1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Dabigatran etexilate			
Name of active ingredient: Anatomical main group: B - Blood and blood forming organs Therapeutic subgroup: B01 - Antithrombotic agents Pharmacological subgroup: B01A - Antithrombotic agents Chemical subgroup: B01AE - Direct thrombin inhibitors Chemical substance: B01AE07 - Dabigatran etexilate.			
Report date: 13 Sep 2019	**Study number:** 1160.253	**Version/Revision:** Version 1.0	**Version/Revision date:**

Title of study:	Non-interventional study describing treatment convenience in patients treated with Dabigatran for Stroke Prophylaxis in Atrial Fibrillation (SPAF).
Keywords:	SPAF; Dabigatran; Treatment convenience; Stroke prophylaxis; NIS
Rationale and background:	Pradaxa® (Dabigatran etexilate) is a direct thrombin inhibitor approved in Europe, USA and many other countries worldwide for a number of indications including the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Data on how patients perceive Pradaxa® treatment in the context of non-valvular atrial fibrillation and anticoagulation management do only exist to a limited degree in Europe. The decision in clinical practice to either use Pradaxa® as one novel anticoagulant or established vitamin K antagonists is based on the Health authorities' recommendations in the positioning report of NOACs. It is the aim of this non-interventional study to describe the patient perception of anticoagulation with a current VKA therapy and subsequent initiation of treatment with Pradaxa® to prevent stroke and systemic embolism while suffering from non-valvular atrial fibrillation (according to its approved indication in the approved dosages of 110 mg or 150 mg twice daily).
Research question and objectives:	To describe patient and physician assessed factors for patient well-being when treated with Pradaxa® for stroke and embolism prevention in non-valvular atrial fibrillation compared to previous antithrombotic treatment (switcher). <u>Primary research interest:</u> To describe patients' perception of their treatment for NVAF using the

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	PACT-Q2 questionnaire at three time points: during the baseline period (when a patient was planned to be switched from VKA to Pradaxa®, to capture VKA treatment perception), after approximately one month of the initiation of Pradaxa® and after approximately 6 months (during the continuation period). Secondary Research interest: Characterisation of patient population in Spain: 1) Demographic data (age, gender, comorbidities and concomitant medication). 2) Obtaining elements assessed by the physician to calculate the HAS-BLED score during the baseline period. 3) Obtaining elements assessed by the physician to calculate the CHA_2DS_2-VASc score during the baseline period. 4) Analytical evaluation of kidney function and calculation of creatinine clearance using the Cockcroft-Gault formula. 5) Initial Pradaxa® dose. 6) Reasons for changing the dose of Pradaxa® or discontinuing Pradaxa®/VKAs.
Study design:	Prospective, non-interventional national, multi-centre, observational study based on newly collected data. The study enrolled patients in Spain with NVAF who were treated with VKAs and subsequently started Pradaxa®, and who gave their consent. Patients were monitored for a period of six months. Data were collected at three time points: 1. After the indication for Pradaxa® (baseline period) 2. 30-45 days after starting treatment with Pradaxa® (initial period) 3. 150-210 days after starting treatment with Pradaxa® (continuation period)

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Setting:	It was initially planned to include 1087 patient from approximately 200 sites. At the end of the study, data of NVAF patients were collected from 73 cardiology and non-specialist sites in Spain in 4 autonomous communities (Andalucía, Cataluña, País Vasco, and Galicia).
Subjects:	Patients who met all the inclusion criteria and none of the exclusion criteria indicated below were considered eligible to take part in the study: **Inclusion criteria** 1. Granting informed consent in writing prior to enrolment. 2. Patients of both sexes ≥ 18 years of age with a diagnosis of NVAF. 3. Patients treated continuously with VKAs for stroke prophylaxis for at least six months prior to the baseline visit. 4. Patients switching to treatment with Pradaxa® in accordance with the recommendations of the competent health authorities described in the therapeutic positioning report for NOACs and the authorisations of the various autonomous communities. **Exclusion criteria** 1. Contraindications for the use of Pradaxa® or VKAs described in the Summary of Product Characteristics (SmPC). 2. Patients receiving Pradaxa® or VKAs for any reason other than stroke prophylaxis in NVAF. 3. Participation in any clinical trial of an investigational medicinal product or medical device.
Variables and data sources:	***For primary objective:*** PACT-Q2 questionnaire (baseline, initial period and continuation period).

