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Final Report of the details about the methodology to evaluate the use of educational material as a risk minimization activity (EMA Follow-Up Measure 42)

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Marketing authorization holder	Novartis Europharm Limited Frimley Business Park Camberley GU16 7SR United Kingdom
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Research question and objectives	The objective of the survey is to evaluate the effectiveness of the educational material for healthcare professionals and patients used as part of the Tasigna® risk management plan
Countries of study	France, Germany, Italy, Spain, and United Kingdom

Marketing authorization holder

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Table of Contents

1 Abstract

Title

Final Report of the details about the methodology to evaluate the use of educational material as a risk minimization activity (EMA Follow-Up Measure 42)

Keywords

Chronic myeloid leukemia (CML), Philadelphia chromosome, nilotinib, risk management plan (RMP)

Rationale and background

In line with the European Medicines Agency (EMA) Post-Authorisation Measure (PAM)/Follow-Up Measure (FUM) MEA 042, Novartis committed to provide details about the methodology to evaluate the use of educational material as a risk minimization activity. This study included a detailed survey to evaluate the use of the TASIGNA® educational material, which was agreed with the EMA on 02 May 2013 (EMA/272076/2013).

Research question and objectives

The objective of the survey was to evaluate the effectiveness of the TASIGNA educational material used as part of the TASIGNA RMP for healthcare professionals (HCPs) and patients.

The main objectives were to:

- Evaluate physician's receipt and review as well as their understanding of the educational materials
- 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 was a multi-centre, observational, international study including cross-sectional physician and patient surveys in the context of TASIGNA prescription and treatment.

Setting

The study was conducted in 5 European countries (France, Germany, Italy, Spain, and the United Kingdom) where TASIGNA is commercially available.

[redacted]

Subjects and study size, including dropouts

Subjects consisted of TASIGNA prescribers in 5 European countries (United Kingdom [UK], France, Germany, Spain, and Italy) and patients with CML treated with TASIGNA by the eligible prescribers in 3 European countries (UK, Germany, and Spain). Patients were not contacted directly by the sponsor or contract research organization but only through their physicians. Healthcare professionals were identified from sponsor lists or commercially available prescriber lists.

Variables and data sources

Data were collected via self-administered, online, 19-question physician and patient electronic surveys. The surveys included multiple choice and close-ended questions related to the understanding of the educational material for TASIGNA.

Results

Healthcare professionals

Invitation letters were sent to 1592 HCPs in 5 European countries. By the survey end date (31 Dec 2015), 244 (15.1%) HCPs responded to the survey. Of these respondents, 75 (30.7%) were ineligible (with 62 [25.4%] not having received the educational brochure or received it but did not read it, 8 [3.3%] not asked the question as they had been deemed ineligible by an earlier question, and 5 [2.0%] discontinued the survey without answering the question), 169 (69.3%) HCPs were eligible for participation and 157 (64.3%) HCPs completed the survey.

Of the 157 eligible HCPs who completed the survey, 73 (46.5%) reported that they had received information every time they were in touch with a sales representative, 61 (38.9%) received information when TASIGNA was first launched, and 58 (36.9%) reported receiving information periodically after launch. Most of the HCPs rated the TASIGNA guide for prescription and posology as very useful (91, 58.0%) or mostly useful (57, 36.3%); 9 (5.7%) HCPs rated the guide as somewhat useful, and no HCPs rated the TASIGNA guide as mostly not useful or not useful at all (see Table 1-1).

[redacted]

Table 1-1 Results to questions related to the educational materials in complete respondents - HCPs

Question	Complete Respondents[1], n (%)					
	UK N=14	France N=39	Germany N=9	Spain N=31	Italy N=64	Total N=157
Question 18: When did you receive TASIGNA educational material? (Check all that apply)						
When TASIGNA was first launched (date)	9 (64.3)	10 (25.6)	3 (33.3)	14 (45.2)	25 (39.1)	61 (38.9)
Every time I'm in touch with a sales representative	6 (42.9)	22 (56.4)	2 (22.2)	11 (35.5)	32 (50.0)	73 (46.5)
Periodically (twice a year, etc.)	7 (50.0)	5 (12.8)	2 (22.2)	12 (38.7)	32 (50.0)	58 (36.9)
Do not remember	1 (7.1)	14 (35.9)	4 (44.4)	7 (22.6)	7 (10.9)	33 (21.0)
It is available on demand	5 (35.7)	6 (15.4)	3 (33.3)	9 (29.0)	13 (20.3)	36 (22.9)
I do not know how to ask for more Guides	1 (7.1)	0	0	0	0	1 (0.6)
Question 19: How do you rate the TASIGNA Guide for prescription and posology?						
Very useful	6 (42.9)	20 (51.3)	6 (66.7)	16 (51.6)	43 (67.2)	91 (58.0)
Mostly useful	8 (57.1)	15 (38.5)	3 (33.3)	15 (48.4)	16 (25.0)	57 (36.3)
Somewhat useful	0	4 (10.3)	0	0	5 (7.8)	9 (5.7)
Mostly not useful	0	0	0	0	0	0
Not useful at all	0	0	0	0	0	0

[1] A respondent will be considered as complete if all questions are answered.
Source: HCP Table 3

Question 5 to Question 17 in the HCP survey (see Appendix 3) related to understanding the risks associated with TASIGNA. Responses to the questions were categorized as "correct response" and "incorrect responses"; "I don't know" was always categorized as an incorrect response. The correct response rates across the 13 HCP survey questions ranged from 28.0% to 99.4%.

The questions with low correct response rates for HCPs included Question 9 and Question 16. For Question 9 (Patients who are unable to swallow TASIGNA capsules can be counseled to disperse the content of each TASIGNA capsule), 47.1% of HCPs correctly answered that TASIGNA should be dispersed in a teaspoon of applesauce and taken immediately; however, another 20.4% of HCPs selected "all of the above", which included the correct option to disperse in applesauce as well as the incorrect option to disperse TASIGNA in water. Another low percentage of correct responses was seen for Question 16 for "both correct options" (28.0%; If treatment with strong CYP3A4 inhibitors or antiarrhythmic medications or strong CYP3A4 inducers cannot be avoided, what should you do?), Although 1 correct option (Closely monitor the individual for prolongation of the QT interval if transient interruption of TASIGNA is not possible) had a response rate of 94.9%, the other correct option (Interrupt therapy with TASIGNA if possible) had a response rate of 32.5%.

Patients

Selected HCPs were asked to provide invitation letters to their patients for participation in the survey. A subset of 165 eligible HCPs from 3 European countries (UK, Germany, and Spain) were sent a total of 167 patient recruitment packs (2 HCPs requested recruitment packets to be resent)containing 1195 invitation letters that could have been distributed to their patients. In order to minimize the burden on HCPs and protect the confidentiality of patients who were invited to participate, the HCPs were not asked to keep a log of who their invitations were distributed to or how many were distributed. Therefore, the number of invitation letters actually issued to patients is unknown. Of these, 11 patients responded to the survey, of which 10 (90.9%) were eligible and completed the survey.

All 10 (100.0%) patients responded "Yes" to the statements that the brochure "Important Information About How to Take Your Medication" provided important safety information about TASIGNA and that it told when and how to take TASIGNA. Seven (70.0%) patients responded "Yes" to the statement that the information in the educational brochure indicates which food to avoid with TASIGNA. Eight (80.0%) patients reported having received educational material from the physician who prescribed them TASIGNA (1 [10.0%] patient reported that the materials were provided by another healthcare professional, and 1 [10.0%] patient could not recall who provided the materials), and all 10 (100.0%) patients reported that the educational materials were clearly explained to them. Six (60.0%) patients reported that they found the TASIGNA educational brochure useful, and 3 (30.0%) patients reported that they found the TASIGNA educational brochure both interesting and useful.

Question 9 to Question 17 in the patient survey (see Appendix 4) related to understanding the risks associated with TASIGNA. Responses to the questions were categorized as "correct response" and "incorrect responses"; "I don't know" was categorized as an incorrect response. The correct response rates for the 10 patients who completed the survey ranged from 30.0% to 100.0%.

For the 10 patients, the questions with low correct response rates included Question 10 and 1 component of Question 13. For Question 10, 3 (30.0%) correctly responded that each TASIGNA capsule may be dispersed in 1 teaspoon of applesauce and taken immediately in case you are unable to swallow capsules, while another 3 (30.0%) responded "does not apply to me" and 4 (40.0%) responded "I don't know. For Question 13, 4 (40.0%) correctly responded "Yes" they should avoid certain vitamins and herbal supplements when taking TASIGNA, while 3 (30.0%) responded "No" and 3 (30.0%) responded "I don't know.

Discussion

In general, the results suggest that the TASIGNA educational material was effective in communicating important safety information to HCPs, which was demonstrated in the number of questions with high correct response rates.

For HCPs who received and read the materials, the rates of correct responses about the risks associated with TASIGNA were greater than 80%, which is a commonly used knowledge rate threshold in the United States (Food and Drug Administration 2012), for the majority of the questions, i.e., 8 of the 13 questions (range: 81.5% to 99.4%).

The correct response rates for the patient survey questions were ≥60% for 9 of the 10 questions (range: 60.0% to 100.0%), excluding 1 component question to Question 13. Although knowledge was demonstrated for the key elements of how to take TASIGNA in Question 9 (range: 90.0% to 100.0%) and cardiac risks in Questions 14 and 16 (90.0% for both), very limited conclusions about patient awareness can be derived from these results due to low patient participation in this observational study. It is not uncommon to see low patient participation rates for these types of surveys as participation is voluntary and without incentive (Galea S 2007). Further, patients were not contacted directly by the sponsor or contract research organization but only through their physicians.

Conclusion

Based on the assessment of the interim report (dated 07 Dec 2015), the Committee for Medicinal Products for Human Use (CHMP) concluded on 10 Nov 2016 that the Post Authorization Measure (PAM) was considered fulfilled and no further action was required by Novartis.

The purpose of this final report is to include the 4 additional HCP responses that were submitted after the data cut-off (31 July 2015) of the interim report. As expected, the results remain in line with those provided in the interim report:

- In general, these results reflect a good understanding of the TASIGNA educational material for HCPs as correct response rates for the questions about the risks associated with TASIGNA were greater than 80% for the majority of the questions.
- However, very limited conclusions about patient awareness can be derived from the results due to the low patient participation in this observational study. Further, because the total number of respondents was low, no conclusion can be drawn about the effect of the demographic characteristics on the rates of knowledge and behavior in the broader treated population.

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2 List of abbreviations

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BCR-ABL	Breakpoint Cluster Region-Abelson
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CML	Chronic Myelogenous Leukemia
CRO	Contract Research Organization
CYP3A4	Cytochrome P450 3A4
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FAQ	Frequently Asked Question
FUM	Follow-up Measure
HCP	Healthcare Professional
MSL	Medical Science Liaison
PAM	Post Authorization Measure
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
Ph+	Philadelphia Chromosome Positive
REMS	Risk Evaluation and Mitigation Strategies
RMP	Risk Management Plan
[redacted]	[redacted]
UK	United Kingdom

[redacted]

3 Investigators

[redacted]

4 Other responsible parties

The administrative structure of the study, including internal and external participants, is described in Appendix 2.

Novartis and [redacted] staff analyzed this study and authored this report. The signatures of the sponsor's responsible medical officer, and the report authors are provided separately.

