Boehringer Ingelheim

Protocol for non-interventional studies based on existing data:

Document Number:	**c12696196-01**
BI Study Number:	1160.219
BI Investigational Product(s):	PRADAXA (dabigatran)
Title:	Validation of predictors for oral anticoagulant medication choice using EMR data (Phase 3b of the BI/BWH Pradaxa study program)
Protocol version identifier:	1.0
Date of last version of protocol:	02 November 2016
PASS:	No
EU PAS register number:	Not available yet
Active substance:	Dabigatran etexilate
Medicinal product:	Pradaxa
Product reference:	EU/1/08/442/001-019
Procedure number:	EMEA/H/C/000829
Joint PASS:	Not applicable
Research question and objectives:	The research question is whether select patient characteristics that may be incompletely captured by insurance claims data, differ between dabigatran and warfarin initiators. Objectives: 1) Descriptive: To identify select clinical covariates from electronic medical records that might be associated with initiation of oral anticoagulant medications (dabigatran or warfarin) in NVAF patients at risk for stroke and are not usually well captured in the associated claims database 2) Prediction Rule: To assess how well EMR-based clinical characteristics can be captured on the basis of claims data only 3) Assess Balance: To assess the potential for unmeasured confounding in dabigatran vs warfarin comparative effectiveness and safety studies based on administrative claims

	databases
Country(-ies) of study:	US
Author:	[redacted]
Marketing authorisation holder(s):	Boehringer Ingelheim
MAH contact person:	[redacted]
Date:	02 November 2016

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2. LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACEI	Angiotensin-converting Enzyme Inhibitor
AES	Advanced Encryption Standard
AF	Atrial Fibrillation
ALT	Serum Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BB	Beta Blocker
BI	Boehringer Ingelheim
BMI	Body Mass Index
BWH	Brigham and Women's Hospital
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHA_2DS_2-VASc	Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65-74, Sex Category
$CHADS_2$	Congestive Heart Failure, Hypertension, Age> 75, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack
CHF	Congestive Heart Failure
CI	Confidence Interval
CONSORT	Consolidated Standards for Reporting Trials
CPT	Current Procedural Terminology
Cr	Creatinine
DM	Diabetes Mellitus
DVT	Deep Venous Thromboembolism
Dx	Diagnosis
EMR	Electronic Medical Records
ESC	European Society of Cardiology
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
H2 Receptor	Histamine H2 Receptor
HAS-BLED	Hypertension, Abnormal Liver/Renal function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (Age >65), Drugs-Alcohol usage
HbA1c	Hemoglobin A1C
HCPC	Healthcare Common Procedure Coding
hdPS	High-dimensional Propensity Score
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	Intracerebral Hemorrhage
INR	International Normalized Ratio
ITT	Intent-To-Treat
IRB	Institutional Review Board
ISF	Investigator Site File

LDL	Low Density Lipoprotein
LOS	Length of Stay
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
NOAC	New Oral Anticoagulant
NSAID	Non-steroidal Anti-inflammatory Drug
NVAF	Non-valvular Atrial Fibrillation
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PGP	P-glycoprotein
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
PS	Propensity Score
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral Vascular Disease
PY	Person-Year
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RR	Relative Risk
SAH	Subarachnoid Hemorrhage
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SD	Standard deviation
TIA	Transient Ischemic Attack
t.i.d.	ter in die (3 times a day)
US	United States
VTE	Venous Thromboembolism

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa® (Dabigatran etexilate), or warfarin			
Name of active ingredient: Dabigatran etexilate or warfarin			
Protocol date: 02 November 2016	**Study number:** 1160.219	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Association of select EMR-based covariates with oral anticoagulant medication selection Version and date: Version 1.0, 02 November 2016 [redacted]		
Rationale and background:	A study of safety/effectiveness of dabigatran is being conducted in health insurer claims databases that may incompletely capture select variables representing covariates. This validation study seeks to ascertain a select set of covariates in electronic medical records (EMRs) linked to a subset of patients within the insurance claims data in order to assess the potential for unmeasured confounding in observational studies based on insurance claims databases only.		
Research question and objectives:	The research question is whether select patient characteristics that may be incompletely captured by insurance claims data differ between dabigatran and warfarin initiators. Objectives: 1) Descriptive: To identify select clinical covariates from electronic medical records that might be associated with initiation of oral anticoagulant medications (dabigatran or warfarin) in patients with NVAF at risk for stroke and are not usually well captured in the associated claims database. 2) Prediction Rule: To quantify the association between EMR-based clinical characteristics and patterns of insurance claims		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa® (Dabigatran etexilate), or warfarin			
Name of active ingredient: Dabigatran etexilate or warfarin			
Protocol date: 02 November 2016	**Study number:** 1160.219	**Version/Revision:** 1.0	**Version/Revision date:**
Research question and objectives:	3) Assess Balance: To assess the potential for unmeasured confounding in dabigatran vs warfarin comparative effectiveness and safety studies based on administrative claims databases		
Study design:	A validation study		
Population:	Patients from an US health insurance database (electronic medical records) with a recorded diagnosis of atrial fibrillation without evidence of valvular etiology and at risk for stroke who initiate dabigatran or warfarin between October 2010 and December 2014 (This date range corresponds to the available matched cohort date range). Inclusion criteria: • A recorded diagnosis of atrial fibrillation. • Initiation of anticoagulant medication (dabigatran or warfarin). • At least 18 years of age on the date of anticoagulant initiation. • CHA_2DS_2-VASc score ≥ 1 • Presence of electronic medical records (for the EMR-based subset) Exclusion criteria: • Patients with missing or ambiguous age or sex information. • Patients with evidence of valvular disease. • Patients with less than 12 months enrolment preceding the date of anticoagulant initiation. • Patients with a dispensing of any oral anticoagulant during the 12 months preceding the date of anticoagulant initiation • Patients with a nursing home stay during baseline • Unmatched dabigatran/warfarin initiators		

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Protocol date: 02 November 2016	**Study number:** 1160.219	**Version/Revision:** 1.0	**Version/Revision date:**
Variables:	Patient characteristics derived from insurance claims (claims-based covariates) This study will characterize patients initiating oral anticoagulant medications with respect to select characteristics, some of which might be reflected differently in claims data compared to electronic medical records prior to and including the date of initiation. These characteristics from EMR data are usually treated as covariates but will be considered outcomes in this validation study. These characteristics include: Primary Outcomes • Obesity • Smoking • Alcohol consumption • Abnormal renal function • Bleeding history or predisposition • Renal function (estimated GFR) • Serum Creatinine • Abnormal liver function Secondary Outcomes • Duration of atrial fibrillation • History of adherence • History/duration of hypertension • Uncontrolled Hypertension (for HAS-BLED) • History/duration of CHF • Prior TIA • Diabetes • Hyperlipidemia		

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Name of finished medicinal product: Pradaxa® (Dabigatran etexilate), or warfarin			
Name of active ingredient: Dabigatran etexilate or warfarin			
Protocol date: 02 November 2016	**Study number:** 1160.219	**Version/Revision:** 1.0	**Version/Revision date:**
Variables:	• HAS-BLED Score • Use of antiplatelets or NSAIDs (needed for HAS-BLED) [redacted]		
Data sources:	This study will be conducted within MarketScan data linked to electronic medical records.		
Study size:	Study cohort: approximately 15,000 dabigatran initiators PS-matched to 15,000 warfarin initiators EMR-linked subset: approx. 5.5% of the study cohort.		
Data analysis:	• Analyses will describe the presence in the claims data of each EMR-based clinical characteristic among initiators of dabigatran and initiators of warfarin. • A prediction algorithm to identify in the claims data each of the EMR-based clinical characteristic will be developed. The prediction algorithm will be estimated using a regression model that uses each of the EMR characteristic as the model outcome and all available claims-based covariates as predictors. • Strength of association between each EMR-based covariate and medication choice will guide quantitative assessments of potential confounding of the association between anticoagulant and clinical outcomes.		
Milestones:	Draft Protocol: September 2013 Final Protocol: November 2016 Draft Report: July 2017 Final Report: September 2017		

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Contract	June 2012
Draft protocol	September 2013
Final protocol	November 2016
Start of data collection	15 November 2016
End of data collection	15 May 2017
First draft report	July 2017
Registration in the EU PAS register	November 2016
Final report of study results:	September 2017

7. RATIONALE AND BACKGROUND

A number of new oral anticoagulants are being developed and marketed to replace vitamin K antagonists, one of the most important drugs in modern medicine. [P11-11875] Unlike vitamin K antagonists, these new drugs do not require dose titration involving intensive therapeutic monitoring of prothrombin time to achieve target anticoagulation within a narrow therapeutic range. In Phase III studies, these drugs were found to be therapeutically advantageous or non-inferior over warfarin. In the coming years, as many as six new anticoagulants could be on the market and a lack of valid comparative evidence will hinder prescriber and payor decision-making.

Pharmacoepidemiologic studies based on large administrative claims databases are increasingly utilized for that purpose; however, these data are collected for reasons unrelated to research, and as a result, might not contain sufficient information on important confounders, such as body mass index, smoking, family history, or alcohol consumption, leading to residual confounding. Several approaches have been proposed to address the issue of unmeasured confounding, and internal validation studies, based on additional data obtained for a subset of participants in the main study population is one of them. Such studies offer specific advantages since they are more representative of the main study population and allow application of methods that do not require assumptions about the direction of confounding. [R13-2768]

This protocol is for a validation study conducted within a cohort of patients initiating dabigatran or warfarin during October 2010 – December 2014 time period and matched on propensity score (PS). The study will involve targeted data ascertainment from linked patients for enhanced covariate assessment via extraction from electronic medical records using existing electronic data including pre-defined variables, with the goal of describing the presence of covariates not typically present or insufficiently measured in claims data in dabigatran users as compared to users of warfarin and assessing the potential for confounding in the comparative safety research that will be undertaken in other phases of the study program.

8. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are:

1) Descriptive: To identify select clinical covariates from electronic medical records that might be associated with initiation of oral anticoagulant medications (dabigatran or warfarin) in patients with NVAF at risk for stroke and are not usually well captured in the associated claims database.
2) Prediction Rule: To quantify the association between EMR-based clinical characteristics and patterns of insurance claims
3) Assess Balance: To assess the potential for unmeasured confounding in dabigatran vs warfarin comparative effectiveness and safety studies based on administrative claims databases

9. RESEARCH METHODS

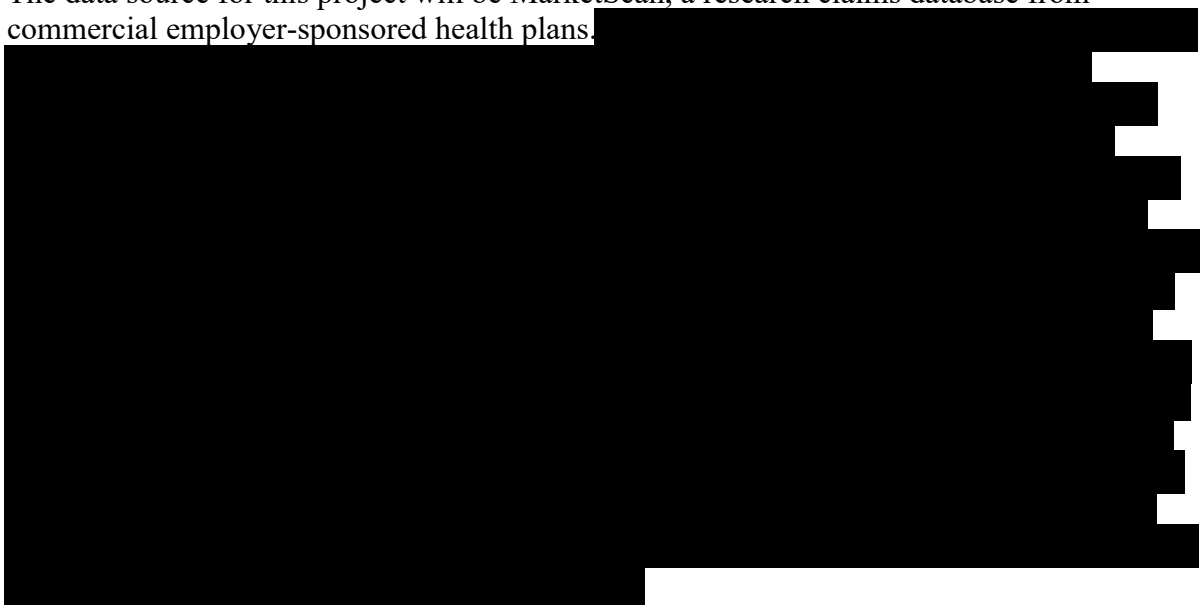
9.1 STUDY DESIGN

This study represents a form of internal validation study that will involve selection of a patient sample, extraction of medical record data, and analyses that will have implications for potential confounding in comparative studies of dabigatran effect.

This study will be conducted within a cohort of NVAF patients at risk for stroke initiating dabigatran or warfarin during October 2010 – December 2014 time period identified in MarketScan research claims database based on Protocol 1160.207 (Sequential Expansion of Comparative Effectiveness of Oral Anticoagulants).

9.2 SETTING

The data source for this project will be MarketScan, a research claims database from commercial employer-sponsored health plans.



9.3 VARIABLES

9.3.1 Exposures

The primary exposure is new initiation of warfarin or dabigatran. Initiators are defined as no anticoagulation with *any oral anticoagulant* in the 12 months before the index prescription. Comparison between these two groups of initiators will be made with respect to variables obtained from the EMR among patients who have been matched on the propensity score derived from insurance claims data.

9.3.2 Outcomes

EMR-based clinical characteristics that are typically used as covariates will be treated as outcomes in this validation study. Unless otherwise noted, all of these outcomes will have an indicator for being recorded in EMR (Present, Y/N). Index date is the date of dabigatran or

warfarin initiation. All characteristics will be assessed prior and including the medication initiation date (index date). The characteristics presented in Table 1 reflect likely availability in the EMR.

9.3.2.1 Primary outcomes

- Obesity
- Smoking
- Alcohol consumption
- Abnormal renal function
- Bleeding history or predisposition
- Renal function (estimated GFR)
- Serum Creatinine
- Abnormal liver function

9.3.2.2 Secondary outcomes

- Duration of atrial fibrillation
- History of adherence
- History/duration of hypertension
- Uncontrolled Hypertension (for HAS-BLED)
- History/duration of CHF
- Prior TIA
- Diabetes
- Hyperlipidemia
- HAS-BLED Score
- Use of antiplatelets or NSAIDs (needed for HAS-BLED)

[redacted]

Table 1 Outcome definitions

Outcome	Definition	Present	Categories if present
Primary			
Obesity	Calculated BMI >30 or recorded "obesity"	Y/N	Obese, not-obese based on note of obesity or recorded BMI>30.
Smoking	Any note on smoking	Y/N	Current & past combined and nonsmoker & not noted combined.
Alcohol consumption	Any note on alcohol use	Y/N	Alcohol use (any); No use
Abnormal renal function	Any note of: Dialysis, renal transplant Serum Creatinine >1.3 mg/dL	Y/N	
Bleeding history or predisposition	Any note of: Major bleeding requiring hospitalization or blood transfusion or causing a decrease in hemoglobin level of > 2 g/L	Y/N	
Renal function	Estimated GFR closest to index dispensing	Y/N	The value
Serum Creatinine	Closest to the index date	Y/N	The value
Abnormal liver function	Any note of: Liver disease, cirrhosis, Active hepatitis C Active hepatitis B Active hepatitis A AST/ALT >3X upper limit of normal *Absence of any note would be considered as absence of the disease*	Y/N	

Table 1 (cont'd) Outcome definitions

Outcome	Definition	Present	Categories if present
Secondary			
Duration of atrial fibrillation	Years/months prior to initiation of dabigatran/warfarin	Y/N	Number of months prior to index date for the earliest note
History of adherence	Any note of patient adherence/lack thereof in EMR	Y/N	Non-adherent Adherent
History/duration of hypertension	Any note of: Hypertension SBP >120 mmHg Hypertension drugs	Y/N	Number of months prior to index date for the earliest date
Uncontrolled Hypertension (for HASBLED)	SBP >160 mmHg using the most recent information prior to index date	Y/N	
History/duration of CHF	Any note of: CHF	Y/N	Number of months prior to index date for the earliest note
Prior TIA	Any note of TIA	Y/N	Also, number of months prior to index date if noted
Diabetes	Any note of: Diabetes *Absence of any note of diabetes will be considered as absence of the disease*	Y/N	
Hyperlipidemia	Any note of; Hyperlipidemia, dyslipidemia, LDL>130 mg/dl		
HAS Bled Score	As recorded (if recorded) or calculated from EMR data. [redacted]	Recorded/ calculated /none	The value
Use of antiplatelets or NSAIDs (needed for HASBLED)	Use of aspirin, clopidogrel, prasugrel, ticagrelor or NSADs (within 1 month or on the index date)	Y/N	
INR	Closest to the index date	Y/N	The value

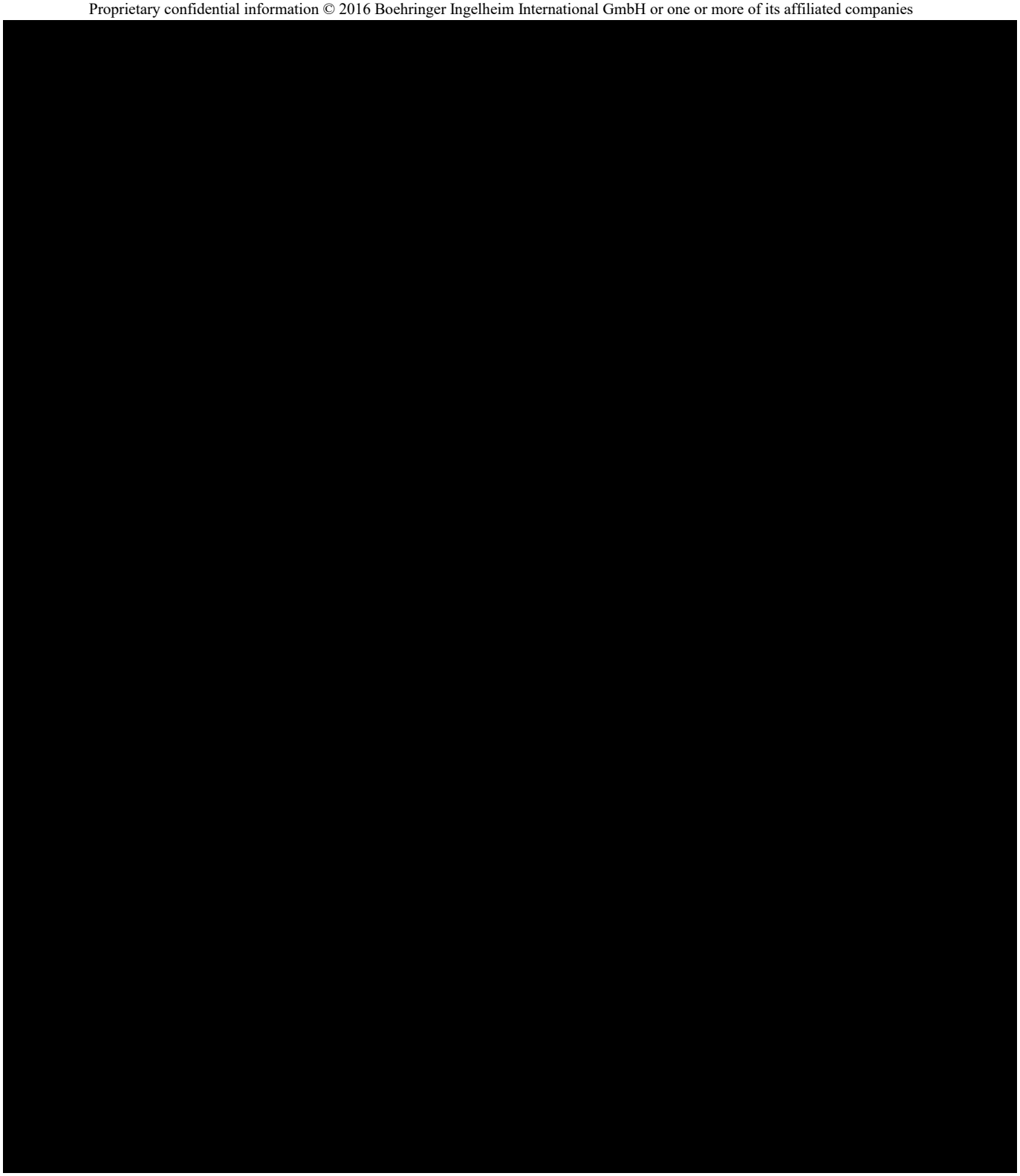
Table 2 Components of HAS-BLED bleeding risk score*

