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Oncology Global Medical Affairs

Non-Interventional Study Protocol (PASS)

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REDACTED PROTOCOL

Title	Survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycemia when using alpelisib
Protocol version identifier	v00
Date of last version of protocol	08-Jun-2021
EU PAS register number	Study not registered
Active substance	Alpelisib (ATC code L01XX65)
Medicinal product	Piqray® (alpelisib)
Product reference	EU/1/20/1455/001-009
Procedure number	EMEA/H/C/004804

Name of marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	The objective of this survey is to confirm whether HCPs received the Piqray educational material, and to assess their knowledge and behavior around management of hyperglycemia in patients treated with Piqray
Country (-ies) of study	Four to 8 countries from the European Union (EU)/European Economic Area (EEA). These countries may include Austria, Luxembourg, Norway, Slovenia, Sweden, and the Netherlands plus up to 2 additional countries depending on timing and approval of commercialization of Piqray in additional EU/EEA countries.
Author	[redacted], PhD, MPH; [redacted]; [redacted]

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FMV	Fair Market Value
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
MBC	Metastatic Breast Cancer
NCA	National Competent Authority
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted], PhD, MPH [redacted], [redacted]
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2 Abstract

Title

Survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycemia when using alpelisib

Version and date

V00; 08 Jun 2021

Name and affiliation of main author

[redacted], PhD, MPH

[redacted]

Rationale and background

Piqray (alpelisib) is indicated in the EU/EEA in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (MBC) with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy (Novartis 2020). Hyperglycemia is an expected on-target effect of PI3K inhibition (Goncalves et al 2018). To minimise the risk of hyperglycemia, Piqray was approved with a requirement for an additional risk minimization measure using an educational material. Piqray Prescriber's/HCP guide for hyperglycemia was agreed in the Piqray EU RMP v1.3 (dated 19 May 2020), for which EC Decision was granted on 28 May 2020. Specifically, oncologists/healthcare professionals (HCPs) prescribing Piqray in the EU/EEA will be provided with the Piqray Prescriber's/HCP Guide for hyperglycemia (educational material). The educational material aims to provide oncologists/HCPs prescribing Piqray with additional measures/guidance prior to, and during treatment with Piqray for the identification and management of hyperglycemia.

As part of the European Risk Management Plan (RMP) v2.1 (dated 16 Dec 2020) for Piqray, Novartis is required to conduct a Post-authorisation Safety Study (PASS) to assess the effectiveness of the Piqray educational material among HCPs who treat patients with locally advanced or MBC in the EU/EEA. This study is designed and conducted in accordance with Good Pharmacovigilance Practices (GVP) Modules VIII and XVI for a Category 3 PASS.

The PASS utilises a cross-sectional survey study design. In general, only a survey can assess knowledge. Therefore, a survey is considered the optimal methodological approach for this study.

Research question and objectives

The objective of this survey is to confirm that HCPs received the Piqray educational material and to assess HCPs' knowledge and management of hyperglycemia in patients treated with Piqray.

The primary objective is to assess HCPs' knowledge and understanding of the key information included in the Piqray Prescriber's/HCP Guide for hyperglycemia:

- Risk of hyperglycemia and its potential risk factors
- Signs and symptoms of hyperglycemia
- Recommendations for monitoring for hyperglycemia prior to, and during, treatment with Piqray
- Recommendations for managing hyperglycemia during treatment with Piqray

The primary endpoint is a composite endpoint based on the percentages of HCPs with correct responses to all questions included in the composite regarding the above information.

Secondary objectives are:

- Assess HCPs' reported levels of receipt, and reading, of the Piqray Prescriber's/HCP Guide for hyperglycemia

- Assess HCPs' knowledge levels for each survey question regarding knowledge of, and management of, hyperglycemia
- Assess the primary source from which HCPs learned about the messages included in the Piqray Prescriber's/HCP Guide for hyperglycemia

Study design

This is a multinational, non-interventional, cross-sectional survey conducted among HCPs based in the EU/EEA who prescribe Piqray. The survey will assess the knowledge of HCPs prescribing Piqray in relation to the management of hyperglycemia in patients treated with Piqray. The survey will endeavor to collect a minimum to 30-50 completed surveys.

The survey will be conducted in 4 to 8 countries from the EU/EEA. These countries may include Austria, Luxembourg, Norway, Slovenia, Sweden, and the Netherlands plus up to 2 additional countries depending on timing and approval of commercialization of Piqray in additional EU/EEA countries. A sample of HCPs who may/do prescribe Piqray will be recruited from the target population of HCPs who manage care for patients with locally advanced or MBC.

A web-based survey approach will be used to collect data in all selected countries. Information collected will include receipt and reading of the Piqray educational material, and knowledge of key messages included in the Piqray educational materials.

Recruitment will take place a minimum of 6 months following the reimbursement and launch (availability on the market) of Piqray in each participating country.

The survey is anticipated to be open for a minimum of 3 months in each country. Follow-up reminders will be sent to non-respondents to support achieving the target sample size and reducing the impact of selection bias.

Setting and study population

The target population is HCPs who were part of the Piqray educational materials dissemination list in any of the participating countries.

Variables

The survey questionnaire includes a survey introduction and screening questions to ensure the HCP is eligible to participate in the survey.

Outcomes/endpoint variables

Primary endpoint:

- Levels of knowledge of the risk of hyperglycemia, and risk factors for hyperglycemia,
- Levels of knowledge of signs and symptoms of hyperglycemia,
- Levels of knowledge of recommendations for monitoring for hyperglycemia prior to, and during, treatment with Piqray, and
- Levels of knowledge of recommendations for managing hyperglycemia during treatment with Piqray.

The primary endpoint is prescribers' knowledge of the risk of hyperglycemia with Piqray and practices recommended to minimize this risk, expressed as the weighted composite percentage of HCPs with correct responses to the key question set. Success criteria on the primary endpoint is defined as a composite knowledge level of at least 70% across these key questions.

Secondary endpoint questions

- Levels of reported receipt and reading of the Piqray Prescriber's/HCP Guide for hyperglycemia, assessed as the percentages of HCPs who report receipt and reading of the same
- HCPs' knowledge levels for each survey question regarding knowledge of, and management of, hyperglycemia, assessed as the percentages of HCPs with correct responses to each question

- The distribution of responses regarding the primary source from which HCPs learned about the messages included in the Piqray Prescriber's/HCP Guide for hyperglycemia, assessed as the percentages of HCPs who report using each of the possible sources as the primary source they used.

Data sources

HCPs will be recruited from the target population of oncologists/HCPs who may prescribe Piqray, and were on the lists for dissemination of the Piqray Prescriber's/HCP Guide for hyperglycemia. If after two reminders the target sample size has not been achieved, the sample may be supplemented through additional outreach based on internet research or outreach through applicable professional societies.

