NOVARTIS

Global Clinical Epidemiology

Non-Interventional Study Protocol

Study Protocol Number AMN107A2001

Title	Details about the methodology to evaluate the use of educational material as a risk minimization activity (EMA Follow-Up Measure 42)
Protocol version identifier	v0.0
Date of last version of protocol	14 January 2014
EU PAS register number	Study not registered
Active substance	Nilotinib (ATC code L01XE08)
Medicinal product	Tasigna (nilotinib)
Product reference	Not applicable
Procedure number	EMEA/H/C/000798
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom

Joint PASS	No
Research questions and objectives	The objective of the proposed survey is to evaluate the effectiveness of the educational material for healthcare professionals and patients/caregivers used as part of the Tasigna® risk management plan
Country (-ies) of study	United Kingdom, France, Germany, Spain, Italy
Author	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
MAH contact person	[redacted]

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2 List of abbreviations

AE	Adverse Event
CML	Chronic Myeloid Leukemia
CML-CP	Chronic Myeloid Leukemia chronic phase
CRF	Case Report/Record Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare Professional
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
NIS	Non-interventional Study
OTC	Over the counter
PASS	Post-Authorization Safety Study
Ph+ CML	Phuiladelphia positive Chronic Myeloid Leukemia
PI	Principal Investigator
REB	Research Ethics Board
REMS	Risk Evaluation and Minimization Strategy
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOP	Standard Operations Procedure
[redacted]	[redacted]
WHO	World Health Organization

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

4 Abstract

Title

Details about the methodology to evaluate the use of educational material as a risk minimization activity

Version and date

V.0.0

Name and affiliation of main author

[redacted]

Rationale and background

In line with EMA Post-Authorisation Commitment/Follow-Up-Measure (FUM) 42, Novartis committed to provide details about the methodology to evaluate the use of educational material as a risk minimization activity. This protocol provides a detailed survey to evaluate the use of the Tasigna educational material, with which the EMA agreed on 02 May 2013 (EMA/272076/2013).

Research question and objectives

The objective of the proposed survey is to evaluate the effectiveness of the educational material used as part of the Tasigna® Risk Management Plan (RMP) for healthcare professionals and patients/caregivers. Specifically, to

- Evaluate physician's receipt and review as well as their understanding of the educational material
- Evaluate the physician's assessment of the effectiveness of the educational materials as tools to convey important safety information to physicians who prescribe Tasigna
- Assess patient's understanding of the patient educational material to confirm that patients have received and reviewed as well as understood the material

Study design

This is a multi-centre, observational, international, cross-sectional physician and patient survey in the context of Tasigna prescription and treatment

Population

Tasgina prescriber's in 5 EU countries and patients with CML treated by the eligible prescribers

Variables

See questionnaires

Data sources

Prescribers and patients survey

Study size

50 prescribers and patients per participating country

Data analysis

Descriptive statistics al global level and stratifications per country

Milestones

Start of data collection: 15 January 2014

End of data collection: 30 April 2014

Final report of study results: 30 July 2014

5 Amendments and updates

None

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	15 January 2014
End of data collection	30 April 2014
Final report of study results	30 July 2014

7 Rationale and background

Chronic myeloid leukemia (CML) is a myeloproliferative disease associated with a characteristic chromosomal translocation called the Philadelphia chromosome. The term Philadelphia chromosome describes a specific chromosomal abnormality resulting from a reciprocal translocation between chromosome 9 and 22, generating the BCR-ABL gene. BCR-ABL is a constitutively active tyrosine kinase and drives the pathology of CML.

The initial, chronic phase of CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. If untreated, the disease progresses to an accelerated phase, marked by the presence of primitive blast cells in the bone marrow and peripheral blood, followed by a terminal blast crisis phase. The therapeutic concept of inhibition of the BCR-ABL tyrosine kinase is an effective treatment modality for Ph+ CML.