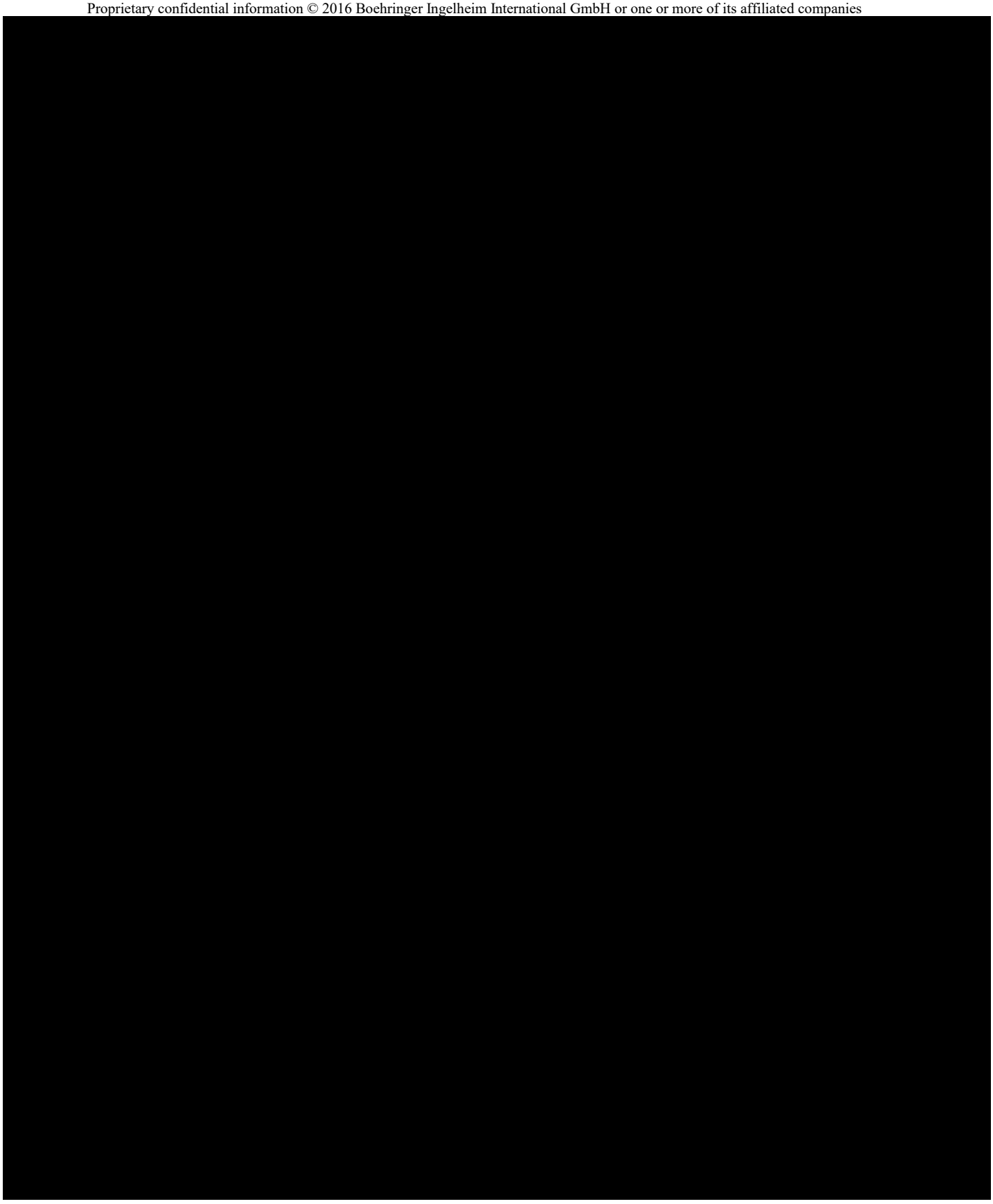
HAS-BLED item	Points
Hypertension (uncontrolled)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding history or predisposition (anemia)	1
Labile INR	1
Elderly	1
Drugs or alcohol (1 point each)	1 or 2

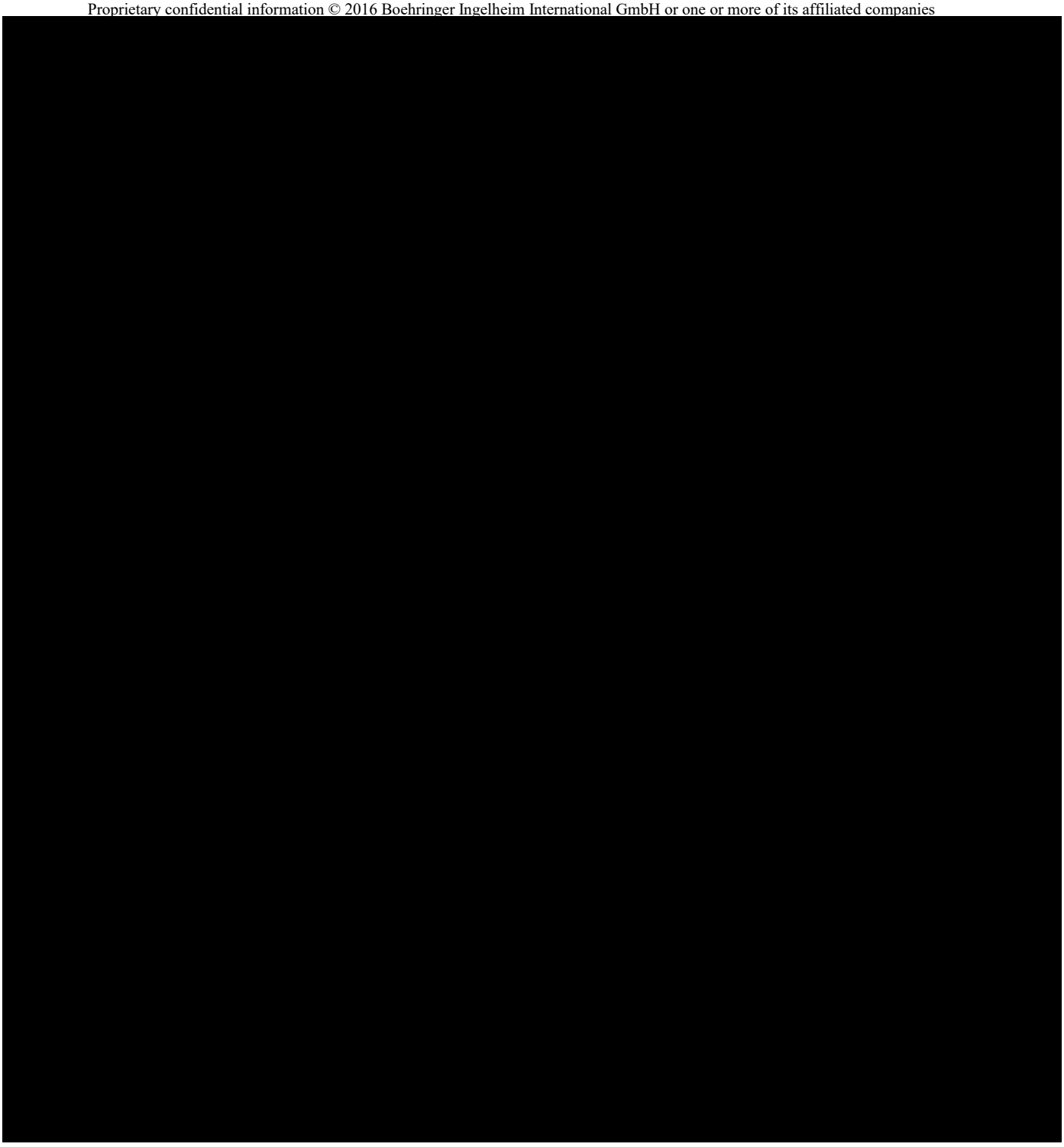
*HAS-BLED score is calculated by adding the specified points for each of the conditions listed. [R10-6394]

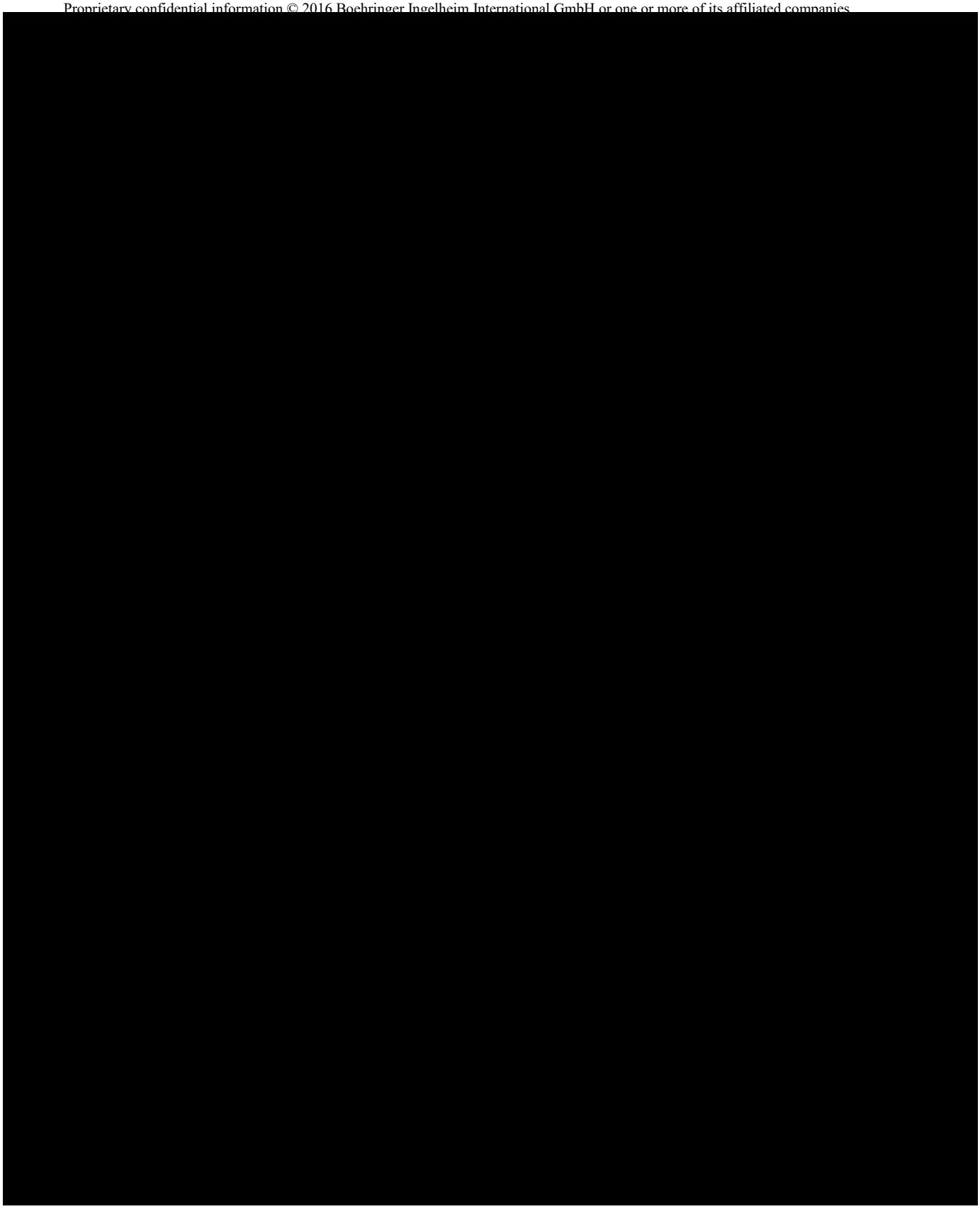
[redacted]