Invitations to participate in the survey will be sent to at least 1000 HCPs by either email (preferred) or by post mail (if email is not available) using the available contact information.

Study size

The primary evaluation criteria are prescribers' knowledge of the risk of hyperglycemia with Piqray and practices recommended to minimize this risk, expressed as the weighted composite percentage of HCPs with correct responses to the key question set. The sample size is based on the primary endpoint. With a targeted weighted composite knowledge level of ≥70% for the primary endpoint. HCPs allows estimation of a minimum HCP knowledge level of at least 70% with a precision of 9.4%.

Data analysis

The primary analysis set will include all HCPs who have completed at least one of the endpoint questions in the survey.

All analyses will be performed using appropriate statistical software (e.g., SAS® Version 9 or later). Data analyses will be descriptive. For continuous variables, counts, means (with standard deviations), medians (with interquartile ranges, minimum, and maximum) will be provided. For categorical variables, frequencies and percentages (with 95% CI) will be provided. Missing data will be reported, but no replacement or imputation will be performed.

Survey administrative details (e.g., the number of invited HCPs, the number and percentage of responding HCPs, the number and percentage of eligible vs. ineligible HCPs, and the number and percentage of HCPs with partially vs. fully completed surveys) and analysis sets will be described overall and by country.

Respondent characteristics/covariates will be summarized overall and by country.

Frequencies, percentages, and corresponding 95% 2-sided CI will be used to summarize the primary and secondary endpoints overall and by country.

For the primary endpoint, the point estimate of the weighted average composite percentage of HCPs who provide correct responses to the key question set will be estimated and assessed against the 70% threshold.

Milestones

Planned dates of study milestones:

Start date of data collection: October 2021

Last date of data collection: October 2022

Submission of final report of study results: 30 April 2023

3 Amendments and updates

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Registration in the EU PASS register	Prior to start of data collection
Start of data collection	October 2021
End of data collection	31 Oct 2022
Submission of final report of study results	30 April 2023

5 Rationale and background

Piqray (alpelisib) is an orally administered alpha specific PI3K inhibitor indicated in the EU/EEA in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (MBC) with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy (Novartis, 2020). Hyperglycemia is an expected on-target effect of PI3K inhibition since targeting p110α can block glucose uptake into skeletal muscle and adipose tissue, resulting in hyperglycemia (Goncalves et al 2018). To minimise the risk of hyperglycemia (including life-threatening and fatal events), Piqray was approved with a requirement for additional risk minimization measure using an educational material. Piqray Prescriber's/HCP guide for hyperglycemia was agreed in the Piqray EU RMP v1.3 (dated 19 May 2020), for which EC Decision was granted on 28 May 2020. Specifically, oncologists/healthcare professionals (HCPs) prescribing Piqray in the EU/EEA will be provided with the Piqray Prescriber's/HCP Guide for hyperglycemia (educational material), as agreed in the Piqray European Risk Management Plan (RMP), version 1.3 (dated 19.May.2020). The educational material aims to provide oncologists/HCPs prescribing Piqray with additional measures/guidance prior to, and during, treatment with Piqray, for the identification and management of hyperglycemia.

As part of the European Risk Management Plan (RMP) for Piqray, Novartis is required to conduct a Post-authorisation Safety Study (PASS) to assess the effectiveness of the Piqray educational materials among HCPs who treat patients with locally advanced or MBC in the EU/EEA. After Novartis has obtained approval of the educational materials from each concerned National Competent Authority (NCA) where Piqray will be commercialized and has disseminated these educational materials, this PASS will be conducted to assess the effectiveness of the Piqray educational materials among HCPs who prescribe Piqray in the EU/EEA. This study will be designed and conducted in accordance with Good Pharmacovigilance Practices (GVP) Modules VIII and XVI for a Category 3 PASS.

The PASS utilises a cross-sectional survey study design. In general, only a survey can assess knowledge. Therefore, a survey is considered the optimal methodological approach for understanding prescribers' knowledge of safe-use conditions for treating patients with Piqray.

Surveys are an accepted methodology to evaluate knowledge of educational materials and are referenced as an appropriate tool in Module XVI of GVP.

6 Research question and objectives

The objective of this survey, amongst oncologists/HCPs prescribing Piqray in selected countries in the EU/EEA, is to confirm that they received the educational material and to assess their knowledge, understanding and management of hyperglycemia in patients treated with Piqray.

Assessing, firstly, the dissemination of the educational material, and upon receipt of the material assess prescribing physicians' knowledge, understanding and behavior relating to the management of hyperglycemia as detailed in the educational material and SmPC provided. The educational material provides additional guidance to the SmPC, for prior to and during treatment with Piqray, on the management of hyperglycemia, particularly focusing on testing fasting glucose (FG) and HbA1c, and optimizing blood glucose levels prior to treatment initiation; monitoring FG and HbA1c during treatment; and management of hyperglycemia if it occurs.

6.1 Primary objective

Assess HCPs' knowledge of the key information included in the Piqray Prescriber's/HCP Guide for hyperglycemia:

- Risk of, and risk factors for, hyperglycemia
- Signs and symptoms of hyperglycemia
- Recommendations for monitoring for hyperglycemia prior to, and during, treatment with Piqray
- Recommendations for managing hyperglycemia during treatment with Piqray

The primary endpoint is a composite endpoint based on the percentages of HCPs with correct responses to all questions included in the composite regarding the above information