5 Milestones

The data collection period for the final analysis was 05 Dec 2014 to 31 Dec 2015. The date of the interim report was 07 Dec 2015. The date of this final report is 27 Apr 2017 and was only created to include 4 additional HCP responses that became available after the original interim report was produced.

6 Rationale and background

TASIGNA® (nilotinib) is a potent and selective Breakpoint Cluster Region-Abelson (BCR-ABL) inhibitor that was rationally designed to improve binding affinity to the BCR-ABL protein (Weisberg et al 2005). It is approximately 30 times more potent in vitro than imatinib against the wild-type kinase and is active against most of the common imatinib-resistant BCR-ABL kinase domain mutants with the exception of T315I (O'Hare et al 2005, Weisberg et al 2006, Manley et al 2010).

TASIGNA® (nilotinib) is approved in the European Union (EU) for the treatment of adult patients with:

- Newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase, and
- Chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

The safety profile of TASIGNA is established (Saglio et al 2010). As part of additional risk minimization measures, the Tasigna Risk Management Plan (RMP) includes educational materials highlighting the key safety messages, targeting healthcare professionals (HCPs) and patients.

[redacted]

Key elements included in the RMP educational material are:

- Brief background on TASIGNA, its authorised indication and posology.
- Information on the cardiac risks associated with the use of TASIGNA.
- That TASIGNA is metabolised by cytochrome P450 3A4 (CYP3A4) and that strong inhibitors (such as grapefruit juice) or inducers (in particular St John's Wort) of this enzyme may significantly affect exposure to TASIGNA.
- That CYP inhibitors may increase the potential for adverse drug reactions, in particular QT interval prolongation.
- Not to eat food within 2 hours before and at least 1 hour after taking TASIGNA because food effects how TASIGNA is absorbed.

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

For HCPs:

- "HCP Risk Management Letter"
- "A Guide to the Dosing and Administration of TASIGNA"

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

For patients:

- "Important Information About How to Take Your Medication"

Where feasible and where required by local laws and regulations, the Novartis Affiliate in each country in which TASIGNA is licensed must ensure that the RMP educational material is distributed.

In line with the European Medicines Agency (EMA) Post-Authorisation Measure/Follow-Up-Measure (FUM) 042, Novartis committed to provide details about the methodology to evaluate the effectiveness of the TASIGNA educational material as a risk minimization activity. The survey/questionnaire was approved by the EMA on 02 May 2013 (EMA/272076/2013). Results of this survey will help assess the effectiveness of the educational materials as a risk minimization measure and whether there is need to modify the educational materials. The data collection period for the final analysis for this survey was 05 Dec 2014 to 31 Dec 2015. The date of this interim report was 07 Dec 2015 and the date of this final report is 14 Mar 2017 and was only created to include 4 additional HCP responses that became available after the original interim report was produced.

[redacted]

7 Research question and objectives

The objective of the patient and HCP surveys was to evaluate the effectiveness of the TASIGNA educational material for HCPs and patients used as part of the TASIGNA RMP. The prescriber survey was conducted in 5 European countries: France, Germany, Italy, Spain, and the United Kingdom (UK). The patient survey was conducted in 3 European countries: Germany, Spain, and the UK. The patient survey was not conducted in France or Italy as the educational materials were not distributed to patients in these 2 countries due to local regulations.

The objectives of the surveys were to:

- Evaluate physician's receipt and review as well as their understanding of the TASIGNA 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 patients' understanding of the patient educational material, to confirm that patients have received and reviewed as well as understood the material.

8 Amendments and updates to the protocol

There were no amendments or updates to the protocol.

9 Research methods

The protocol is provided in Appendix 1. The final HCP questionnaire and patient questionnaire are provided in Appendix 3 and Appendix 4, respectively.

9.1 Study design

This was a multi-centre, observational, international study collecting data by cross-sectional physician and patient surveys in the context of TASIGNA prescription and treatment. The surveys were performed under conditions of routine clinical practice and did not interfere with any aspect of the patient's clinical management. The surveys were sponsored by Novartis and conducted by a global contract research organization (CRO).

To ensure comprehension of the invitation and survey questions, all of the physician and patient materials were provided in the local country language. The surveys and invitations as well as any reminder letters were all translated by a certified translation company.

The surveys were offered only online. The final survey design was based on experience from risk management evaluation studies previously completed by Novartis and the CRO. The CRO has designed and conducted assessment surveys in over 25 European countries to evaluate prescriber understanding of risk messages. Recruitment and analytic strategies included in the survey protocol were similar to those programs.

[redacted]

9.2 Setting

The study was conducted in 5 European countries (France, Germany, Italy, Spain, and the UK. In order to ascertain the use of TASIGNA in routine clinical practice, physicians and patients were asked to answer questions based on information provided in the educational materials. To ensure that a sufficient number of patients and physicians could be identified to participate in the survey, 50 completed physician surveys per country was the target. If, within a given timeframe, 50 completed physician surveys were not feasible, the sponsor considered 30 physician surveys per country (150 in total) as an acceptable target. Physicians primarily consisted of oncologists/haematologists who were either in the sponsor's database and were contacted by the sponsor previously or were selected by directly contacting CML treatment centres. More than 1 physician could be recruited per centre, depending on the size of the centre. Since the prescriber questionnaire was based on the physician's understanding and accomplishment of the sponsor's prescription directions, no influence based on the recruitment centre was expected.

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

Healthcare professionals were asked to provide invitation letters to their patients for participation in the patient survey. A subset of HCPs from 3 European countries (UK, Germany, and Spain) were sent a total of 167 patient recruitment packs (2 HCPs requested recruitment packets to be resent) containing 1195 invitation letters that could have been distributed to their patients. In order to minimize the burden on HCPs and protect the confidentiality of patients who were invited to participate, the HCPs were not asked to keep a log of who their invitations were distributed to or how many were distributed. Therefore, the actual number of invitation letters issued to patients by the HCPs is unknown. The sponsor planned to recruit 50 patients per country; however, since CML is a rare disease, the sponsor considered 30 patients per country an acceptable target.

9.3 Subjects

9.3.1 Inclusion criteria

Physicians were required to meet all the following inclusion criteria:

- Oncology-haematology specialist.
- Having prescribed TASIGNA in the preceding 12 months at the time of survey.

Patients were required to meet all the following inclusion criteria:

- CML patient who had been prescribed TASIGNA within 12 months of the date the patient started the survey.
- Providing informed consent in accordance with local national requirements (where required).

9.3.2 Exclusion criteria

- Patients were not included if they were prescribed TASIGNA as part of a clinical trial (i.e., outside of routine practice).

No specific exclusion criteria had been defined for physicians; however, physicians were not considered eligible if they responded "Have not received the Novartis brochure "Guideline to the Dosing and Administration of TASIGNA" and "Have received the Novartis brochure but have not read it".

9.3.3 Prescriber recruitment

An invitation to participate in the survey was sent to prescribers by email or mail, based on local permissions, who were identified either in the sponsor's database and were contacted by the sponsor previously or were selected by directly contacting CML treatment centres. Three reminder invitations were sent by email, if allowed, to prescribers who had not completed the survey. For those invited by mail, invitations were sent by mail with 3 reminder mailings after the initial invitations.

The prescriber survey invitations directed the recipient to access the survey website to complete the survey. A unique code was included in the invitation. The code was entered on the landing page of the survey website prior to access being granting to take the survey and was deactivated after use to minimize fraud. The survey had to be completed in a single session and would time out after 30 minutes of inactivity.

9.3.4 Patient recruitment

Healthcare professionals were asked to provide invitation letters to their patients for participation in the survey. A subset of 165 eligible HCPs from 3 European countries (UK, Germany, and Spain) were sent a total of 167 patient recruitment packs (2 HCPs requested recruitment packets to be resent) containing 1195 invitation letters that could have been distributed to their patients. In order to minimize the burden on HCPs and protect the confidentiality of patients who were invited to participate, the HCPs were not asked to keep a log of who their invitations were distributed to or how many were distributed. Therefore, the actual number of invitation letters issued to patients by the HCPs is unknown. If the desired response rate was not achieved after the first invitation, then second and third reminder invitations were sent by email. The patient survey invitation presented the patient with information for completing the survey online via the survey website.

There were 72 patient recruitment packets sent to physicians initially, then the sponsor's field force (medical science liaisons [MSLs]) delivered 95 additional packets directly to HCPs to increase participation. Patient survey recruitment packets were translated into the required local languages and included:

- An Introductory Letter to the HCP (outlines the objective of the survey, process for recruiting patients, and explains that the surveys have been approved by EMA)
- Patient survey invitation letters (5 to 10)
- Brief Instruction Guide
- Frequently Asked Questions (FAQs) Laminated Card

[redacted]

9.4 Variables

The instrument for data collection was a survey developed by the sponsor, which was similar to one already used in the United States in the context of the local Risk Evaluation and Mitigation Strategy (REMS). Before data inclusion, the electronic Case Report/Record Form (eCRF) was tested by the CRO's [redacted]. The survey was translated into the required languages and administered using the web-based modality.

Participants (HCPs and patients) received a survey invitation to participate. The survey invitation included information on how to access the survey online and instructions on the use of the electronic data capture (EDC) system. Each invitation included a unique code which the respondent entered into the system in order to access the survey. The code was deactivated after use to minimize fraud. The survey had to be completed in a single session or the session would time out.

The web-based survey was self-administered online through a secure website. The CRO was required to design, build, and maintain a web-based EDC system to collect the data and to store the survey data and other relevant study information. An electronic 'Help Desk' was also provided for all participants in order to log specific queries and obtain additional information.

9.5 Data sources and measurement

9.5.1 Data sources

Data were collected via a physician survey and a patient survey. Both physicians and patients recorded information in an electronic Data Collection Tool. Patients were asked to acknowledge informed consent on an initial webpage before their data could be included in accordance with local national requirements (where required).

No link was possible between the sponsor and patient respondents.

Prescribers in each country were asked to provide survey invitations to their patients being treated with TASIGNA and to motivate their participation in the survey. This was intended to recruit a total of 50 completed patient surveys per country where patient educational material can be provided by local law.

9.5.2 Measurements

The surveys consisting of multiple-choice and close-ended questions were used to measure understanding of the educational material associated with TASIGNA.

The outcome was the proportion of respondents answering each question associated with TASIGNA correctly. Responses to the questions related to the knowledge, attitudes and behaviours (Questions 5 to Question 17 in the HCP survey, and Question 9 to Question 18 in the patient survey) were categorized as "correct response" and "incorrect responses" as detailed in the correct answer document. "I don't know" was categorized as an incorrect response.

This study was observational. The survey did not solicit reports of adverse drug reactions (ADRs). Safety-related questions contained in the survey were those associated with TASIGNA.

[redacted]

9.6 Bias

The following were measures that minimised bias:

- Respondents who worked for, or had immediate family members who worked for, Novartis (survey sponsor) or the CRO (survey administrator) were excluded.
- No link was possible between the sponsor and patient respondents.
- [redacted] operated an EudraLex Annex 11 compliant platform for the entry, storage, manipulation, analysis and transmission of electronic information.
- The instrument for data collection was a survey (developed by the sponsor) in similar form to those already used in the US in the context of the local REMS.
- Respondents were provided a unique code during the recruitment process and were asked to provide the code to gain access to the online survey. The code was deactivated after use to minimize the possibility of fraud. The survey had to be completed in a single session and the session would time out after 30 minutes of inactivity.
- Response options presented in a list were randomized to minimize positional bias as the order of questions has been shown to influence responses.
- The survey was constructed so that all questions had to be answered in sequence and the respondent could not skip forward or backward in the survey.