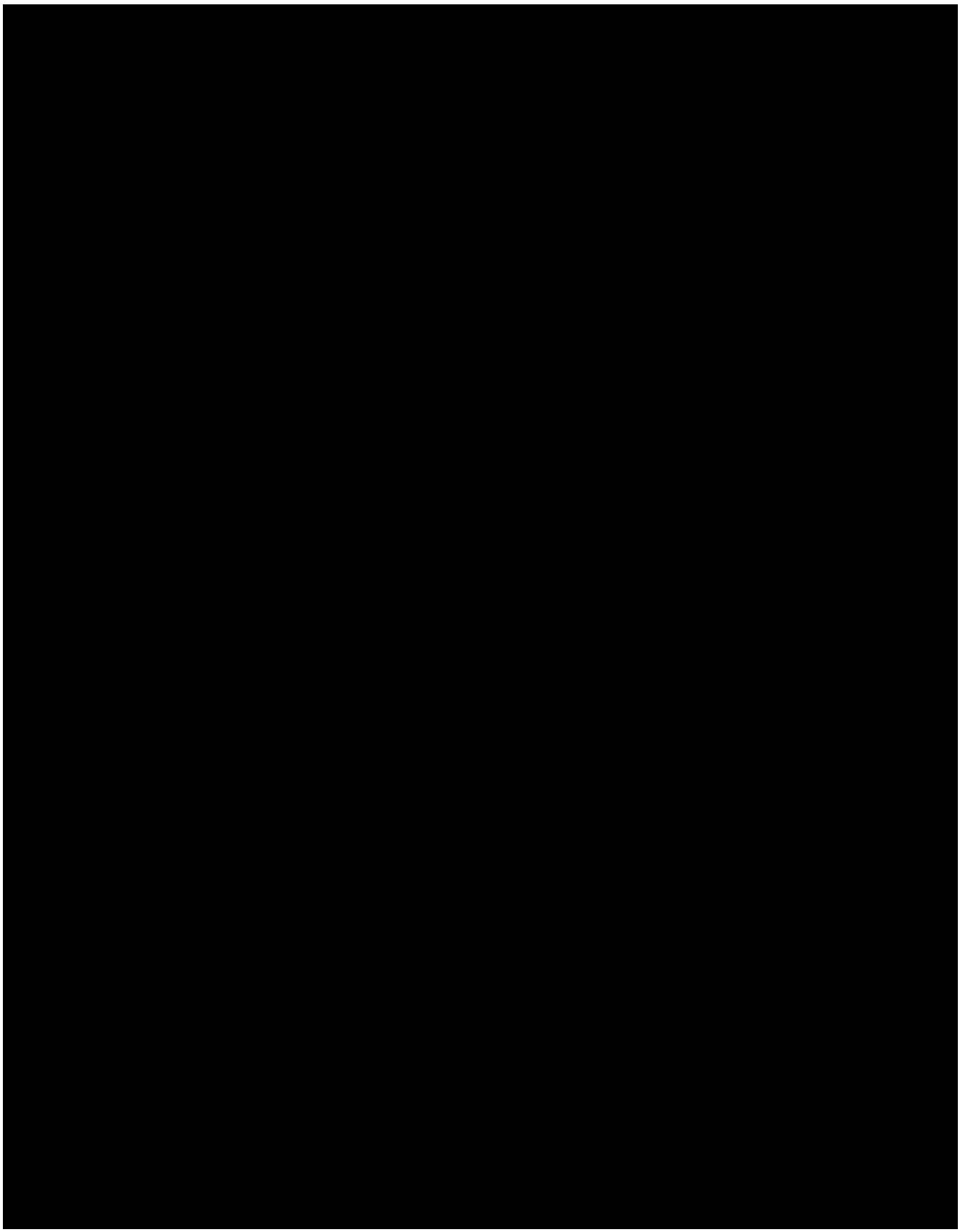
[redacted]