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	For secondary objectives: Characterisation of patients according to: - Age - Gender - CHA_2DS_2-VASc score - HAS-BLED score - Kidney function (creatinine clearance) - Risk factors associated with stroke and/or haemorrhage in the medical history and baseline period - Comorbidities - Concomitant medication - Duration of previous treatment with VKAs - Reasons for changing the dose of Pradaxa® or discontinuing Pradaxa®/VKAs - Pradaxa® dose The study was based on new data collection. Questionnaires completed by the patients. Patient characteristics completed by physician's judgement and patient medical records.		
Statistical methods:	In this non-interventional study, cross-sectional data at study baseline and longitudinal follow-up data over 6 months was collected for non-valvular AF patients with a current VKA therapy and subsequent initiation of Pradaxa®. The main analysis population consisted of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria). Mean PACT-Q2 scores at second and last assessment were compared with the scores at baseline using Wilcoxon signed-rank test. Likewise, mean PACT-Q2 scores at last assessment were compared with the scores		

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	at second assessment. Due to the nature of this non-interventional study, analyses were descriptive in nature and p-values from statistical models were used for explorative purposes. Patient demographic and disease characteristics at baseline were summarised descriptively for all eligible patients. No interim analysis was conducted for this study.		

Results:

671 patients (planned number: 1087 patients) were enrolled in this study: 223 patients were enrolled in Andalucía, 229 patients in Cataluña, 88 patients in País Vasco, and 131 patients in Galicia.

Of the 671 patients recruited, 659 patients were considered eligible (that is, they received Pradaxa® and did not have any important protocol violations) for the analysis of the study objectives and could be used for the analysis.

The summary of patient's characteristics is presented below (data reported as number and percentage of patients n (%), except for quantitative variables in which mean±SD has been reported):

Socio-demographic data	
Gender	**659 (100.0%)**
Male	384 (58.3%)
Female	275 (41.7%)
Age (n, (mean±SD))	659, (73.12±9.39)
Age categories	**659 (100.0%)**
≤65 years	132 (20.0%)
>65 years	527 (80.0%)
Race	**659 (100.0%)**
Caucasian	638 (96.8%)
Latin American	19 (2.9%)
North African	2 (0.3%)
Haemorrhagic risk and thromboembolic risk	
Haemorrhagic risk (HAS-BLED)	**659 (100.0%)**
Low risk (score 0)	23 (3.5%)
Moderate risk (score 1-2)	435 (66.0%)
High Risk (score ≥3)	201 (30.5%)
Haemorrhagic risk (HAS-BLED) (mean±SD)	2.10 ±0.98
Thromboembolic risk (CHA_2DS_2-VASc)	**659 (100.0%)**
Low risk (score 0 in male and 1 in female)	8 (1.2%)
Moderate risk (score 1 in male and 2 in female)	60 (9.1%)
High Risk (score ≥2 in male and ≥3 in female)	591 (89.7%)
Thromboembolic risk (CHA_2DS_2-VASc) (mean±SD)	3.60 ±1.56
Kidney function	
Serum creatinine (mg/dl) (n, (mean±SD))	237 (0.94±0.31)
Creatinine clearance (ml/min) (Cockcroft-Gault) (n, (mean±SD))	643 (73.91±22.72)
Stages of kidney disease (based on Cockcroft-Gault)	**643 (100.0%)**
No kidney failure (> 80 ml/min)	211 (32.8%)

