Boehringer Ingelheim

Clinical Trial Report

BI Trial Number:	1160.149
EudraCT Number:	Not applicable.
BI Investigational Product:	Pradaxa®
Title:	Post-authorisation study to evaluate the effectiveness of the risk minimisation activities in the treatment of SPAF.
Clinical Phase:	IV
GCP Compliance:	No **USA 21 CFR 312.120:** Not applicable
Authors:	[redacted] Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Principal/Coord. Investigator:	Not applicable.
Institute/ Department:	Not applicable.
Date of Report:	12 Feb 2016
Dates of Trial:	From 12 Feb 2015 To 17 Aug 2015
Additional Reports:	Not applicable.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** Not applicable	
BI Investigational Product: Dabigatran etexilate (mesilate)		**Page:** 1 of 5	
Report Date: 12 Feb 2016	**Trial No. / Doc. No.:** 1160.149	**Dates of Trial:** 12 Feb 2015 - 17 Aug 2015	**Date of Revision:** Not applicable

Title of Trial:	Post-authorisation study to evaluate the effectiveness of the risk minimisation activities in the treatment of SPAF
Principal/Coordinating Investigator:	Not applicable in this survey.
Trial Sites:	411 healthcare professionals in 8 European countries [58 in Bulgaria (BG), 64 in Czech Republic (CZ), 69 in Germany (DE), 1 in Denmark (DK), 62 in Spain (ES), 50 in France (FR), 46 in Slovakia (SK), and 61 in United Kingdom (UK)] .
Publications:	None.
Clinical Phase:	Not applicable. Survey
Objectives:	The objective of this survey was to evaluate the effectiveness of the risk minimization measure, the Pradaxa® educational package, and with this to evaluate the understanding of prescribers and patients of the information contained in the SPAF Prescriber Guide and Patient Alert Card in different regions of the European Union (EU)
Methodology:	Cross-sectional survey. Pradaxa® prescribing healthcare professionals and Pradaxa® treated patients were randomly selected and interviewed (face-to-face).
No. of Subjects:	
Planned:	Entered: 400 healthcare professionals (50 per country) and 800 patients with atrial fibrillation (100 per country)
Actual:	Enrolled: 411 healthcare professionals and 802 patients with atrial fibrillation
	Entered: 411 healthcare professionals and 802 patients with atrial fibrillation
Diagnosis:	Atrial fibrillation (applicable for patients only)
Main Criteria for Inclusion:	Physicians: Current prescribers of Pradaxa® for stroke prevention in patients with atrial fibrillation (AF).
	Patients: AF patients on treatment with Pradaxa®.
BI Investigational Product:	Pradaxa®; dabigatran etexilate (mesilate)
Dose:	Not applicable.

Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** Not applicable	
BI Investigational Product: Dabigatran etexilate (mesilate)		**Page:** 2 of 5	
Report Date: 12 Feb 2016	**Trial No. / Doc. No.:** 1160.149	**Dates of Trial:** 12 Feb 2015 – 17 Aug 2015	**Date of Revision:** Not applicable

Mode of Admin.:	Not applicable.
Batch No.:	Not applicable.
Comparator Product:	Not applicable.
Duration of Treatment:	Not applicable.
Criteria for Evaluation:	1. Physicians' knowledge and recommendations to their patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®. The evaluation was based on the physicians' interview responses to questions regarding the "Prescriber Guide". 2. Patients' understanding of the disease, bleeding signs, what to do in case of bleeding and how to deal with emergency situations. The evaluation was based on the patients' interview responses to questions regarding the information received through the "Patient Alert Card".
Statistical Methods:	All analyses were descriptive. For both physician and patient surveys, all percentages and means were presented for the following groups: – The entire populations for physicians and for patients – Stratified by country (UK, DE, ES, FR, DK, BG, CZ and SK) – Patients stratified by those who had received the risk minimization materials and those who had not. – Physicians stratified for each country for the two medical specialty groups (i.e., general practitioners, cardiologists) Patients were further stratified by age groups (<75 years and ≥75 years). The results of this subgroup analysis are provided in Section 15, but are not presented in detail in this report, because only minor differences between the two subgroups were observed.
SUMMARY - CONCLUSIONS:	
Trial Subjects and Compliance with Trial Protocol:	A total of 411 physicians [124 primary care physicians (PCPs) and 287 cardiologists] and 802 AF-patients in 8 European countries participated in this survey. All of the participants were either prescribers (physicians) or current consumers (patients) of Pradaxa®. The proportion of male patients was slightly higher than that of females (54% vs. 46%) and 60% of the patients were less than 75 years old. Eighty-two

Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** Not applicable	
BI Investigational Product: Dabigatran etexilate (mesilate)		**Page:** 3 of 5	
Report Date: 12 Feb 2016	**Trial No. / Doc. No.:** 1160.149	**Dates of Trial:** 12 Feb 2015 – 17 Aug 2015	**Date of Revision:** Not applicable

	percent of the patients reported concomitant diseases other than AF, which required drug treatment. These were most frequently diabetes (36%), arterial hypertension (27%) and/or congestive heart failure (25%). In 42% of the patients, Pradaxa® was their first blood thinning medication for AF. In the total patient group, approximately half of them (49%) has taken Pradaxa® since 1-12 months. Shorter exposures were reported by only 5%. When considering the median exposure times, it was found that patients having received the Patient Alert Card had a 6-month shorter exposure than patients who had not or could not remember having received it (8.0 vs. 14.0 months). Besides this difference, the two patient groups were absolutely comparable with regard to demographics and medical history.
Efficacy / Clinical Pharmacology / Other Results:	<u>Physicians' knowledge and recommendations to their patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®:</u> The majority of physicians (65%) stated that they had received the Patient Alert Card, mostly did this at start of the Pradaxa® treatment. Most of them (61%) handed it out to their AF-patients without selection of a certain patient group. The dispensing was the highest in UK (100%) and DE (99%) and the lowest (57%) in FR. As of September 2014 the Patient Alert Card was also distributed directly to the patient via the Pradaxa® trade pack. Overall, 71% of the physicians stated that they had received the Prescriber Guide (maximum: 97% in CZ, minimum: 36% in FR). More than 90% of the physicians who had received the educational pack in the different countries were satisfied with the information provided in the Prescriber Guide. Only in FR, 72% of those physicians who had received the Prescriber Guide were satisfied and the remaining 28% had not read it yet. All physicians were aware of the importance of determining and controlling of the patients' renal function for correct Pradaxa® dosing. The majority of physicians also knew about the correct dosing of patients. In risk patients, physicians tended to recheck the prescriber guide/literature first or would tend to prescribe lower doses than expected based on the patient profile. There was a high awareness of risk factors for bleeds. Only for specific risk factors like concomitant treatment with P-glycoprotein inhibitors or presence of bacterial endocarditis, the percentages of physicians replying "don't know" amounted to up to 34%. The physicians knew at least one suitable laboratory parameter [ecarin clotting time (ECT), thrombin time (TT), diluted thrombin time (dTT), and activated partial thromboplastin time (aPTT)], but nearly 20% of them were not aware of the unreliability of prothrombin time (international

Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** Not applicable	
BI Investigational Product: Dabigatran etexilate (mesilate)		**Page:** 4 of 5	
Report Date: 12 Feb 2016	**Trial No. / Doc. No.:** 1160.149	**Dates of Trial:** 12 Feb 2015 – 17 Aug 2015	**Date of Revision:** Not applicable

	normalized ratio; INR) in patients on Pradaxa®. Actions to be taken for surgeries or invasive procedures were more familiar. The answers regarding actions physicians would take in case of bleeds were variable and dependent on the physicians' routine and available technical equipment. Less than 50% would assess the patient's anticoagulation status first and/or would apply diuresis measurement (46% and 35%, respectively), but the physicians would discontinue Pradaxa® either immediately or in case of hemorrhagic complications (65% and 56%, respectively). Overall, some regional differences were observed, but across all countries, physicians were familiar with the content of the Prescriber Guide and applied the instructions as intended. In general, cardiologists appeared to be better informed than PCPs about the treatment of AF-patients with Pradaxa® and would less frequently check the Prescriber Guide than PCPs. <u>Patients' understanding of the disease, bleeding signs, what to do in the event of bleeding and how to deal with emergency situations:</u> Fifty-five percent of the interviewed patients had received the Patient Alert Card, had read it and understood its content. Most of the remaining patients, who had not received the Patient Alert Card, felt well informed by their treating physicians. The Patient Alert Card was completed with the patient-specific information in about 80% of the cases, and this was mostly done by the dispensing person. In general, all patients, irrespective of having received the Patient Alert Card or not, were well informed about their treatment and the actions to be taken in case of serious complications. The vast majority of patients knew about the anticoagulant effect of Pradaxa® (89%) and were well aware of the importance of the regular intake of the drug (>99%), potential side effects (bruising: 54%, bleeding: 52%), and the consequences associated with an arbitrary discontinuation. Patients having received the Patient Alert Card were even better informed, which confirms the patients' understanding of its content. In case of bleeding complications or surgery, most patients would behave correctly, irrespective of having received the Patient Alert Card or not.
Safety Results:	Safety data were not systematically collected in this survey. Spontaneous reports during the interviews were forwarded to the sponsor's pharmacovigilance unit for further processing.
Conclusions:	This survey in 8 preselected EU countries demonstrates a good educational

Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** Not applicable	
BI Investigational Product: Dabigatran etexilate (mesilate)		**Page:** 5 of 5	
Report Date: 12 Feb 2016	**Trial No. / Doc. No.:** 1160.149	**Dates of Trial:** 12 Feb 2015 – 17 Aug 2015	**Date of Revision:** Not applicable

level of prescribers and patients about the safety messages for Pradaxa® with some regional differences. The information given by the Prescriber Guide and the Patient Alert Card has been assessed by the study attendees as sufficiently informative and adequate.

Potential for improvements in the logistical distribution of the educational material to prescribers identified by this survey will be taken up by BI in the near future by adequate measures such as mailing and personal contacts to further improve the education and information related to key safety messages for Pradaxa®. The Patient Alert Card is directly distributed to the patient per Pradaxa® trade packs as of September 2014.

3. MAIN PART TABLES OF CONTENTS

APPENDICES - TABLES OF CONTENT

The following appendices of the Clinical Trial Report are provided as separate documents. Please see page 1 of these documents for further details.

Section 16, 16.1, and 16.1.1 are combined into one document. Similarly, sections 16.2 and 16.2.1 are combined into one document.

16. APPENDICES

16.1 TRIAL INFORMATION

16.1.1 Protocol and amendments
16.1.2 Sample case report form
16.1.3 List of IRBs or IECs and consent forms
16.1.4 List and description of investigators and sites
16.1.5 Signature of principal or coordinating investigator
16.1.6 Listing of subjects receiving test drugs from specified batch
16.1.7 Randomisations scheme
16.1.8 Audit certificates
16.1.9 Documentation of statistical and pharmacokinetic analysis
16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used
16.1.11 Publications based on the trial
16.1.12 Important publications referenced in the report

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects – disposition of subjects
16.2.2 Subjects excluded from the efficacy analysis
16.2.3 Protocol violations
16.2.4 Demographic data
16.2.5 Exposure - compliance and - or drug concentration data
16.2.6 Individual efficacy response data
16.2.7 Adverse event listings

LIST OF IN-TEXT TABLES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AF	Atrial fibrillation
ASA	Acetylsalicylic acid
ASS	Acetylsalicylsäure (Engl.: acetylsalicylic acid)
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
BG	Bulgaria
BI	Boehringer Ingelheim
BID	Twice daily
COPD	Chronic obstructive pulmonary disease
CHMP	Committee for Medicinal Products for Human Use
CZ	Czech Republic
DE	Germany
DK	Denmark
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
EMA	European Medicines Agency
ES	Spain
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FR	France
FUM	Follow-up measurement
ID	Identification
IEC	Independent ethics committee
INN	International non-proprietary name
INR	International normalized ratio
IRB	Institutional review board
Max	Minimum
Min	Maximum

N	Number (of patients/physicians)
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OD	Once daily
PCP	Primary care physician
PE	Pulmonary embolism
pVTEp	Primary prevention of venous thromboembolism
Q1	25%-quartile
Q3	75%-quartile
SAE	Serious adverse event
SK	Slovakia
SmPC	Summary of product characteristics
SPAF	Stroke prevention in atrial fibrillation
TIA	Transient ischemic attack
ToC	Table of contents
TT	Thrombin time
UK	United Kingdom

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

Involvement of an ethics committee or institutional review board was not applicable in this study. Prior to initiation of this study, the study protocol was reviewed and approved by the European Medicines Agency (EMA).