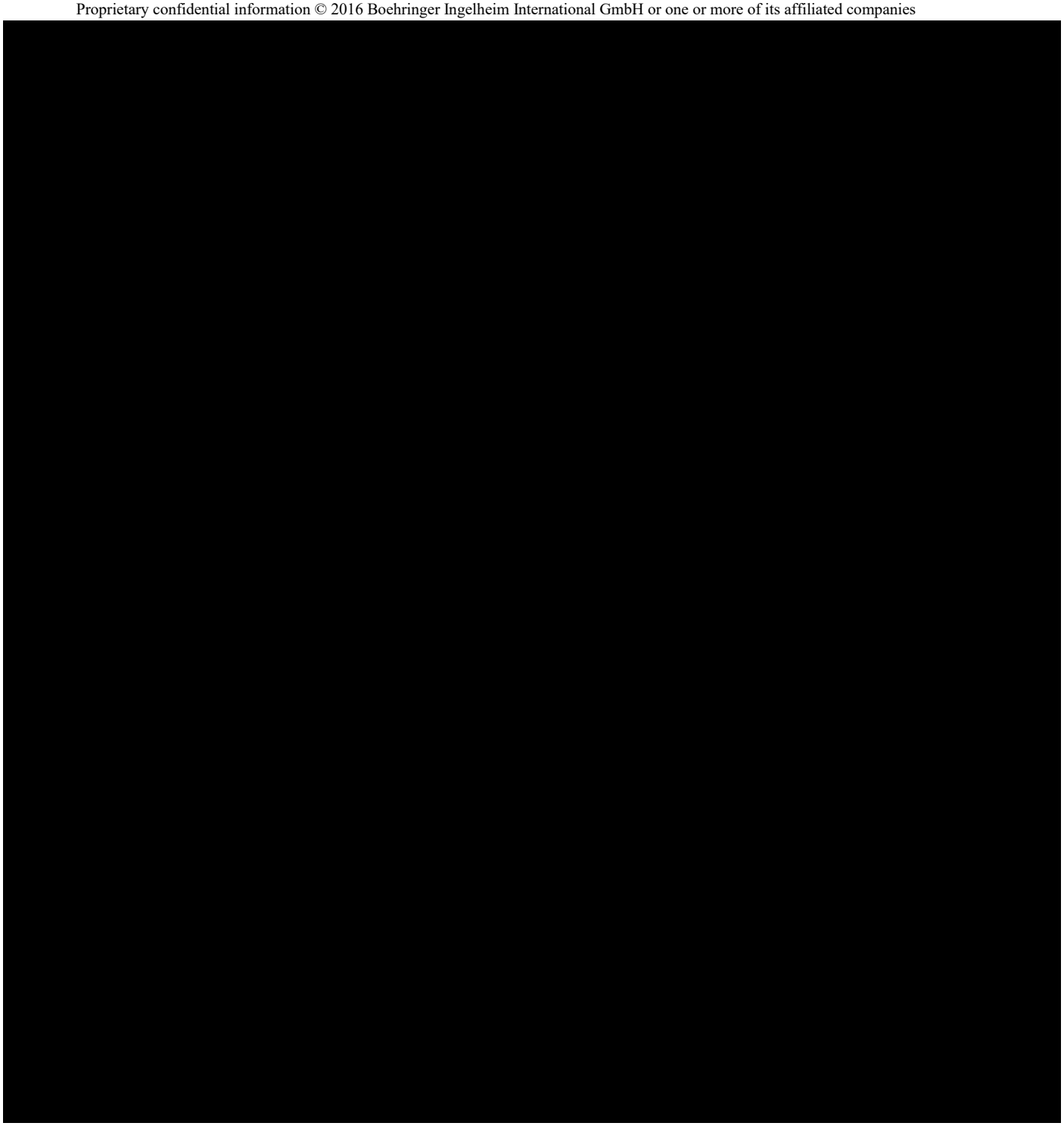


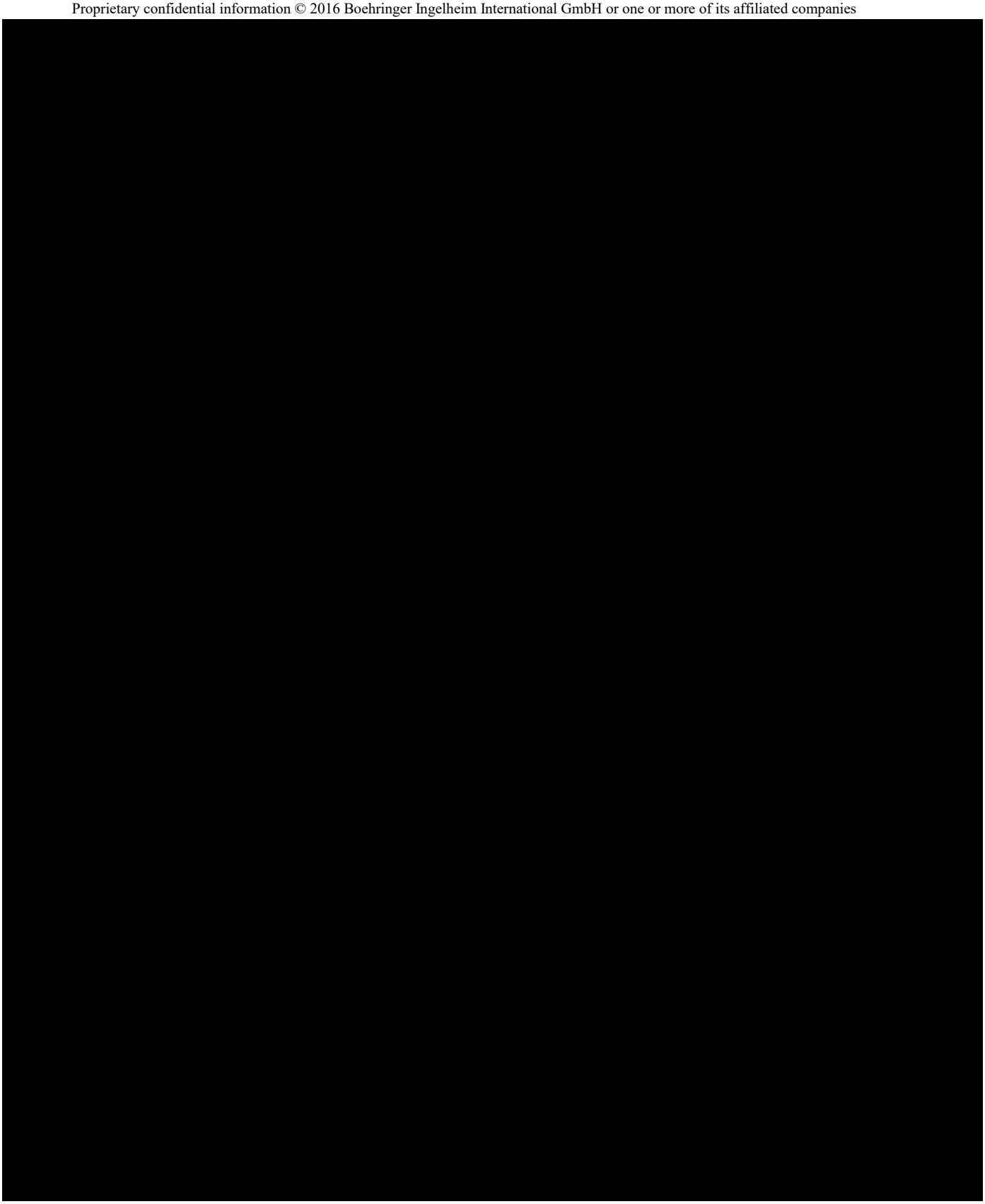


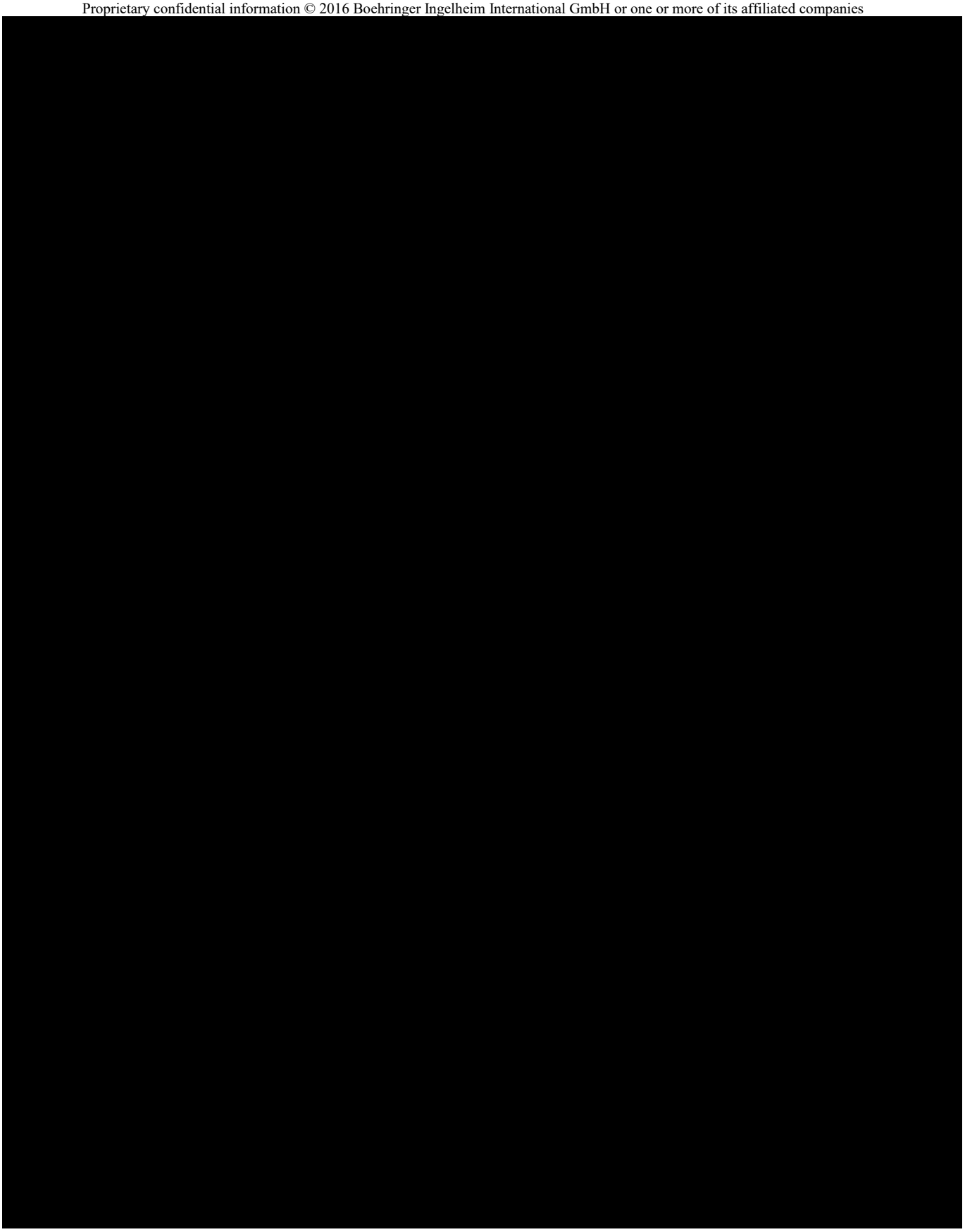












[redacted]

9.4 DATA SOURCES

The data source for this project will be data from MarketScan, a research claims database from commercial employer-sponsored health plans, through December 2014. [redacted]

9.5 STUDY SIZE

This study will identify covariates that represent potential confounding variables among dabigatran and warfarin users within a sampled population. The ability to identify a covariate and the precision for estimating potential confounding from the covariate will depend on the numbers of patients from whom electronic medical record data is extracted, and features of the covariate itself, such as how certain it is to be recorded in the medical record and whether binary (yes/no) or other.

The PS-matched dabigatran and warfarin initiators during Oct 2010– December 2013 period are approximately 20,000 each. Assuming that 5.5% of this study group will be linked to EMR, the EMR-linked subset up to Dec 2013 will consist of approximately 1100 patients in each exposure group.

The precision of estimated prevalence for a covariate obtained from the EMR depends on the prevalence of the covariate, and the sample size. With 10,000 dabigatran initiators, this study will estimate a patient characteristic that has a 10% prevalence with considerable precision (the 95% confidence interval will be 9.4% to 10.6%) (Table 7). A characteristic not captured in claims, but present in the medical record with a prevalence of 10% to 20% is plausibly a confounding variable and so this table enumerates characteristics with these prevalences. The table has not been extended below 10% since such lower prevalence characteristics have progressively less ability to produce meaningful confounding, so that while the study will have less precision to estimate such a characteristic, validation of the presence for such a low prevalence characteristic becomes unnecessary. At the other end of the range presented in the table, a characteristic with a prevalence above 20% will be identified with even greater precision, so that it also does not need to be depicted in the table.

Table 7 Precision of Estimates for Proportion Measures

Numerator	Denominator	Prevalence	95% CI	Precision (s.e.)
10	100	10%	4.9%-17.6%	3.0%
100	1,000	10%	8.2%-12.0%	0.9%
1,000	10,000	10%	9.4%-10.6%	0.3%
10,000	100,000	10%	9.8%-10.2%	0.1%
100,000	1,000,000	10%	9.9%- 10.1%	0.003%
20	100	20%	12.7%-29.2%	4.0%
200	1,000	20%	17.6%-22.6%	1.3%
2,000	10,000	20%	19.2%-20.8%	0.4%
20,000	100,000	20%	19.8%-20.2%	0.1%
200,000	1,000,000	20%	19.9%- 20.1%	0.004%

[redacted]

9.7 DATA ANALYSIS

9.7.1 Main analysis

Representativeness of EMR

We will assess whether the subpopulation with linked EMR data is a representative sample of the full MarketScan cohort of oral anticoagulant medication initiators. In the full MarketScan cohort, the proportion of each exposure group with linked EMR data available will be determined. We will evaluate the claims-based covariates in the linked and non-linked subpopulations, separately by exposure group as well as overall, by examining prevalences

for categorical covariates and means and standard deviations for continuous covariates. These data will be summarized as in the example Table 8 and will allow us to determine if there are any patient characteristics that are over-represented or under-represented in the EMR subpopulation. If EMR linkage is only available for a subset with considerably different characteristics than the full cohort or among a subset where the propensity score balance is not retained, then further remedies might be applied such as stratification or weighting.

Table 8 Association between claims-based covariates and EMR linkage.

Claims-based covariate	**Dabigatran initiators**		**Warfarin initiators**	
	N=		**N=**	
	Linked	**Not linked**	**Linked**	**Not linked**
Proportion (N)				
Age				
Age category 18-35				
Age category 36-64				
Age category 65-74				
Age category 75+				
Sex				
…				

Objective 1: Descriptive

The analyses for this objective will occur within the subpopulation of individuals with linked EMR data and will focus on describing the EMR-based clinical characteristics for the dabigatran and warfarin initiators. This table will provide an evaluation of the association between the EMR clinical characteristics and initiation of dabigatran or warfarin. [redacted]

The prevalence of each category for categorical characteristics and the mean and standard deviation for continuous characteristics will be calculated (as shown in the example Table 9). This analysis will aid in identifying EMR characteristics that are unbalanced across exposure groups and are therefore potential unmeasured confounders after PS matching.

Table 9 EMR clinical characteristics in matched dabigatran and warfarin initiators

EMR clinical characteristic	Dabigatran initiators	Warfarin initiators
	N=	N=
[redacted]		
Smoking		
Alcohol consumption		
Obesity		
…		

Note: anticoagulant initiation [redacted] are based on claims data

We will seek to define variables derived from the EMR in a manner that reduces missingness. Accordingly, most variables will be defined as presence or non-presence in the EMR, which we will take as a proxy of being medically-recognized. For example, if smoking is noted in the medical record, it will be recorded as present, if it is not present, it will be assumed that the patient does not smoke. We will also evaluate the patterns of missing data in the EMR clinical characteristics.

Objective 2: Prediction Rule

Within the EMR linked subpopulation, a prediction model will be developed [redacted] with particular focus on covariates that are found to represent potentially important unmeasured confounding in the primary analysis. Specifically, a logistic regression model (potentially a multinomial logistic regression, depending on the number of categories for the EMR characteristic) will be estimated [redacted] that uses the EMR covariate as the model outcome and all available claims-based covariates as predictors. [redacted] For [redacted] continuous EMR-based characteristic, a linear regression model will be estimated. Coefficients from these models will be reported as well as prediction accuracy, defined by the R2 statistic.

[redacted]

Objective 3: Potential Unmeasured Confounding Assessment

To assess the potential for confounding, we will conduct a series of logistic regression analyses that predict exposure (dabigatran versus warfarin) from covariates. [redacted]

[redacted]

9.7.2 Further analysis

None defined.

9.8 QUALITY CONTROL

All aspects of data analysis will be conducted according to standard procedures of the Division of Pharmacoepidemiology. Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst will review the program along with input and output data sets, and for select steps of the project will employ double programming techniques to reduce the potential for programming errors.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This is a validation study and we are not assessing the association between EMR-based patient characteristics and clinical outcomes.

The source claims data include limitations with respect to certainty of the capture of exposure, covariates, and outcomes. As a comprehensive insurance database, essentially all billable medical services will result in claims for reimbursement, so that the certainty of capture is tied to likelihood of a claim being submitted to the insurer.