6.2 Secondary objectives

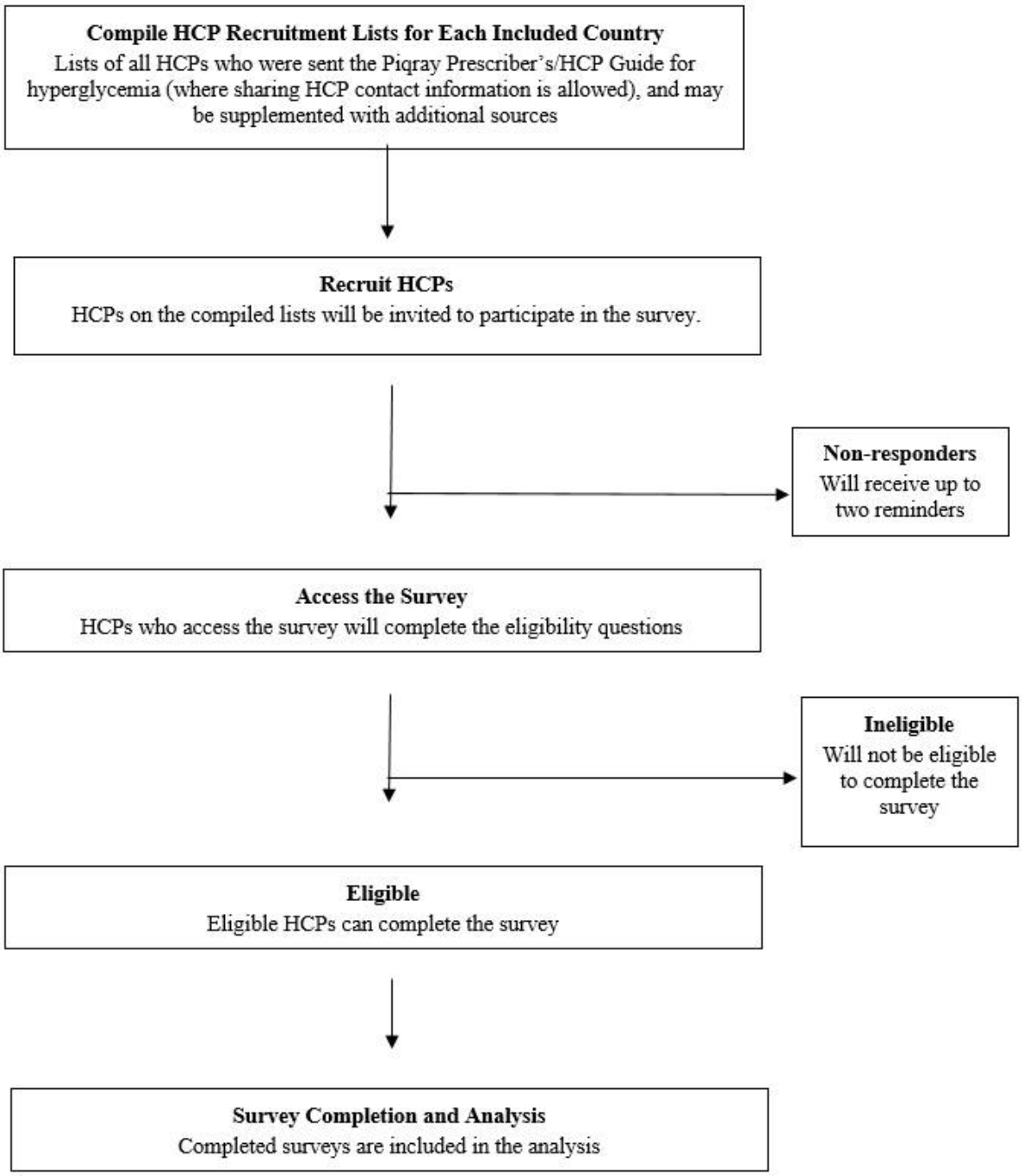
- Assess HCPs' reported levels of receipt, and reading, of the Piqray Prescriber's/HCP Guide for hyperglycemia
- Assess HCPs' knowledge levels for each survey question regarding knowledge of, and management of, hyperglycemia
- Assess the primary source from which HCPs learned about the messages included in the Piqray Prescriber's/HCP Guide for hyperglycemia

7 Research methods

7.1 Study design

Figure 7-1 provides a study flow chart.

Figure 7-1 Study flow chart



This is a multinational, non-interventional, cross-sectional survey to evaluate the effectiveness of the educational materials for Piqray. The survey will be conducted among HCPs based in the EU/EEA who prescribe Piqray. The survey will assess the knowledge of HCPs prescribing Piqray in relation to the management of hyperglycemia in patients treated with Piqray. The survey will endeavor to collect a minimum of 30 to 50 completed surveys.

The PASS will be conducted in 4 to 8 countries from the EU/EEA. This includes 6 countries where Piqray is planned to be reimbursed and commercially available within 1 year of Piqray's centralized marketing authorization approval on 27 July 2020 (European Commission [EC] decision date); specifically, Austria, Luxembourg, Norway, Slovenia, Sweden, and the Netherlands. Up to 2 additional countries may be included, depending on the timing and approval of commercialization of Piqray in additional EU/EEA countries relative to the survey study milestones and requirements. A sample of HCPs who may/do prescribe Piqray will be recruited from the target population of HCPs who manage care for patients with locally advanced or MBC. The final list of countries will also consider geography and market share (for example, small countries with only a few HCPs prescribing Piqray may be excluded).

A web-based survey approach will be used to collect data in all selected countries. Information collected will include receipt and reading of the Piqray educational material, and knowledge of key messages included in the Piqray educational materials.

Recruitment will take place a minimum of 6 months following the reimbursement and launch (availability on the market) of Piqray in each participating country. Since Piqray launch will be staggered, the intention is to implement the survey at different times depending on each country's reimbursement date, but at a fixed period after each country's launch. This reduces the chance of any bias introduced by some HCPs prescribing Piqray having longer or shorter durations of experience with the Piqray.

The survey is anticipated to be open for a minimum of 3 months in each country. Follow-up reminders will be sent to non-respondents to support achieving the target sample size and reducing the impact of selection bias.

7.2 Setting

The target population is HCPs who were part of the Piqray educational materials dissemination list in any of the participating countries.

The target groups for dissemination of the Piqray educational material were established by Novartis, as agreed with each NCA, and as outlined in Annex IID are HCPs who manage care for patients with locally advanced or MBC and may intend to prescribe Piqray.

7.2.1 Inclusion criteria

- Has prescribed Piqray to at least 1 locally advanced or MBC patient within 6 months prior to completing the survey.
- Provides permission to share their anonymized responses in aggregate with EMA or NCAs, if requested.

7.2.2 Exclusion criteria

HCPs who are direct employees of Novartis, the EMA (or any other regulatory bodies), or [redacted]

7.3 Variables

The survey questionnaire includes a survey introduction and screening questions to ensure the HCP is eligible to participate in the survey. The main survey questions are described in Sections 7.3.1 through 7.3.3, and Table 7-1.

7.3.1 Outcomes/endpoint variables

Primary endpoint:

- Levels of knowledge of the risk for hyperglycemia, and risk factors for hyperglycemia, (survey question 4A, 6),
- Levels of knowledge of signs and symptoms of hyperglycemia (survey questions 5A-C),
- Levels of knowledge of recommendations for monitoring for hyperglycemia prior to, and during, treatment with Piqray (survey questions 8A-C, 10, 15) and
- Levels of knowledge of recommendations for managing hyperglycemia during treatment with Piqray (survey questions 12-14).

The primary endpoint is a composite endpoint that combines correct responses given by HCPs to questions included in the composite. Specifically, the primary endpoint is a weighted composite knowledge score aggregated across the following survey questions: 4A, 5A-C, 6, 8A-C, 10, and 12-15. It is calculated as the number of all correctly answered questions divided by the number of all answered questions (i.e. questions that were answered either correct and not correct – unanswered questions are excluded).

Success criteria on the primary endpoint is defined as a weighted composite knowledge level of at least 70% across these key questions.