5.2 ETHICAL CONDUCT OF THE TRIAL

The survey was carried out in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs). Data protections laws applied.

5.3 SUBJECT INFORMATION AND CONSENT

In order to access patients with atrial fibrillation (AF) in this survey, Pradaxa® prescribing physicians were to ask all of their patients treated with Pradaxa® if they were interested in participating in this survey. This means that physicians should approach all of their patients on Pradaxa® at the same time, thus, giving each patient an equal opportunity of participating in the research project. Patients willing to participate were given the contact details of the field agency and an identification (ID) code representing their treating physician.

6. INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

This survey was conducted in 8 European countries: Bulgaria (BG), Czech Republic (CZ), Denmark (DK), France (FR), Germany (DE), Spain (ES), Slovakia (SK), and the United Kingdom (UK).

Sponsor:	Boehringer Ingelheim Pharma GmbH & Co. KG
Trial Clinical Monitor:	[redacted] Medicine, TA Cardiology Boehringer Ingelheim Pharma GmbH & Co. KG
Team Member Medicine:	[redacted] Medicine, TA Cardiology Boehringer Ingelheim Pharma GmbH & Co. KG
Conduct, data management and statistical analysis:	[redacted]
Medical Writing:	[redacted]

7. INTRODUCTION

7.1 MEDICAL BACKGROUND

With approval of the Stroke Prevention in Atrial Fibrillation (SPAF) indication (EMA/H/C/X/13/G in August 2011) EMA/CHMP requested the introduction of a risk minimization measure. Boehringer Ingelheim (BI) was requested to implement an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/ use Pradaxa®. This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Pradaxa® and providing guidance on how to manage that risk.

BI agreed to the content of the educational material consisting of a prescriber guide per approved and indication and a patient alert cared, together with a communication plan with EMA /CHMP, followed by subsequent approval by the national competent authorities prior to the distribution of the educational pack. Moreover, it was agreed that the educational pack must be available for distribution for any approved therapeutic indication prior to the launch of the new indication in the member state. The physician educational package contains the Summary of Product Characteristics (SmPC), a Prescriber Guide and a Patient Alert Card. The aim of the Prescriber Guide and a Patient Alert Card is the following:

- Prescriber Guide focused on appropriate use and recommendations for dose reduction in at risk populations, management of overdose situations, the use of coagulation tests and the interpretation thereof.

- Patient Alert Card to reinforce patient counseling about signs and symptoms of bleeding, the importance of treatment compliance and the necessity to inform Health Care Providers that they are taking Pradaxa® in case of any surgery or invasive procedure.

Furthermore, EMA/CHMP imposed a post authorization measure to evaluate the effectiveness of the aforementioned risk minimization measure (educational pack) for use of Pradaxa® in the SPAF indication. The present report provides the results of study 1160.149 measuring the effectiveness of the educational pack for use of Pradaxa® in the SPAF indication.

7.2 DRUG PROFILE

Pradaxa® is provided as hard capsules, each containing 75, 110 or 150 mg of the active substance dabigatran etexilate (as mesilate).

Pradaxa® is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, such as prior stroke or transient ischemic attack (TIA), age ≥ 75 years, heart failure (NYHA Class ≥ II) diabetes mellitus, or hypertension, and is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), prevention of recurrent DVT and PE, and primary prevention of venous thromboembolism (pVTEP) in adults.

8. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

8.1 RATIONALE FOR PERFORMING THE TRIAL

To evaluate effectiveness of risk minimization measure, i.e., educational pack (Prescriber Guide and Patient Alert Card) for use in the SPAF indication.

8.2 TRIAL OBJECTIVES

The objective of this survey was to evaluate the effectiveness of the educational pack and to collect data on physicians' awareness and understanding of the content of the Pradaxa® Prescriber Guide summarizing the potential risk of bleeding during treatment with Pradaxa® and providing guidance on how to manage that risk.

Furthermore, the trial objective was to measure the extent to which risk awareness is communicated to patients via the Prescriber Guide and via the Patient Alert Card. The data collected with AF patients were intended to show if and how well this information was received and understood.

This survey was performed to provide data on:

1. Physician's knowledge and recommendations to their AF patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®.

2. Patients' understanding of the disease, bleeding signs, what to do in the event of bleeding and how to deal with emergency situations.

8.3 BENEFIT - RISK ASSESSMENT

No direct benefit or risk was associated with this survey.

9. TRIAL METHODOLOGY AND INVESTIGATIONAL PLAN

9.1 OVERALL TRIAL DESIGN AND PLAN - DESCRIPTION

This was a cross-sectional survey in which the names of both BI and EMA as well as of respondents remained anonymous. Additionally, physician and patient names or initials etc., which would make the participants identifiable, were not recorded nor were they connected with each other. In order to have an as meaningful sample as possible, face-to-face interviews with patients and physicians were conducted.

In order to guarantee a sound database for the interpretation of results on physicians' and patients' understanding of treatment with Pradaxa®, a total of 1200 respondents were to be interviewed throughout the survey, 400 physicians and 800 patients.

The survey was conducted in 8 European countries (Bulgaria, Czech Republic, Denmark, France, Germany, Italy, Slovakia, Spain and United Kingdom). These countries were selected and mutually agreed upon with the EMA to cover a representative sample.

In each country, n=50 health care professionals [cardiologists and, in some countries, also primary care physicians (PCPs] and n=100 AF patients receiving treatment with Pradaxa® were to be recruited.

Countries were selected to represent heterogeneous regions across Europe with differing cultures, economies and healthcare systems, thus, increasing generalizability. From the list of Pradaxa® prescribers provided by each country, a minimum of 250 PCPs and 250 cardiologists (in BG, CZ and SK, 500 cardiologists) were to be chosen at random within each country in order to achieve at least 25 responders of each physician specialty type (in BG, CZ and SK, 50 cardiologists), when assuming a 10% response rate. In an attempt to derive a representative group of patients, physicians who consented to participate were given a set of form letters and asked to distribute a letter to every patient currently on treatment with Pradaxa®; the letter provided a brief description of the survey and invited the patient to contact the Surveyor by phone if he/she was considering participation. A set of letters also included the same predefined physician code, and these sets with differing codes were distributed randomly to participating physicians via mail. The purpose of this code was to identify a 'pool' of candidates with the same code from which patients were then sampled at random to be contacted for conducting the survey.

Generalizability of estimates was enhanced due to the following: 1) Physicians within each country were identified at random to participate, 2) physicians were asked to identify all patients currently on treatment with Pradaxa® and were provided the form letter regarding survey information, 3) among those patients who contacted the Surveyor with the same code, 2 or 3 were chosen at random to participate. These survey methodology considerations supported the evaluation and/or reduction of bias in estimates derived, and also supported generalizability of findings.

The research was highly standardized. The master English questionnaires were translated into local languages, allowing for a standardized approach in all countries. Interviewers with medical experience conducted the interviews following a standardized in-depth briefing of all field agencies.

After EMA/CHMP protocol approval, the questionnaires were slightly adapted to the local situation (e.g., instructions for adverse event reporting, local product name, and some other editorial changes), if necessary.

9.2 DISCUSSION OF TRIAL DESIGN - INCLUDING THE CHOICE OF CONTROL GROUPS

A survey including face-to-face interviews was the appropriate method to investigate the objectives of the imposed follow-up measurement FUM. The preference of face-to-face interviews over web-based telephone interviews was due to the following reasons:

1. Stimuli (Patient Alert Card and Prescriber Guide) were shown to the respondents during the interview. Web-based could be difficult in some geographies, as these respondent might have limited access to the internet. Furthermore, web-based interviews with elderly people were assumed to add further limitations (e.g., computer access or skills), which could also bias the data as the patient sample would have been selective.

2. Interviews could be conducted in the field, i.e., at the clinicians' workplace or at the location which was most convenient for the patients. Conducting the interviews in a central location could bias the research by recruiting only patients fit enough to travel and take part in a studio venue.

3. For some patients, following the interview on the telephone could be demanding, i.e., due to hearing loss, unable to concentrate, etc., which could potentially impact the reliability of the data.

Control groups were not applicable in this survey.

9.3 SELECTION OF TRIAL POPULATION

In order to qualify for this survey, physicians needed to be current prescribers of Pradaxa® for stroke prevention in patients with AF.

A target list of all Pradaxa® prescribers in each country was provided to the research agency, from which physicians were randomly recruited, but representing the geographical spread of the country. A minimum of n=500 prescribers had to be listed to achieve n=50 per country before beginning fieldwork.

AF patients qualified for this study, if they were currently receiving treatment with Pradaxa®.

Recruitment of patients required close adherence to data protection laws. Physicians were not allowed to pass on the name of patients for research purposes. In order to access AF patients in this research, physicians were to ask all of their patients treated with Pradaxa® if they are interested in participating in this study. Physicians were to approach all of their patients on Pradaxa® at the same time, thus, giving each patient an equal opportunity of participation. Patients willing to participate were given the contact details of the field agency and an identification (ID) code representing their treating physician. The ID code allowed recruiters to identify patients from a specific physician to limit recruitment to only two or three patients per physician. The research aimed to recruit patients from a maximum number of physicians to obtain a geographical spread. Thus, the patients who made the contact first, showing their interest and willingness to participate in the research, but the agency's random selection from the pool of patients calling from a specific physician minimized any possible bias of a pre-selection made by the physician. Postponing fieldwork with physicians until patient recruitment and partial fieldwork was completed further minimized the possibility that physicians could only recruit their "model" patients. Not knowing the purpose of the patient research by slightly delaying the physician fieldwork on the Prescriber Guide avoided physicians pre-selecting patients based on their own interview experience.

Furthermore, physicians were made aware that physician and patient data were analyzed separately and not connected to each other, allowing physicians to consider each Pradaxa® treated patient as a potential candidate for the survey.

As the objectives of the patient research (i.e., Patient Alert Cards) were not disclosed to physicians, a personal interest in offering only certain patients the opportunity of being included was not to be expected. Additionally, physicians were informed that, in order to ensure valid and reliable data, the patient sample should be as representative as possible for the underlying patient population, thus, requiring to include patients with, for example, different disease histories or knowledge levels on disease and treatment.

9.3.1 Main diagnosis for trial entry

For patients only: AF with one or more risk factors, such as prior stroke or transient ischemic attack (TIA), age ≥ 75 years, heart failure (NYHA Class ≥ II) diabetes mellitus, or hypertension.

9.3.2 Inclusion criteria

Physicians: Current prescribers of Pradaxa® for stroke prevention in patients with atrial fibrillation (AF).