CML has a yearly incidence of 1-2 cases/100,000 persons and a median age at presentation of 45 to 55 years (Faderl et al 1999). CML starts as an indolent disease with a chronic phase that untreated leads to an accelerated phase and finally progresses to a blast crisis. Until 1998 patients identified with CML had a grim prognosis, when imatinib was used for the first time, in patients refractory or intolerant to interferon alfa. The introduction of imatinib for the treatment of CML patients changed the course and prognosis of this disease, producing complete hematologic responses in more than 95% of patients with a large proportion of cytogenetic and molecular responses and good long-term results.

Tasigna (nilotinib) is a potent and selective inhibitor of the tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive (Ph+) leukemia cells.

Nilotinib is indicated for treatment of adult patients with newly diagnosed Ph+ CML in chronic phase (CML-CP) as well Ph+ CML-CP and Ph+ CML in accelerated phase (CML-AP) with resistance or intolerance to prior therapy including imatinib.

The Tasigna risk management plan includes educational materials for selected safety concerns, targeting healthcare professionals and patients/caregivers. Key elements included in the educational brochure are:

- Brief background on Tasigna, its authorised indication and posology
- Information on the cardiac risks associated with the use of Tasigna
    - That Tasigna can cause prolongation of the QT interval and that patients at risk of arrhythmia, especially torsade de pointes, should not be prescribed Tasigna.
    - The need to avoid co-prescription with any other medicines that might prolong the QT interval
    - Caution in prescribing to patients with a history of or risk factors for coronary heart disease
    - That Tasigna may cause fluid retention, cardiac failure and pulmonary oedema
- That Tasigna is metabolised by CYP3A4 and that strong inhibitors or inducers of this enzyme may significantly affect exposure to Tasigna.
    - That inhibitors may increase the potential for adverse drug reactions in particular QT interval prolongation.
    - To warn patients about OTC medicines in particular St John's Wort
- The need to inform patients about the effects of food on Tasigna
    - Not to eat within two hours before and one hour after taking Tasigna
    - The need to avoid foods such as grapefruit juice which inhibit CYP3A4 enzymes

The following educational materials for healthcare providers (physician/pharmacist/nurse) and patients have been developed in support of the Tasigna RMP.

For HCPs:

- "HCP Risk Management Letter "
- "Guideline to the Dosing and Administration of Tasigna".

These pieces are mandatory for the Novartis Affiliate to use in the local market.

For the Patients and Caregivers:

- "Important information on How to Take Your Medication"

This brochure is the mandatory piece for the Novartis affiliate to use is, where feasible and where allowed by local laws and regulations. Other optional materials are available on the company intranet site to use in communicating to patients.

8 Research question and objectives

The objective of the proposed project is to evaluate the effectiveness of the educational material for healthcare professionals and patients/caregivers used as part of the Tasigna risk management plan. The survey is proposed to be conducted in 5 European countries (Germany, France, UK, Italy and Spain).

Specifically:

- to evaluate physician's receipt and review as well as their understanding of the educational material
- to evaluate the physician's assessment of the effectiveness of the educational materials, as tools to convey important safety information to physicians who prescribe Tasigna
- to assess patients' understanding of the patient educational material, to confirm that patients have received and reviewed as well as understood the material

9 Research methods

9.1 Study design

This is a multi-centre, observational, international, cross-sectional physician and patient survey in the context of Tasigna prescription and treatment. This study will be performed under conditions of routine clinical practice and will not interfere with any aspect of the patient's clinical management.

9.2 Setting

The study will be conducted in the five largest European countries (France, Germany, Italy, Spain and the United Kingdom) to ensure that a sufficient number of patients and physicians can be identified to participate in the survey. In order to ascertain the use of Tasigna in routine clinical practice and thus answering questions regarding the provided educational materials, 50 completed physician surveys per country is the target. If within a given timeframe, 50 completed physician surveys are not feasible, Novartis considers 30 physicians per country (150 physicians in total) as an acceptable target. Physicians will primarily consist of oncologists/haematologists who are either in the Sponsor's database and thus have been contacted by the Sponsor previously, or they will be selected by directly contacting CML treatment centres. More than one physician can be recruited per centre, depending on the size of the centre. Since the questionnaire is based on the individual's understanding and accomplishment of the Sponsor's prescription directions, no influence based on the recruitment centre is expected.