Secondary endpoint questions:

- Levels of reported receipt and reading of the Piqray Prescriber's/HCP Guide for hyperglycemia, assessed as the percentages of HCPs who report receipt and reading of the same (survey questions 1, 2)
- HCPs' knowledge levels for each survey question regarding knowledge of, and management of, hyperglycemia, assessed as the percentages of HCPs with correct responses to each question (individual responses to survey questions 4-15)
- The distribution of responses regarding the primary source from which HCPs learned about the messages included in the Piqray Prescriber's/HCP Guide for Hyperglycemia**,** assessed as the percentages of HCPs who report using each of the possible sources as the primary source they used (survey question 3).

Table 7-1 Outcomes/endpoints collected in the survey

Study objective domains assessed	Corresponding variable (original data collected; all are categorical variables)	Operational definition/derivation "Calculated as the percentage of HCPs who..."
HCPs' knowledge of the risk for hyperglycemia and risk factors for hyperglycemia	Knowledge that hyperglycemia is a risk associated with treatment with Piqray (key question)	"Checked" question 4A
	Knowledge that pneumonitis is a risk associated with treatment with Piqray	"Checked" question 4B
	Knowledge that severe cutaneous reactions are a risk associated with treatment with Piqray	"Checked" question 4C
	Knowledge that suicidal ideation is not a risk associated with treatment with Piqray	"Not checked" question 4D
	Knowledge that onychomycosis is not a risk associated with treatment with Piqray	"Not checked" question 4E
	Knowledge that being diabetic/pre-diabetic, having a fasting blood glucose >13.9 mmol/L(250 mg/dL), and being 75 years of age or older are additional risk factors for developing hyperglycemia while taking Piqray (key question)	"Checked" only "body mass index <30 kg/m^2 "for question 6
HCPs' knowledge of the signs and symptoms of hyperglycemia	Knowledge that excessive thirst is a sign/symptom of hyperglycemia (key question)	"Checked" question 5A
	Knowledge that increased frequency or amount of urination is a sign/symptom of hyperglycemia (key question)	"Checked" question 5B
	Knowledge that increased appetite with weight loss is a sign/symptom of hyperglycemia (key question)	"Checked" question 5C
	Knowledge that inability to swallow is not a sign/symptom of hyperglycemia	"Not checked" question 5D
	Knowledge that yellowing of the skin is not a sign/symptom of hyperglycemia	"Not checked" question 5E
	Knowledge that difficulty breathing is a sign/symptom of hyperglycemia (key question)	"Checked" question 5F
	Knowledge that nausea and/or vomiting is a sign/symptom of hyperglycemia (key question)	"Checked" question 5G
	Knowledge that headache is a sign/symptom of hyperglycemia (key question)	"Checked" question 5H
HCPs' knowledge of recommendations for monitoring for hyperglycemia prior to, and during, treatment with Piqray	Knowledge that for patients at higher risk for developing hyperglycemia, an HCP/endocrinologist experienced in the treatment of hyperglycemia should be consulted	Checked "false" to question 7
	Knowledge that a fasting glucose and HbA1c should be obtained before a patient starts treatment with Piqray (key question)	"Checked" question 8A
	Knowledge that the patient's level of blood glucose should be optimized, as applicable, before a patient starts treatment with Piqray (key question)	"Checked" question 8B

Study objective domains assessed	Corresponding variable (original data collected; all are categorical variables)	Operational definition/derivation "Calculated as the percentage of HCPs who..."
	Knowledge that the patient should be counselled about the risk of hyperglycemia before a patient starts treatment with Piqray (key question)	"Checked" question 8C
	Knowledge that the dose of their current antihyperglycemia medication, if applicable, does not need to be increased before a patient starts treatment with Piqray	"Not checked" question 8D
	Knowledge that the Piqray Prescriber's/HCP Guide for Hyperglycemia and SmPC does not require a diabetologist to be consulted for patients who are not diabetic before a patient starts treatment with Piqray	"Not checked" question 8E
	Knowledge that "the monitoring schedule of fasting glucose levels for patients receiving Piqray is the same for all patients with, and without, risk factors for hyperglycemia" is not correct	Checked "false" to question 9
	Knowledge of when a FPG test should be performed after starting treatment with Piqray (key question)	Checked "at weeks 1, 2, 4, 6, and 8, after treatment start, then monthly thereafter" to question 10
	Knowledge of the frequency for HbA1c testing to be performed for all patients treated with Piqray	Checked "4 weeks after treatment start, then every 3 months thereafter" to question 11
	Knowledge of what frequency should fasting glucose be monitored when hyperglycemia occurs and patients are treated with antihyperglycemic medications (key question)	Checked "weekly for at least 8 weeks, followed by once every 2 weeks, and consider consultation with a healthcare professional with expertise in the treatment of hyperglycemia" to question 15
HCPs' knowledge of recommendations for managing hyperglycemia during treatment with Piqray	Knowledge that for fasting glucose values that are ≤250 mg/dL (≤13.9 mmol/L), no Piqray dose adjustment is required, and it is recommended to manage by initiating or intensifying oral antihyperglycemic treatment (key question)	Checked "true" to question 12
	Knowledge of which fasting glucose values require Piqray dosing to be interrupted (key question)	Checked "any fasting glucose value >250 mg/dL (>13.9 mmol/L) to question 13
	Knowledge that "if Piqray dosing is interrupted due to elevations in fasting glucose >250 mg/dL (>13.9 mmol/L), and fasting glucose decreases to ≤160 mg/dL (≤8.9 mmol/L) within 3-5 days under appropriate antihyperglycemia treatment, Piqray can	Checked "false" to question 14

Study objective domains assessed	Corresponding variable (original data collected; all are categorical variables)	Operational definition/derivation "Calculated as the percentage of HCPs who..."
	be resumed at the starting dose level of 300 mg/day" is not accurate (key question)	
Assess whether HCPs received and read the Piqray Prescriber's/HCP Guide for Hyperglycemia	Received the **Guide for HCPs**	Checked "Yes" to question 1
	Read the **Guide for HCPs**	Checked "Yes, all of it" + "Yes, some of it" to question 2
Primary source of the indication, precautions for use, and potential risks for Piqray	Response choices: Piqray SmPC, Piqray **Guide for HCPs**, NCA website, Professional society or congress, Piqray product website, EMA website, Clinical practice guidelines, Novartis representative, Other	Checked each of the response choices to question 3

Note: Please see Appendix 13.1 for a full list of survey questions

7.3.2 Exposure/independent variables of interest

The survey does not evaluate outcomes related to exposure to a medicinal product. However, it does evaluate the effectiveness of the Piqray educational material, and therefore, the exposure of interest can be considered as the Piqray **Guide for HCPs**.

7.3.3 Other covariates/control variables

Covariates include HCP characteristics as shown in Table 7-2.