Patients: AF patients on treatment with Pradaxa®.

9.3.3 Exclusion criteria

Patients and physicians (verbally) unwilling to participate in the survey.

Note: Only patients willing to participate were to voluntarily contact the agency. At the beginning of each interview, all participants were again explicitly asked about their willingness for participation.

9.3.4 Monitoring of drop-outs

The research monitored all physicians contacted and not willing to take part in the research or not meeting the screening criteria. All patients contacting the research agency, indicating their interest to participate, who did not meet the screening criteria or met the criteria but were not selected, were tracked.

9.3.5 Removal of subjects from therapy or assessment

Removal of patients from therapy was at the discretion of the treating physician. Removal of patients from therapy during the interview was not applicable, because of this single point evaluation.

All patients and physicians were free to discontinue the interview at any time.

9.3.5.1 Removal of individual subjects

Not applicable.

9.3.5.2 Discontinuation of the trial by the sponsor

The sponsor reserved the right to discontinue the survey at any time.

9.4 TREATMENTS

9.4.1 Treatments administered

For patients, premise for participation in this survey was the intake of Pradaxa®.

9.4.1.1 Identity of BI investigational product and comparator product

Not applicable.

9.4.1.2 Method of assigning subjects to treatment groups and randomization

Not applicable.

9.4.1.3 Selection of doses in the trial

Not applicable.

9.4.1.4 Drug assignment and administration of doses for each subject

Not applicable.

9.4.1.5 Blinding and procedures for unblinding

Not applicable.

9.4.1.5.1 Blinding

Not applicable.

9.4.1.5.2 Procedures for emergency unblinding

Not applicable.

9.4.1.6 Packaging - labelling, and re-supply

Not applicable.

9.4.1.7 Storage conditions

Not applicable.

9.4.1.8 Drug accountability

Not applicable.

9.4.2 Concomitant therapy, restrictions, and rescue treatment

Not applicable.

9.4.2.1 Rescue medication, emergency procedures, and additional treatments

Not applicable.

9.4.2.2 Restrictions

Not applicable.

9.4.3 Treatment compliance

Not applicable.

9.5 VARIABLES AND THEIR ASSESSMENT

9.5.1 Flow chart and schedule of assessments

Single face-to-face interviews were conducted for this survey. Each physician interview lasted approximately 30 minutes and each patient interview approximately 15 minutes.

9.5.2 Efficacy - Clinical pharmacology

This was not an investigation of the efficacy of Pradaxa® in terms of a certain therapeutic effect, but an evaluation of the effectiveness of the educational pack provided to physicians and patients ("Pradaxa® Prescriber Guide for Stroke Prevention in Atrial Fibrillation" and "Patient Alert Card", respectively) within the scope of the sponsor's risk minimization activities.

9.5.2.1 Endpoints of efficacy

1. Physicians' knowledge and recommendations to their patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®. The evaluation to be was based on the physicians' interview responses to questions regarding the "Prescriber Guide".

2. Patients' understanding of the disease, bleeding signs, what to do in case of bleeding and how to deal with emergency situations. The evaluation was based on the patients' interview responses to questions regarding the information received from the prescribing healthcare professional and the "Patient Alert Card".

9.5.2.2 Assessment of efficacy

Physician interviews

The physician questionnaire used for the interviews included the following topics/chapters:

1. Background Information
2. Physician receipt of Prescriber Guides and Patient Alert Cards
3. Distribution of Patient Alert Cards to patients
4. Awareness of daily dosing in different patient types
5. Awareness of patient populations at higher risk of bleeding
6. Actions taken in case of surgery/interventions and bleeding events
7. Assessing anticoagulation status
8. Presentation of Prescriber Guide and Patient Alert Card to those who can't remember: Receipt and distribution of Patient Alert Cards to patients

Patient interviews

The patient questionnaire used for the interviews included the following topics/chapters:

1. Background Information
2. Receipt of Patient Alert Card and awareness of content
3. Awareness of daily dosing and intake instructions
4. Awareness of side effects
5. Actions to be taken in case of bleeding events and surgery/interventions
6. Awareness of implications, if discontinuing use

7. Presentation of Alert Card to those who can't remember: Receipt and awareness of content

9.5.3 Safety

Not applicable.

9.5.3.1 Endpoints of safety

Not applicable.

9.5.3.2 Assessment of adverse events and serious adverse events

All interviewers were trained on the definition of adverse events (AEs). In the event, a physician or patient mentioned an AE during the interview, the interviewer together with the physician or patient was to complete an Adverse Event Form and fax it to the sponsor's pharmacovigilance units.

9.5.3.2.1 Definitions of adverse events

AE were defined according to standard definitions (i.e., any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related).

9.5.3.2.2 Adverse event and serious adverse event reporting

Adverse events reported during the study were documented and reported according to standard processes. All (S)AEs were to be reported to the sponsor's pharmacovigilance unit within 24 hours after becoming aware.

9.5.3.3 Assessment of safety laboratory parameters

Not applicable.

9.5.4 Other

Not applicable.

9.5.5 Appropriateness of measurements

Not applicable.

9.6 DATA QUALITY ASSURANCE

The research was highly standardized. The master English questionnaires were translated into local languages, allowing for a standardized approach in all countries. Interviewers with medical experience conducted the interviews following a standardized in-depth briefing of all field agencies.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and analytical plans

9.7.1.1 Statistical design – model

Not applicable.

9.7.1.2 Null and alternative hypotheses

Not applicable.

9.7.1.3 Planned analyses

For both Physician and Patient Surveys, all estimates of proportions and means were to be presented for the following groups: The entire populations for physicians and for patients, stratified by country, and stratified by those who had received the risk minimization materials and those who had not. For each country or combination of countries, relative frequencies were to be presented separately for the two medical specialty groups (i.e., PCPs, cardiologists) and the patient age subgroups (i.e., <75 years, ≥75 years).

The results of the subgroup analysis by age are not presented in detail in this report, because only minor differences became apparent between the two age classes. The corresponding data are presented in Tables 15.2.1:97 to 15.2.1:134.

9.7.1.3.1 Analyses of the primary endpoints

9.7.1.3.1.1 Physicians' survey

With regard to the Physicians' Survey, for all individual questions with pre-defined answer options, relative frequencies for all response categories were to be presented. For open-ended questions, such as, e.g., "Other – please specify", answers were to be analyzed by elaborating a code frame and coding of all answers, followed by the calculation and presentation of the relative frequencies of answers. For each of the four patient profile questions, a descriptive analysis of the reasons given for selecting a particular dosage was to be conducted to uncover physicians' prescribing rationale and describe current usage practices. As far as possible in qualitative analysis, probable differences between countries or physician subgroups were to be documented.

9.7.1.3.1.2 Patients' survey

With regard to the Patients' Survey, for all questions with pre-defined answer options, relative frequencies for all response categories were to be presented. For open-ended questions, such as, e.g., "Other – please specify", answers were to be analyzed by elaborating a code frame and coding of all answers, followed by the calculation and presentation of the relative frequencies of answers.

9.7.1.3.2 Analyses of the secondary endpoints

Not applicable.

9.7.1.3.3 Safety analyses

Not applicable.

All AEs which were reported in this survey were forwarded to the sponsor's pharmacovigilance unit, but were not analyzed within the scope of this study.

9.7.1.3.4 Interim analyses

Not applicable.

9.7.1.4 Handling of missing data and outliers

Because both physicians and patients were personally interviewed, the probability of missing data was very low. However, surveyors were to document whether the physician or patient terminated the survey for lack of time (i.e., items after a certain question were left blank) and the respective cases were to be excluded from the analysis. In case of missing data for other reasons, such items were coded as "don't know/no answer".

9.7.2 Determination of sample size

Almost all summary statistics from the survey are proportions, and these proportions were expected to encompass the entire range between 0 and 1. In addition, within each country the planned sample size for physicians was relatively low; thus Wilson's method was chosen to derive confidence intervals for all categorical response rates (proportions). Varying proportions from P=0 to P=1 at 0.05 intervals, for sample sizes of 50 physicians and 100 patients 95% confidence Intervals using Wilson's method were derived. It was found that for sample size of 50 Physicians per country, the maximum deviation from the observed proportion was <0.14, and, thus, the maximum width of the confidence interval was <0.28. For a sample size of 100 patients, the maximum deviation from the observed proportion was <0.10, and, thus, the maximum width of the confidence interval was <0.20. For the entire sample of physicians across 8 countries (N=400), the maximum deviation was estimated to be <0.05 and the maximum width was <0.10. For the entire sample of patients across 8 countries (N=800), the maximum deviation was estimated to be <0.04 and the maximum width was <0.08.

The Wilcoxon score intervals for the different numbers of patients and physicians are presented in Tables 3.7:1 to 3.7:4 in section 3.7 of the protocol (Appendix 16.1.1).

9.8 CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

According to protocol, 50 physicians and 100 AF-patients were planned to be enrolled in each of the 8 countries. This recruitment goal was not always met (especially in DK, where only 1 of the planned 50 physicians and 43 of the planned 100 patients were willing to participate). Therefore, recruitment in other countries was adjusted to achieve the total planned sample size of 400 physicians and 800 patients. For details, see also Section 10.1.

10. TRIAL SUBJECTS AND COMPLIANCE WITH TRIAL PROTOCOL

10.1 DISPOSITION OF SUBJECTS

A total of 411 physicians (124 PCPs and 287 cardiologists) and 802 AF-patients in 8 European countries participated in this survey.

The distribution of physicians and patients across countries is displayed in Table10.1:1.

Table 10.1:1 Regional distribution of survey participants

Country	Physicians			Patients
	Total	Cardiologists	PCPs	Total
All	411	287 (70%)	124 (30%)	802
DE	69	34 (49%)	35 (51%)	212
ES	62	31 (50%)	31 (50%)	118
FR	50	25 (50%)	25 (50%)	92
UK	61	29 (48%)	32 (52%)	67
DK	1	-	1 (100%)	43
BG	58	58 (100%)	-	103
CZ	64	64 (100%)	-	108
SK	46	46 (100%)	-	59

Source Data: see Table 15.2.1:1 and 15.2.1:59

The data in Table 10.1:1 show that the highest numbers of both physicians and patients participated in DE, CZ and ES. The planned numbers of physicians and patients per country (n=50 and n=100, respectively) were not always met. Especially in DK, only 1 physician and 43 patients were interested in the participation.

In those countries, where both cardiologists and PCPs are treating AF-patients, the proportions of both professional groups were well balanced.

10.2 DATASETS ANALYZED

The data from all survey participants were included in the analysis. The analysis of the patient survey stratified patients by those who had received the Patient Alert Card (n=445) and those who had not (n=357; see Table 15.2.1:59).

10.3 PROTOCOL VIOLATIONS

No protocol violations were identified. All of the participants were either prescribers (physicians) of Pradaxa® or patients on treatment with Pradaxa®.

10.4 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

10.4.1 Physicians

Of the 411 participating physicians, 199 (48%) worked in private practices and 212 (52%) in hospitals with out-patient care (see Table15.2.1:2). There were marked regional differences, e.g., 90% of the physicians in DE worked in private practices but only 8% in ES.

Similar regional differences were also seen with regard to the type of hospital the respective 212 physicians worked at (see Table 15.2.1:3). Overall, 41% of them worked at a academic/teaching hospital and 33% in a community hospital. The highest proportion of physicians working at an academic/teaching hospital was found in UK (75%) and the highest proportion working at a community hospital were found in DE (57%). Private hospitals and ambulant care clinics were the workplaces of 14-15% of the physicians overall. Especially in FR, a large proportion of physicians (63%) worked at a private clinic, and in BG, a similar proportion (56%) worked at ambulant care clinics.