Each physician will be asked to complete a survey with questions related to the information given in the brochure "A Guide to the Dosing and Administration of TASIGNA" and the "HCP Risk Management Letter".

The survey will aim to provide data on a maximum of 50 physician respondents per country.

A subset of physicians invited to take the online survey will be encouraged to invite their patients to participate in the patient survey. Novartis aims to recruit 50 patients per country; However, because CML is a rare disease it might not be feasible to attain participation of 50 patients per country. Consequently Novartis will consider 30 patients an acceptable target if not more patients commit to the survey within a given timeframe. Also, if in a given country the educational brochure could not have been provided to patients for legal reasons, no patients will be recruited in the respective country.

Participating physicians must meet the following criteria at the study start:

1. Oncology-haematology specialist.
2. Have prescribed Tasigna in the preceding 12 months at the time of survey.

Included patients must meet the following criteria:

1. CML patient who has been prescribed Tasigna within 12 months of the date the patient starts the survey.
2. Provides informed consent in accordance with local national requirements (where required).

No specific non-eligibility criteria have been defined for physicians.

Patients will not be included if they were prescribed Tasigna as part of a clinical trial (i.e. outside of routine practice).

9.3 Variables

The instrument for data collection is a survey developed by Novartis and in similar form already used in the US in the context of the local REMS. Before data inclusion, the e-CRF will be tested by the [redacted] team. The survey will be translated and administered using the following modality: web based.

All participants will receive a survey invitation to participate. The survey invitation will include information on how to access the survey online and instructions on the use of the electronic data capture (EDC) system. Each invitation will include a unique code which the respondent must enter into the system in order to access the survey. The code is deactivated after the survey is completed to minimize fraud.

The web based survey is self-administered, online through a secure website. [redacted] will be required to design, build and maintain a web-based electronic data capture (EDC) system to collect the data and to store the survey data and other relevant study information. An electronic **'Help Desk'** will also be provided for all participants in order to log specific queries and obtain additional information.

Recorded data will be quality checked. [redacted] operates an EU Annex 11 compliant platform for the entry, storage, manipulation, analysis and transmission of electronic information. Data migrated to the final study database will also be validated by the Statistical Department to ensure its quality, prior to any data analyses

Refer to Annex 3.1 for proposed physicians' survey

Refer to Annex 3.2 for proposed patient's survey

9.4 Data sources

Data will be collected via a physician survey and a patient survey. Both Physicians and patients will record all information in an electronic Data Collection Tool (eDCT). Patients will be asked to provide informed consent before their data can be included in accordance with local national requirements (where required).

No link will be possible between the sponsor and patient respondents.

[redacted] will follow its own internal SOPs that have been reviewed and approved by Novartis.

For prescribers with email addresses, an invitation to participate in the survey will be sent by e-mail. If the desired response rate is not achieved after the first invitation, then a second reminder invitation will be sent by email. If the target is still not achieved, then an additional email will be made to prescribers randomly selected from the list until the desired sample size is obtained. The invitation will direct the prescriber to the survey website to complete the survey. For those prescribers without e-mail addresses, invitations will be sent by mail following the same pattern of two mailings following the initial invitations. The prescriber survey invitations will direct the recipient to access the survey website to complete the survey. A unique code will be included in the invitation. The code is entered on the landing page of the survey website prior to access being granting to take the survey. The unique code is deactivated after the survey is completed.

A minimum of 6 – 10 prescribers per country will be asked to provide survey invitations to their patients being treated with Tasigna and to motivate their participation in the proposed survey. This should allow recruitment of 4 - 12 patients to complete the survey per physician (for a total of 50 completed patient surveys per country where patient educational material can be provided by local law).