	Mild kidney failure (50-80 ml/min)	385 (59.9%)
	Moderate kidney failure (30-49 ml/min)	44 (6.8%)
	Severe kidney failure (15-29 ml/min)	3 (0.5%)
	End-stage kidney failure/dialysis (< 15 ml/min)	0 (0.0%)
	History of stroke	**659 (100.0%)**
	Yes	106 (16.1%)
	No	553 (83.9%)
	History of bleeding, anaemia or predisposition to bleeding	**659 (100.0%)**
	Yes	54 (8.2%)
	No	605 (91.8%)
	Comorbidities	**659 (100.0%)**
	Yes	425 (64.5%)
	No	231 (35.1%)
	Not assessed	3 (0.5%)
	Type of most frequent diseases and/or surgeries *(a patient might have specified ≥1 event)*	
	Arterial hypertension	351 (53.3%)
	Others	182 (27.6%)
	Diabetes mellitus	159 (24.1%)
	Ischemic heart disease or Heart failure	136 (20.6%)
	Ischaemic stroke	88 (13.4%)
	Concomitant medications	**659 (100.0%)**
	Yes	597 (90.6%)
	No	62 (9.4%)
	Previous treatment with VKAs	
	Duration, Months (mean, SD)	47.83 (46.51)
	n, (%)	**659 (100.0%)**
	Acenocoumarol	625 (94.8%)
	Warfarin	34 (5.2%)
	Reasons for no longer receiving Pradaxa® at Visit 2	**26 (100.0%)**
	Change of treatment (by patient or by investigator)	8 (30.8%)
	Diarrhea, gastrointestinal discomfort, rectorrhagia, dyspepsia	10 (38.5%)
	Exitus	1 (3.8%)
	Others	7 (26.9%)
	Reasons for no longer receiving Pradaxa® at Visit 3	**27 (100.0%)**
	Change of treatment (by patient or by investigator)	7 (25.9%)

Diarrhea, gastrointestinal discomfort, rectorrhagia, dyspepsia	7 (25.9%)
Exitus	6 (22.2%)
Others	7 (25.9%)
Reasons for switching from VKA to Pradaxa® *(a patient might have specified ≥1 reason)*	**659 (100%)**
Poor INR control	484 (73.4%)
Patient's decision	137 (20.8%)
Other	113 (17.1%)
Reasons for dose change during the Follow-up period	**15 (2.3%)**
From 150 mg/bid to 110 mg/bid at Visit 2	**5 (0.8%)**
High risk of bleeding	2 (0.3%)
Moderate renal failure	1 (0.2%)
Other	2 (0.3%)
From 110 mg/bid to 150 mg/bid at Visit 2	**1 (0.2%)**
Other (insufficient dose related with patient weight)	1 (0.2%)
From 150 mg/bid to 110 mg/bid at Visit 3	**7 (1.2%)**
Moderate renal failure	3 (0.5%)
>80 years	2 (0.3%)
Other	2 (0.3%)
From 110 mg/bid to 150 mg/bid at Visit 3	**2 (0.3%)**
Other (Filtration improvement, Highest efficacy)	2 (0.3%)

PACT-Q2 score increased significantly (p<0.0001 based on Wilcoxon signed-rank test) after approximately 1 month (visit 2) and after 6 months (visit 3) of Pradaxa® treatment, compared with baseline, which means that patient convenience and satisfaction with Pradaxa® was higher than with the previous anticoagulation therapies. In addition, PACT-Q2 scores between visit 2 and 3 were further improved (p<0.0001). The summary of changes in PACT-Q2 between Visit1, 2 and 3 is presented below:

Changes in PACT-Q2 questionnaire scores: COMPARISONS VISIT 1 vs VISIT 2

DOMAINS	Visit 1	Visit 2	p
Convenience (range from 0 to 100)			
Mean (SD)	59.86 (25.39)	80.96 (16.98)	p<0.0001
95% CI	(57.65 ; 62.06)	(79.48 ; 82.43)	
Median (P25; P75)	60.58 (40.38 ; 80.77)	84.62 (71.15 ; 96.15)	
(Min; Max)	(0.00 ; 100.00)	(26.92 ; 100.00)	
Valid N	512	512	