Across all countries, the majority of physicians belonged to the age groups 40-49 years (28% in total) and 50-62 years (54% in total; see Table 15.2.1:4).

Table 10.4.1:1 displays the median number of AF-patients treated for stroke prevention per month and the number of AF-patients initiated on Pradaxa® in the previous 6 months. The by far highest median number of patients treated for stroke prevention per month was found in DE (median: 60). In all other countries, the corresponding numbers ranged from 25 (in DK) to 40 (in ES). Less pronounced were the regional differences in the median number of AF-patients newly prescribed Pradaxa®. Here, the median number was the lowest in DK (median: 1) and the highest in BG and SK (median: 20).

Table 10.4.1:1 Number of treated AF-patients (all physicians)

	Number of AF-patients treated for stroke prevention per month (N=411)	**Number of AF-patients initiated on Pradaxa® treatment in the past 6 months (N=411)**
Median	35.0	10.0
[Minimum - Maximum]	[2 - 400]	[1 - 300]

Source Data: see Tables 15.2.1:5 and 15.2.1:6

In countries, where AF-patients are treated both by cardiologists and PCPs, the number of AF-patients treated per month was approximately twice as high for cardiologists (Table 15.2.1:5).

10.4.2 Patients

As shown in Table 10.4.2:1, the proportion of male patients was slightly higher than that of females (54% vs. 46%) and 60% of the patients were less than 75 years old. Most of the patients (69%) had a person (family/friends) who was also instructed by the physician on the patient's proper intake of Pradaxa® and actions to be taken in case of any unexpected events.

Overall, the 2 subgroups of patients having received the Patient Alert Card or not were absolutely comparable. The regional differences with regard to these parameters were minor. For details, see also Tables 15.2.1:67 to 15.2.1:69.

Table 10.4.2:1 Demographic characteristics (all patients)

	Total	**Patient Alert Card received**	
		Yes	**No**
	N = 802	**N = 445**	**N = 357**
Sex			
Male	432 (54%)	235 (53%)	197 (55%)
Female	370 (46%)	210 (47%)	160 (45%)
Age group			
< 75 years	480 (60%)	266 (60%)	214 (60%)
≥ 75 years	322 (40%)	179 (40%)	143 (40%)
Also other persons (family/friends) instructed by the physician on the patient's Pradaxa® treatment?			
Yes	518 (65%)	305 (69%)	213 (60%)
No	282 (35%)	139 (31%)	143 (40%)
No answer	2 (0%)	1 (0%)	1 (0%)

Source Data: see Tables 15.2.1:67 to 15.2.1:69.

Eighty-two percent of the patients reported concomitant diseases other than AF, which required drug treatment (Table 10.4.2:2). These were most frequently diabetes (36%), arterial hypertension (27%) and/or congestive heart failure (25%).

Again, there were no relevant differences between the two subgroups or between countries. For details, see also Tables 15.2.1:70 and 15.2.1:71.

Table 10.4.2:2 Concomitant diseases (all patients)

	Total	Patient Alert Card received	
		Yes	No
	N = 802	N = 445	N = 357
Concomitant diseases with drug treatment?			
No	141 (18%)	73 (16%)	68 (19%)
Yes	661 (82%)	372 (84%)	289 (81%)
Most frequent (≥15%) concomitant diseases:	n = 661	n = 372	n = 289
Diabetes	235 (36%)	146 (39%)	89 (31%)
Arterial hypertension	177 (27%)	99 (27%)	78 (27%)
Congestive heart failure	163 (25%)	96 (26%)	67 (23%)
Osteoarthritis	134 (20%)	85 (23%)	49 (17%)
Respiratory disorders (asthma, COPD)	114 (17%)	69 (19%)	45 (16%)
(Ischemic) stroke	105 (16%)	53 (14%)	52 (18%)

COPD = chronic obstructive pulmonary disease.
Source Data: see Tables 15.2.1:70 and 15.2.1:71.

In 42% of the patients, Pradaxa® was their first blood thinning medication for AF (Table 10.4.2:3). In the remaining 58% of patients, the most common previous medications were vitamin K antagonists (Marcumar or Sintrom) and/or acetylsalicylic acid (68% and 20% of the pre-treated patients, respectively). Sintrom, which was taken by 20% of the pre-treated patients, was only reported by patients from ES and BG, where this drug is available only.

The duration of the prior treatment of AF was highly flexible among patients. However, the longest median duration of 5.0 year was seen with acetylsalicylic acid (2.0 years for Marcumar and Sintrom). The longest median duration of the acetylsalicylic acid intake was observed in FR (8.0 years), CZ (8.0 years) and SK (7.1 years) and the shortest in ES (2.5 years), DE and DK (3.0 years each). For details, see also Tables 15.2.1:60 to 15.2.1:66.

There were no relevant differences between the two subgroups with regard to prior AF treatment.

Table 10.4.2:3 Prior treatment of AF (all patients)

	Total	**Patient Alert Card received**	
		Yes	**No**
	N = 802	**N = 445**	**N = 357**
Prior intake of blood thinning medication for AF?			
No	337 (42%)	189 (42%)	148 (41%)
Yes	465 (58%)	256 (58%)	209 (59%)
Most frequent (≥20%) previous blood thinning medications for AF:	n = 465	n = 256	n = 209
Marcumar	223 (48%)	143 (56%)	80 (38%)
Acetylsalicylic acid	93 (20%)	52 (20%)	41 (20%)
Sintrom	92 (20%)	26 (10%)	66 (32%)
Duration of pre-treatment [years] (Median; Min - Max)			
Marcumar	2.0 [0.01 – 20.0]	2.0 [0.08 – 18.0]	2.5 [0.01 – 20.0]
Acetylsalicylic acid (ASS, ASS 100, ASA)	5.0 [0.08 – 25.0]	5.0 [0.08 – 25.0]	5.0 [0.25; 20.9]
Sintrom	2.0 [0.04 – 15.0]	2.0 [0.08 – 10.0]	2.0 [0.04 – 15.0]

Source Data: see Tables 15.2.1:60 to 15.2.1:63, and 15.2.1:66.

10.5 EXTENT OF EXPOSURE

In the total patient group, approximately half of them (49%) have taken Pradaxa® since 1-12 months (Table 10.5:1). Shorter exposures were reported by only 5%.

For details, including the data by country, see Table 15.2.1:78.

Table 10.5:1 Patient reported extent of exposure to Pradaxa® (all patients)

Duration of Pradaxa® treatment [Months]	**Total**	**Patient Alert Card received**	
		Yes	**No**
	N = 802	**N = 445**	**N = 357**
Categorical:			
< 1	44 (5%)	34 (8%)	10 (3%)
1-12	394 (49%)	235 (53%)	159 (45%)
13-24	214 (27%)	92 (21%)	122 (34%)
25-36	90 (11%)	47 (11%)	43 (12%)
< 36	32 (4%)	13 (3%)	19 (5%)
Missing	28 (3%)	24 (5%)	4 (1%)
Summary statistics:	n = 774	n = 421	n = 353
Median	12.0	8.0	14.0
Q1 – Q3	4.0 – 24.0	3.0 – 24.0	6.0 – 24.0
Min – Max	0.13 – 120.0	0.23 – 93.0	0.13 – 120.0

Q1 = 25%-quartile, Q3 = 75%-quartile
Source Data: see Table 15.2.1:78.

10.6 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable.

11. EFFICACY - CLINICAL PHARMACOLOGY EVALUATION

As already described in Section 9.5.2, this was not an investigation of the efficacy of Pradaxa® in terms of a certain therapeutic effect, but an evaluation of the effectiveness and understanding of the educational pack provided to physicians and patients ("Pradaxa® Prescriber Guide for Stroke Prevention in Atrial Fibrillation" and "Patient Alert Card", respectively) within the scope of the sponsor's risk minimization activities.

The survey provides data on:

1. Physician's knowledge and recommendations to their patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®

2. Patients' understanding of the disease, bleeding signs, what to do in case of bleeding and how to deal with emergency situations

In the following sections, the results of the physician interviews (Section 11.1.3.1) and of the patients interviews (Section 11.1.3.2) are presented.

11.1 EFFICACY RESULTS

11.1.1 Primary endpoint

Not applicable.

11.1.2 Secondary endpoints

Not applicable.

11.1.3 Further endpoints

11.1.3.1 Physician's knowledge and recommendations to their patients on appropriate dosing and minimizing the risk of bleeding when treated with Pradaxa®

11.1.3.1.1 Handling of the "Patient Alert Card – Pradaxa®"

The majority of physicians (65%) stated that they had received the Patient Alert Card, and most of them (61%) handed it out to their AF-patients without selection of a certain patient group. Moreover, most of the physicians who distributed it to their patients, handed it out at start of the Pradaxa® treatment.

However, there were marked regional differences in the handling of the Patient Alert Card. E.g., more than 90% of the physicians in DE and CZ remembered the receipt of the Patient Alert Card, but less than one third of the physicians in ES and UK did (31% and 28%, respectively). Similar differences were seen in the prescribers' selection of patients who were handed out the Patient Alert Card. In some countries (DE, ES, BG and CZ), at least two thirds of the physicians handed it out to all AF-patients, whereas this applied to less than 50%

of the physicians in FR, UK and SK. The most striking finding in this regard was that 43% of the physicians in FR, who stated that they had received the Patient Alert Card, did not forward it to their patients at all.

Those physicians who dispensed the Patient Alert Card to their patients, mostly did it upon initiation of therapy, irrespective of the country.

A summary of these data is shown in Table 11.1.3.1.1:1. The corresponding data by physicians' specialization are shown in (Tables 15.2.1:9 to 15.2.1:11).

Table 11.1.3.1.1:1 Physicians' handling of Patient Alert Card (all physicians)

	Total	**DE**	**ES**	**FR**	**UK**	**DK**	**BG**	**CZ**	**SK**
Patient Alert Card received?	N = 411	N = 69	N = 62	N = 50	N = 61	N = 1	N = 58	N = 64	N = 46
Yes	65%	97%	31%	56%	28%	0%	71%	91%	80%
No	28%	1%	60%	34%	56%	100%	26%	5%	13%
Don't know	7%	1%	10%	10%	16%	0%	3%	5%	7%
Type of patients provided with Patient Alert Cards [a]	n = 267	n = 67	n = 19	n = 28	n = 17	n = 0	n = 41	n = 58	n = 37
Patients needing add. support	28%	6%	11%	25%	29%	0%	32%	36%	62%
All AF-patients	61%	90%	79%	32%	47%	0%	66%	53%	32%
Other persons	3%	3%	5%	0%	24%	0%	0%	3%	0%
Not handed out	8%	1%	5%	43%	0%	0%	2%	7%	5%
Time of dispensing Patient Alert Cards [b]	n = 237	n = 64	n = 17	n = 16	n = 13	n = 0	n = 40	n = 52	n = 35
At treatment initiation	86%	98%	94%	88%	85%	0%	70%	94%	69%
At any time during treatment	7%	0%	6%	0%	8%	0%	10%	6%	23%
On demand	6%	2%	0%	13%	8%	0%	20%	0%	9%

[a] Only physicians who stated to have received the Patient Alert Card.
[b] Only physicians who stated to hand out the Patient Alert Card.
Source Data: see Tables 15.2.1:9 to 15.2.1:11.