Table 7-2 Covariates collected in the survey

Original data collected	Variable type	Operational definition/derivation
Primary medical specialty	Categorical	Surgeon/surgical oncologist, radiation oncologist/radiologist, medical oncologist, other
Years working with oncology patients	Categorical	Less than 5 years, 5 to <10 years, 10 to <15 years, >15 years, prefer not to answer
Number of patients for which the HCP has prescribed Piqray within the past 12 months	Categorical	1-5, 6-10, >10, don't know/am not sure
Last time prescribed Piqray	Categorical	Less than 3 months ago, 3 to <6 months ago, don't know/am not sure
Investigator in a Piqray clinical trial	Categorical	Yes, No, don't know/am not sure

7.4 Data sources

A minimum sample of 30 to 50 HCPs from the included countries will be recruited from the target population of oncologists/HCPs who may prescribe Piqray and were on the lists for dissemination of the Piqray Prescriber's/HCP Guide for hyperglycemia. To endeavor to achieve

a larger sample than 30-50 completed surveys, recruitment will remain open until the end of the data collection period, and will not be closed early even if 50 completed surveys have been reached sooner. If after two reminders the target sample size has not been achieved, the sample may be supplemented through additional outreach based on internet research or outreach through applicable professional societies. Additionally, up to 2 additional countries may be included, depending on the timing and approval of commercialization of Piqray in additional EU/EEA countries relative to the survey study milestones and requirements (in each country, recruitment must take place a minimum of 6 months following the reimbursement and launch of Piqray, and must be open a minimum of 3 months before the end of data collection period).

Invitations to participate in the survey will be sent to approximately 1000 HCPs by either email (preferred) or by post mail (if email is not available) using the available contact information. The invitation letter will include information about the survey, a unique code, and instructions for accessing the survey. The unique code will be used to track who has already completed a survey so that reminders are only sent to HCPs who have not yet completed the survey.

All data for the survey will be collected by web-based data capture. The survey will be available for completion in English or native language spoken in participating countries depending on HCPs' preference.

The survey is anticipated to be open for a minimum of 3 months per country, measured from the date the survey is launched/initial invites sent in each country. Metrics will be tracked to monitor survey progress (e.g., number of eligible/ineligible HCPs, number of completed surveys). Follow-up reminders will be sent to non-respondents using the available contact information. Reminders will be sent within 2-4 weeks of the previous invite/reminder, and the maximum number of follow-up attempts per HCP will not exceed two. As an acknowledgement of their time and input, HCPs who complete the survey will receive fair market value (FMV) compensation if allowed, feasible, and in accordance with local regulations. The FMV compensation will be based on a survey that should take 15-20 minutes to complete.

7.5 Study size

Research has shown that response rate in HCP surveys can be expected to be rather low. A recent meta-analysis of data from 23 HCP surveys found the proportions of completers from invited participants ranging from 0.5% to 26.0% in each survey, with a pooled estimated proportion of 2.1% (95% confidence interval [CI]: 2.1 to 2.2) based on a fixed effects model, or 4.7% (95% CI: 3.0 to 6.6) based on a random effects model. For example, up to 10,000 eligible physicians must be contacted to obtain 200 completed questionnaires (Artime et al 2019).

It is estimated that response rates in the range of 4-5% are achievable; as a result, to approximately1000 potentially eligible physicians must be contacted to obtain 30 to 50 completed questionnaires based on the estimated response rate. Table 7-3 provides an estimate of the maximum number of Piqray prescribers in each of the potential participating countries. Up to 2 additional countries may be included in the survey depending on the timing and approval of commercialization of Piqray in additional EU/EEA countries relative to the survey study milestones and requirements.

Table 7-3 Estimated maximum number of potential Piqray prescribers

Country	# Potential prescribers	Reimbursement status
Austria	280	Reimbursed
Luxembourg	20	Reimbursed
Norway	175	Pending review outcome
Slovenia	30	Reimbursed
Sweden	340	Reimbursed
The Netherlands	100	Reimbursed
Total	945	

The primary evaluation criteria (i.e., endpoints) are prescribers' knowledge of the risks of hyperglycemia with Piqray and practices recommended to minimize this risk, expressed as the weighted composite percentage of HCPs with correct responses to the key question set. The sample size is based on the primary endpoint.

Table 7-4 provides the precision and corresponding 2-sided 95% exact confidence intervals (CI) around expected levels of knowledge by various numbers of completed surveys for this study. With a targeted weighted composite knowledge level of ≥70% for the primary endpoint, a sample size of 30 to 50 HCPs allows estimation of a minimum HCP knowledge level of at least 70% with a precision ranging between 13.4%-17.4%. To endeavor to achieve a larger sample than 30-50 completed surveys and improve precision of the knowledge level estimates, recruitment will remain open until the end of the data collection period, and will not be closed early even if 50 completed surveys have been reached sooner.

Table 7-4 Precision and 95% confidence intervals for various combinations of sample size and knowledge levels

Sample size	Probable respondent knowledge levels									
	50%		**60%**		**70%**		**80%**		**90%**	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
30	18.7	31.3-68.7	18.4	40.6-77.3	17.4	50.6-85.3	15.5	61.4-92.3	12.2	73.5-97.9
50	14.5	35.5-64.5	14.2	45.2-73.6	13.4	55.4-82.1	11.9	66.3-90.0	9.3	73.2-96.7
100	10.2	39.8-60.2	10.0	49.7-69.7	9.4	60.0-78.8	8.3	70.8-87.3	6.4	82.4-95.1
150	8.3	41.7-58.3	8.1	51.7-67.9	7.6	62.0-77.2	6.7	72.7-86.1	5.2	84.0-94.3
200	7.2	42.9-57.1	7.0	52.9-66.8	6.6	63.1-76.3	5.8	73.8-85.3	4.4	85.0-93.8
300	5.8	44.2-55.8	5.7	54.2-65.6	5.4	64.5-75.1	4.7	75.0-84.4	3.6	86.0-93.2

Note: Calculated using PASS 13 software (Hintze 2014), exact confidence intervals for one proportion (Clopper-Pearson).

7.6 Data management

Survey data collection will be completed on-line in Confirmit, a software platform specifically designed for the creation and delivery of multi-lingual surveys. Data collected will be stored at secure servers and will be maintained to ensure compliance with applicable local and national regulations.

Response sets for multiple-choice questions will be randomised to minimize bias. To minimize likelihood that respondents would look up answers and/or discuss the survey while taking it, respondents will be asked to complete survey in one sitting and will not be allowed to revise their answers after they advance to the next question.

Survey database lock is anticipated to occur shortly after the survey is closed in the last country. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses to knowledge assessment-related questions.

Data management will be in accordance with the [redacted] standard operating procedures (SOPs).