The Patient Survey Recruitment Packet will be housed in a simple 2-pocket folder and will include:

- An Introductory Letter (outlines the objective of the surveys and the process for recruiting patients, and explains that the surveys are EC-approved)
- Brief Instruction Guide
- Frequently Asked Questions (FAQ) Laminated Card

All of these materials will be translated into the required local languages.

The survey invitation presents the patient with the option of completing the survey on-line via the survey website.

9.4.1 Estimated calendar (tentative)

Timelines are estimated and will be dependent upon further discussions and confirmation of specifications and approvals.

Table 9-1 Timeline for assessment of prescribers and patients

Milestone	Estimated timeline	Duration
Field survey	15 Jan 2014 – 30 April 2014	4.0 Months
Data management and analysis	01 May 2014 – 30 June 2014	2.0 Months

Milestone	Estimated timeline	Duration
Final analysis report	30 July 2014	1 Month

9.5 Study size

The survey aims to provide data on a maximum of 50 physicians and patients per country, or a maximum total of 250 physicians and patients; although the final physicians and patient sample size will be dependent on the success in recruiting physicians and patients into the survey.

The inclusion of 250 physicians and patients will allow to estimate different occurrence rates with the following precision level (Table 9-2).

Table 9-2 Precision of estimated rates with a sample size of 250 (2-sided 95% confidence interval)

Estimated rate	Width of confidence interval	Lower limit
50%	12.7%	43.7%
55%	12.6%	48.8%
60%	12.5%	53.6%
65%	12.1%	58.9%
70%	11.7%	63.8%
75%	11.1%	69.3%
80%	10.3%	74.4%
85%	9.2%	80.1%
90%	7.9%	85.4%
95%	5.8%	91.6%

The inclusion of 150 patients - if in 2 out of 5 countries distribution of patient education material would not be allowed and consequently patient surveys would not be conducted - will allow estimating different occurrence rates with the following precision level (Table 9-3).

Table 9-3 Precision of estimated rates with a sample size of 150 (2-sided 95% confidence interval)

Estimated rate	Width of confidence interval	Lower limit
50%	16.6%	41.7%
55%	16.5%	46.3%
60%	16.2%	51.7%
65%	15.8%	56.5%
70%	15.2%	62.0%
75%	14.5%	66.9%
80%	13.4%	72.7%
85%	12.1%	77.9%
90%	10.3%	84.0%
95%	7.9%	89.8%

A sample size of 250 physicians and patients across the five participating study countries and the initial wave of the survey, followed by a potential second wave if warranted after the analysis of the first survey - are appropriate for the evaluation of the understanding and utilization patterns of Tasigna educational materials.

9.6 Data management

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses. In all cases, patient identifiers will not be collected or transmitted to Novartis. All respondents will be given an alphanumeric identifier.

9.7 Data analysis

All analyses will be performed by [redacted] that will develop a report of the survey results, including an overview of the Tasigna Risk Minimization Plan evaluation goals/objectives, design/methodology, survey results, and interpretations.

The following metrics will be reported as part of this analysis. All data will be reported by country and for all countries in aggregate:

- Number of patients and HCPs receiving survey invitations
- Number of patients and HCPs who met eligibility criteria
- Number of completed patient and HCP surveys by internet
- Description of survey participants' characteristics
- Patients
  - Gender, Age
  - Length of CML treatment(s)
- HCPs
  - Medical specialty (if other than hematologists attend CML patients)
  - Type of institution
  - Gender, Age
  - Prescribing level
  - Frequency distribution of responses to each question in each survey
  - Percent of respondents indicating correct response to each key risk message and 95% confidence intervals of the estimates

The final report will be prepared in accordance with ICH Guidelines and any applicable Novartis guidelines and/or templates.

Data will be analysed using SAS system version 9.1 (SAS Institute Inc., Cary, NC, USA) in Windows™ support. All the results will be presented at global level, with only descriptive tables proposed for stratification by country.

Continuous variables will be summarised by the appropriate descriptive statistics: mean, standard deviation, number of valid and missing values, minimum and maximum value. For categorical variables the number and percentage of responses per category will be described. The respective point estimates/proportions will be accompanied by a 95% Confidence Interval (CI).