At the end of the interview, all of the 144 physicians who initially stated that they had not received the Patient Alert Card or did not know/remember were shown a copy of the card and asked again whether they had received or even seen the card. As only 10 of these physicians remembered having seen/received the card, the results of the combined analysis of the two sets did not change the overall picture. For details, see Tables 15.2.1:53 to 15.2.1:58.

11.1.3.1.2 Knowledge of "Pradaxa® Prescriber Guide for Stroke Prevention in Atrial Fibrillation"

Overall, 71% of the physicians stated that they had received the Prescriber Guide, with the highest percentages seen in DE, BG, CZ and SK (all >85%) and the lowest in FR, ES and UK (36-56%). More than 90% of the physicians in the different countries found that the Prescriber Guide provides adequate support. Only in FR, 72% of those physicians who had received the Prescriber Guide were satisfied and the remaining 28% had not read it yet.

For a summary, see Table 11.1.3.1.2:1. Detailed information by the physicians' specialization are given in Tables 15.2.1:7 and 15.2.1:8.

Table 11.1.3.1.2:1 Receipt and assessment of the Prescriber Guide (all physicians)

	Total	**DE**	**ES**	**FR**	**UK**	**DK**	**BG**	**CZ**	**SK**
Prescriber Guide received?	N = 411	N = 69	N = 62	N = 50	N = 61	N = 1	N = 58	N = 64	N = 46
Yes	71%	86%	40%	36%	56%	100%	88%	97%	89%
No	21%	6%	50%	48%	31%	0%	9%	2%	7%
Don't know	8%	9%	10%	16%	13%	0%	3%	2%	4%
Does the Prescriber Guide provide adequate support? [a]	n = 291	n = 59	n = 25	n = 18	n = 34	n = 1	n = 51	n = 62	n = 41
Yes	95%	92%	96%	72%	91%	100%	100%	98%	100%
No	2%	3%	0%	0%	6%	0%	0%	2%	0%
Not read yet	3%	5%	4%	28%	3%	0%	0%	0%	0%

[a] Only physicians who stated to have received the Prescriber Guide.
Source Data: see Tables 15.2.1:7 and 15.2.1:8.

Similar as with the Patient Alert Card, all of the 120 physicians who initially stated that they had not received the Prescriber Guide or did not know/remember were shown a copy of the guide and asked again whether they had received or at least seen it. Twenty-five of these physicians remembered having seen/received the guide, but the results of the combined analysis of the two sets did not change the overall picture. For details, see Tables 15.2.1:49 to 15.2.1:52.

11.1.3.1.3 Knowledge of appropriate laboratory assessments prior to and during Pradaxa® treatment

Physicians were asked which clinical parameters, if any, they routinely measured before prescribing Pradaxa® (Table 15.2.1:12).

The most frequently mentioned parameters referred to renal function, such as "creatinine level" (73%), "creatinine clearance" (72%) and/or "glomerular filtration rate" (64%). As multiple answers were possible, this indicates that all physicians were well aware of the importance of renal function for correct Pradaxa® dosing. Other parameters not relating to renal function were measured by 25% of the physicians.

The regional differences were minor. It was found that physicians in FR first of all determined the creatinine clearance (98%), whereas physicians in UK focused on the glomerular filtration rate (95%).

Later during the interview, physicians were again asked when they determine the creatinine clearance in a patient prescribed Pradaxa® (Table 15.2.1:41). Then, 92% (initially 72%, see above) stated to determine it prior to the first prescription.

During treatment, physicians mostly stated to determine the patients' creatinine clearance either once a year (52%) or when renal function might have worsened (54%). More frequent measurements, i.e., twice to four times per year, were only reported by 12-14% of the physicians in DE, FR and UK.

11.1.3.1.4 Awareness of daily dosing of Pradaxa® in different patient types

Physicians were presented six different profiles of AF-patients and were asked to specify the daily Pradaxa® dosages they would prescribe (see Table 11.1.3.1.4:1).

Profile 1: AF-patient, <80 years old, without other risk factors

In this patient, the recommended dosage according to the Prescriber Guide is 150 mg BID.

Overall, 82% of the physicians spontaneously stated they would prescribe a dose of 150 mg twice daily (BID) as recommended in the Prescriber Guide, with the highest percentages in DE, BG, CZ and SK (all ≥89%). The lowest percentages were seen in FR (60%), ES (69%) and UK (69. A lower dose of 110 mg BID would be prescribed by 9% of all physicians, with the highest percentages being found again in ES (29%) and FR (16%), especially among PCPs (48% and 20%, respectively).

In FR and UK, however, a large proportion of PCPs (18% and 15%, respectively) would first check with the prescriber guide or literature.

For details, see Table 15.2.1:13.

Profile 2: AF-patient, 75-80 years old, low thromboembolic risk, high risk of bleeding

According to the Prescriber Guide, patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Overall, 65% of the physicians would prescribe the recommended reduced dose of 110 mg BID. Higher or lower dosages would be prescribed by less than 5% each. Of note, nearly 20% of the physicians – especially PCPs (68%) in FR – would not prescribe Pradaxa® in this patient population.

Across all countries, the main reasons for the 110 mg BID dosing were the described high hemorrhagic risk and the patient's age.

For details, see Tables 15.2.1:14 to 15.2.1:18.

Profile 3: AF-patient, permanent AF, >80 years old, body weight <50 kg, gastrointestinal bleeds, moderate thromboembolic risk, high risk of bleeding

According to the Prescriber Guide, patients aged 80 years or above should be treated with a daily dose of 220 mg. In addition, the Prescriber Guide mentions low body weight (<50 kg) as factor which may increase the hemorrhagic risk. In this patient, the recommended dosage according to the Prescriber Guide is 110 mg BID.

Overall, 52% of the physicians, in particular in FR (90%), would not prescribe Pradaxa® to such a patient, but still 31%, in particular in CZ (45%) and SK (52%), would prescribe it a reduced dosage of 110 mg BID.

The main reasons given for preferring the 110 mg BID dosing were the high hemorrhagic risk and the patient's age.

For details, see Tables 15.2.1:19 to 15.2.1:23.

Profile 4: AF-patient, 62 years old, treated with verapamil, no increased risk of bleeding

In this patient, the recommended dosage according to the Prescriber Guide is 110 mg BID.

Overall, physicians would prescribe dosages of either 150 mg BID (32%) or 110 mg BID (36%) to such a patient.

The main reasons given for the 150 BID dosing were that the patient had no increased risk of bleeding, the patient's age, recommendations in guidelines, the dosage is standard and their experiences. The main reason for the 110 mg BID dosing were the possible interaction with verapamil.

Fourteen percent of the physicians overall would not prescribe Pradaxa® to such a patient, with the highest percentages seen in DE (25%) and ES (23%). In these countries, first of all the cardiologists (32% and 35%, respectively) had concerns against a Pradaxa® treatment in this case. Of note, 60% of the PCPs in FR would check the prescriber guide or literature first.

For details, see Tables 15.2.1:24 to 15.2.1:28.

Profile 5: AF-patient, intermittent AF, 67 years old, treated with NSAIDs, prior stroke, creatinine clearance 80 ml/min

In this patient, the recommended dosage according to the Prescriber Guide is either 150 mg BID or 110 mg BID. The Prescriber Guide states a dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high. In Table 1 of the Prescriber Guide, NSAIDs are mentioned as factor which may increase the hemorrhagic risk.

Overall, 54% of the physicians would prescribe a dosage of 150 mg BID, and 22% would prescribe a reduced dosage of 110 mg BID.

The main reasons given for the 150 mg BID dosing were that the patient is a risk patient, the patient's stroke history, renal function and the recommendations in guidelines, the dosage is standard and their experiences.

Correspondingly, the main reasons given for the reduced dose of 110 mg BID were that the patient is a risk patient, the high hemorrhagic risk and that the dose is dependent on renal function.

Of all interviewed physicians, 9% (38% in FR) would check the prescriber guide or literature first. A further 9% of the physicians (22% in DE) would not prescribe Pradaxa® to such a patient.

For details, see Tables 15.2.1:29 to 15.2.1:33.

Profile 6: AF-patient, intermittent AF, 62 years old, prosthetic aortic valve replacement, high risk of bleeding, moderate renal impairment (creatinine clearance 40 ml/min)

According to the Prescriber Guide, this patient should not be treated with Pradaxa® since the presence of prosthetic heart valves requiring anticoagulant treatment is listed as contraindication.

There was a common sense across countries not to treat such a patient with Pradaxa®, which stated 81% of all physicians. Thirteen percent of the physicians (n=54) would treat this patient off-label, most of them (n=32 or 8% in total) at a reduced dosage of 110 mg BID. For details, see Tables 15.2.1:34 to 15.2.1:38.

Table 11.1.3.1.4:1 Dosing of Pradaxa® in different AF-patient profiles (all physicians)

Dosing decision	Total N = 411	DE N = 69	ES N = 62	FR N = 50	UK N = 61	DK N = 1	BG N = 58	CZ N = 64	SK N = 46
Profile 1: AF-patient, <80 years old, without other risk factors									
110 mg OD	1%	0%	0%	6%	2%	0%	0%	0%	0%
110 mg BID	9%	4%	29%	16%	7%	0%	3%	0%	7%
150 mg OD	2%	6%	0%	0%	5%	0%	0%	0%	4%
150 mg BID	82%	90%	69%	60%	69%	100%	97%	100%	89%
Other	0%	0%	0%	0%	3%	0%	0%	0%	0%
Check prescriber guide / literature	5%	0%	2%	18%	15%	0%	0%	0%	0%
Profile 2: AF-patient, 75-80 years old, low thromboembolic risk, high risk of bleeding									
110 mg OD	5%	6%	6%	0%	10%	0%	9%	0%	2%
110 mg BID	65%	65%	76%	44%	49%	100%	69%	81%	70%
150 mg OD	1%	4%	3%	0%	2%	0%	0%	0%	0%
150 mg BID	5%	4%	3%	2%	7%	0%	7%	3%	7%
Other	1%	0%	2%	0%	7%	0%	0%	0%	0%
Check prescriber guide / literature	5%	1%	0%	8%	18%	0%	0%	2%	4%
No Pradaxa®	18%	19%	10%	46%	8%	0%	16%	14%	17%
Profile 3: AF-patient, permanent AF, >80 years old, body weight <50 kg, gastrointestinal bleeds, moderate thromboembolic risk, high risk of bleeding									
110 mg OD	5%	6%	10%	0%	10%	0%	5%	2%	2%
110 mg BID	31%	28%	39%	6%	25%	100%	21%	45%	52%
150 mg OD	1%	1%	5%	0%	2%	0%	0%	0%	0%
150 mg BID	1%	0%	5%	0%	0%	0%	2%	0%	0%
Other	2%	3%	2%	0%	10%	0%	0%	0%	2%
Check prescriber guide / literature	7%	3%	2%	4%	26%	0%	2%	5%	9%
No Pradaxa®	52%	59%	37%	90%	28%	0%	71%	48%	33%

(continued)

Table 11.1.3.1.4:1 Dosing of Pradaxa® in different AF-patient profiles (all physicians) – continued