7.7 Data analysis

All analyses will be performed [redacted].

A detailed statistical analysis plan (SAP) describing the planned analysis of the physician questionnaire and data presentation, including table shells, will be developed. The SAP will be finalized prior to database close. Any changes to the SAP will be captured in the final study report as changes to the SAP.

7.7.1 Analysis populations

The primary analysis set will include all HCPs who have completed at least one of the endpoint questions in the survey. Denominators used to calculate descriptive statistics for each survey question will reflect the number of respondents who completed that particular question including responses of "I don't know/am not sure".

7.7.2 Statistical methods

General considerations

All analyses will be performed using appropriate statistical software (e.g., SAS® Version 9 or later).

Data analyses will be descriptive. For continuous variables, counts, means (with standard deviations), medians (with interquartile ranges, minimum, and maximum) will be provided. For categorical variables, frequencies and percentages (with 95% CI) will be provided.

Missing data

Missing data will be reported, but no replacement or imputation will be performed. Descriptive statistics for continuous variables will include the available n, and descriptive statistics for categorical variables will include a category of "missing" when applicable.

Planned analyses

Survey administrative details (e.g., the number of invited HCPs, the number and percentage of responding HCPs, the number and percentage of eligible vs. ineligible HCPs, and the number and percentage of HCPs with partially vs. fully completed surveys) and analysis sets will be described overall and by country.

Respondent characteristics/covariates will be summarized overall and by country.

Frequencies, percentages, and corresponding 95% 2-sided CI will be used to summarize the primary and secondary endpoints overall and by country. Depending on the final distribution of data within each subgroup, subgroup analyses of primary endpoints may also be analyzed by specialty and experience with Piqray.

For the primary endpoint, the point estimate of the weighted average composite percentage of HCPs who provide correct responses to the key question set will be estimated and assessed against the 70% threshold. Where subgroup analyses have small sample sizes (e.g., less than about 30), the results should be handled with caution. Although the 70% threshold is considered success, the associated confidence intervals for small subgroups will be wide, reflecting imprecision.

7.8 Quality control

Steps to be taken to ensure the accuracy and reliability of data will include the selection of qualified study personnel and review of data collection and processing procedures with the study personnel before the study is launched.

7.8.1 Data quality management

Applicable SOPs will be followed to ensure data quality and integrity, including validation and user acceptance testing of the survey database, validation of derived variables and analysis programs, documentation of data cleaning, and description of available data. [redacted] will assure database quality processes are followed in accordance with the data validation plan.

7.8.2 Data recording and document retention

The on-line survey questionnaire asks HCPs to answer questions regarding information included in the Piqray educational material and therefore is the source document in this study.

Survey data will be stored in a secure validated database and shall be treated in compliance with all local applicable laws and regulations.

Study records must be retained for the maximum period required by applicable local regulations. For interventional clinical trials, the retention period in Europe is 25 years. For NIS, the retention period is not always specified in national regulations. Therefore, for this study, documents will be retained for a minimum of 25 years.

7.8.3 Site monitoring

There is no site monitoring in this study. This is a direct-to-HCP survey to evaluate HCPs' understanding of information included in the Piqray educational material. There are no 'sites' in this study and since this is a knowledge assessment survey, monitoring survey responses could bias the study results.

7.9 Limitations of the research methods

The primary limitation of a cross-sectional survey is selection bias due to use of a convenience sample and/or low response rates. A key requirement of this study is that it reflects a representative view across the HCPs who have prescribed Piqray. To minimize selection bias, HCPs will be recruited from a geographically representative sample of countries where Piqray is commercialized. Due to privacy laws, lists of actual prescribers of Piqray in these countries may not be available. Therefore, to promote generalizability, all potential prescribers in the participating countries (i.e., HCPs who were sent the Piqray educational material) will be invited to screen for participation in the survey. To further minimize selection bias:

- HCPs will receive up to 2 reminders to encourage their participation, and
- The eligibility criteria are limited to reflect the real-world EU/EEA population of HCPs prescribing Piqray.

There may be some recall bias associated with HCPs thinking back over time when answering the survey. To minimize this bias, respondents will be limited to those who have prescribed Piqray within the 6 months prior to completing the survey.

7.10 Other aspects

None.

8 Protection of human subjects

Although there are no patients in this study, the HCPs are research subjects. As such, this study will be conducted in compliance with national and EU requirements for ensuring the rights of participants of NIS. HCPs' survey responses will be reported in aggregate and de-identified. The collection and processing of personal data from HCPs will be limited to those data that are necessary to fulfill the objectives of the study. HCPs' personal data will be collected and processed in accordance with General Data Protection Regulation of Europe.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of people participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

Informed consent procedures

There are no patients in this study; the HCPs are considered study subjects. Survey participants will be asked to provide acknowledgement of consent to participate in the survey as part of the on-line consulting agreement completed by HCPs prior to accessing the survey.

9 Management and reporting of adverse events/adverse reactions

This direct-to-HCP survey does not involve collection of patient outcomes and does not involve exposure to Piqray. In this survey, HCPs are the research subjects and will complete a web-based survey via a secure website about their knowledge of information included in the Piqray educational material. The survey questionnaire does not include questions that could potentially identify an adverse event (AE) or special situation report. However, given that this is a physician survey related to understanding how to identify and manage the risk of hyperglycemia associated with Piqray, during survey conduct an HCP may provide unsolicited information to study personnel that could constitute an AE or special situation report. Any AE reports received during survey conduct should follow standard pharmacovigilance procedures for spontaneous reporting.

All AEs that occurred in patients exposed to the Novartis drug, irrespective of seriousness or causality will be reported to Novartis Patient Safety within 24 hours of becoming aware of the event. All reported AEs will be collected and recorded in the Novartis safety database, irrespective of seriousness or causal association.

AEs occurring in patients exposed to a Novartis drug can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report. All AEs identified for non-Novartis products will be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this NIS may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

11 References (available upon request)

Artime E, Qizilbash N, Garrido-Estepa M, et al. (2019) Are risk minimization measures for approved drugs in Europe effective? A systematic review, Expert Opinion on Drug Safety, 18:5, 443-454, DOI: 10.1080/14740338.2019.1612875

European Medicines Agency (2016) The ENCePP Code of Conduct – for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. Available from: http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3amend.pdf (Accessed 11 August 2016).

Goncalves MD, Hopkins BD, Cantley LC. (2018) Phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med;379(21):2052-2062.

Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. ncss.com

International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 25:2-10.

Novartis (2020). Piqray Summary of Product Characteristics, 27 July 2020. Available at: ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf. Accessed 24 May 2021.

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med; 147(8):W163-94.