9.8 Quality control

The entire study will be managed by an international project coordinator at [redacted] who will coordinate all the local project managers and maintain fluid communication with the study Sponsor, the study team and the principal-in-charge at [redacted]. There will be a national project manager in each country in charge of local management and the coordination of local study research associates.

9.8.1 Data quality assurance

Not applicable

9.8.2 Data recording and document retention

Not applicable

9.8.3 Site monitoring

Not applicable

9.9 Limitations of the research methods

Final results will be impacted by the overall number of physicians and patients participating in the survey. Every effort will be done in order to accomplish the pre-fixed sample size for both physicians and patients.

9.10 Other aspects

Not applicable

10 Protection of human subjects

Information on the identity of patients shall be considered as confidential for all effects and purposes. The identity of patients may under no circumstances be revealed nor published. All other parties involved in data management and analysis will receive and subsequently analyse non-identifiable patient data. No link will be possible between the Sponsor and the patient.

This study does not foresee the Sponsor requiring access to patient data. If, in the unlikely event, a patients' identity needs to be revealed for legal reasons or in the case of an audit to evaluate data quality, the study Sponsor will be required to comply at all times with confidentiality legislation and guidelines. The provisions of the European Directive 95/46/CE, governing the protection of data of a personal nature shall be fully respected. A patients' identity will always be a matter for the patient and his/her physician and may not be revealed without the permission of both.

10.1 Data confidentiality

By signing the physician's confidentiality agreement, the physician affirms to Novartis that information provided to the physician by Novartis will be kept in confidence and such information will be divulged to any expert committee, affiliated institution, and employees only under an appropriate understanding of confidentiality with such committee, affiliated institution and employees.

Web-based data will be securely recorded in a central database and tracked using an audit trail. The system will allow retrieval of all data at any time, and will include security elements to prevent anyone other than authorised personnel from accessing data. Each user will have a specific profile, which will limit his/her use of the database and also identify any person who might access any particular piece of information.

A security copy of the database and the application files will be held outside the server housing the web-based study. Security copies will be made on a periodic basis and stored outside this server.

10.2 Confidentiality of patient records

[redacted] will be required to conduct the study so that in the unlikely event that Novartis or any regulatory agency needs to consult and/or copy study documents in order to verify e-CRF data, they will be able to do so in accordance with local regulatory and ethical restrictions.

10.3 Compliance with law audit and debarment

[redacted] shall prepare and maintain complete and accurate study documentation in compliance with good clinical practice standards and applicable national and local laws, rules and regulations and, for each patient participating in the study, promptly record all data in the e-CRFs as required by this protocol.

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients 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 2008), 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).

11 Management and reporting of adverse events/adverse reactions

This study is purely observational. The patient undergoes no additional risk from his/her participation in the study, as inclusion involves no additional diagnostic, evaluative or therapeutic action over and above those deemed appropriate by the patients' physician.

11.1 Safety data collection and reporting

To respond to the questions of this survey the physician is not required to review treatment outcomes or adverse reactions. The survey does not solicit reports of adverse drug reactions (ADRs). While it is not the objective of the survey to collect adverse events, it is possible that a patient will spontaneously report information which meets adverse event criteria. The [redacted] team members supporting this survey will be trained on Novartis adverse event criteria and reporting procedures.

12 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study 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.

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.

13 References (available upon request)

European Medicines Agency (2010) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (Internet) Available from: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000229.jsp&mid=WC0b01ac05801df747> (Accessed 25 June 2013).

Faderl S, Talpaz M, Estrov Z, et al (1999) The biology of chronic myeloid leukemia. N Engl J Med; 341:164-72.

ISPE (2008) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 17:200-8.

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology; 18(6):805-35.