Although more information on covariates is captured in EMR, some data will be missing in EMR as well. In addition, information is assessed during routine medical care (not in a standardized way) and some variation in assessment persists but cannot be studied within the scope of the study.

As in any EMR source, there could be potentially small number of dabigatran initiators and they might not represent dabigatran initiators in the general population. In addition, the data sources for this study are commercial US data sources (based on employed people and their dependents), so they tend to over-represent working-age people. The data are supplemented with elderly through patients with certain types of Medicare coverage (Medicare Advantage); however, elderly with Medicare Advantage tend to be healthier and more likely to still be employed as compared to elderly with other types of Medicare. These features of data may further limit the generalizability in that the results will be most generalizable to US people who are employed. [P13-03077, P13-03078]

9.10 OTHER ASPECTS

Funding: Boehringer Ingelheim GmbH

9.11 SUBJECTS

9.11.1 Study group

The main cohort will consist of patients with NVAF at risk for stroke initiating warfarin and dabigatran, from October 2010 through December 2014.

Inclusion criteria:

- Initiation of an oral anticoagulant is defined by a dispensing of an anticoagulant medication (warfarin or dabigatran) in the source data, with no dispensing of any oral anticoagulant in the prior 12 months. The date of that dispensing will be defined as the index date for that initiation.
- At least one ICD-9 diagnosis code of 427.31 (atrial fibrillation) at any time prior to and including the index date
- At least 12 months (365 days) continuous enrollment, defined as ≤32 days enrollment gap using enrollment and disenrollment dates, preceding the index date
- 18 years of age and older at index date
- CHA_2DS_2-VASc score ≥ 1

Exclusion criteria:

- Patients with a nursing home stay during baseline
- Patients with missing or ambiguous age or sex information.
- Patients with a dispensing of any oral anticoagulant during the 12 months preceding and including the index date
- Patients with documented evidence of valvular disease defined as at least 1 inpatient or outpatient ICD-9 Dx code of [R11-4334]
  394.x (diseases of mitral valve)
  395.x (diseases of aortic valve)
  396.x (diseases of mitral and aortic valve)
  397.x (diseases of other endocardial structures)
  398.9x (other and unspecified rheumatic heart diseases)
  V42.2 (heart valve replaced by transplant)
  V43.3 (heart valve replaced by a mechanical device/prosthesis)
  OR
  ICD-9 procedure code 35.1x (open heart valvuloplasty without replacement), 35.2x (replacement of heart valve) [R03-1232]
  OR
  one of the following CPT codes:
  33660-33665 (atrioventricular valve repair)
  33400-33403 (aortic valve valvuloplasty)
  33420-33430 (mitral valve repair/valvuloplasty/replacement)
  33460 (valvectomy, tricuspid valve, with cardiopulmonary bypass)
  33463-33468 (tricuspid valve repair/valvuloplasty/replacement)
  33475 (replacement, pulmonary valve)

33496 (prosthetic valve dysfunction repair)
0257T (implantation of catheter-delivered prosthetic aortic heart valve; open thoracic approach)
0258T (transthoracic cardiac exposure for catheter-delivered aortic valve replacement; without cardiopulmonary bypass)
0259T (transthoracic cardiac exposure for catheter-delivered aortic valve replacement; with cardiopulmonary bypass)
0262T (implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach)

at any time prior to and including the index date.

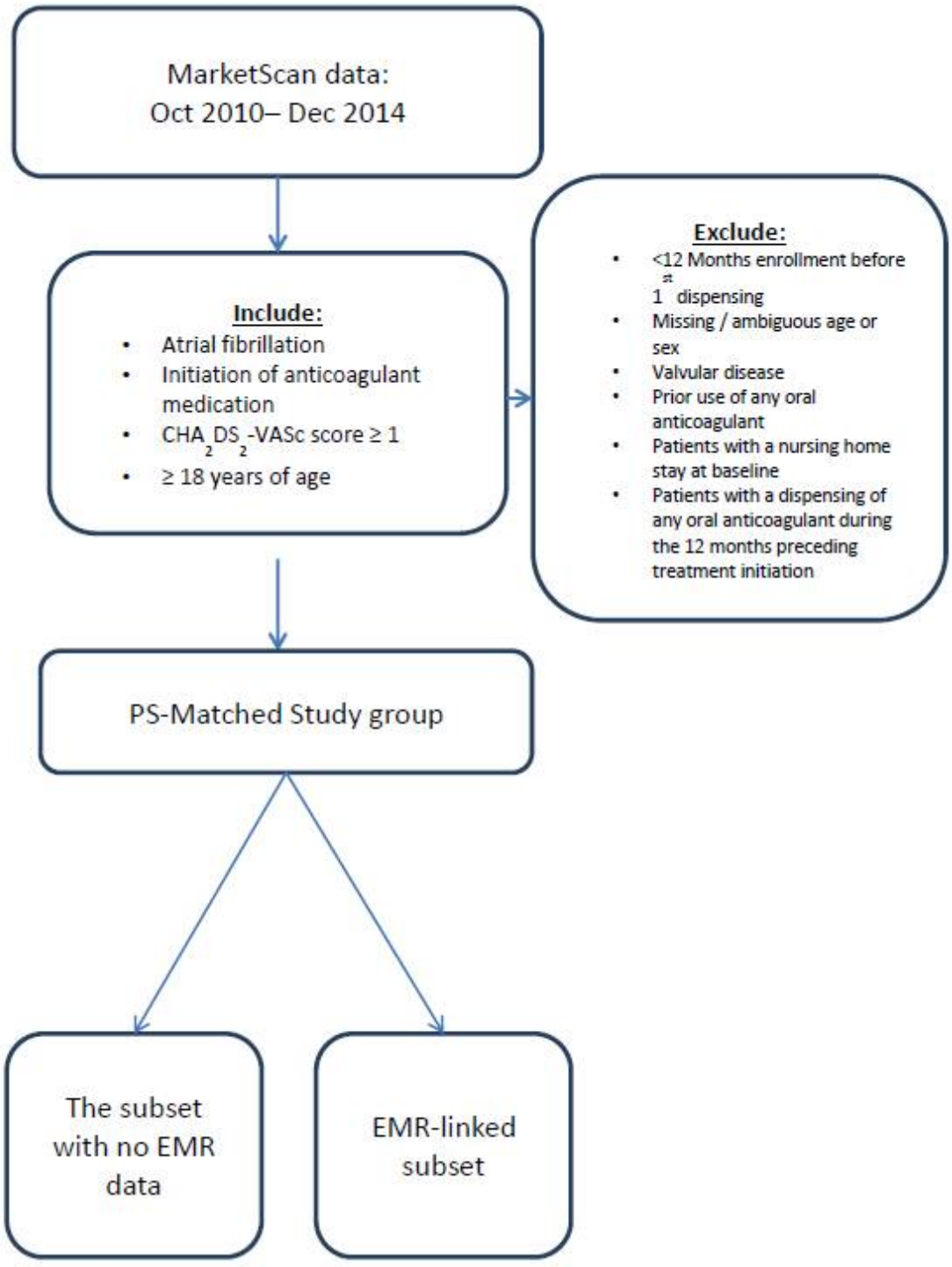
Cohort formation

Initiators of dabigatran and warfarin will be matched on their PS to initiate the treatment of interest (dabigatran) and the calendar quarter of initiation. PS will be derived from predicted probabilities of treatment initiation with dabigatran as compared to warfarin estimated in a logistic regression model that includes all claims-based covariates identified in this protocol [redacted] The PS will be used to match dabigatran initiators to warfarin initiators on a 1:1 fixed ratio basis using a nearest-neighbor algorithm.

9.11.2 EMR-linked subset

From the PS-matched cohorts we will identify patients who have EMR data available. Most analyses will be performed in this group. We expect that the EMR-linked subset is a random subset so that the covariate balance achieved by propensity score matching in the overall cohorts will be retained in the EMR subsets. However, due to chance, some imbalances in baseline characteristics may occur. We will check the average PS among the linked subset and inspect covariates among them prior to proceeding with the analysis. In the event of imbalances, we will proceed with analyses outlined after stratifying by the propensity score.

Figure 1 Patient Selection Flow Chart



We will provide Truven with linkage IDs and exposure indicators. Within the EMR-linked subset, Truven will evaluate the balance of the EMR clinical characteristics across exposure groups (see section 9.7 Data Analysis for detailed description).

9.12 BIAS

Various design and analysis methods will be implemented to reduce the potential for bias in the study. We will employ new-user cohorts of dabigatran and warfarin in order to address differences that might arise in the comparison of newer and older treatments, such as survivor bias and attrition of susceptibles. The comparator cohort will be formed warfarin initiators with similar clinical profiles to dabigatran initiators to reduce confounding by indication. We will employ propensity score matching of dabigatran and warfarin cohorts in order to improve the balance of the cohorts with respect to numerous variables.

As a validation study, the aim of this study is to assess the magnitude of potential confounding that might be present in the main cohort study as a result of non-claims characteristics that are both associated with choice of anticoagulant and predictive of study outcomes.

10. PROTECTION OF HUMAN SUBJECTS

This study will be submitted to the Institutional Review Board (IRB) of [redacted]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As an observational study based on existing data all patient data will be de-identified and analyzed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable for this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim and final reports will consist of a description of the methods, including patient selection and variable definitions along with tabular summaries of cohort characteristics, numbers of patients receiving each anticoagulant and associated follow-up time. Counts of outcomes and corresponding rates and measures of association will be presented. The tabular results will be followed by an interpretive summary along with a discussion of the findings and implications.

Manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences.