9.7 Study size

The survey planned to provide data on a maximum of 50 physicians and patients per country, or a maximum total of 250 physicians and 150 patients, although the final physician and patient sample sizes were dependent on the success in recruiting physicians and patients into the survey. The inclusion of 250 physicians and 150 patients was to allow estimation of rates of knowledge and behaviours with the precision levels shown in Section 9.5 of the protocol (Appendix 1).

9.8 Data transformation

There was no data transformation and no imputation for missing values.

9.9 Statistical methods

9.9.1 Main summary measures

Continuous variables were 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 were described. The respective point estimates/proportions were accompanied by their 95% confidence intervals (CI).

9.9.2 Main statistical methods

The statistical analysis was descriptive; i.e., no formal hypothesis was tested. Counts and percentages were calculated for each question/item in the questionnaire and the proportion with correct responses with associated 95% CIs, when applicable. All questions are presented by country and overall in a frequency table. Exact binomial 2-sided 95% CIs around the percentages were calculated by the method of Clopper and Pearson (Clopper & Pearson 1934) and no adjustment was performed for multiplicity. Unless otherwise indicated, percentages were based on the population to whom a specific question was presented.

Data were managed and described using SAS system version 9.1 (SAS Institute Inc., Cary, North Carolina, United States) in Windows™ support.

9.9.3 Populations

9.9.3.1 Screened population

The screened respondents were the respondents who accessed the online survey with the code and answered at least the first survey question with any response. The participant screening results (i.e., Questions 1 to 4 in the HCP Survey and Questions 1 to 3 and 5 in the Patient Survey) were analysed in the population of the screened respondents.

9.9.3.2 Primary population

The primary population was all eligible respondents who completed the survey (Completed Respondents Population). A respondent was counted as eligible if all inclusion questions were fulfilled and none of the exclusion questions were fulfilled. Respondents who did not complete all inclusion and exclusion questions were not considered as eligible. A respondent was considered as complete if all questions were answered. The survey was constructed so that all questions must be answered in sequence and that the respondent could not skip forward or backward in the survey. This population was used for the entire set with exception of the participant screening results and the survey administration statistics.

9.9.4 Survey administration statistics

Information obtained from the survey was reported as descriptive statistics for the survey administration, survey populations, and the survey questions. All data were reported by country and for all countries in aggregate:

- Number of patients and HCPs receiving survey invitations
- Number of patients and HCPs who participated in the survey
- Number of patients and HCPs who met eligibility criteria
- Number of completed patient and HCP surveys
- Description of eligible survey participants' characteristics

- Patients
  - Gender, age
  - Length of CML treatment(s)
  - Frequency distribution of responses to each question in the survey
  - Percent of respondents indicating correct response to each key risk message and 95% CIs of the estimates
- HCPs
  - Medical specialty (if other than haematologists attend CML patients)
  - Type of institution
  - Gender, age
  - Prescribing level
  - Frequency distribution of responses to each question in the survey
  - Percent of respondents indicating correct response to each key risk message and 95% CIs of the estimates

9.9.5 Missing values

Missing data were not imputed.

9.9.6 Sensitivity analyses

No sensitivity analyses were performed.

9.9.7 Amendments to the statistical analysis plan

There were no amendments to the statistical analysis plan.

9.10 Quality control

Recorded data were quality checked. The CRO operates a EudraLex Annex 11 compliant platform for the entry, storage, manipulation, analysis, and transmission of electronic information. Data migrated to the final study database were also validated by the Statistical Department to ensure its quality prior to any data analyses.

The entire study was managed by an international project coordinator at the CRO who coordinated all the local project managers and maintained communication with the study sponsor, the study team, and the principal-in-charge at the CRO.

10 Results

10.1 Participants

10.1.1 Healthcare professionals

Survey administration statistics for HCPs are presented in Table 10-1.

Across all countries (UK, France, Germany, Spain, and Italy), 1592 invitation letters and 2413 reminder letters were issued to HCPs. By the survey end date (31 Dec 2015), a total of 244 respondents were screened for participation (i.e., the number of respondents who logged into the EDC system with the unique number and answered at least the first question of the survey). Of these respondents, 75 (30.7%) were ineligible (with 62 [25.4%] not having received the educational brochure or received it but did not read it, 8 [3.3%] not asked the question as they had been deemed ineligible by an earlier question, and 5 [2.0%] discontinued the survey without answering the question), 169 (69.3%) HCPs were eligible for participation and 157 (64.3%) HCPs completed the survey.

Table 10-1 Survey administration statistics – HCPs

	UK	France	Germany	Spain	Italy	Total
The number of respondents screened for participation[1], n	23	77	21	44	79	244
The number of respondents eligible for participation[2], n (%)	14 (60.9)	41 (53.2)	11 (52.4)	32 (72.7)	71 (89.9)	169 (69.3)
The number of eligible respondents who completed the survey[2], n (%)	14 (60.9)	39 (50.6)	9 (42.9)	31 (70.5)	64 (81.0)	157 (64.3)

[1] The number of respondents who logged on into the EDC system with the unique number and answered at least the first question of the survey with any response.
[2] Percentages are based on the number of respondents screened for participation.
Source: HCP Table 1.1

Survey participant screening results for HCPs are presented in Table 10-2.

Of the 244 HCPs screened for participation, 243 (99.6%) agreed to take part in the survey. Most screened HCPs were an oncology or hematology specialist (238, 97.5%) and had prescribed TASIGNA in the last 12 months (233, 95.5%). A total of 169 (69.3%) HCPs received and read the TASIGNA (nilotinib) Novartis brochure ("Guideline to the Dosing and Administration of TASIGNA"), while 30 (12.3%) received it but did not read it and 32 (13.1%) did not receive the brochure; the question was not asked to another 8 (3.3%) HCPs and 5 (2.0%) HCPs discontinued.

Table 10-2 Survey participant screening results – HCPs

Question	Screened Respondents[1], n (%)					
	UK N=23	France N=77	Germany N=21	Spain N=44	Italy N=79	Total N=244
Question 1: Do you agree to take part in this survey?						
Yes	23 (100.0)	77 (100.0)	21 (100.0)	44 (100.0)	78 (98.7)	243 (99.6)
No[2]	0	0	0	0	1 (1.3)	1 (0.4)
Question 2: Are you an oncology or hematology specialist?						
Yes	23 (100.0)	77 (100.0)	17 (81.0)	44 (100.0)	77 (97.5)	238 (97.5)
No[2]	0	0	3 (14.3)	0	1 (1.3)	4 (1.6)
Question not asked[3]	0	0	0	0	1 (1.3)	1 (0.4)
Discontinued[4]	0	0	1 (4.8)	0	0	1 (0.4)
Question 3: Have you prescribed TASIGNA in the last 12 months?						
Yes	23 (100.0)	76 (98.7)	17 (81.0)	42 (95.5)	75 (94.9)	233 (95.5)
No[2]	0	1 (1.3)	0	1 (2.3)	1 (1.3)	3 (1.2)
Question not asked[3]	0	0	3 (14.3)	0	2 (2.5)	5 (2.0)
Discontinued[4]	0	0	1 (4.8)	1 (2.3)	1 (1.3)	3 (1.2)
Question 4: Have you read the TASIGNA (nilotinib) Novartis brochure "Guideline to the Dosing and Administration of TASIGNA"?						
Yes, I have received and read it	14 (60.9)	41 (53.2)	11 (52.4)	32 (72.7)	71 (89.9)	169 (69.3)
No, I have received it but not read it[2]	4 (17.4)	16 (20.8)	5 (23.8)	4 (9.1)	1 (1.3)	30 (12.3)
I have not received the brochure[2]	5 (21.7)	18 (23.4)	1 (4.8)	5 (11.4)	3 (3.8)	32 (13.1)
Question not asked[3]	0	1 (1.3)	3 (14.3)	1 (2.3)	3 (3.8)	8 (3.3)
Discontinued[4]	0	1 (1.3)	1 (4.8)	2 (4.5)	1 (1.3)	5 (2.0)

[1] The screened respondents are the respondents who accessed the online survey with the unique code and answered at least the first survey question with any response.
[2] Ineligible to participate in the survey.
[3] Question not asked due to a previous elimination question.
[4] A respondent is counted as discontinued if he/she did not answer all eligibility questions without being identified as ineligible in any of the previous questions.
Note: To demonstrate the proportion of respondents who are eligible based on the number of screened respondents and the main reasons for being ineligible, overall column N is used as the denominator for percentages.

Source: HCP Table 1.2

[redacted]

10.1.2 Patients

Survey administration statistics for patients are presented in Table 10-3.

Across the 3 countries (UK, Germany, and Spain), a total of 11 patients responded to the survey, of which 10 (90.9%) were eligible for participation and completed the survey.

Table 10-3 Survey administration statistics - Patients

	UK	Germany	Spain	Total
The number of respondents screened for participation[1], n (%)	5	0	6	11
The number of respondents eligible for participation[2], n (%)	4 (80.0)	0	6 (100.0)	10 (90.9)
The number of eligible respondents who completed the survey[2], n (%)	4 (80.0)	0	6 (100.0)	10 (90.9)

[1] The number of respondents who logged on into the EDC system with the unique number and answered at least the first question of the survey with any response.
Percentages are based on the number of invitations sent.
[2] Percentages are based on the number of respondents screened for participation.

Source: Patient Table 1.1

Survey participant screening results for patients are shown in Table 10-4.

Of the 11 patients screened, all agreed to take part in the survey. Of the patients who were presented the question, 5 (100.0%) reported that they were being treated for CML, and 5 (100.0%) reported that they had been prescribed TASIGNA in the last 12 months. Ten (90.9%) patients reported receiving and reading the TASIGNA educational brochure "Important Information about How to Take Your Medication" and 1 (9.1%) patient reported receiving it but not reading it.

Table 10-4 Survey participant screening results – Patients

Question	Screened Respondents[1], n (%)			
	UK N=5	Germany N=0	Spain N=6	Total N=11
Question 1: Do you agree to take part in this survey?				
Yes	5 (100.0)		6 (100.0)	11 (100.0)
No[3]	0 (0.0)		0 (0.0)	0 (0.0)
Question 2: Are you being treated for CML (chronic myeloid leukemia)?[2]				
Yes	5 (100.0)		0	5 (100.0)
No[3]	0 (0.0)		0	0 (0.0)
N/A[4]	0		6	6

Question	Screened Respondents[1], n (%)			
	UK N=5	Germany N=0	Spain N=6	Total N=11
Question 3: Have you been prescribed TASIGNA in the last 12 months?[2]				
Yes	5 (100.0)		0	5 (100.0)
No[3]	0 (0.0)		0	0 (0.0)
N/A[4]	0		6	6
Question 5: Did you read the brochure "Important Information About How to Take Your Medication"?				
Yes, I have received and read it	4 (80.0)		6 (100.0)	10 (90.9)
No, I have received but not read it[3]	1 (20.0)		0 (0.0)	1 (9.1)
Not sure/Don't remember[3]	0 (0.0)		0 (0.0)	0 (0.0)

[1] The screened respondents are the respondents who accessed the online survey with the unique code and answered at least the first survey question with any response.
[2] Denominator for percentages is the number of respondents presented the question.
[3] Ineligible to participate in the survey.
[4] Question not asked in Spain.

Source: Patient Table 1.2

10.2 Descriptive data

10.2.1 Healthcare professionals

The description of HCP survey participants (complete respondents) is presented in Table 10-5.