Annex 1 - List of stand-alone documents

None

Annex 2 - ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evaluation of the use of educational material as a risk minimization activity

Study reference number:

AMN107A2001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection [1]	☒	☐	☐	13
1.1.2 End of data collection [2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

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Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	9
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	11
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

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Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	11
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments:

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

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

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☐	☒	☐	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12

Comments:

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Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

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Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☒	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	13

Comments:

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Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

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Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☒	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	27
8.1.3 Covariates?	☐	☒	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style,	☐	☒	☐	

Section 8: Data sources	Yes	No	N/A	Page Number(s)
etc.)				
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

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Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	14

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	15
10.3 Are descriptive analyses included?	☒	☐	☐	15
10.4 Are stratified analyses included?	☒	☐	☐	15
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

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Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on	☒	☐	☐	16

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)				
11.3 Are methods of quality assurance described?	☒	☐	☐	16
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☒	☐	
12.1.2 Information biases? (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. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	17

Comments:

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Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	17
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	17
13.3 Have data protection requirements been described?	☒	☐	☐	17

Comments:

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Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**

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

Comments:

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

Comments:

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[redacted]

Annex 3 - Additional information

Annex 3.1 - Proposed survey for healthcare providers

1. Have you read the TASIGNA (nilotinib) Novartis brochure "Guideline to the Dosing and Administration of TASIGNA"?

   ☐ Yes, I have received and read it
   ☐ No, I have received it but not read it
   ☐ I have not received the brochure

   Only HCPs that responded "Yes" should respond to the rest of the survey

2. Can you identify any of the safety warnings for TASIGNA from the list below? (*Check all that apply*.)

	True	False	I don't know
TASIGNA may prolong the QT interval	O	O	O
TASIGNA should not be used in patients with long QT syndrome and uncorrected hypokalemia or hypomagnesemia	O	O	O
TASIGNA should be used with caution in patients with a history of uncontrolled or significant cardiac disease	O	O	O

3. How do you prescribe (doses and administration) TASIGNA for newly diagnosed Ph+ CML patients and Imatinib resistant or intolerant patients?

Indication	300 mg twice daily	300 mg once daily	400 mg twice daily	400 mg once daily
newly diagnosed Ph+ CML CP patients	O	O	O	O
Imatinib resistant or intolerant Ph+ CML CP and AP patients	O	O	O	O

4. Patients should be advised (*check all that apply*)

	Yes	No	I don't know
to avoid food 2 hours before and at least 1 hour after taking TASIGNA	O	O	O
that TASIGNA should not be taken at any time with grapefruit juice or grapefruit products	O	O	O
to take TASIGNA on a full stomach	O	O	O
to swallow TASIGNA whole with water	O	O	O
To take TASIGNA twice daily approximately 12 hours apart, around the same time each day	O	O	O

5. Intake of food together with TASIGNA increases the bioavailability (serum concentration) of TASIGNA and may subsequently increase the risk of QT prolongation. *(Select one)*

- ☐ True
- ☐ False
- ☐ I don't know

6. Patients who are unable to swallow TASIGNA capsules can be counseled to disperse the content of each TASIGNA capsule *(Select one)*
   - ☐ In a teaspoon of applesauce and take the content immediately
   - ☐ In a glass of water and drink the content immediately.
   - ☐ In a teaspoon of milk and take the content immediately.
   - ☐ All of the above.

7. What guidance do you give to your patient if he/she has forgotten to take a dose of TASIGNA (>2 hours after the scheduled dose)? *(Select one)*
   - ☐ To take the missed dose as soon as he/she realizes the oversight.
   - ☐ To wait until next dose time and then follow the planned dose schedule.
   - ☐ To take the double dose once at the next planned dose schedule.