12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Not applicable	07 Jun 2021	Survey invitation letter

12.2 Annex 2 – ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycemia when using alpelisib

EU PAS Register® number: To be assigned when study is registered
Study reference number (if applicable): CYBL719C2005 (protocol #)

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				4
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

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

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)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
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, other design)	☒	☐	☐	5, 7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1, 7.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.3.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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)	☒	☐	☐	9

Comments:

Measures of occurrence are a) levels of knowledge, expressed as the proportions of respondents with correct answers to questions regarding knowledge of information included in Piqray HCP Guide, and b) levels of receipt and reading of the Piqray HCP Guide, expressed as the proportions of respondents reporting they have received/read this document.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7.2, 7.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 7.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	7.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.4 Disease/indication	☐	☐	☒	
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.1, 7.2, 7.4

Comments:

This is a cross-sectional study of HCPs who have prescribed Piqray. Age, sex, disease, and duration of follow-up are all not applicable.

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 categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a non-interventional study that aims to test knowledge related to risk minimisation for Piqray. Although the Piqray HCP Guide may be considered an educational intervention, exposure to it/use of it is not specifically required in order to participate in this study.

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?	☒	☐	☐	6, 7.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	5, 7.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	6.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

Confounding: Assess the primary source from which HCPs learned about messages included in the Piqray Prescriber's/HCP Guide for Hyperglycemia

Section 8: Effect measure 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)	☒	☐	☐	7.7

Comments:

Effect modifiers are anticipated to include: specialty and experience with Piqray. However, given the overall small N, the ability to assess impact of effect modifiers will be limited.

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)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3
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)	☒	☐	☐	7.3.1, 7.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3
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), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.3 Covariates and other characteristics?	☐	☐	☒	
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 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7.2
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

An independent statistical development plan will be developed to provide further details. Due to the overall small N, the ability to perform subgroup analyses for confounding, sensitivity, etc. is limited.

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)	☒	☐	☐	7.6, 7.8.2
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Results will be communicated to applicable health authorities within the agreed timeframe.

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?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	

Section 12: Limitations	Yes	No	N/A	Section Number
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 uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8

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?	☒	☐	☐	3

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)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: [redacted] PhD, MPH

Date: 03/June/2021

Signature: [redacted]

12.3 Annex 3 – Additional information

None.

13 Appendices

13.1 Appendix – HCP Survey questionnaire

SURVEY QUESTIONNAIRE

Note to Reviewers:

1. Items in RED font are programming instructions and will not be seen by HCPs who complete the survey.
2. Items in *italics* are information for questionnaire reviewers and will also not be seen by HCPs who complete the survey.

Please enter your Unique ID to participate in the survey. Your Unique ID was provided in your survey invitation.
Unique ID: _____ ➔ **IF ENTERED, PROCEED TO COUNTRY AND LANGUAGE SELECTION, OTHERWISE, TERMINATE SURVEY**

The above section will only appear for respondents who did not receive their invitation directly by email from the survey software.

Surveys sent by post will include a unique ID in their invitation letter, which will need to be entered.

Correct responses are ticked as ✓ and will be removed for the versions used for pre-testing and the actual survey.
Key questions for the primary endpoint are noted in brackets.

Please select your country and preferred language from the list below:	
□ Country 1 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ Country 2 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ Country 3 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ Country 4 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ Country 5 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ Country 6 (language or English)	➔ PROCEED TO SURVEY INTRODUCTION
□ My country is not listed	➔ THANK AND TERMINATE
[Termination Language for Non-Qualified Candidates:]	

Once country/language is selected, the survey introduction is displayed in local language (next page).

SURVEY INTRODUCTION

On behalf of Novartis Europharm Limited (Novartis), [redacted] is conducting a survey among healthcare professionals who have prescribed Piqray to patients with metastatic breast cancer. **Novartis is required to perform this survey in line with the requirements of the Piqray Risk Management Plan for Europe.** The overall goal of this study is to evaluate the effectiveness of the Piqray risk minimization measures. Participation in this survey is voluntary.

The survey is expected to take up to 20 minutes to complete and is recommended to be completed in one sitting.

To complete the survey, you must meet study eligibility criteria. Please be assured that your individual answers will be held confidential. This study will summarize aggregated results provided by all participating healthcare professionals in order to protect the confidentiality of your individual answers.

You may withdraw from the survey at any time, in which case the information you have already provided will not be used in the final study report.

Please click on the NEXT button to verify that you qualify for this survey and to complete the required documentation for participation.

When HCPs click on the NEXT button, the country-specific on-line letter agreement will be displayed. NOTE TO PROGRAMMER: INSERT COUNTRY-SPECIFIC ON-LINE SURVEY AGREEMENT.

[BEGIN SURVEY SCREENING QUESTIONS]

S1. Do you provide your permission to share your anonymized survey responses, aggregated with all other survey responses, with the European Medicines Agency or National Competent Authorities?

□ Yes ➔ **PROCEED TO S2**

□ No ➔ Based on your answer, you are not eligible to take this survey. Thank you for your interest.

S2. Have you prescribed Piqray to at least 1 patient with locally advanced or metastatic breast cancer within the past 6 months?

□ Yes ➔ **PROCEED TO S3**

□ No ➔ Based on your answer, you are not eligible to take this survey. Thank you for your interest.

S3. Are you a direct employee of Novartis, the European Medicines Agency, or [redacted]?

□ Yes ➔ Based on your answer, you are not eligible to take this survey. Thank you for your interest.

□ No ➔ **PROCEED TO MAIN SURVEY**

[Termination Language for Non-Qualified Candidates:]

Thank you for your interest in participating in this survey. However, you are not eligible to complete this survey. We look forward to your potential participation in a future study.

[Language for Qualified Candidates:]
Thank you for your responses. You qualify for this survey. Please click on the NEXT button to proceed to the main survey.

[END SURVEY SCREENING QUESTIONS]

MAIN SURVEY

[Preamble 1]: These questions are about important product information for Piqray. Please be sure to review all response choices for each question before answering each question.

1. Did you receive the "Piqray Prescriber's/HCP **Guide for Hyperglycemia"** that reminds healthcare professionals about certain how to identify, and manage, hyperglycemia in patients treated with Piqray?