A total of 137 (87.3%) respondents reported that they had personally treated 5 or more CML patients in the last 12 months. Most (119, 75.8%) prescribers reported that they practiced as an oncologist/haematologist for 10 years or more. Most of the respondents reported spending most of their time working in either a public/university setting (57, 36.3%) and/or specialist cancer/oncology/haematology centre (47, 29.9%).

Table 10-5 Description of survey responses by complete respondents – HCPs

Question	Complete Respondents[1], n (%)					
	UK N=14	France N=39	Germany N=9	Spain N=31	Italy N=64	Total N=157
Question 20: How many CML patients did you personally treat - including all new and follow-up cases - in the last 12 months?						
Less than 5 patients	1 (7.1)	9 (23.1)	0	2 (6.5)	8 (12.5)	20 (12.7)
5 or more patients	13 (92.9)	30 (76.9)	9 (100.0)	29 (93.5)	56 (87.5)	137 (87.3)
Question 21: For how many years have you practiced as an oncologist/haematologist?						
Less than 5 years	0	1 (2.6)	1 (11.1)	1 (3.2)	6 (9.4)	9 (5.7)
5 to less than 10 years	3 (21.4)	7 (17.9)	0	5 (16.1)	14 (21.9)	29 (18.5)
10 to less than 15 years	5 (35.7)	11 (28.2)	3 (33.3)	7 (22.6)	20 (31.3)	46 (29.3)
15 to less than 20 years	2 (14.3)	13 (33.3)	3 (33.3)	9 (29.0)	11 (17.2)	38 (24.2)
More than 20 years	4 (28.6)	7 (17.9)	2 (22.2)	9 (29.0)	13 (20.3)	35 (22.3)
Question 22: In what setting do you spend most of your time working? (check all that apply)						
Specialist cancer / oncology / haematology centre	2 (14.3)	2 (5.1)	1 (11.1)	4 (12.9)	38 (59.4)	47 (29.9)
Teaching / university hospital	5 (35.7)	8 (20.5)	0	15 (48.4)	3 (4.7)	31 (19.7)
Public / university setting	3 (21.4)	9 (23.1)	0	24 (77.4)	21 (32.8)	57 (36.3)
Public / Non-university hospital	2 (14.3)	16 (41.0)	0	2 (6.5)	17 (26.6)	37 (23.6)
District / regional general (NHS) hospital	6 (42.9)	4 (10.3)	0	1 (3.2)	0	11 (7.0)
Private clinic / office based	0	5 (12.8)	8 (88.9)	0	1 (1.6)	14 (8.9)
Other	0	0	2 (22.2)	0	1 (1.6)	3 (1.9)

[1] A respondent will be considered as complete if all questions are answered.

Source: HCP Table 2

10.2.2 Patients

A description of patient survey participants (complete respondents) is presented in Table 10-6.

Of the 10 patients who completed the survey, 6 (60.0%) reported that they had been taking TASIGNA for more than 12 months. The genders of the patient respondents were equally represented by 5 (50.0%) males and 5 (50.0%) females. The respondents had a mean age of 51.1 ±11.65 years. Five patients reported their highest level of education as less than high school, while 1 (10.0%) reported having some high school, 1 (10.0%) some college, 2 (20.0%) graduating college, and 1 (10.0%) having a graduate degree.

Table 10-6 Description of survey participants in complete respondents – Patients

Question	Complete Respondents[1]			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Question 4: For how long have you been taking TASIGNA?, n (%)				
Less than or equal to 6 months	0 (0.0)		3 (50.0)	3 (30.0)
7-12 months	0 (0.0)		0 (0.0)	0 (0.0)
More than 12 months	4 (100.0)		2 (33.3)	6 (60.0)
Not sure/Don't remember	0 (0.0)		1 (16.7)	1 (10.0)
Question 19: Are you male or female?, n (%)				
Male	3 (75.0)		2 (33.3)	5 (50.0)
Female	1 (25.0)		4 (66.7)	5 (50.0)
Question 20: What is your age?[2]				
Age (completed life years)				
n	4		6	10
Mean	57.0		47.2	51.1
SD	4.69		13.59	11.65
Min	51		31	31
Max	62		68	68
Question 21: What is the highest level of education you have completed?, n (%)				
Less than high school	1 (25.0)		4 (66.7)	5 (50.0)
Some high school	0 (0.0)		1 (16.7)	1 (10.0)
High school graduate	0 (0.0)		0 (0.0)	0 (0.0)
Some college	1 (25.0)		0 (0.0)	1 (10.0)
College graduate	1 (25.0)		1 (16.7)	2 (20.0)
Graduate degree	1 (25.0)		0 (0.0)	1 (10.0)

[1] A respondent will be considered as complete if all questions are answered.
[2] Age at survey completion in completed life years.

Source: Patient Table 2

[redacted]

10.3 Outcome data

10.3.1 Healthcare professionals

Responses to questions related to the educational material by respondents who completed the survey are shown in Table 10-7.

Of the 157 eligible HCPs who completed the survey, 73 (46.5%) reported that they had received information every time they were in touch with a sales representative, 61 (38.9%) when TASIGNA was first launched, and 58 (36.9%) reported receiving information periodically. Most HCPs rated the TASIGNA guide for prescription and posology as very useful (91, 58.0%) or mostly useful (57, 36.3%); 9 (5.7%) rated it somewhat useful, and no HCPs rated the TASIGNA guide as mostly not useful or not useful at all.

Table 10-7 Results to questions related to the educational materials in complete respondents – HCPs

Question	Complete Respondents[1], n (%)					
	UK N=14	France N=39	Germany N=9	Spain N=31	Italy N=64	Total N=157
Question 18: When did you receive TASIGNA educational material? (Check all that apply)						
When TASIGNA was first launched (date)	9 (64.3)	10 (25.6)	3 (33.3)	14 (45.2)	25 (39.1)	61 (38.9)
Every time I'm in touch with a sales representative	6 (42.9)	22 (56.4)	2 (22.2)	11 (35.5)	32 (50.0)	73 (46.5)
Periodically (twice a year, etc.)	7 (50.0)	5 (12.8)	2 (22.2)	12 (38.7)	32 (50.0)	58 (36.9)
Do not remember	1 (7.1)	14 (35.9)	4 (44.4)	7 (22.6)	7 (10.9)	33 (21.0)
It is available on demand	5 (35.7)	6 (15.4)	3 (33.3)	9 (29.0)	13 (20.3)	36 (22.9)
I do not know how to ask for more Guides	1 (7.1)	0	0	0	0	1 (0.6)
Question 19: How do you rate the TASIGNA Guide for prescription and posology?						
Very useful	6 (42.9)	20 (51.3)	6 (66.7)	16 (51.6)	43 (67.2)	91 (58.0)
Mostly useful	8 (57.1)	15 (38.5)	3 (33.3)	15 (48.4)	16 (25.0)	57 (36.3)
Somewhat useful	0	4 (10.3)	0	0	5 (7.8)	9 (5.7)
Mostly not useful	0	0	0	0	0	0
Not useful at all	0	0	0	0	0	0

[1] A respondent will be considered as complete if all questions are answered.

Source: HCP Table 3

10.3.2 Patients

Responses to questions related to the educational material by respondents who completed the survey for patients are shown in Table 10-8.

All 10 (100.0%) patients responded "Yes" to the statements that the TASIGNA educational brochure "Important Information about How to Take Your Medication" provided important safety information about TASIGNA and that it told when and how to take TASIGNA. Seven (70.0%) patients responded "Yes" to the statement that the information in the educational brochure indicated which food to avoid with TASIGNA.

Eight (80.0%) patients reported receiving the TASIGNA education material from the physician who prescribed them TASIGNA, and all 10 (100.0%) patients reported that the educational materials were clearly explained to them. Six (60.0%) patients reported that they found the TASIGNA brochure useful, and 3 (30.0%) reported that they found the TASIGNA brochure both interesting and useful.

Table 10-8 Results to questions related to the educational materials in complete respondents – Patients

Question	Complete Respondents[1], n (%)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Question 6: What kind of information is contained in the brochure "Important Information About How to Take Your Medication"?				
It provides me with important safety information about TASIGNA				
Yes	4 (100.0)		6 (100.0)	10 (100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
It tells me when and how to take TASIGNA				
Yes	4 (100.0)		6 (100.0)	10 (100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
It tells me which foods to avoid with TASIGNA				
Yes	2 (50.0)		5 (83.3)	7 (70.0)
No	0 (0.0)		1 (16.7)	1 (10.0)
I don't know	2 (50.0)		0 (0.0)	2 (20.0)

Question	Complete Respondents[1], n (%)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Question 7: Who gave you this educational informational material for TASIGNA?				
The physician who prescribed me TASIGNA	4 (100.0)		4 (66.7)	8 (80.0)
Another healthcare professional	0 (0.0)		1 (16.7)	1 (10.0)
Someone else	0 (0.0)		0 (0.0)	0 (0.0)
I don't remember	0 (0.0)		1 (16.7)	1 (10.0)
Question 8: When you were given this packet of informational materials, were the materials clearly explained to you?				
Yes	4 (100.0)		6 (100.0)	10 (100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
Question 22: How did you like the TASIGNA Brochure(s)?				
Interesting and useful	1 (25.0)		2 (33.3)	3 (30.0)
Useful	3 (75.0)		3 (50.0)	6 (60.0)
Not useful	0 (0.0)		1 (16.7)	1 (10.0)
Misleading	0 (0.0)		0 (0.0)	0 (0.0)
I did not understand it	0 (0.0)		0 (0.0)	0 (0.0)
I started reading, but did not finish it	0 (0.0)		0 (0.0)	0 (0.0)

[1] A respondent was considered as complete if all questions were answered.

Source: Patient Table 3

10.4 Main results

10.4.1 Healthcare professionals

Responses to all questions related to HCP understanding of the risks associated with TASIGNA by complete respondents are presented in Table 10-9.

Of the 157 eligible respondents who completed the survey, most correctly identified as “True” statements that TASIGNA may prolong the QT interval (155, 98.7%), TASIGNA should not be used in patients with long QT syndrome and uncorrected hypokalaemia or hypomagnesaemia (142, 90.4%), and that TASIGNA should be used with caution in patients with a history of uncontrolled or significant cardiac disease (156, 99.4%) (Question 5).

Most HCPs correctly identified that they should prescribe TASIGNA at 300 mg twice daily for newly diagnosed Ph + CML CP patients (149, 94.9%) and 400 mg twice daily for imatinib resistant or intolerant Ph+ CML CP and AP patients (133, 84.7%) (Question 6).

Most HCPs correctly responded "Yes" to the statement that patients should be advised to avoid food 2 hours before and at least 1 hour after taking TASIGNA (153, 97.5%), TASIGNA should not be taken at any time with grapefruit juice or grapefruit products (149, 94.9%), to take TASIGNA whole with water (150, 95.5%), and to take TASIGNA twice daily approximately 12 hours apart around the same time each day (155, 98.7%). Most HCPs correctly responded "No" to taking TASIGNA on a full stomach (133, 84.7%) (Question 7).

Most (109, 69.4%) HCPs correctly responded "Yes" to the statement that the intake of food together with TASIGNA increases the bioavailability (serum concentration) of TASIGNA and may subsequently increase the risk of QT prolongation (Question 8).

Almost half (74, 47.1%) of HCPs correctly responded that if patients are unable to swallow the TASIGNA capsule whole, the content of the hard capsules may be dispersed in 1 teaspoon of applesauce and taken immediately (Question 9).