8. Are you aware of any dose adjustments or modification guidance for TASIGNA?
   - ☐ No
   - ☐ Yes
   - ☐ I don't know

9. Which of the situations below might warrant dose interruption or dose adjustments? (*Check all that apply*)
   - ☐ hematologic toxicities (including neutropenia and thrombocytopenia) that are not related to underlying leukemia
   - ☐ when clinically significant moderate or severe non-hematologic toxicity develops
   - ☐ Grade 3 or 4 lipase increase
   - ☐ Grade 3 bilirubin or hepatic transaminase increase
   - ☐ Grade 1 or 2 lipase increase

10. When should ECGs be conducted for TASIGNA (nilotinib) patients? (*Check all that apply*)
    - ☐ Before starting TASIGNA (at baseline)
    - ☐ As clinically indicated
    - ☐ Fourteen days after starting TASIGNA and periodically thereafter

11. Hypokalemia and hypomagnaesemia must be corrected prior to TASIGNA administration and electrolytes should be monitored periodically.
    - ☐ False
    - ☐ True

☐ I don't know

12. Which of the following carry a risk of drug interactions with TASIGNA and should be avoided if possible? (*Check all that apply*)

☐ Strong CYP3A4 inhibitors
☐ Strong CYP3A4 inducers
☐ St Johns Wort
☐ Certain antiarrhythmic medicines such as amiodarone
☐ Medications or supplements known to prolong QT interval
☐ Consumption of green tea (> 3 cups a day)

13. If treatment with strong CYP3A4 inhibitors or antiarrhythmic medications or strong CYP3A4 inducers cannot be avoided, what should you do? *(Check all that apply)*

☐ Interrupt therapy with TASIGNA if possible
☐ Closely monitor the individual for prolongation of the QT interval if transient interruption of TASIGNA is not possible
☐ No attention is needed

14. Identify preexisting conditions from the list below which require that TASIGNA is used with caution. *(Check all that apply)*

☐ Congenital long QT syndrome
☐ Patients with a history of uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia
☐ Patients with hepatic impairment. Hepatic impairment has a modest effect on the pharmacokinetics of TASIGNA
☐ Patients with a history of pancreatitis. Serum lipase should be checked periodically
☐ Patients with a history of central neurologic disease such as seizures

15. When did you receive TASIGNA educational material? *(Check all that apply)*

☐ When TASIGNA was first launched (*the country launch date will be included in survey here*)
☐ Every time I'm in touch with a sales representative
☐ Periodically (twice a year, etc.)
☐ Do not remember
☐ It is available on demand
☐ I do not know how to ask for more Guides

16. How do you rate the TASIGNA Guide for prescription and posology?

☐ Very useful

- ☐ Mostly useful
- ☐ Somewhat useful
- ☐ Mostly not useful
- ☐ Not useful at all

17. How many CML patients did you personally treat – including all new and follow-up cases – in the last 12 months?

- ☐ below 5 patients
- ☐ 5 or more patients

18. For how many years have you practiced as an oncologist/ hematologist?

- ☐ Less than 5
- ☐ 5 to less than 10
- ☐ 10 to less than 15
- ☐ 15 to less than 20
- ☐ More than 20 years

19. In what setting do you spend most of your time working? *(to be adapted for every country*). *(Check all that apply)*

- ☐ Specialist cancer / oncology/ haematology centre
- ☐ Teaching / university hospital
- ☐ Public / university hospital
- ☐ Public / Non-university hospital
- ☐ District/ regional general (NHS) hospital
- ☐ Private clinic / office based
- ☐ Other

Annex 3.2 - Proposed survey for patients

1. For how long have you been taking TASIGNA?

   ☐ less than or equal to 6 months
   ☐ 7-12 months
   ☐ more than12 months
   ☐ Not sure/Don't remember

2. Did you read the brochure "Important Information About How to Take Your Medication"? (Note: the exact title of the brochure will be adjusted to reflect the respective local title) (Select one)

   ☐ Yes, I have received and read it
   ☐ No, I have received but not read it
   ☐ Not sure/Don't remember

   STOP if NO or DON'T REMEMBER is selected under question 2.