Dosing decision	Total N = 411	DE N = 69	ES N = 62	FR N = 50	UK N = 61	DK N = 1	BG N = 58	CZ N = 64	SK N = 46
Profile 4: AF-patient, 62 years old, treated with verapamil, no increased risk of bleeding									
110 mg OD	1%	1%	2%	0%	3%	0%	0%	0%	0%
110 mg BID	36%	38%	24%	36%	11%	100%	31%	69%	46%
150 mg OD	3%	6%	3%	2%	7%	0%	0%	3%	2%
150 mg BID	32%	19%	40%	22%	51%	0%	55%	14%	26%
Other	0%	0%	2%	0%	0%	0%	0%	0%	0%
Check prescriber guide / literature	13%	12%	6%	34%	23%	0%	5%	5%	7%
No Pradaxa®	14%	25%	23%	6%	5%	0%	9%	9%	20%
Profile 5: AF-patient, intermittent AF, 67 years old, treated with NSAIDs, prior stroke, creatinine clearance 80 ml/min									
110 mg OD	2%	3%	0%	0%	5%	0%	3%	0%	0%
110 mg BID	22%	25%	29%	18%	11%	100%	31%	23%	15%
150 mg OD	3%	3%	3%	2%	5%	0%	5%	0%	7%
150 mg BID	54%	42%	53%	34%	56%	0%	45%	73%	76%
Other	0%	0%	2%	0%	0%	0%	0%	0%	0%
Check prescriber guide / literature	9%	6%	2%	38%	18%	0%	3%	2%	2%
No Pradaxa®	9%	22%	11%	8%	5%	0%	12%	2%	0%
Profile 6: AF-patient, intermittent AF, 62 years old, prosthetic aortic valve replacement, high risk of bleeding, moderate renal impairment (creatinine clearance 40 ml/min)									
110 mg OD	3%	4%	3%	0%	7%	0%	2%	0%	2%
110 mg BID	8%	12%	10%	4%	7%	0%	9%	8%	4%
150 mg OD	1%	0%	5%	0%	2%	0%	0%	0%	0%
150 mg BID	2%	6%	2%	2%	2%	0%	0%	0%	0%
Other	1%	1%	3%	0%	0%	0%	0%	0%	0%
Check prescriber guide / literature	5%	6%	6%	6%	13%	0%	2%	0%	2%
No Pradaxa®	81%	71%	71%	88%	70%	100%	88%	92%	91%

Abbreviations: AF = atrial fibrillation, BID = twice daily, NSAIDs = non-steroidal anti-inflammatory drugs, OD = once daily.
Source Data: see Tables 15.2.1:13, 15.2.1:14, 15.2.1:19, 15.2.1:24, 15.2.1:29 and 15.2.1:34.

11.1.3.1.5 Instruction of patients on proper intake of Pradaxa®

Approximately two thirds (68%) of all physicians stated that they instruct their patients on the proper intake of the Pradaxa® capsules (Section 15, Table 39). However, there were large regional differences in the corresponding proportions. These were the highest in BG (100%), DE (93%) and CZ (80%), and the lowest in UK (30%) and FR (40%).

Instructions mostly encompass telling the patients to swallow the capsules as a whole (82%), not to open it (33%) and/or to take the capsules twice daily (13%). In FR, however, the instructions focus more frequently on telling the patients that the capsules are to be taken twice per day (65%), to be taken during a meal (45%) and/or that they are to be taken with enough water (30%). For details, see Table 15.2.1:40.

11.1.3.1.6 Knowledge (based on the information provided in the Prescriber Guide) of potential risk factors for bleedings in patients treated with Pradaxa®

Physicians were given a list with different patient characteristics and were asked to give their assessment (yes/no/don't know) of the associated risks for bleeding when treated with Pradaxa®.

The percentages of physicians stating that the different factors may represent a potential risk for bleeding were high (>80%). For details see Table 11.1.3.1.6:1. Concomitant intake of P-glycoprotein inhibitors or presence of bacterial endocarditis was less frequently mentioned as potential risk factors for bleeding (52% and 49%, respectively). These, together with "brain, spinal or ophthalmic surgery" as risk factor, were also the categories which were most frequently (up to 34% in total) answered with "don't know" across all countries and especially by PCPs.

There were ≥10% "don't know" answers regarding the potential bleeding risk for "increased creatinine level (>1.25 mg/dl)" in UK, CZ and SK, for "low body weight (<50 kg)" in ES and UK, "treatment with acetylsalicylic acid" in ES and UK, for "treatment with clopidogrel" in ES, and for "Type 2 diabetes mellitus patients" in FR, UK, BG, CZ and SK. These uncertainties were especially present in PCPs.

For further details, see Tables 15.2.1:42 and 15.2.1:43.

Table 11.1.3.1.6:1 Factors rated by the physicians as potential risk factors for bleedings in patients treated with Pradaxa® (all physicians)

Potential risk factor for bleedings	**Total** N = 411	**DE** N = 69	**ES** N = 62	**FR** N = 50	**UK** N = 61	**DK** N = 1	**BG** N = 58	**CZ** N = 64	**SK** N = 46
Age >75 years	75%	77%	71%	50%	89%	100%	88%	73%	76%
Moderate renal impairment	79%	74%	81%	72%	59%	100%	86%	94%	89%
Increased creatinine level	68%	68%	71%	76%	54%	100%	83%	63%	63%
P-glycoprotein inhibitor co-medication	52%	64%	53%	30%	39%	0%	38%	67%	70%
Low body weight (<50 kg)	80%	78%	69%	88%	79%	100%	76%	81%	91%
Treatment with ASA	84%	86%	69%	88%	85%	100%	81%	88%	96%
Treatment with NSAIDs	87%	88%	76%	92%	93%	100%	86%	81%	96%
Treatment with clopidogrel	89%	90%	81%	94%	89%	100%	88%	84%	100%
Congenital or acquired coagu-lation disorders	91%	93%	82%	96%	90%	100%	95%	89%	96%
Thrombocytopenia or functional platelet defects	87%	83%	89%	94%	89%	100%	83%	86%	91%
Active ulcerative GI disease	92%	80%	82%	100%	98%	100%	91%	98%	98%
Recent GI bleed	95%	96%	85%	100%	100%	100%	95%	94%	96%
Recent biopsy or major trauma	82%	72%	81%	90%	89%	100%	79%	81%	83%
Recent intracranial hemorrhage	93%	93%	82%	100%	95%	100%	91%	97%	91%
Type 2 diabetes	19%	22%	34%	6%	16%	100%	24%	13%	13%
Brain, spinal, ophthalmologic surgery	67%	43%	71%	76%	70%	100%	69%	63%	83%
Bacterial endocarditis	49%	55%	31%	46%	39%	100%	50%	64%	61%

Abbreviations: ASA = acetylsalicylic acid, GI = gastrointestinal, NSAIDs = non-steroidal anti-inflammatory drugs.
Source Data: see Table 15.2.1:43.

11.1.3.1.7 Knowledge of actions (based on the information provided in the Prescriber Guide) to be taken with Pradaxa® in case of surgery or invasive procedures

Physicians were asked which actions with regard to Pradaxa® treatment need to be taken in case of surgery or other invasive procedures.

Overall, 78% of the physicians stated that all patients must temporarily discontinue their Pradaxa® treatment, 16% were of the opinion that treatment interruption is only necessary in patients at higher risk, and 6% didn't know, but would check with the prescriber guide or literature. Only 2 physicians from ES stated that patients should continue their Pradaxa® treatment without interruption.

The highest percentage of physicians who would interrupt Pradaxa® treatment in case of surgery was seen in BG and CZ (88% and 89%, respectively) and the lowest ones in UK (62%) followed by DE (75%). However, the highest percentage of physicians who would check with the prescriber guide or literature first was also present in UK (26%), whereas the remaining 25% of physicians in DE thought that only patients at higher risk should interrupt the treatment in case of surgery. Only 1 physician each in ES and BG stated that no action with regard to Pradaxa® treatment was required.

A summary of these data is shown in Table 11.1.3.1.7:1. Further details, also broken down by the physicians' specialization, are provided in Table 15.2.1:44.

Table 11.1.3.1.7:1 Actions to be taken with Pradaxa® in case of surgery or invasive procedures (all physicians)

Actions to be taken in case of surgery	**Total** N = 411	**DE** N = 69	**ES** N = 62	**FR** N = 50	**UK** N = 61	**DK** N = 1	**BG** N = 58	**CZ** N = 64	**SK** N = 46
Nothing – all patients should continue treatment	0%	0%	2%	0%	0%	0%	2%	0%	0%
All patients must temporarily discontinue Pradaxa®	78%	75%	76%	78%	62%	0%	88%	89%	78%
Patients at higher risk must temporarily discontinue Pradaxa®	16%	25%	18%	16%	11%	100%	9%	8%	22%
Don't know – check with prescriber guide / literature	6%	0%	5%	6%	26%	0%	2%	3%	0%

Source Data: see Table 15.2.1:44.

11.1.3.1.8 Assessment of adequate parameters for the determination of the patients' anticoagulation status (based on the information provided in the Prescriber Guide)

Physicians were to rate five parameters for the determination of the patients' anticoagulation status for their adequacy: prothrombin time (international normalized ratio; INR), ecarin clotting time (ECT), thrombin time (TT), diluted thrombin time (dTT), and activated partial thromboplastin time (aPTT). All of these parameters are mentioned in the Prescriber Guide. The results of these ratings are shown in Table 11.1.3.1.8:1.

With the exception of the physicians in UK (48%) and ES (50%), the majority (>70%) of physicians in all other countries knew that INR determination is not suitable to assess the anticoagulation status in patients on Pradaxa®. APTT was assessed as adequate parameter by 45%, ECT by 38%, TT by 34% and dTT by 29% of the physicians. The proportions of physicians who replied "don't know" to a specific method amounted to up to 43% (for dTT).

Across all countries, it was found that the "don't know" answers were more frequently given by PCPs than by cardiologists. For details, see Table 15.2.1:45.

Table 11.1.3.1.8:1 Adequacy of methods for the determination of the anticoagulation status (all physicians)

Method **Decision**	**Total** N = 411	**DE** N = 69	**ES** N = 62	**FR** N = 50	**UK** N = 61	**DK** N = 1	**BG** N = 58	**CZ** N = 64	**SK** N = 46
INR									
Yes	18%	17%	40%	4%	30%	0%	19%	6%	4%
No	70%	80%	50%	82%	48%	100%	74%	73%	89%
Don't know	12%	3%	10%	14%	23%	0%	7%	20%	7%
ECT									
Yes	38%	54%	47%	6%	18%	100%	41%	45%	52%
No	29%	19%	23%	50%	26%	0%	45%	20%	24%
Don't know	33%	28%	31%	44%	56%	0%	14%	34%	24%
TT									
Yes	34%	43%	44%	20%	38%	100%	41%	19%	26%
No	43%	42%	35%	48%	34%	0%	45%	50%	50%
Don't know	23%	14%	21%	32%	28%	0%	14%	31%	24%
aPTT									
Yes	45%	52%	50%	4%	34%	0%	55%	53%	61%
No	33%	25%	29%	36%	34%	0%	40%	39%	30%
Don't know	22%	23%	21%	60%	31%	100%	5%	8%	9%
dTT									
Yes	29%	30%	24%	8%	15%	0%	41%	41%	46%
No	28%	25%	40%	32%	25%	0%	38%	16%	20%
Don't know	43%	45%	35%	60%	61%	100%	21%	44%	35%

Abbreviations: aPTT = activated partial thromboplastin time, dTT = diluted thrombin time, ECT = ecarin clotting time, TT = thrombin time, INR = international normalized ratio.
Source Data: see Table 15.2.1:45.

11.1.3.1.9 Assessment of measures to be taken in case of bleedings

If a patient reported a bleeding event, most of the physicians would discontinue Pradaxa® treatment either immediately (65%) or in case of hemorrhagic complications only (56%). Less than half of the physicians (46%) would determine the anticoagulation status first, and only 35% would consider diuresis management. Overall, 50% of the physicians stated that they would not apply diuresis. The remaining 16% stated that they didn't know.