Most (140, 89.2%) HCPs correctly responded that if a patient has forgotten to take a dose (>2 hours after the scheduled dose) to wait until the next dose time and then follow the planned dose schedule (Question 10).

Most (132, 84.1%) HCPs correctly responded "Yes" to the question, "Are you aware of any dose adjustment or modification guidance for TASIGNA?" (Question 11). Most (128, 81.5%) HCPs identified all 4 correct options that might warrant a dose interruption or adjustment (Question 12).

Over two thirds (108, 68.8%) of HCPs identified both correct options for the question "When should ECGs be conducted for TASIGNA (nilotinib) patients?", while most (150, 95.5%) responded "before starting TASIGNA [at baseline]" (Question 13). Most (153, 97.5%) HCPs correctly responded "True" to the statement that hypokalaemia and hypomagnaesemia must be corrected prior to TASIGNA administration and electrolytes should be monitored periodically (Question 14).

Over half (91, 58.0%) of HCPs identified all 5 correct options for the question "Which of the following carry a risk of drug interactions with TASIGNA and should be avoided if possible?", while most (151, 96.2%) selected "medications or supplements known to prolong QT interval" (Question 15). To the question "If treatment with strong CYP3A4 inhibitors or antiarrhythmic medications or strong CYP3A4 inducers cannot be avoided, what should you do?", most (149, 94.9%) HCPs selected 1 correct option (to closely monitor the individual), while 44 (28.0%) identified both correct options (Question 16).

Most (129, 82.2%) HCPs correctly selected all 4 correct options when asked to identify pre-existing conditions from the list that required TASIGNA to be used with caution (Question 17).

[redacted]

Table 10-9 Responses to all questions related to understanding the risks associated with Tasigna in complete respondents – HCPs.

Question	Complete Respondents[1], n (%) [95% CI[2]]					
	UK N=14	France N=39	Germany N=9	Spain N=31	Italy N=64	Total N=157
Question 5: Can you identify any of the safety warnings for TASIGNA from the list below?						
TASIGNA may prolong the QT interval						
True[3]	14 (100.0) [76.8 - 100.0]	38 (97.4) [86.5 - 99.9]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	63 (98.4) [91.6 - 100.0]	155 (98.7) [95.5 - 99.8]
False	0	0	0	0	0	0
I don't know	0	1 (2.6)	0	0	1 (1.6)	2 (1.3)
TASIGNA should not be used in patients with long QT syndrome and uncorrected hypokalemia or hypomagnesemia						
True[3]	12 (85.7) [57.2 - 98.2]	35 (89.7) [75.8 - 97.1]	8 (88.9) [51.8 - 99.7]	30 (96.8) [83.3 - 99.9]	57 (89.1) [78.8 - 95.5]	142 (90.4) [84.7 - 94.6]
False	0	1 (2.6)	1 (11.1)	1 (3.2)	5 (7.8)	8 (5.1)
I don't know	2 (14.3)	3 (7.7)	0	0	2 (3.1)	7 (4.5)
TASIGNA should be used with caution in patients with a history of uncontrolled or significant cardiac disease						
True[3]	13 (92.9) [66.1 - 99.8]	39 (100.0) [91.0 - 100.0]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	64 (100.0) [94.4 - 100.0]	156 (99.4) [96.5 - 100.0]
False	1 (7.1)	0	0	0	0	1 (0.6)
I don't know	0	0	0	0	0	0
Question 6: How do you prescribe (doses and administration) TASIGNA for newly diagnosed Ph + CML CP patients and Imatinib resistant or intolerant Ph+ CML CP and AP patients?						
Newly diagnosed Ph + CML CP patients						
300 mg twice daily[3]	14 (100.0) [76.8 - 100.0]	34 (87.2) [72.6 - 95.7]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	62 (96.9) [89.2 - 99.6]	149 (94.9) [90.2 - 97.8]
300 mg once daily	0	0	0	1 (3.2)	0	1 (0.6)
[redacted]				0	1 (1.6)	6 (3.8)

400 mg once daily	0	0	0	0	1 (1.6)	1 (0.6)
Imatinib resistant or intolerant Ph + CML CP and AP patients						
300 mg twice daily	0	5 (12.8)	1 (11.1)	9 (29.0)	9 (14.1)	24 (15.3)
300 mg once daily	0	0	0	0	0	0
400 mg twice daily[3]	14 (100.0) [76.8 - 100.0]	34 (87.2) [72.6 - 95.7]	8 (88.9) [51.8 - 99.7]	22 (71.0) [52.0 - 85.8]	55 (85.9) [75.0 - 93.4]	133 (84.7) [78.1 - 90.0]
400 mg once daily	0	0	0	0	0	0
Question 7: Patients should be advised						
To avoid food 2 hours before and at least 1 hour after taking TASIGNA						
Yes[3]	12 (85.7) [57.2 - 98.2]	37 (94.9) [82.7 - 99.4]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	64 (100.0) [94.4 - 100.0]	153 (97.5) [93.6 - 99.3]
No	1 (7.1)	1 (2.6)	0	0	0	2 (1.3)
I don't know	1 (7.1)	1 (2.6)	0	0	0	2 (1.3)
That TASIGNA should not be taken at any time with grapefruit juice or grapefruit products						
Yes[3]	12 (85.7) [57.2 - 98.2]	37 (94.9) [82.7 - 99.4]	8 (88.9) [51.8 - 99.7]	30 (96.8) [83.3 - 99.9]	62 (96.9) [89.2 - 99.6]	149 (94.9) [90.2 - 97.8]
No	1 (7.1)	0	0	0	0	1 (0.6)
I don't know	1 (7.1)	2 (5.1)	1 (11.1)	1 (3.2)	2 (3.1)	7 (4.5)
To take TASIGNA on a full stomach						
Yes	0	14 (35.9)	1 (11.1)	3 (9.7)	4 (6.3)	22 (14.0)
No[3]	13 (92.9) [66.1 - 99.8]	24 (61.5) [44.6 - 76.6]	8 (88.9) [51.8 - 99.7]	28 (90.3) [74.2 - 98.0]	60 (93.8) [84.8 - 98.3]	133 (84.7) [78.1 - 90.0]
I don't know	1 (7.1)	1 (2.6)	0	0	0	2 (1.3)
To swallow TASIGNA whole with water						
Yes[3]	12 (85.7) [57.2 - 98.2]	36 (92.3) [79.1 - 98.4]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	62 (96.9) [89.2 - 99.6]	150 (95.5) [91.0 - 98.2]
No	0	2 (5.1)	0	0	1 (1.6)	3 (1.9)
I don't know	2 (14.3)	1 (2.6)	0	0	1 (1.6)	4 (2.5)

[redacted]

To take TASIGNA twice daily approximately 12 hours apart, around the same time each day						
Yes[3]	14 (100.0) [76.8 - 100.0]	39 (100.0) [91.0 - 100.0]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	62 (96.9) [89.2 - 99.6]	155 (98.7) [95.5 - 99.8]
No	0	0	0	0	1 (1.6)	1 (0.6)
I don't know	0	0	0	0	1 (1.6)	1 (0.6)
Question 8: Intake of food together with TASIGNA increases the bioavailability (serum concentration) of TASIGNA and may subsequently increase the risk of QT prolongation.						
True[3]	4 (28.6) [8.4 - 58.1]	22 (56.4) [39.6 - 72.2]	7 (77.8) [40.0 - 97.2]	22 (71.0) [52.0 - 85.8]	54 (84.4) [73.1 - 92.2]	109 (69.4) [61.6 - 76.5]
False	2 (14.3)	4 (10.3)	2 (22.2)	5 (16.1)	5 (7.8)	18 (11.5)
I don't know	8 (57.1)	13 (33.3)	0	4 (12.9)	5 (7.8)	30 (19.1)
Question 9: Patients who are unable to swallow TASIGNA capsules can be counseled to disperse the content of each TASIGNA capsule.						
In a teaspoon of applesauce and take the content immediately.[3]	8 (57.1) [28.9 - 82.3]	15 (38.5) [23.4 - 55.4]	6 (66.7) [29.9 - 92.5]	6 (19.4) [7.5 - 37.5]	39 (60.9) [47.9 - 72.9]	74 (47.1) [39.1 - 55.2]
In a glass of water and drink the content immediately.	5 (35.7)	14 (35.9)	2 (22.2)	16 (51.6)	14 (21.9)	51 (32.5)
In a teaspoon of milk and take the content immediately.	0	0	0	0	0	0
All of the above.	1 (7.1)	10 (25.6)	1 (11.1)	9 (29.0)	11 (17.2)	32 (20.4)
Question 10: 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)?						
To take the missed dose as soon as he/she realizes the oversight.	1 (7.1)	2 (5.1)	0	1 (3.2)	11 (17.2)	15 (9.6)
To wait until next dose time and then follow the planned dose schedule.[3]	13 (92.9) [66.1 - 99.8]	36 (92.3) [79.1 - 98.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	52 (81.3) [69.5 - 89.9]	140 (89.2) [83.2 - 93.6]
To take the double dose once at the next planned dose schedule.	0	1 (2.6)	0	0	1 (1.6)	2 (1.3)
Question 11: Are you aware of any dose adjustments or modification guidance for TASIGNA?						
No	2 (14.3)	8 (20.5)	1 (11.1)	3 (9.7)	2 (3.1)	16 (10.2)

[redacted]

Yes[3]	11 (78.6) [49.2 - 95.3]	29 (74.4) [57.9 - 87.0]	8 (88.9) [51.8 - 99.7]	24 (77.4) [58.9 - 90.4]	60 (93.8) [84.8 - 98.3]	132 (84.1) [77.4 - 89.4]
I don't know	1 (7.1)	2 (5.1)	0	4 (12.9)	2 (3.1)	9 (5.7)
Question 12: 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[3]	14 (100.0) [76.8 - 100.0]	38 (97.4) [86.5 - 99.9]	9 (100.0) [66.4 - 100.0]	29 (93.5) [78.6 - 99.2]	57 (89.1) [78.8 - 95.5]	147 (93.6) [88.6 - 96.9]
When clinically significant moderate or severe non-hematologic toxicity develops[3]	12 (85.7) [57.2 - 98.2]	35 (89.7) [75.8 - 97.1]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	60 (93.8) [84.8 - 98.3]	146 (93.0) [87.8 - 96.5]
Grade 3 or 4 lipase increase[3]	13 (92.9) [66.1 - 99.8]	34 (87.2) [72.6 - 95.7]	9 (100.0) [66.4 - 100.0]	29 (93.5) [78.6 - 99.2]	60 (93.8) [84.8 - 98.3]	145 (92.4) [87.0 - 96.0]
Grade 3 bilirubin or hepatic transaminase increase[3]	13 (92.9) [66.1 - 99.8]	36 (92.3) [79.1 - 98.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	58 (90.6) [80.7 - 96.5]	146 (93.0) [87.8 - 96.5]
Grade 1 or 2 lipase increase	0	5 (12.8)	1 (11.1)	2 (6.5)	5 (7.8)	13 (8.3)
Identified all 4 correct options[3]	11 (78.6) [49.2 - 95.3]	31 (79.5) [63.5 - 90.7]	9 (100.0) [66.4 - 100.0]	25 (80.6) [62.5 - 92.5]	52 (81.3) [69.5 - 89.9]	128 (81.5) [74.6 - 87.3]
Question 13: When should ECGs be conducted for TASIGNA (nilotinib) patients? (Check all that apply)						
Before starting TASIGNA (at baseline)[3]	13 (92.9) [66.1 - 99.8]	36 (92.3) [79.1 - 98.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	62 (96.9) [89.2 - 99.6]	150 (95.5) [91.0 - 98.2]
As clinically indicated[3]	11 (78.6) [49.2 - 95.3]	31 (79.5) [63.5 - 90.7]	5 (55.6) [21.2 - 86.3]	24 (77.4) [58.9 - 90.4]	42 (65.6) [52.7 - 77.1]	113 (72.0) [64.3 - 78.8]
Fourteen days after starting TASIGNA and periodically thereafter	5 (35.7)	15 (38.5)	8 (88.9)	20 (64.5)	28 (43.8)	76 (48.4)
Identified both correct options[3]	10 (71.4) [41.9 - 91.6]	28 (71.8) [55.1 - 85.0]	5 (55.6) [21.2 - 86.3]	23 (74.2) [55.4 - 88.1]	42 (65.6) [52.7 - 77.1]	108 (68.8) [60.9 - 75.9]
Question 14: Hypokalemia and hypomagnaesemia must be corrected prior to TASIGNA administration and electrolytes should be monitored periodically.						
True[3]	14 (100.0) [76.8 - 100.0]	37 (94.9) [82.7 - 99.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	63 (98.4) [91.6 - 100.0]	153 (97.5) [93.6 - 99.3]
False	0	0	0	0	0	0
I don't know	0	2 (5.1)	0	1 (3.2)	1 (1.6)	4 (2.5)