3. What kind of information is contained in the brochure "Important Information About How to Take Your Medication"?

	Yes	No	I don't know
It provides me with important safety information about TASIGNA	O	O	O
It tells me when and how to take TASIGNA	O	O	O
It tells me which foods to avoid with TASIGNA	O	O	O

4. Who gave you this educational informational material for TASIGNA? *(Select one)*

   ☐ The physician who prescribed me TASIGNA
   ☐ Another healthcare professional
   ☐ Someone else
   ☐ I don't remember

5. When you were given this packet of informational materials, were the materials clearly explained to you?

   ☐ Yes
   ☐ No

6. How should you take TASIGNA? *(Select all that apply)*

	Yes	No	I don't know
On an empty stomach (at least 2 hours after a meal)	O	O	O
On a full stomach	O	O	O
Swallow whole with water, do not chew	O	O	O

After taking TASIGNA wait at least 1 hour before you eat	O	O	O
If you take 4 capsules of TASIGNA per day, you should take 2 capsules each 12 hours apart, around the same time each the day	O	O	O
If you take 4 capsules of TASIGNA per day, you can take them at 4 times over the day	O	O	O

7. In case you are unable to swallow capsules, how should you take TASIGNA?
   - ☐ Each TASIGNA capsule may be dispersed in one teaspoon of applesauce and taken immediately
   - ☐ Each TASIGNA capsule may be dispersed into a glass of fruit juice and drunk
   - ☐ Each TASIGNA capsule may be dispersed into a soup dish and taken along with lunch/dinner
   - ☐ I don't know
   - ☐ This does not apply to me

8. What should you do if you have forgotten to take a dose of TASIGNA well after the scheduled time (> 2 hours)? *(Select one)*
   - ☐ Take the missed dose as soon as you realize the oversight
   - ☐ Wait until next dose time and follow the planned dose schedule
   - ☐ Take the double-dose of TASIGNA once on the next planned dose schedule

9. What should you do if you are sick and experience vomiting after taking TASIGNA? *(Select one)*
   - ☐ Take another dose of TASIGNA and inform your doctor at the next visit
   - ☐ Do not take another dose and speak to your doctor immediately
   - ☐ Take the double-dose of TASIGNA once on the next planned dose schedule

10. What should you avoid at any time when taking TASIGNA? *(Select all that apply)*

	Yes	No	I don't know
Grapefruit juice, grapefruit products or any supplement containing grapefruit extracts	O	O	O
Apples, apple juice	O	O	O
Certain vitamins and herbal supplements	O	O	O

11. You should tell your doctor if you have a heart disorder or are taking medication for the heart or if you have heart rhythm abnormalities/QT prolongation or a family history of it. *(Select one)*
   - ☐ False
   - ☐ True
   - ☐ I don't know

12. Is it correct that grapefruit products can influence an enzyme in your body and as a consequence an increased amount of TASIGNA will be circulating in your blood and may cause side effects? *(Select one)*

    ☐ Yes
    ☐ No
    ☐ I don't know

13. In case you faint or experience an irregular heartbeat while taking TASIGNA, you should contact your physician immediately? *(Select one)*

    ☐ True
    ☐ False
    ☐ I don't know

14. Do you know that you need to avoid medicines that are strong CYP3A4 inhibitors (your doctor will determine if any of your medicines are strong CYP3A4 inhibitors)?

    ☐ Yes
    ☐ No

15. Which of the following should you discuss with your doctor while taking TASIGNA? *(Select all that apply)*

	Yes	No	I don't know
Any changes in my prescription medication	O	O	O
Any changes in medications I can buy without a prescription	O	O	O
Any changes in vitamins/herbal supplements	O	O	O

16. Are you male or female?

    ☐ Male
    ☐ Female

17. What is your age?_____(range = 16-99) *[only numeric values can be entered]*

18. What is the highest level of education you have completed (to be adjusted on a per country level)?

    ☐ Less than high school
    ☐ Some high school
    ☐ High school graduate
    ☐ Some college
    ☐ College graduate
    ☐ Graduate degree

19. How did you like the TASIGNA Brochure(s)?

- ☐ Interesting and useful
- ☐ Useful
- ☐ Not useful
- ☐ Misleading
- ☐ I did not understand it
- ☐ I started reading, but did not finish it