Again, there were large regional differences between the ratings of measures. For example "discontinuation of Pradaxa® only in the event of hemorrhagic complications", 28% of the physicians in DE, but 80% of the physicians in SK would do this. Another example may be

the assessment of the anticoagulation status. Here, 12% of the physicians in FR, but 74% of the physicians in ES would do this.

A summary of these data is shown in Table 11.1.3.1.9:1. For details, see Tables 15.2.1:47 and 15.2.1:48.

Table 11.1.3.1.9:1 Measures to be taken in case of bleedings (all physicians)

Measure **Decision**	**Total** N = 411	**DE** N = 69	**ES** N = 62	**FR** N = 50	**UK** N = 61	**DK** N = 1	**BG** N = 58	**CZ** N = 64	**SK** N = 46
Assess anticoagu-lation status first									
Yes	46%	19%	74%	12%	41%	100%	72%	42%	65%
No	44%	67%	23%	78%	51%	0%	21%	38%	35%
Don't know	9%	14%	3%	10%	8%	0%	7%	20%	0%
Diuresis management									
Yes	35%	28%	53%	18%	23%	0%	45%	28%	50%
No	50%	55%	40%	68%	56%	0%	47%	41%	43%
Don't know	16%	17%	6%	14%	21%	100%	9%	31%	7%
Discontinue Pradaxa® immediately									
Yes	65%	86%	61%	54%	51%	0%	76%	73%	48%
No	29%	12%	27%	42%	36%	100%	21%	20%	52%
Don't know	6%	3%	11%	4%	13%	0%	3%	6%	0%
Discontinue Pradaxa® only for hemorrhagic complications									
Yes	56%	28%	58%	54%	56%	100%	55%	69%	80%
No	36%	58%	42%	44%	36%	0%	33%	19%	20%
Don't know	8%	14%	0%	2%	8%	0%	12%	13%	0%

Source Data: see Table 15.2.1:47.

11.1.3.2 Patients' information by the "Patient Alert Card – Pradaxa®"

11.1.3.2.1 Receipt and content assessment of the Patient Alert Card

Of the 802 patients in this survey, 430 (54%) spontaneously stated that they had at least heard of the Patient Alert Card, and 416 of them remembered its receipt[1]. Fourteen patients had heard of the card, but hadn't received it. Of the 430 patients spontaneously remembered the card, 310 (72%) either received it from the Pradaxa® prescribing or from someone else (103 patients or 24%). Most of the patients who didn't receive it from their prescribing physician either found it in the drug package (13%) or received it from the pharmacist (7%). Of the 372 patients who spontaneously didn't remember the card spontaneously, further 29 patients[2] remembered the receipt after being shown it by the interviewer. Thus, a total of 445 patients actually had the Patient Alert Card.

As with the dispensing of the Patient Alert Card by the physicians (see Section 11.1.3.1.1), regional differences became apparent. In DE, ES, BG and CZ, the majority of patients (≥56%) received the card from their physicians who also prescribed the drug, whereas in FR, DK, and UK, at least 50% of these patients had other sources for it (mostly as part of the drug package). Seventy-three percent of the 414 patients who stated to have the Patient Alert Card at the beginning of the interview had received it with their very first Pradaxa® prescription.

For details, see Tables 15.2.1:73 to 15.2.1:75.

Across all countries, 90% of the patients who had the Patient Alert Card also had read it (minimum: 76% in FR; maximum: 100% in DK and SK; see Section 15, Table 75). The main reason for not reading the card was that patients thought they knew everything from their doctors (19 patients or 46% of the patients who didn't read it) or that they were not interested in this information (7 patients or 17%; see Table 15.2.1:76).

Six patients (15%) stated that it was difficult to read because of the small font size and 2 patients (5%) did not read it because they were not fluent enough in the language (did not understand properly) or found the language not appropriate (too scientific/too many medical details).

As shown in Table 11.1.3.2.1:1, the patient-specific information on the back of the card (name, date of birth, indication for dosage and Pradaxa® dosage) was completed in 89% of the cases, and this was mostly done by the physicians or the person who dispensed the Patient Alert Card (see Table 15.2.1:77).

Similar to the handling of the Patient Alert Card by the physicians in the different countries, also the completion of the information was very country-specifically dealt with: Especially in

[1] Including two patients who initially stated they had received the Patient Alert Card, but replied in the next question that they hadn't received it. I.e., actually 114 patients confirmed the receipt at the beginning of the interview.
[2] Excluding the two patients who initially stated they had received the Patient Alert Card, but replied in the next question that they hadn't received it. These two patients remembered again the receipt of the card upon being shown it at the end of the interview.

DE (82%), the card was completed primarily by the dispensing person (e.g., physician, pharmacist), whereas in FR (59%), this was primarily done by the patients themselves.

The highest proportions of cards left blank were found in SK (28%), CZ (21%) and UK (20%).

Table 11.1.3.2.1:1 Completion of the Patient Alert Card with patient-specific information (all patients who had received the Patient Alert Card)

Patient Alert Card completed by the dispensing person?	**Total** N = 414	**DE** N = 171	**ES** N = 35	**FR** N = 37	**UK** N = 15	**DK** N = 28	**BG** N = 34	**CZ** N = 76	**SK** N = 18
Yes, completion by the doctor / the dispensing person	61%	82%	66%	27%	13%	50%	53%	53%	33%
No, completion by patient	22%	6%	9%	59%	33%	36%	47%	25%	39%
Not sure / don't know	6%	5%	14%	3%	33%	7%	0%	1%	0%
No, left empty	11%	6%	11%	11%	20%	7%	0%	21%	28%

Source Data: see Table 15.2.1:77.

11.1.3.2.2 Information about the drug effect

In order to assess the familiarity of the patients with the content of the Patient Alert Card, patients who initially stated that they had never heard of this card and/or never received it were shown the card, and 31 of these patients remembered the card and 29 its receipt. Thus, overall, a total of 445 patients had familiarity with the card (see Tables 15.2.1:74 and 15.2.1:87).

All patients were then read out a list of possible reasons for the intake of Pradaxa® and asked to assess their correctness.

The data in Table 11.1.3.2.2:1 show that the vast majority (89%) of patients was well informed and knew about the blood-thinning effect of Pradaxa®, irrespective of having received the Patient Alert Card or not. However, there were marked uncertainties with regard to the effects on heart beat and lung function. Here, patients who had received the Patient Alert Card were better informed. Considering all of the three potential effects mentioned, the best informed patients came from DE, FR and DK. For details, see Table 15.2.1:80.

Table 11.1.3.2.2:1 Information about the Pradaxa® drug effect (all patients)

Reason for intake of Pradaxa®	**Total**	**Patient Alert Card received**	
		Yes	**No**
	N = 802	**N = 445**	**N = 357**
Pradaxa® prevents clots by making my blood less "sticky"			
Correct	**717 (89%)**	**408 (92%)**	**309 (87%)**
Not correct	63 (8%)	28 (6%)	35 (10%)
Don't know	22 (3%)	9 (2%)	13 (4%)
Pradaxa® helps to regulate my heart beat			
Correct	324 (40%)	126 (28%)	198 (55%)
Not correct	**434 (54%)**	**296 (67%)**	**138 (39%)**
Don't know	44 (5%)	23 (5%)	21 (6%)
Pradaxa® allows my lungs to take in more air / it helps me to breathe better			
Correct	184 (23%)	60 (13%)	124 (35%)
Not correct	**554 (69%)**	**351 (79%)**	**203 (57%)**
Don't know	64 (8%)	34 (8%)	30 (8%)

Note: Correct answers printed in bold.
Source Data: see Table 15.2.1:80.

11.1.3.2.3 Information about the intake of Pradaxa®

All but two patients from FR knew that they need to take Pradaxa® every day (Table 15.2.1:79). These two patients reported that they need to take it on demand only, i.e., whenever they feel they need it.

Similarly, all but three patients (1 from FR and 2 from UK) reported to swallow the capsules as a whole (Table 15.2.1:82).

11.1.3.2.4 Information about potential side-effects of the Pradaxa® treatment as described in the Patient Alert Card

Table 11.1.3.2.4:1 shows that patients who had received the Patient Alert Card were well aware of their increased risk of bruising and other bleeds, which are the most relevant side-effects of the Pradaxa® treatment and which are both described in the Patient Alert Card. This knowledge was less pronounced among patients who had not received this card. Bruising and bleeds were also the two items for which the smallest uncertainties (≤20%) existed. No relevant differences in the assessment of other signs and symptoms read out during the interview were observed between patients having received the Patient Alert Card and those who did not.

Regarding regional differences, the highest awareness of the risk of bruising was seen in DE (75%), CZ (66%) and DK (65%) and the lowest in BG (17%) and SK (36%). For bleeds, the highest awareness was seen in FR (68%) and DE (66%) and the lowest in SK (17%), BG (36%) and UK (39%). For details, see Table 15.2.1:83.

Table 11.1.3.2.4:1 Information about potential side-effects (all patients)

Potential side-effect of Pradaxa® (as described in the Patient Alert Card)	**Total**	**Patient Alert Card received**	
		Yes	**No**
	N = 802	**N = 445**	**N = 357**
Bruising			
Correct	**437 (54%)**	**296 (67%)**	**141 (39%)**
Not correct	217 (27%)	81 (18%)	136 (38%)
Don't know	148 (18%)	68 (15%)	80 (22%)
Skin fungal disease			
Correct	43 (5%)	29 (7%)	14 (4%)
Not correct	**499 (62%)**	**280 (63%)**	**219 (61%)**
Don't know	260 (32%)	136 (31%)	124 (35%)
Bleeding (e.g., hematoma of the skin, tar stools, blood in urine, nose bleed)			
Correct	**421 (52%)**	**282 (63%)**	**139 (39%)**
Not correct	245 (31%)	98 (22%)	147 (41%)
Don't know	136 (17%)	65 (15%)	71 (20%)
Gastrointestinal problems (e.g., flatulence, diarrhea, dyspepsia)*			
Correct	222 (28%)	141 (32%)	81 (23%)
Not correct	**339 (42%)**	**176 (40%)**	**163 (46%)**
Don't know	241 (30%)	128 (29%)	113 (32%)
Hair loss			
Correct	46 (6%)	32 (7%)	14 (4%)
Not correct	**486 (61%)**	**260 (58%)**	**226 (63%)**
Don't know	270 (34%)	153 (34%)	117 (33%)
Fatigue/feeling sleepy/lethargic			
Correct	174 (22%)	97 (22%)	77 (22%)
Not correct	**338 (42%)**	**184 (41%)**	**154 (43%)**
Don't know	290 (36%)	164 (37%)	126 (35%)

* Gastrointestinal problems are known side-effects of Pradaxa®. These are described in the package insert but not in the Patient Alert Card, which focuses on correct intake of the tablets and on bleedings.

Note: Correct answers in accordance with the Patient Alert Card are printed in bold.
Source Data: see Table 15.2.1:83.

11.1.3.2.5 Information about actions to be taken in special situations

If patients experienced bleeds with prolonged bleeding times, 63% of the patients would immediately contact their physicians or nurses for their advice, and 30% of the patients would stop the intake of Pradaxa® and then immediately contact their physicians/nurses. Four percent of patients would continue their treatment and 2% would stop treatment, both groups without informing their physicians/nurses. In this regard, no relevant differences between patients with and without Patient Alert Cards were detectable. The same applies when comparing the different countries. For details, see Table 15.2.1:84.

In case of surgery, 96% of the patients stated that they would tell their treating physician about their intake of Pradaxa®. The remaining 4% would continue their treatment without informing the physician, gave no answer or would do something else (not further specified). Again, no relevant differences between patients with and without Patient Alert Cards were detectable. The same applies when comparing the different countries. For details, see Table 15.2.1:85.