[redacted]

Question 15: 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[3]	14 (100.0) [76.8 - 100.0]	33 (84.6) [69.5 - 94.1]	9 (100.0) [66.4 - 100.0]	25 (80.6) [62.5 - 92.5]	59 (92.2) [82.7 - 97.4]	140 (89.2) [83.2 - 93.6]
Strong CYP3A4 inducers[3]	9 (64.3) [35.1 - 87.2]	27 (69.2) [52.4 - 83.0]	8 (88.9) [51.8 - 99.7]	27 (87.1) [70.2 - 96.4]	52 (81.3) [69.5 - 89.9]	123 (78.3) [71.1 - 84.5]
St John's Wort[3]	11 (78.6) [49.2 - 95.3]	24 (61.5) [44.6 - 76.6]	9 (100.0) [66.4 - 100.0]	27 (87.1) [70.2 - 96.4]	58 (90.6) [80.7 - 96.5]	129 (82.2) [75.3 - 87.8]
Certain antiarrhythmic medicines such as amiodarone[3]	10 (71.4) [41.9 - 91.6]	27 (69.2) [52.4 - 83.0]	8 (88.9) [51.8 - 99.7]	25 (80.6) [62.5 - 92.5]	52 (81.3) [69.5 - 89.9]	122 (77.7) [70.4 - 84.0]
Medications or supplements known to prolong QT interval[3]	14 (100.0) [76.8 - 100.0]	38 (97.4) [86.5 - 99.9]	9 (100.0) [66.4 - 100.0]	29 (93.5) [78.6 - 99.2]	61 (95.3) [86.9 - 99.0]	151 (96.2) [91.9 - 98.6]
Consumption of green tea (>3 cups a day)	4 (28.6)	11 (28.2)	2 (22.2)	14 (45.2)	22 (34.4)	53 (33.8)
Identified all 5 correct options[3]	6 (42.9) [17.7 - 71.1]	15 (38.5) [23.4 - 55.4]	7 (77.8) [40.0 - 97.2]	18 (58.1) [39.1 - 75.5]	45 (70.3) [57.6 - 81.1]	91 (58.0) [49.8 - 65.8]
Question 16: 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[3]	8 (57.1) [28.9 - 82.3]	14 (35.9) [21.2 - 52.8]	2 (22.2) [2.8 - 60.0]	5 (16.1) [5.5 - 33.7]	22 (34.4) [22.9 - 47.3]	51 (32.5) [25.2 - 40.4]
Closely monitor the individual for prolongation of the QT interval if transient interruption of TASIGNA is not possible[3]	13 (92.9) [66.1 - 99.8]	37 (94.9) [82.7 - 99.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	60 (93.8) [84.8 - 98.3]	149 (94.9) [90.2 - 97.8]
No attention is needed	0	0	0	1 (3.2)	0	1 (0.6)
Identified both correct options[3]	7 (50.0) [23.0 - 77.0]	12 (30.8) [17.0 - 47.6]	2 (22.2) [2.8 - 60.0]	5 (16.1) [5.5 - 33.7]	18 (28.1) [17.6 - 40.8]	44 (28.0) [21.2 - 35.7]
Question 17: Identify pre-existing conditions from the list below that require that TASIGNA is used with caution. (Check all that apply)						
Congenital long QT syndrome[3]	13 (92.9) [66.1 - 99.8]	37 (94.9) [82.7 - 99.4]	9 (100.0) [66.4 - 100.0]	30 (96.8) [83.3 - 99.9]	62 (96.9) [89.2 - 99.6]	151 (96.2) [91.9 - 98.6]

[redacted]

Patients with a history of uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia[3]	14 (100.0) [76.8 - 100.0]	39 (100.0) [91.0 - 100.0]	8 (88.9) [51.8 - 99.7]	31 (100.0) [88.8 - 100.0]	61 (95.3) [86.9 - 99.0]	153 (97.5) [93.6 - 99.3]
Patients with hepatic impairment. Hepatic impairment has a modest effect on the pharmacokinetics of TASIGNA[3]	13 (92.9) [66.1 - 99.8]	32 (82.1) [66.5 - 92.5]	9 (100.0) [66.4 - 100.0]	29 (93.5) [78.6 - 99.2]	53 (82.8) [71.3 - 91.1]	136 (86.6) [80.3 - 91.5]
Patients with a history of pancreatitis. Serum lipase should be checked periodically[3]	13 (92.9) [66.1 - 99.8]	38 (97.4) [86.5 - 99.9]	9 (100.0) [66.4 - 100.0]	31 (100.0) [88.8 - 100.0]	62 (96.9) [89.2 - 99.6]	153 (97.5) [93.6 - 99.3]
Patients with a history of central neurologic disease such as seizures	2 (14.3)	18 (46.2)	3 (33.3)	10 (32.3)	11 (17.2)	44 (28.0)
Identified all 4 correct options[3]	12 (85.7) [57.2 - 98.2]	30 (76.9) [60.7 - 88.9]	8 (88.9) [51.8 - 99.7]	28 (90.3) [74.2 - 98.0]	51 (79.7) [67.8 - 88.7]	129 (82.2) [75.3 - 87.8]

[1] A respondent will be considered as complete if all questions are answered.
[2] Exact binomial 2-sided 95% confidence intervals around the percentages calculated by the method of Clopper and Pearson and no adjustment was performed for multiplicity.
[3] Correct answer.
Source: HCP Table 4

[redacted]

10.4.2 Patients

Responses to all questions related to understanding the risks associated with TASIGNA by patients who completed the survey are shown in Table 10-10.

All 10 (100.0%) eligible patients who completed the survey correctly identified that they should take TASIGNA on an empty stomach, they should swallow it whole with water, that they should not chew the capsule, and that they should take 2 capsules each 12 hours apart around the same time each the day if they take 4 capsules of Tasigna per day. All 10 (100.0%) patients correctly responded "No" to the statements that they should take TASIGNA on a full stomach, that if the patient takes 4 capsules of TASIGNA per day, he/she can take them at 4 times over the day. Nine (90.0%) patients correctly responded "Yes" to the statement that after taking TASIGNA wait at least 1 hour before eating (Question 9).

Three (30.0%) patients correctly responded that each TASIGNA capsule content may be dispersed in 1 teaspoon of applesauce and taken immediately, while 4 (40.0%) responded "I don't know" and 3 (30.0%) responded "This does not apply to me" (Question 10).

Seven (70.0%) patients correctly responded they if they've forgotten to take a dose (>2 hours), they should wait until next dose time and follow the planned schedule (Question 11).

Seven (70.0%) patients correctly responded that if they are sick and experience vomiting after taking TASIGNA, they should not take another dose and should speak to their doctor immediately (Question 12).

All 10 (100.0%) patients correctly responded that they should avoid grapefruit juice, grapefruit products, or any supplement containing grapefruit extracts when taking TASIGNA and 8 (80.0%) correctly responded they do not have to avoid apples or apple juice. Four (40.0%) patients correctly responded "Yes" that they should avoid vitamins and herbal supplements, while 3 (30.0%) responded "No" or "I don't know" (Question 13).

Nine (90.0%) patients correctly responded "True" to the question that they should tell their doctor if they have a heart disorder or are taking medication for the heart or if they have heart rhythm abnormalities/QT prolongation or a family history of it (Question 14).

Eight (80.0%) patients correctly responded "True" to the question "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?" (Question 15).

Nine (90.0%) patients correctly responded "True" to the question "In case you faint or experience an irregular heartbeat while taking TASIGNA, you should contact your physician immediately?" (Question 16).

Six (60.0%) patients correctly responded "Yes" when asked if they knew they needed to avoid medicines that are strong CYP3A4 inhibitors (Question 17).

All 10 (100.0%) patients correctly responded "Yes" they should discuss any changes in their prescription medicine with their doctor while taking TASIGNA. Eight (80.0%) patients correctly responded "Yes" they should discuss any changes in medicine they buy without a prescription and 6 (60.0%) patients correctly responded they should discuss any changes in vitamins/herbal supplements (Question 18).

Table 10-10 Responses to all questions related to understanding the risks associated with Tasigna in complete respondents – Patients

Question	Complete Respondents[1], n (%; 95% CI)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Question 9: How should you take TASIGNA?				
On an empty stomach (at least 2 hours after a meal)				
Yes[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
On a full stomach				
Yes	0 (0.0)		0 (0.0)	0 (0.0)
No[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
Swallow whole with water, do not chew				
Yes[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
After taking TASIGNA wait at least 1 hour before you eat				
Yes[2]	4 (100.0; 39.8 - 100.0)		5 (83.3; 35.9 - 99.6)	9 (90.0; 55.5 - 99.7)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		1 (16.7)	1 (10.0)
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				
Yes[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)

Question	Complete Respondents[1], n (%; 95% CI)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
If you take 4 capsules of TASIGNA per day, you can take them at 4 times over the day				
Yes	0 (0.0)		0 (0.0)	0 (0.0)
No[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
Question 10: 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[2]	1 (25.0; 0.6 - 80.6)		2 (33.3; 4.3 - 77.7)	3 (30.0; 6.7 - 65.2)
Each TASIGNA capsule may be dispersed into a glass of fruit juice and drunk	0 (0.0)		0 (0.0)	0 (0.0)
Each TASIGNA capsule may be dispersed into a soup dish and taken along with lunch/dinner	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	1 (25.0)		3 (50.0)	4 (40.0)
This does not apply to me	2 (50.0)		1 (16.7)	3 (30.0)
Question 11: What should you do if you have forgotten to take a dose of TASIGNA well after the scheduled time (> 2 hours)?				
Take the missed dose as soon as you realize the oversight	1 (25.0)		2 (33.3)	3 (30.0)
Wait until next dose time and follow the planned dose schedule[2]	3 (75.0; 19.4 - 99.4)		4 (66.7; 22.3 - 95.7)	7 (70.0; 34.8 - 93.3)
Take the double-dose of TASIGNA once on the next planned dose schedule	0 (0.0)		0 (0.0)	0 (0.0)
Question 12: What should you do if you are sick and experience vomiting after taking TASIGNA?				
Take another dose of TASIGNA and inform your doctor at the next visit	1 (25.0)		2 (33.3)	3 (30.0)
Do not take another dose and speak to your doctor immediately[2]	3 (75.0; 19.4 - 99.4)		4 (66.7; 22.3 - 95.7)	7 (70.0; 34.8 - 93.3)
Take the double-dose of TASIGNA once on the next planned dose schedule	0 (0.0)		0 (0.0)	0 (0.0)
Question 13: What should you avoid at any time when taking TASIGNA?				
Grapefruit juice, grapefruit products or any supplement containing grapefruit extracts				
Yes[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)