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13.1 PUBLISHED REFERENCES

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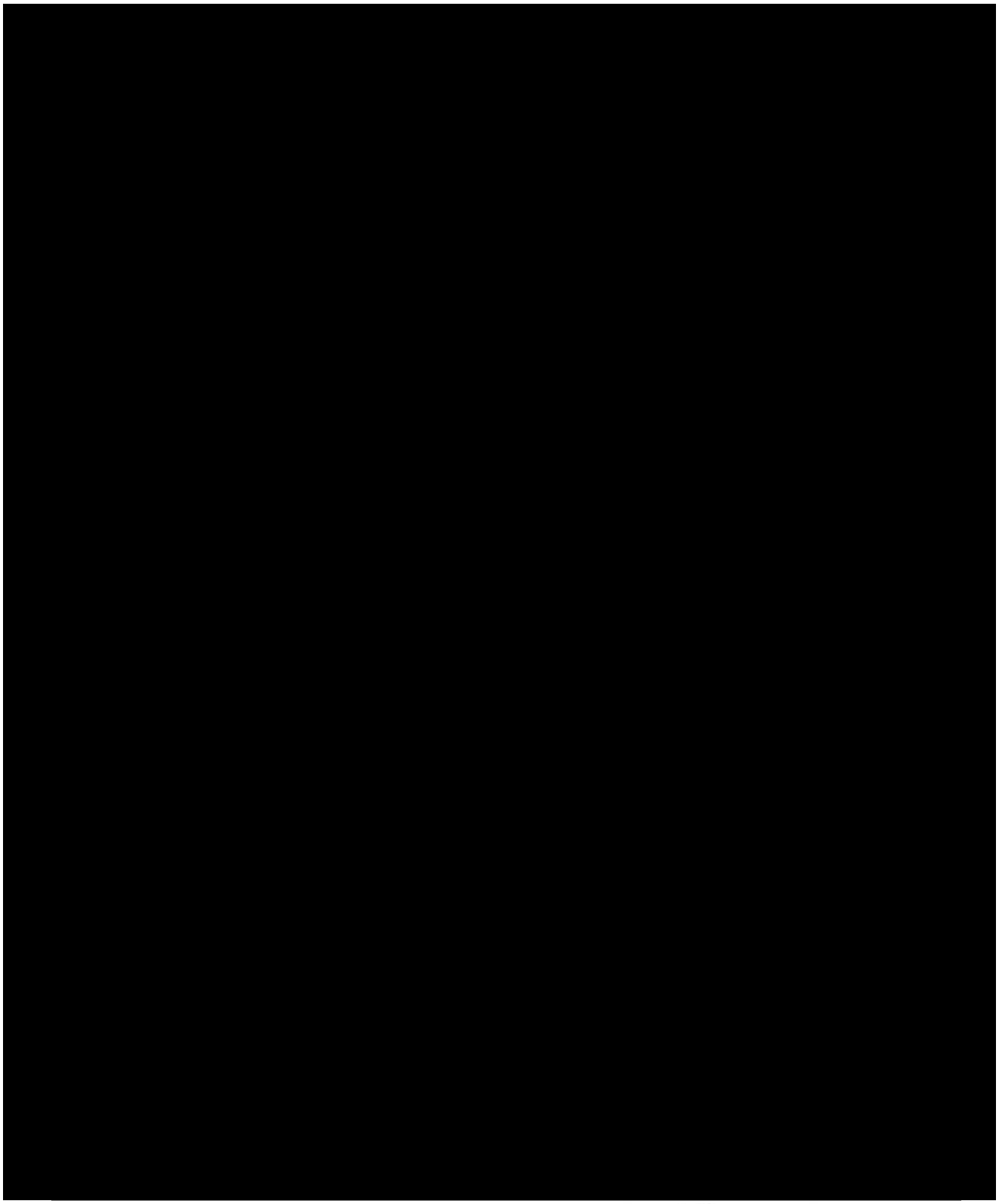
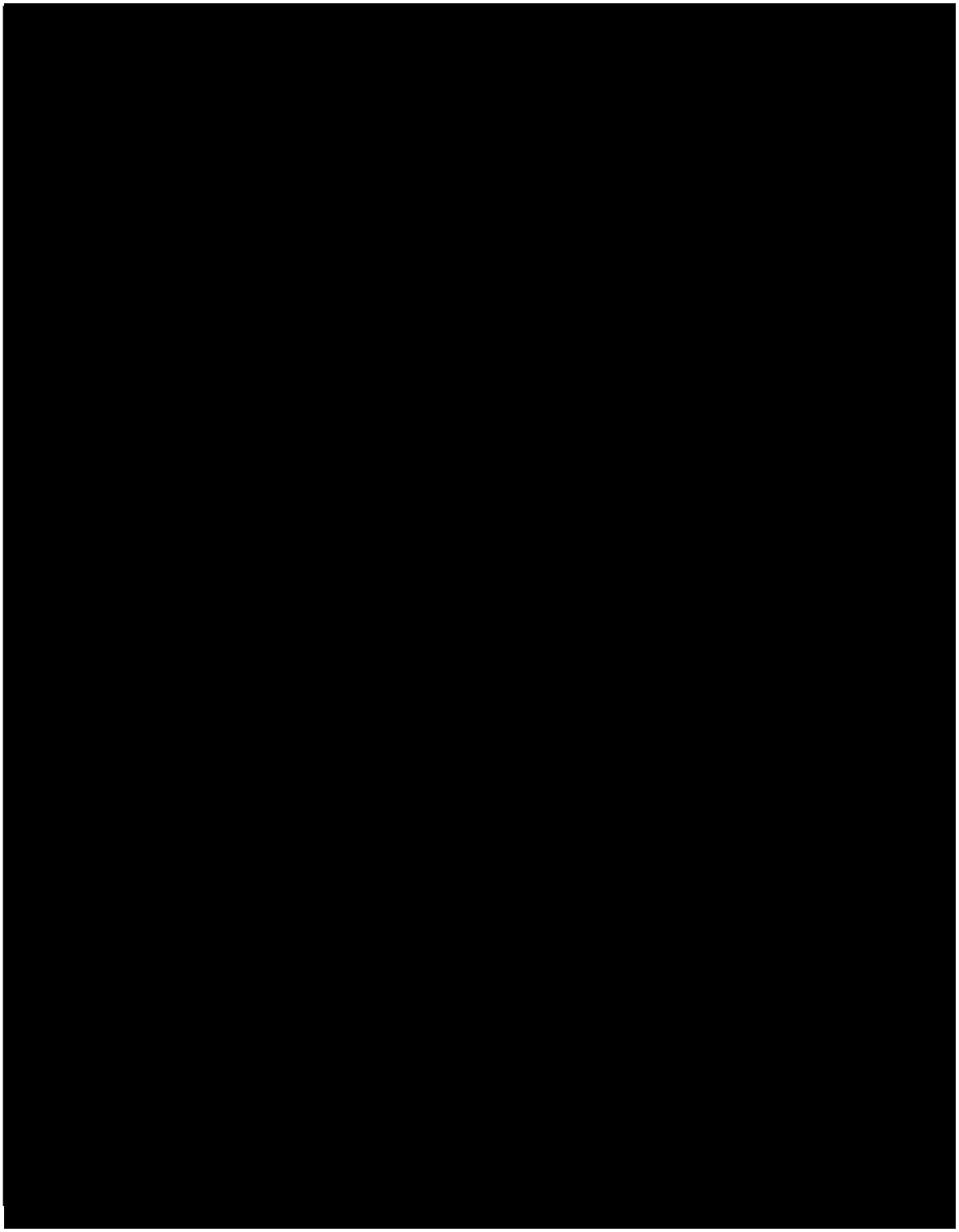
13.2 UNPUBLISHED REFERENCES