11.1.3.2.6 Information about potential consequences, if stopping Pradaxa® treatment against medical advice

Most of the patients (78%) were informed that stopping Pradaxa® treatment against medical advice could make the blood begin to clot and become “sticky”, 74% knew that they could get a stroke and 55% knew that they could get a heart attack. Only some patients stated that nothing would happen or didn’t know (3% and 4%, respectively).

The differences with regard to the awareness of potential consequences between patients with and without Patient Alert Card were minor, but there was a trend towards better information in patients having received the card. Minor differences were also seen among the different countries. For details, see Table 15.2.1:86.

11.1.4 Drug dose - drug-concentration - and relationship to response

Not applicable.

11.1.5 Statistical - analytical issues

Not applicable.

11.2 CLINICAL PHARMACOLOGY RESULTS

Not applicable.

11.3 OTHER RESULTS

Not applicable.

11.4 EFFICACY - CLINICAL PHARMACOLOGY CONCLUSIONS

Overall, the understanding of the content of the Prescriber Guide for Pradaxa® and the Patient Alert Card was good. Seventy-one and 65% of the physicians spontaneously remembered the receipt of the Prescriber Guide and the Patient Alert Card, respectively.

The Prescriber Guide provides adequate support for 95% of the physicians having received it. The majority of physicians are well informed about the two approved dose levels for Pradaxa. The patient profiles were assessed differently to some extent; increased bleeding risk by concomitant treatment with P-glycoprotein inhibitors or presence of bacterial endocarditis was less frequently known.

In general, physicians are well informed about the importance of monitoring renal function in AF patients and when treated with Pradaxa. Physicians know at least one suitable laboratory parameter for the determination of the patients' anticoagulation status as described in the Prescriber Guide.

Actions taken with Pradaxa® in the event of bleeds are as expected varying and according to the options described in the Prescriber Guide. Physicians are well aware of actions to be taken for surgeries or invasive procedures as described in the Prescriber Guide.

Across all countries, cardiologists appeared to be better informed about treating AF-patients with Pradaxa® than PCPs. The information level and content of the Prescriber Guide was generally rated as sufficient and adequate.

Most physicians dispense the Patient Alert Card to their AF-patients when they first prescribe Pradaxa®, without selection of a certain patient group. As of September 2014 the Patient Alert Card was also distributed via the Pradaxa trade pack.

More than 50% of the interviewed patients had received the Patient Alert Card and had read it. Most of the remaining patients who had not received the Patient Alert Card felt well informed by their treating physicians. The Patient Alert Card was completed with the patient-specific information in about 80% of the cases, and this was mostly done by the dispensing person.

In general, patients are informed about the blood-thinning effect of Pradaxa® and are well aware of the importance of the regular intake of the drug and the consequences associated with an arbitrary discontinuation. Here, patients having received the Patient Alert Card were better informed. In case of bleeding complications or surgery, most patients would follow medical instructions, irrespective of having received the Patient Alert Card or not.

In conclusion, this survey in 8 preselected EU countries demonstrates a good educational level of prescribers and patients about the safety messages for Pradaxa® with some regional

differences. The information given by the Prescriber Guide and the Patient Alert Card has been assessed by the study attendees as sufficiently informative and adequate.

Potential for improvements in the logistical distribution of the educational material to prescribers identified by this survey will be taken up by BI in the near future by adequate measures such as mailing and personal contacts to further improve the education and information related to key safety messages for Pradaxa®. The Patient Alert Card is directly distributed to the patient per Pradaxa® trade packs as of September 2014.

12. SAFETY EVALUATION

As this was a market survey investigating the effectiveness of risk minimization procedures, a safety evaluation per se is not applicable.

12.1 ADVERSE EVENTS

12.1.1 Brief summary of adverse events

Spontaneous adverse event reports during the interviews were collected and forwarded to the sponsor's pharmacovigilance unit for further processing.

12.1.2 Display of adverse events

Not applicable.

12.2 DEATHS - OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

Not applicable.

12.3 CLINICAL LABORATORY EVALUATION

Not applicable.

12.4 VITAL SIGNS - PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Not applicable.

12.5 SAFETY CONCLUSIONS

Not applicable.

13. DISCUSSION AND OVERALL CONCLUSIONS

The present survey was conducted to measure the effectiveness of risk minimization activities for the indication SPAF, i.e., the educational pack consisting of the Prescriber Guide and the Patient Alert Card. The data collected with AF patients were intended to show if and how well this information was received and understood.

A total of 411 physicians (124 PCPs and 287 cardiologists) and 802 AF-patients in 8 European countries participated in this survey. Seventy-one and 65% of the physicians spontaneously remembered the receipt of the Prescriber Guide and the Patient Alert Card, respectively. Fifty-five percent of the patients had the Patient Alert Card.

The content of Prescriber Guide for Pradaxa® and the Patient Alert Card were well known by the participating physicians.

No "target recall rates" for comparable physician and patient information materials are available. The spontaneous recall rates observed in this survey were markedly higher than in similar surveys on other information material conducted by the responsible research organization (data on file at [redacted]).

Marked regional differences became apparent with regard to the distribution of the Patient Alert Card. Although no specific selection of patients was made in any of the countries, most of the physicians in DE, ES, BG and CZ handed the card out to their patients, whereas in FR, less than half of the physicians who had the card also forwarded it to their patients. This was also confirmed by the patients. Those who had the Patient Alert Card in FR, had primarily taken it from the Pradaxa® package. Most physicians who dispensed the cards, dispensed them with the patients' first Pradaxa® prescription. As of September 2014, the Patient Alert Card is also distributed directly to the patient with the Pradaxa® trade pack in all EU countries.

Regional differences were also seen with respect to recalling whether the Prescriber Guide has been received Prescriber Guide. With the exception of FR and ES, more than 85% of the physicians spontaneously remembered the receipt of the Prescriber Guide and more than 90% of them also read it and rated its content as an adequate support. Especially in FR, less than 50% of the physicians remembered the receipt, and of those who had it, nearly 30% didn't read it. This, however, does not imply that physicians in FR are not sufficiently informed about treating AF-patients with Pradaxa®. In the context of the questions on correct dosing of special patient populations, it was found that physicians in FR frequently obtain the relevant information from literature. Some discrepancies with regard to dosing of patients with different risk profiles was observed in all countries. Across all countries, physicians tended to prescribe lower doses or even exclude patients from a treatment with Pradaxa®, but the vast majority would adhere to the recommended dosages. Only single physicians would prescribe a once daily intake. All physicians were well aware of the importance of monitoring renal function before and during treatment for the correct dosing of Pradaxa®. The way renal function (e.g., creatinine clearance or glomerular filtration rate) is determined is according to clinic/practice standards.

Physicians in all countries were also well aware of common risk factors for bleedings, which are to be considered for correct dosing. The only exceptions were "concomitant treatment with P-glycoprotein inhibitors" and "presence of bacterial endocarditis". Approximately half of the physicians were not aware or unsure of their impact on the patient's risk for bleeds.

Variable responses were given with regard to the measures the physicians would take if a patient reported a bleed, but responses were in accordance with the information provided in the Prescriber Guide. Whether the anticoagulation status should be determined first, whether diuresis management is appropriate, whether Pradaxa® should be immediately discontinued or only when hemorrhagic complications arise, was rated very differently by the physicians. This, however, is common medical management and reflection to a certain extent therapeutic freedom. It may also be associated with the availability of equipment and the type and severity of the bleed and/or the patient's risk profile the physicians had in mind, when they answered this question. Diuresis management was considered by 35% of the physicians only, and also less than half of the physicians would assess the patient's anticoagulation status first. Assessment of the patient's anticoagulation status may be indicated to avoid excessing high exposure. Physicians knew at least one suitable laboratory parameter to be determined for this purpose, but still nearly 20% would also consider INR. The knowledge about the type of laboratory parameters other than INR (i.e., ECT, TT, dTT and/or aPTT) appeared to be dependent on local standards, but all were consistent with the recommendations in the Prescriber Guide.

A broader consensus existed for actions to be taken in the event of surgery or other invasive procedures. More than 90% of the physicians were aware that treatment interruption may be indicated, and nearly 80% of the physicians stated that temporary treatment discontinuation is necessary in all patients. Only 2 physicians (<1%) stated that no action with the Pradaxa® intake is required, and 6% would check with the Prescriber Guide or literature first.

Overall, physicians specialized in cardiology were better informed about treating AF-patients with Pradaxa® than PCPs. Especially with regard to the correct dosing of risk patients, assessment of risk factors for bleeds, or determination of the anticoagulation status, PCPs were more uncertain and would check the Prescriber Guide/literature more frequently than cardiologists. This finding, however, was not surprising, taking into account the large variety of indications PCPs usually treat and the comparably low number of AF-patients among their customers, which amounts to approximately 50% of those treated by cardiologists. Thus, the Prescriber Guide constitutes a valuable source of information, in particular for PCPs.

A second aspect of this survey was to evaluate the level of information in AF-patients treated with Pradaxa®. More than half of the patients had received the Patient Alert Card either from their treating physician, the pharmacist, or took it from the drug package. It was found that the vast majority of these patients were interested in the information provided in the card, as 90% of the patients also read it. The primary reason for not reading it was that these patients felt well informed by their physician. Only few patients (n=8) had difficulties with the language/ terminology or font size. The patient-specific information on the card, which is intended as source of information for other healthcare professionals, was completed in nearly

80% of the cases, and this was mostly done by the treating physicians or the persons who dispensed the Patient Alert Card. Completion by the patients themselves was primarily seen in FR (59%).

About 90% both of receivers and non-receivers of the Patient Alert Card knew about the anticoagulant effect of Pradaxa®, but a markedly higher proportion of non-receivers erroneously assumed that Pradaxa® also affects heart rate and lung function. The information level about the two main and relevant potential side-effects of bruising and bleeding, which are described in the card, was clearly higher in patients who had received the card. Approximately 65% of the patients with the card were aware of their increased risk of bruising and bleeding. The corresponding percentage in patients not having the card was less than 40%.

At the same time, all patients, irrespective of having the card or not, would behave correctly when it comes to important, clinically relevant events, e.g., if they experienced prolonged bleeding times or had to undergo surgery or other invasive procedures. Only single patients (2% or n=13) would discontinue the intake of Pradaxa® for prolonged bleeding times without informing their treating physician or nurse, and also single patients (4% or n=28) would not inform the physician in case of surgery or other interventions. This is also in accordance with the finding that all but three patients were well informed about the correct intake of Pradaxa®, the necessity to take the drug daily, and the possible consequences associated with an arbitrary discontinuation of the therapy. Regional differences in this regard were minor. Therefore, it can be concluded that physicians in all participating countries provide their patients with sufficient information on the main items of the therapy, i.e., on the correct intake of Pradaxa®, and on how to behave in special situations.

In conclusion, this survey in 8 preselected EU countries demonstrates a good educational level of prescribers and patients about the safety messages for Pradaxa® with some regional differences. The information given by the Prescriber Guide and the Patient Alert Card has been assessed by the study attendees as sufficiently informative and adequate.

Potential for improvements in the logistical distribution of the educational material to prescribers identified by this survey will be taken up by BI in the near future by adequate measures such as mailing and personal contacts to further improve the education and information related to key safety messages for Pradaxa®. The Patient Alert Card is directly distributed to the patient per Pradaxa® trade packs as of September 2014.

14. REFERENCE LIST

Not applicable for survey 1160.149.