23 %	53 %	85 %	24 %	4%	3%	37 %	2%

Table 4: Summary of Contacts by Country: Year 3

	UK	DE	NO	DK	LU	SE	FI	AT	NL	FR	BL	IT	SP	IE	BG	SK	GR	PL
# of Physicians Contacted	258	447	16	470	52	700	290	163	248	71	50	68	64	31	358	415	13	424
# of Physicians Screened	48	358	0	43	2	44	23	137	19	48	10	49	64	11	2	6	0	6
# of Physicians Completed Survey	40	40	0	15	0	15	15	15	15	40	10	40	40	10	10	10	10	15
% of Physicians Contacted Who Completed Survey	16 %	9%	0%	3%	0%	2%	5%	9%	6%	56 %	20 %	59 %	63 %	32 %	3%	2%	77 %	4%

Table 5: Number (%) of HCPs who Received the Educational Materials by Caprelsa Prescribing Status

	Total Prescribers (n=342)		Year 1 (n=80)		Year 2 (n=105)		Year 3 (n=157)	
Prescribers	n	%	n	%	n	%	n	%
Received materials	232	68%	54	68%	74	70%	104	66%
Do not receive materials	61	18%	15	19%	18	17%	28	18%
Do not know	49	14%	11	14%	13	12%	25	16%

	Total Non-Prescribers (n=686)		Year 1 (n=261)		Year 2 (n=242)		Year 3 (n=183)	
Non-Prescribers	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
Received materials	133	19%	52	20%	50	21%	31	17%
Do not receive materials	375	55%	150	57%	129	53%	96	52%
Do not know	178	26%	59	23%	63	26%	56	31%

Table 6: Percent of HCPs with Correct Responses by Materials Received

	Total Received materials (n=365)	Year 1 (n=106)	Year 2 (n=124)	Year 3 (n=135)
Received materials	**%**	**%**	**%**	**%**
Correct Responses (net)	78%	76%	78%	80%
Incorrect Responses (net)	22%	24%	22%	20%
	Total Did not receive materials (n=384)	**Year 1 (n=134)**	**Year 2 (n=133)**	**Year 3 (n=117)**
Did not receive materials	**%**	**%**	**%**	**%**
Correct Responses (net)	58%	52%	59%	65%
Incorrect Responses (net)	42%	48%	41%	35%

Table 7: Correct Response for Each Question by Year by Respondents Who Received Materials

% of Physicians Who Received Materials Answering Each Question Correctly (Only correct answers are shown below)	Year 1 (n=106)	Year 2 (n=124)	Year 3 (n=135)
Q2. Please indicate whether you believe each of the following statements to be true or false:			
Torsade de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered Caprelsa (vandetanib) (True)	80%	85%	87%
Caprelsa (vandetanib) can prolong the QT interval in a dose-dependent manner (True)	91%	97%	95%
Year 1: Caprelsa (vandetanib) should not be administered to patients with hypokalaemia under any circumstances (False) Year 2: Caprelsa (vandetanib) can be administered to patients with hypokalaemia under certain circumstances (True)	45%	48%	47%
Monitoring of serum electrolytes is not required for Caprelsa (vandetanib) patients (False)	80%	77%	81%
Monitoring for QT prolongation should occur after any reduction of Caprelsa (vandetanib) dose due to QT prolongation, or for any dose interruption greater than 2 weeks (True)	85%	85%	90%
Q3. Imagine that you have been treating a medullary thyroid cancer patient with Caprelsa (vandetanib). During a follow-up appointment, he states that he has a headache and has been suffering from confusion. An ECG reveals he has a QTc interval greater than 500 ms. Which one of the following courses of action would you be most likely to take?			
Immediately perform a MRI of the brain to ascertain if the patient has PRES and stop Caprelsa (vandetanib) until QTc returns to less than 450 ms. Dosing can then be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed, correction of possible electrolyte imbalance has been made and the patient is found not to have PRES	78%	71%	79%
Q4. To the best of your knowledge, what is the recommended frequency of ECGs to monitor QT interval for patients on Caprelsa (vandetanib)?			

At baseline and at 1,3, 6 and 12 weeks after starting Caprelsa (vandetanib) and every three months for at least a year thereafter	77%	86%	84%
Q5. How often should a patient on Caprelsa (vandetanib) receive a patient alert card (a card separate from the package leaflet) that contains patient safety information for Caprelsa (vandetanib)?			
With each prescription	34%	44%	42%
Q6. Please indicate whether you consider each of the following patients to be appropriate candidates for Caprelsa (vandetanib)?			
Congenital long QTc syndrome (Not Appropriate)	91%	91%	88%
A QTc interval of <480 ms (Appropriate)	81%	83%	84%
A history of uncompensated heart failure (Not Appropriate)	75%	79%	76%
Pre-existing hypertension that is currently controlled (Appropriate)	95%	90%	97%
A history of hypocalcaemia, hypokalaemia, and/or hypomagnesemia which has been corrected (Appropriate)	81%	75%	83%

Table 8: Incorrect Response for Each Question by Year by Respondents Who Received Materials

% of Physicians Who Received Materials Answering Each Question Incorrectly (Only correct answers are shown below)	Year 1 (n=106)	Year 2 (n=124)	Year 3 (n=135)
Q2. Please indicate whether you believe each of the following statements to be true or false:			
Torsade de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered Caprelsa (vandetanib) (True)	20%	15%	13%
Caprelsa (vandetanib) can prolong the QT interval in a dose-dependent manner (True)	9%	3%	5%
Year 1: Caprelsa (vandetanib) should not be administered to patients with hypokalaemia under any circumstances (False) Year 2: Caprelsa (vandetanib) can be administered to patients with hypokalaemia under certain circumstances (True)	55%	52%	53%
Monitoring of serum electrolytes is not required for Caprelsa (vandetanib) patients (False)	20%	23%	19%

Monitoring for QT prolongation should occur after any reduction of Caprelsa (vandetanib) dose due to QT prolongation, or for any dose interruption greater than 2 weeks (True)	15%	15%	10%
Q3. Imagine that you have been treating a medullary thyroid cancer patient with Caprelsa (vandetanib). During a follow-up appointment, he states that he has a headache and has been suffering from confusion. An ECG reveals he has a QTc interval greater than 500 ms. Which one of the following courses of action would you be most likely to take?			
Immediately perform a MRI of the brain to ascertain if the patient has PRES and stop Caprelsa (vandetanib) until QTc returns to less than 450 ms. Dosing can then be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed, correction of possible electrolyte imbalance has been made and the patient is found not to have PRES	22%	29%	21%
Q4. To the best of your knowledge, what is the recommended frequency of ECGs to monitor QT interval for patients on Caprelsa (vandetanib)?			
At baseline and at 1,3, 6 and 12 weeks after starting Caprelsa (vandetanib) and every three months for at least a year thereafter	23%	14%	16%
Q5. How often should a patient on Caprelsa (vandetanib) receive a patient alert card (a card separate from the package leaflet) that contains patient safety information for Caprelsa (vandetanib)?			
With each prescription	66%	56%	58%
Q6. Please indicate whether you consider each of the following patients to be appropriate candidates for Caprelsa (vandetanib)?			
Congenital long QTc syndrome (Not Appropriate)	9%	9%	12%
A QTc interval of <480 ms (Appropriate)	19%	17%	16%
A history of uncompensated heart failure (Not Appropriate)	25%	21%	24%
Pre-existing hypertension that is currently controlled (Appropriate)	5%	10%	3%
A history of hypocalcaemia, hypokalaemia, and/or hypomagnesemia which has been corrected (Appropriate)	19%	25%	17%