Question	Complete Respondents[1], n (%; 95% CI)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Apples, apple juice				
Yes	0 (0.0)		0 (0.0)	0 (0.0)
No[2]	4 (100.0; 39.8 - 100.0)		4 (66.7; 22.3 - 95.7)	8 (80.0; 44.4 - 97.5)
I don't know	0 (0.0)		2 (33.3)	2 (20.0)
Certain vitamins and herbal supplements				
Yes[2]	2 (50.0; 6.8 - 93.2)		2 (33.3; 4.3 - 77.7)	4 (40.0; 12.2 - 73.8)
No	1 (25.0)		2 (33.3)	3 (30.0)
I don't know	1 (25.0)		2 (33.3)	3 (30.0)
Question 14: 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.				
True[2]	3 (75.0; 19.4 - 99.4)		6 (100.0; 54.1 - 100.0)	9 (90.0; 55.5 - 99.7)
False	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	1 (25.0)		0 (0.0)	1 (10.0)
Question 15: 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?				
True[2]	4 (100.0; 39.8 - 100.0)		4 (66.7; 22.3 - 95.7)	8 (80.0; 44.4 - 97.5)
False	0 (0.0)		1 (16.7)	1 (10.0)
I don't know	0 (0.0)		1 (16.7)	1 (10.0)
Question 16: In case you faint or experience an irregular heartbeat while taking TASIGNA, you should contact your physician immediately?				
True[2]	3 (75.0; 19.4 - 99.4)		6 (100.0; 54.1 - 100.0)	9 (90.0; 55.5 - 99.7)
False	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	1 (25.0)		0 (0.0)	1 (10.0)
Question 17: 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[2]	1 (25.0; 0.6 - 80.6)		5 (83.3; 35.9 - 99.6)	6 (60.0; 26.2 - 87.8)
No	3 (75.0)		1 (16.7)	4 (40.0)

Question	Complete Respondents[1], n (%; 95% CI)			
	UK N=4	Germany N=0	Spain N=6	Total N=10
Question 18: Which of the following should you discuss with your doctor while taking TASIGNA?				
Any changes in my prescription medication				
Yes[2]	4 (100.0; 39.8 - 100.0)		6 (100.0; 54.1 - 100.0)	10 (100.0; 69.2 - 100.0)
No	0 (0.0)		0 (0.0)	0 (0.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
Any changes in medications I can buy without a prescription				
Yes[2]	3 (75.0; 19.4 - 99.4)		5 (83.3; 35.9 - 99.6)	8 (80.0; 44.4 - 97.5)
No	1 (25.0)		1 (16.7)	2 (20.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)
Any changes in vitamins/herbal supplements				
Yes[2]	2 (50.0; 6.8 - 93.2)		4 (66.7; 22.3 - 95.7)	6 (60.0; 26.2 - 87.8)
No	2 (50.0)		2 (33.3)	4 (40.0)
I don't know	0 (0.0)		0 (0.0)	0 (0.0)

[1] A respondent will be considered as complete if all questions are answered.
[2] Correct answer.
Source: Patient Table 4

10.5 Other analyses

There were no other analyses.

10.6 Adverse events/adverse reactions

This survey was observational. The survey did not include any free text or open-ended questions, and did not collect any information on adverse events. There was no additional risk to a patient from his/her participation in the survey, as participation involved no additional diagnostic, evaluative, or therapeutic action over and above those deemed appropriate by the patient's physician. To respond to the questions of this survey, the physician was not required to review treatment outcomes or adverse reactions.

11 Discussion

11.1 Key results

Healthcare Professionals

Invitation letters were sent to 1592 HCPs in 5 European countries (UK, France, Germany, Spain, and Italy). By the survey end date (31 Dec 2015), 244 HCPs responded to the survey and were screened for participation. Of these respondents, 75 (30.7%) were ineligible (with 62 [25.4%] not having received the educational brochure or received it but did not read it, 8 [3.3%] not asked the question as they had been deemed ineligible by an earlier question, and 5 [2.0%] discontinued the survey without answering the question), 169 (69.3%) HCPs were eligible for participation and 157 (64.3%) HCPs completed the survey.

Of the 157 eligible HCPs who completed the survey, 73 (46.5%) reported that they had received information every time they were in touch with a sales representative, 61 (38.9%) when TASIGNA was first launched, and 58 (36.9%) reported receiving information periodically (twice a year, etc.). There were 91 (58.0%) HCPs who rated the TASIGNA guide for prescription and posology as very useful, 57 (36.3%) mostly useful, and 9 (5.7%) as somewhat useful; no HCPs rated the TASIGNA guide as mostly not useful or not useful at all.

The correct response rates across the 13 HCP survey questions related to understanding the risks associated with TASIGNA (Question 5 to Question 17) ranged from 28.0% to 99.4%.

The questions with low correct response rates for HCPs included Question 9 and Question 16. For Question 9 (Patients who are unable to swallow TASIGNA capsules can be counseled to disperse the content of each TASIGNA capsule), 47.1% of HCPs correctly answered that TASIGNA should be dispersed in a teaspoon of applesauce and taken immediately; however, another 20.4% of HCPs selected “all of the above”, which included the correct option to disperse in applesauce as well as the incorrect option to disperse TASIGNA in water. Another low percentage was seen for Question 16 for “both correct options” (28.0%; If treatment with strong CYP3A4 inhibitors or antiarrhythmic medications or strong CYP3A4 inducers cannot be avoided, what should you do?), Although 1 correct option (Closely monitor the individual for prolongation of the QT interval if transient interruption of TASIGNA is not possible) had a response rate of 94.9%, the other correct option (Interrupt therapy with TASIGNA if possible) had a response rate of 32.5%.

Patients

Selected HCPs were asked to provide invitation letters to their patients for participation in the survey. A subset of 165 eligible HCPs from 3 European countries (UK, Germany, and Spain) were sent a total of 167 patient packs (2 HCPs requested recruitment packets to be resent) containing 1195 invitation letters that could have been distributed to their patients. In order to minimize the burden on HCPs and protect the confidentiality of patients who were invited to participate, the HCPs were not asked to keep a log of who their invitations were distributed to or how many were distributed. Therefore, the actual number of invitation letters issued to patients by the HCPs is unknown. Of these, 11 patients responded to the survey, of which 10 (90.9%) were eligible and completed the survey.

[redacted]

All 10 (100.0%) patients responded "Yes" to the statements that the TASIGNA educational brochure "Important Information about How to Take Your Medication" provided important safety information about TASIGNA and that it indicated when and how to take TASIGNA. Seven (70.0%) patients responded "Yes" to the statement that the information in the educational brochure clarified which food to avoid with TASIGNA. Eight (80.0%) patients reported having received the education material from the physician who prescribed them TASIGNA, and all 10 (100.0%) patients reported that the educational materials were clearly explained to them. Six (60.0%) patients reported that they found the TASIGNA educational brochure useful, with 3 (30.0%) reporting that they found the TASIGNA brochure both interesting and useful.

The correct response rates across the 10 patient survey questions related to understanding the risks associated with TASIGNA (Question 9 to Question 18) ranged from 30.0% to 100.0%. For the 10 patients, the questions with low correct response rates included Question 10 and 1 component of Question 13. For Question 10, 3 patients (30.0%) correctly responded that each TASIGNA capsule may be dispersed in 1 teaspoon of applesauce and taken immediately in case you are unable to swallow capsules, while another 3 (30.0%) responded "does not apply to me" and 4 (40.0%) responded "I don't know", which were categorized as incorrect responses. For Question 13, 4 patients (40.0%) correctly responded "Yes" they should avoid certain vitamins and herbal supplements when taking TASIGNA, while 3 (30.0%) responded "No" and 3 (30.0%) responded "I don't know", which were categorized as incorrect responses.

11.2 Limitations

Final results were impacted by the overall number of physicians and patients participating in the survey. In order to accomplish the target sample size for both physicians and patients, efforts made to try to increase HCP and patient response during the course of the study included the following:

- Increased the number of identified HCPs with motivated and active patients
- Enlisted support of local medical directors to follow-up with MSLs
- Two waves of patient packets were sent, increasing the total number of patient packets sent to HCPs
- MSLs hand delivered packets to HCPs
- The survey window was extended

In particular, analysis of the protocol objectives for patients is limited by the low patient response rate (only 10 patients completed the survey out of a target of 150). Recruitment of patients was particularly challenging due to the inability to contact patients directly given the stringent patient confidentiality regulations in Europe. If in a given country the educational brochure could not be provided to patients for legal reasons, no patients were recruited in the respective country, which is why patients were only recruited in 3 countries. However, 1195 invitation letters were made available to HCPs in an effort to achieve adequate participation. Although, as previously noted, the actual number of invitation letters issued to patients by the HCPs is unknown.

11.3 Interpretation

In general, the results suggest that the TASIGNA educational material was effective in communicating important safety information to HCPs, which was demonstrated in the number of questions with high correct response rates.

For HCPs who received and read the materials, the rates of correct responses about the risks associated with TASIGNA were greater than 80%, which is a commonly used knowledge rate threshold in the US (Food and Drug Administration 2012), for the majority of the questions, i.e., 8 of the 13 questions (range: 81.5% to 99.4%).

The correct response rates for the patient survey questions were at or greater than 60% for 9 of the 10 questions (range: 60.0% to 100.0%), excluding 1 component question to Question 13. Although knowledge was demonstrated for the key elements of how to take TASIGNA in Question 9 (range: 90.0% to 100.0%) and cardiac risks in Questions 14 and 16 (90.0% for both), very limited conclusions about patient awareness can be derived from these results due to low patient participation in this observational study. It is not uncommon to see low patient participation rates for these types of surveys as participation is voluntary and without incentives (Galea S 2007). Further, patients were not contacted directly by the sponsor or contract research organization but only through their physicians.

11.4 Generalizability

The results are not generalizable to the larger populations because of the inadequate representation due to low patient participation despite due diligence in recruitment.

12 Other information

Not applicable.

13 Conclusion

Based on the assessment of the interim report (dated 07 Dec 2015), the Committee for Medicinal Products for Human Use (CHMP) concluded on 10 Nov 2016 that the Post Authorization Measure (PAM) was considered fulfilled and no further action was required by Novartis.

The purpose of this final report is to include the 4 additional HCP responses that were submitted after the data cut-off (31 July 2015) of the interim report. As expected the results remain in line with those provided in the interim report:

- In general, these results reflect a good understanding of the TASIGNA educational material for HCPs as correct response rates for the questions about the risks associated with TASIGNA were greater than 80% for the majority of the questions.
- However, very limited conclusions about patient awareness can be derived from the results due to the low patient participation in this observational study. Further, because the total number of respondents was low, no conclusion can be drawn about the effect of the demographic characteristics on the rates of knowledge and behavior in the broader treated population.