Satisfaction with anticoagulant treatment (range from 0 to 100)		
Mean (SD)	49.15 (17.88)	69.35 (14.26)	p<0.0001
95% CI	(47.59 ; 50.70)	(68.11 ; 70.59)	
Median (P25; P75)	50.00 (39.29 ; 60.71)	67.86 (60.71 ; 78.57)	
(Min; Max)	(0.00 ; 100.00)	(21.43 ; 100.00)	
Valid N	511	511	

Changes in PACT-Q2 questionnaire scores: COMPARISONS VISIT 1 vs VISIT 3

DOMAINS	Visit 1	Visit 3	p
Convenience (range from 0 to 100)			
Mean (SD)	60.19 (25.59)	84.29 (15.19)	p<0.0001
95% CI	(57.92 ; 62.46)	(82.95 ; 85.64)	
Median (P25; P75)	61.54 (40.38 ; 80.77)	88.46 (75.00 ; 96.15)	
(Min; Max)	(0.00 ; 100.00)	(26.92 ; 100.00)	
Valid N	491	491	
Satisfaction with anticoagulant treatment (range from 0 to 100)			
Mean (SD)	49.44 (17.74)	73.19 (14.80)	p<0.0001
95% CI	(47.86 ; 51.01)	(71.88 ; 74.51)	
Median (P25; P75)	50.00 (39.29 ; 60.71)	75.00 (64.29 ; 82.14)	
(Min; Max)	(0.00 ; 100.00)	(21.43 ; 100.00)	
Valid N	489	489	

Changes in PACT-Q2 questionnaire scores: COMPARISONS VISIT 2 vs VISIT 3

DOMAINS	Visit 2	Visit 3	p
Convenience (range from 0 to 100)			
Mean (SD)	80.95 (17.01)	84.23 (15.24)	p<0.0001
95% CI	(79.44 ; 82.47)	(82.88 ; 85.59)	
Median (P25; P75)	84.62 (71.15 ; 96.15)	88.46 (75.00 ; 96.15)	
(Min; Max)	(26.92 ; 100.00)	(26.92 ; 100.00)	
Valid N	486	486	
Satisfaction with anticoagulant treatment (range from 0 to 100)			
Mean (SD)	69.54 (14.22)	73.30 (14.66)	p<0.0001
95% CI	(68.26 ; 70.81)	(71.99 ; 74.61)	
Median (P25; P75)	67.86 (60.71 ; 78.57)	75.00 (64.29 ; 82.14)	

	(Min; Max) (21.43 ; 100.00) (21.43 ; 100.00) Valid N 483 483
	Subgroup analyses showed no differences in treatment convenience and treatment satisfaction among different age groups, but there were differences among genders: at visit 3, males had higher mean convenience scores and females had higher mean satisfaction scores. There were also some differences among the autonomous communities, with patients from Basque Country being the ones with higher scores in convenience and treatment satisfaction at Visit 2 and Visit 3. The treatment convenience score at Visit 3 was also higher in patients with low-moderate risk of thromboembolism (according to CHA_2DS_2-VASc scale). With regards to the safety analysis, a total of 69 patients reported 82 adverse events, of which 18 (22.0%) were serious and 64 (78.0%) non-serious events. 6% of patients (n=39) suffered an adverse drug reaction related to the study treatment and most of them were non-serious reactions. Adverse drug reactions were mainly of gastrointestinal origin, with dyspepsia being the most frequent of them. 24 patients (3.7%) discontinued due to a drug-related adverse event. 8 patients died during the study (for some patients more than 1 adverse event with fatal outcome was reported) but only one patient died due to 2 SAEs assessed by the investigator as related with study treatment (lower and upper gastrointestinal hemorrhage).
Conclusion:	Patients with non-valvular atrial fibrillation switched to and treated with Pradaxa® for stroke and embolism prevention have shown better satisfaction and convenience with the treatment, as compared to baseline when treated with vitamin K antagonists. This is probably related to the fact that Pradaxa® has less practical limitations and does not require frequent anticoagulation monitoring. The reported serious and non-serious adverse drug reactions in this study were consistent with known/listed side effects of Pradaxa®. Overall, no changes were observed in the safety profile for Pradaxa®.
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