   □ Yes

   □ No ➔ **PROCEED TO QUESTION 3**

   □ I don't know/am not sure ➔ **PROCEED TO QUESTION 3**

2. Did you read or review the "Piqray Prescriber's/HCP **Guide for Hyperglycemia"**?

   □ Yes, all of it
   □ Yes, some of it
   □ No
   □ I don't know/am not sure

3. What is the **primary source** you use to learn about the indication, precautions for use, and potential risks for Piqray? (please tick only 1 response)

   □ Piqray Summary of Product Characteristics

   □ Piqray Prescriber's/HCP **Guide for Hyperglycemia**

   □ National Competent Authority website

   □ Professional Society or Congress

   □ The Piqray product website

   □ The European Medicines Agency website

   □ Clinical practice guidelines

   □ A representative from Novartis

   □ Other (not listed above)

   □ I do not know/am not sure

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THE FIRST 8 RESPONSE OPTIONS]

4. Listed below are several risks. Which of these risks are associated with treatment with Piqray?

		Check the box if associated with treatment with Piqray
A	Hyperglycemia [KEY QUESTION]	✓
B	Pneumonitis	✓
C	Severe cutaneous reactions	✓
D	Suicidal ideation	☐
E	Onychomycosis	☐
F	I don't know/am not sure	☐

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THESE 5 QUESTIONS]

5. Hyperglycemia is a reversible, on target effect of treatment with Piqray. Which of the following signs and symptoms should patients be counselled about to help identify and mitigate the risk of hyperglycemia? (check all that apply)

		Sign/symptom of hyperglycemia
A	Excessive thirst [KEY QUESTION]	✓
B	Increased frequency or amount of urination [KEY QUESTION]	✓
C	Increased appetite with weight loss [KEY QUESTION]	✓
D	Inability to swallow	☐
E	Yellowing of the skin	☐
F	Difficulty breathing [KEY QUESTION]	✓
G	Nausea and/or vomiting [KEY QUESTION]	✓
H	Headache [KEY QUESTION]	✓
I	I don't know/am not sure	☐

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THESE 8 QUESTIONS]

6. Which of the following is NOT a risk factor for patients to develop hyperglycemia when receiving treatment with Piqray?

□ Diabetic or pre-diabetic
□ Fasting glucose >250 mg/dL (13.9 mmol/L)
✓ Body mass index <30 kg/m^2
□ Age ≥75 years
□ I don't know/am not sure

[ON-LINE SURVEY - PROGRAMMER: RANDOMISE THE ORDER OF THE FIRST 4 RESPONSE OPTIONS]

7. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, please indicate if the following statement is True or False: For patients at higher risk for developing hyperglycemia, there is no need to consult with a healthcare professional or endocrinologist experienced in the treatment of hyperglycemia.

□ True

✓False

□ I don't know/am not sure

8. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, to mitigate risk of hyperglycemia, which of the following should be performed before a patient starts treatment with Piqray?

		Check the box if the action should be performed
A	Obtain a fasting glucose and HbA1c	✓
B	Optimize the patient's level of blood glucose, as applicable	✓
C	Counsel the patient about the risk of hyperglycemia	✓
D	Increase the dose of their current antihyperglycemic medication, if applicable	□
E	Consult with a diabetologist for all patients, even if they are not diabetic	□
F	I don't know/am not sure	□

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THESE 5 QUESTIONS]

9. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, please indicate if the following statement is True or False: The monitoring schedule of fasting glucose levels for patients receiving Piqray is the same for patients with, and without, risk factors for hyperglycemia.

   □ True

   ✓False

   □ I don't know/am not sure

10. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, at what frequency should fasting glucose testing be performed for all patients treated with Piqray?

   □ Weekly for the first 3 months of treatment, then monthly thereafter
   ✓At weeks 1, 2, 4, 6, and 8 after treatment start, then monthly thereafter
   □ Daily for the first 2 weeks of treatment, then at Weeks 4, 6, and 8, then monthly thereafter
   □ I don't know/am not sure

   [ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THE FIRST 3 RESPONSE OPTIONS]

11. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, at what frequency should HbA1c testing be performed for all patients treated with Piqray?

   □ Monthly for the first 3 months of treatment, then quarterly thereafter
   ✓4 weeks after treatment start, then every 3 months thereafter
   □ Monthly for the first 6 months of treatment, then annually thereafter
   □ I don't know/am not sure

   [ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THE FIRST 3 RESPONSE OPTIONS]

12. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, please indicate if the following statement is True or False: For fasting glucose values that are ≤250 mg/dL (≤13.9 mmol/L), no Piqray dose adjustment is required. It is recommended to manage by initiating or intensifying oral antihyperglycemic treatment.

   ✓ True

   □ False

   □ I don't know/am not sure

13. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, which of the following fasting glucose values (blood) that are elevated (above the upper limit of normal) require Piqray dosing to be interrupted?

   □ Any fasting glucose value >160 mg/dL (>8.9 mmol/L)

   □ Any fasting glucose value >200 mg/dL (>27.8 mmol/L

□ Any fasting glucose value >200 mg/dL (>27.8 mmol/L

✓Any fasting glucose value >250 mg/dL (>13.9 mmol/L

□ I don't know/am not sure

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THE FIRST 3 RESPONSE OPTIONS]

14. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, please indicate if the following statement is True or False: If Piqray dosing is interrupted due to elevations in fasting glucose >250 mg/dL (>13.9 mmol/L), and fasting glucose decreases to ≤160 mg/dL (≤8.9 mmol/L) within 3-5 days under appropriate antihyperglycemia treatment, Piqray can be resumed at the starting dose level of 300 mg/day. [KEY QUESTION]

□ True

✓False

□ I don't know/am not sure

15. According to the Piqray Prescriber's/HCP **Guide for Hyperglycemia** and SmPC for Piqray, when hyperglycemia occurs and patients are treated with antihyperglycemic medication, at what frequency should fasting glucose continue to be monitored? [KEY QUESTION]

□ Daily for the first 4 weeks, then weekly for the next 8 weeks

✓ Weekly for at least 8 weeks, followed by once every 2 weeks, and consider consultation with a healthcare professional with expertise in the treatment of hyperglycemia.

□ As clinically indicated

□ I don't know/am not sure

[ON-LINE SURVEY - PROGRAMMER: RANDOMIZE THE ORDER OF THE FIRST 3 RESPONSE OPTIONS]

PARTICIPANT CHARACTERISTICS

[Preamble 2]: There are just a few more questions to help us combine your answers with other answers we have received, and to help us interpret the survey results.

16. What is your primary medical specialty? (Please tick 1 response only)

□ Surgeon/surgical oncologist
□ Radiation oncologist/radiologist
□ Medical oncologist
□ Other

17. Approximately how many years have you been working with oncology patients?

- ◻ <5 years
- ◻ 5 to <10 years
- ◻ 10 to <15 years
- ◻ ≥15 years
- ◻ Prefer not to answer

18. Within the past 12 months, for approximately how many patients have you prescribed Piqray?

- ◻ 1-5
- ◻ 6-10
- ◻ >10
- ◻ I don't know/am not sure

19. When was the last time that you prescribed Piqray?

- ◻ <3 months ago
- ◻ 3 to <6 months ago
- ◻ I don't know/am not sure

20. Have you been an investigator for one of the Piqray clinical trials?

- ◻ Yes
- ◻ No
- ◻ I don't know/am not sure

CLOSING

Thank you for taking the time to complete this survey.

You may now close this browser.