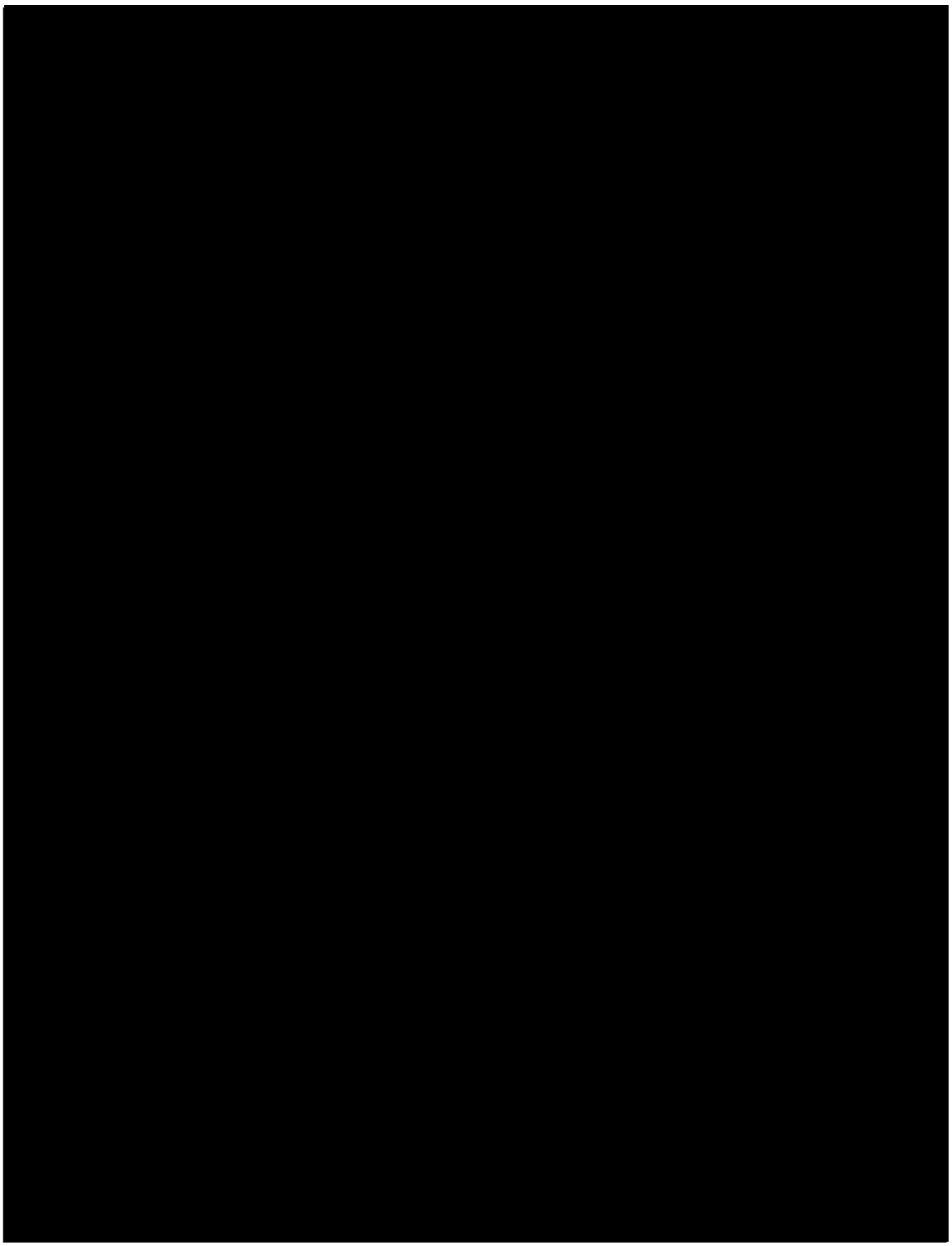
None

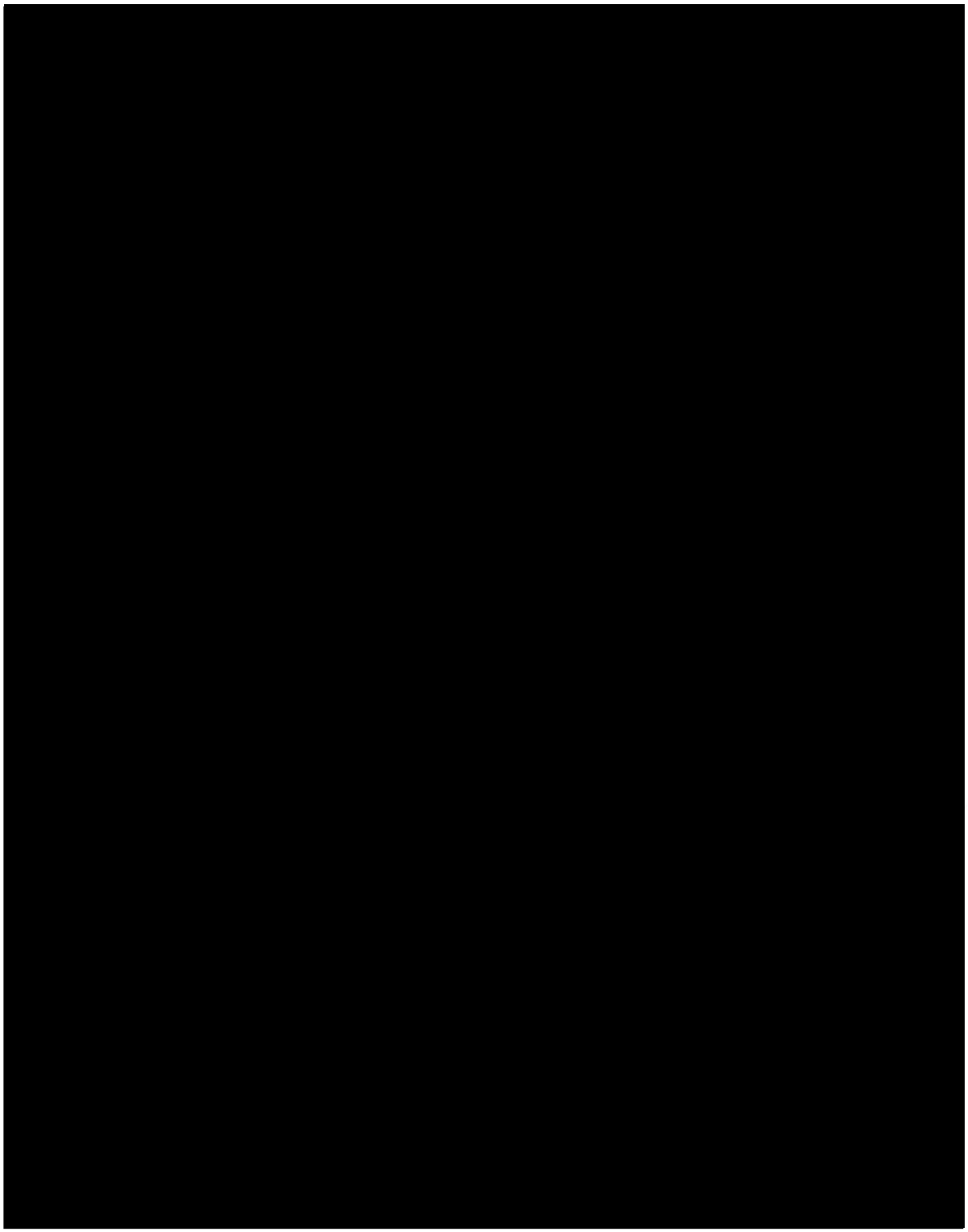
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

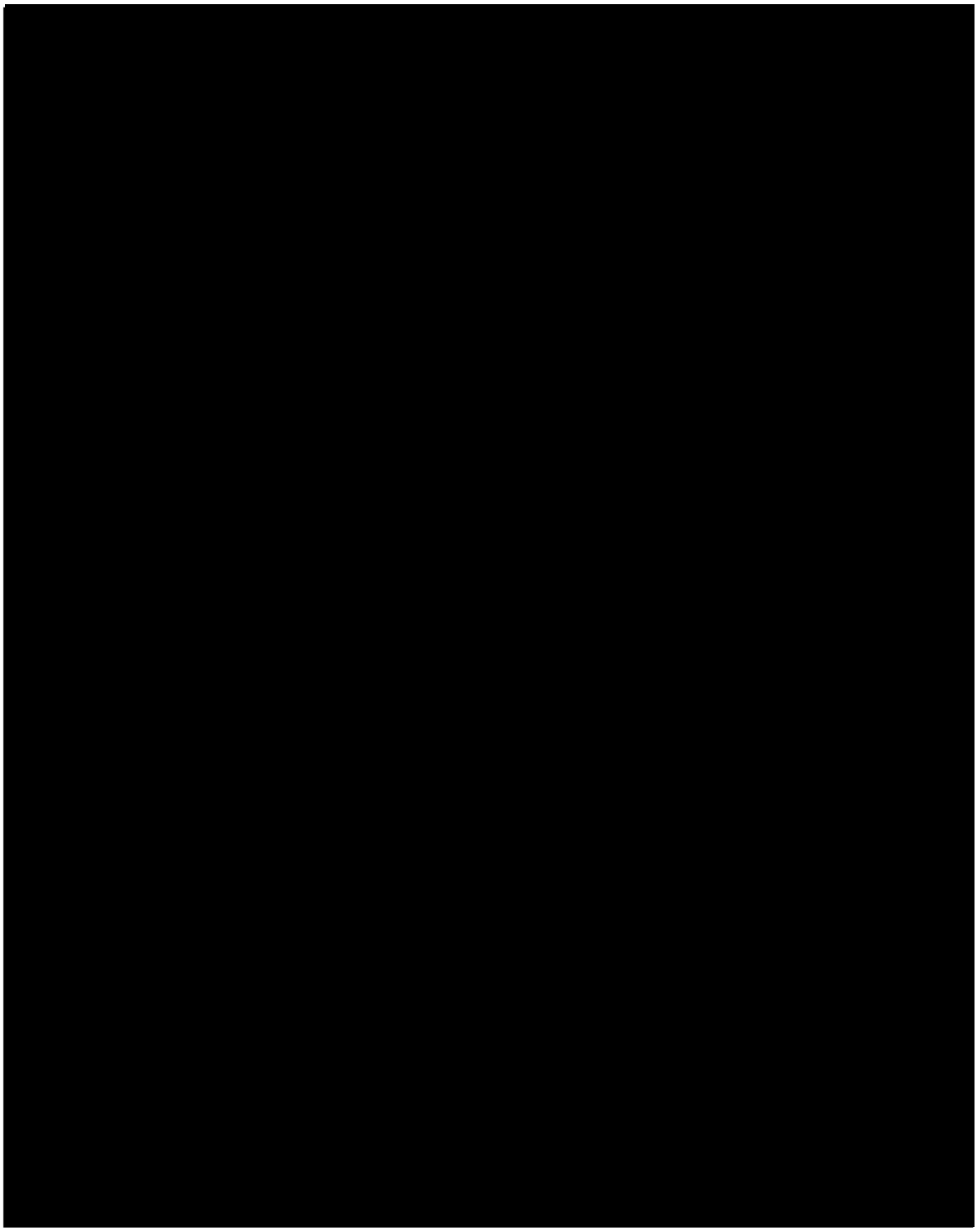
None

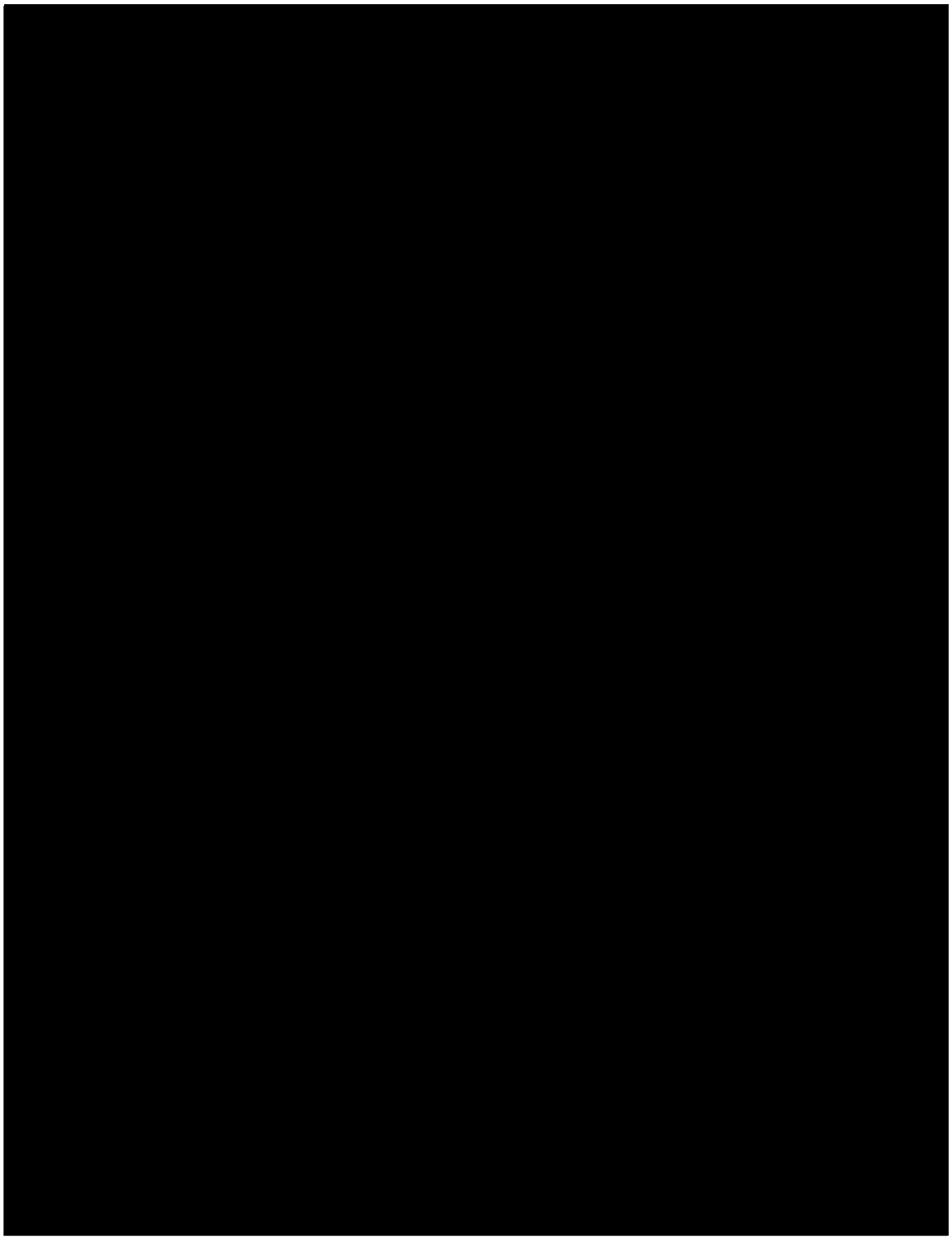












ANNEX 3. ADDITIONAL INFORMATION

None