[redacted]

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Appendices

Appendix 1: Study protocol

[redacted]

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

[redacted]

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]

29 JAN 2014
Date

[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]

[redacted]

1 Table of contents

List of tables

[redacted]

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]

[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.

[redacted]

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] 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

[redacted]

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:

[redacted]

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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]

[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)*

[redacted]

- ☐ 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

[redacted]

☐ 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

[redacted]

- ☐ 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

[redacted]

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

[redacted]

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)?

[redacted]

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

[redacted]

Appendix 2: Study administrative structure

Administrative structure for Study AMN107A2001

	Name of Institution	Address of Institution	Responsibility and Scope of Activities
Sponsor	Novartis Pharmaceuticals Corporation	One Health Plaza East Hanover, NJ 07936-1080 USA	All aspects of the trial unless otherwise indicated
Data Management	[redacted]		Database management and quality control
Statistics			Prepare the analysis plan for the protocol and combine and analyze data from all centers participating in this protocol
Medical Writing			Write the Clinical Study Report with the guidance of the Novartis Study Lead and Global Brand Medical Director.
Randomization	NA	NA	No randomization was used in the AMN107A2001 study
Field Monitoring	N/A	N/A	N/A
Laboratory Assessment	N/A	N/A	N/A
Site of Study Drug Manufacturing -<Nilotinib>	N/A	N/A	N/A
Site of Study Drug Manufacturing -<placebo>	NA	NA	N/A
Site of Study Drug Manufacturing - <active comparator>	NA	NA	N/A
Site of Study Drug Release in Europe	N/A	N/A	N/A
Location where Trial Master files are located	Novartis Pharma AG	mDOC WSJ-433.2 Novartis Campus 4056 Basel Switzerland	TMFs are located at [redacted] until the trial is completed, at which point files are stored in Basel, Switzerland.

Appendix 3: Healthcare Provider Survey

Novartis, the Marketing Authorization Holder of TASIGNA (nilotinib), is surveying healthcare professionals about TASIGNA. The questionnaire will take no more than 20 minutes to complete.

Disclaimer

This is a non-interventional study sponsored by Novartis. A non-interventional study is a study in which individuals are only observed and certain outcomes are measured. The aim of this non-interventional study is to evaluate the use of educational material as a risk minimization activity. Taking part in this study is voluntary; you are under no obligation to participate. You may refuse to participate in the study or stop participating in the study at any time without any interference with your medical care, penalty or loss of any rights or benefits to which you are otherwise entitled.

How We Use Your Information

You have been selected because you are in the Novartis list of possible TASIGNA prescribers. Your answers to the study questionnaire will be combined with those from other respondents and reported in anonymous form to Novartis. If you are eligible to take the survey, complete all the questions, download and return the honorarium payment form, you will receive an honorarium of [redacted] This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you and is not aimed at creating any incentives to prescribe. It is solely aimed at compensating you for the time spent on the study. Prescription and/or dispensing of Tasigna, is and will remain in accordance with the conditions of good medical practice and independently of your possible participation in this study. Your name and address will be used to send you the honorarium after you complete the study questionnaire.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your answers will be kept strictly confidential. In order to protect your identity, all your information to be collected in this study will be completely anonymized with a code assigned to your data. This code, along with your information/data, will be used by Novartis and its representatives only for the study purposes mentioned above. Your privacy will be protected; however, research study records may be inspected by the EMA or local country Ethics Committees. Your choice to allow Novartis to use your information is entirely voluntary but necessary to take part in this study.

If you have any questions about the collection and use of information about you, or would like to exercise rights that you may have regarding this information please contact the TASIGNA Study Support team at: [redacted]

[redacted]

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at [redacted]

By answering YES to the question below you confirm that you have read this document, you understand the purpose of this study and you authorize the use of your personal data for sending the honorarium after you complete the questionnaire.

1. Do you agree to take part in this survey?
   - ❍ Yes
   - ❍ No

2. Are you an oncology or hematology specialist?
   - ❍ Yes
   - ❍ No

3 Have you prescribed TASIGNA in the last 12 months?
   - ❍ Yes
   - ❍ No

4. 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

5. Can you identify any of the safety warnings for TASIGNA from the list below?

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

[redacted]

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

Indication	**300 mg twice daily**	**300 mg once daily**	**400 mg twice daily**	**400 mg once daily**
Newly diagnosed Ph + CML CP patients	❍	❍	❍	❍
Imatinib resistant or intolerant Ph + CML CP and AP patients	❍	❍	❍	❍

7. Patients should be advised

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

8. Intake of food together with TASIGNA increases the bioavailability (serum concentration) of TASIGNA and may subsequently increase the risk of QT prolongation.
   - ❍ True
   - ❍ False
   - ❍ I don't know

9. Patients who are unable to swallow TASIGNA capsules can be counseled to disperse the content of each TASIGNA capsule.
   - ❍ 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.

[redacted]

10. 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)?
    - ❍ 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.

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

12. 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

13. 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

14. Hypokalemia and hypomagnaesemia must be corrected prior to TASIGNA administration and electrolytes should be monitored periodically.
    - ❍ True
    - ❍ False
    - ❍ I don't know

15. 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 John's Wort
    - ❑ Certain antiarrhythmic medicines such as amiodarone
    - ❑ Medications or supplements known to prolong QT interval
    - ❑ Consumption of green tea (> 3 cups a day)

[redacted]

16. 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

17. Identify pre-existing conditions from the list below that 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

18. When did you receive TASIGNA educational material? *(Check all that apply.)*
    - ❑ When TASIGNA was first launched, 01 Jan 2008
    - ❑ 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

19. How do you rate the TASIGNA Guide for prescription and posology?
    - ❍ Very useful
    - ❍ Mostly useful
    - ❍ Somewhat useful
    - ❍ Mostly not useful
    - ❍ Not useful at all

20. How many CML patients did you personally treat – including all new and follow-up cases – in the last 12 months?
    - ❍ Less than 5 patients
    - ❍ 5 or more patients

[redacted]

21. 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

22. In what setting do you spend most of your time working? *(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

[redacted]

Appendix 4: Patient Survey

You have been prescribed TASIGNA. Novartis, a multinational pharmaceutical company, is conducting a study in major EU countries to evaluate the use of educational materials as a risk minimization activity.

Before you begin, we would like to share some general information about this non-interventional study. A non-interventional study is a study in which individuals are only observed and certain outcomes are measured. This means that the treatment you have been provided was prescribed in the usual manner, in accordance with the conditions of good medical practice and independently of your possible participation in this study. The information collected in the study questionnaire you are about to take will help us to know if patients understand important information about taking TASIGNA. The survey will take up to 20 minutes.

There are no known risks to you in participating in this study. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the study will not affect your ability to receive or take TASIGNA.

There is no individual medical information collected in the survey for this non-interventional study

How We Use Your Information

Your participation in this study is entirely voluntary. You may refuse to participate or you may withdraw from this study at any time without any interference with your medical care, penalty or loss of any rights or benefits to which you are otherwise entitled.

Your answers to the survey questions will be combined with answers given by other Tasigna patients in other European countries. All answers will be put together and reported in anonymous form to Novartis, the Marketing Authorization Holder of TASIGNA.

You may not directly benefit from participating in this study. The information collected from patients participating in this study might be of possible future benefit to you and other patients treated with Tasigna.

In no way are you waiving your legal rights by signing this consent form nor does your signature release the study doctors, Novartis or involved institutions from their legal and professional responsibilities.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you.

- All information that is collected about you during the course of the survey will be kept strictly confidential. You will not be asked to provide your name or address in order to take the survey. A code will be assigned to your data.
- Data collected during the study may be sent to researchers in countries where the laws do not protect your privacy to the same extent as the law in Germany. However, Novartis will take all reasonable steps to protect your privacy.

[redacted]

- Your answers will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey.
- Neither Novartis nor its contractors will sell, transfer, or rent your information. Your privacy will be protected; however, research study records may be inspected by the European Medicines Agency (EMA) and your country's Ethics Committee that reviews research studies to make sure they are safe for participants. The EMA and your country's Ethics Committee have reviewed and approved this research study and survey.
- Your choice to allow Novartis to use your information is entirely voluntary but necessary to take part in this study.

How to Learn More About TASIGNA

The information in this study should not take the place of talking with your healthcare professional.

If you have any questions about your condition or treatment, or if you would like more information about TASIGNA, talk to your healthcare professional.

How to Learn More About This Study

If you have questions about or problems with the study, please contact the Help Desk at [redacted]

By answering YES to the first question, you say that you have read this document. You understand the purpose of this non-interventional study and you consent to participate in this non-interventional study unless and until you revoke it.

Thank you for your interest in this survey.

1. Do you agree to take part in this survey?
   - ❍ Yes
   - ❍ No

2. Are you being treated for CML (chronic myeloid leukemia)?
   - ❍ Yes
   - ❍ No

3. Have you been prescribed TASIGNA in the last 12 months?
   - ❍ Yes
   - ❍ No

[redacted]

4. For how long have you been taking TASIGNA?
   - ❍ Less than or equal to 6 months
   - ❍ 7-12 months
   - ❍ More than 12 months
   - ❍ Not sure/Don't remember

5. Did you read the brochure "Wichtige Informationen über die Einnahme Ihres Arzneimittels"?
   - ❍ Yes, I have received and read it
   - ❍ No, I have received but not read it
   - ❍ Not sure/Don't remember

6. What kind of information is contained in the brochure "Wichtige Informationen über die Einnahme Ihres Arzneimittels"?

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

7. Who gave you this educational informational material for TASIGNA?
   - ❍ The physician who prescribed me TASIGNA
   - ❍ Another healthcare professional
   - ❍ Someone else
   - ❍ I don't remember

8. When you were given this packet of informational materials, were the materials clearly explained to you?
   - ❍ Yes
   - ❍ No

9. How should you take TASIGNA?

	Yes	**No**	**I don't know**
On an empty stomach (at least 2 hours after a meal)	❍	❍	❍
On a full stomach	❍	❍	❍
Swallow whole with water, do not chew	❍	❍	❍
After taking TASIGNA wait at least 1 hour before you eat	❍	❍	❍
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	❍	❍	❍
If you take 4 capsules of TASIGNA per day, you can take them at 4 times over the day	❍	❍	❍

[redacted]

10. 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

11. What should you do if you have forgotten to take a dose of TASIGNA well after the scheduled time (> 2 hours)?
    - ❍ 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

12. What should you do if you are sick and experience vomiting after taking TASIGNA?
    - ❍ 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

13. What should you avoid at any time when taking TASIGNA?

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

14. 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.
    - ❍ True
    - ❍ False
    - ❍ I don't know

15. 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?
    - ❍ True
    - ❍ False
    - ❍ I don't know

[redacted]

16. In case you faint or experience an irregular heartbeat while taking TASIGNA, you should contact your physician immediately?
    - ❍ True
    - ❍ False
    - ❍ I don't know

17. 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

18. Which of the following should you discuss with your doctor while taking TASIGNA?

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

19. Are you male or female?
    - ❍ Male
    - ❍ Female

20. What is your age?

    _____

21. What is the highest level of education you have completed?
    - ❍ Less than high school
    - ❍ Some high school
    - ❍ High school graduate
    - ❍ Some college
    - ❍ College graduate
    - ❍ Graduate degree

22. 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

[redacted]

Appendix 5: Signatures

Physical signature page provided separately