1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Evaluation of potential off label use of dabigatran etexilate in Europe: A drug utilisation study in Cegedim France, Denmark, and CPRD UK 26 August 2016 [redacted] RTI Health Solutions		
Keywords:	Dabigatran, OACs, drug utilisation, off-label, atrial fibrillation		
Rationale and background:	Dabigatran etexilate (Pradaxa) is an oral anticoagulant that was approved in Europe in 2008 for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery. In August 2011, dabigatran etexilate was also approved for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) with one or more risk factors [P11-09429]. A third indication for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and secondary prevention of recurrent DVT and PE in adults has been in place since June 2014. Under a regulatory pharmacovigilance commitment, the European Medicines Agency (EMA) endorsed a study protocol (V2.0, dated 8 March 2012) for a multidatabase drug utilisation study (DUS) to evaluate the potential off-label use of dabigatran etexilate outside of the atrial fibrillation indication. The protocol was revised to include several Pradaxa label updates and changes in target countries based on final reimbursement conditions. The revised study protocol, V4.0 dated 19 May 2014, was endorsed by the EMA Committee for Medicinal Products for Human Use (CHMP) on 24 July 2014.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
Research question and objectives:	The main objectives of this study were the following: • To estimate the proportion of off-label use in new users of dabigatran etexilate according to the electronically recorded clinical indication or generated proxies for indication, as available in each database. • To describe the characteristics of new users of dabigatran etexilate, including dose, demographics, clinical indication, morbidity, and use of other medications prior to the first captured prescription, stratified by usage sub-group: on- or off-label use.		
Study design:	Descriptive, observational, multinational, European cross-sectional study of new users of dabigatran etexilate that characterised on- and off-label status and other medical characteristics at the time of the first captured dabigatran etexilate prescription.		
Setting:	The study was implemented using data collected in three data sources and countries: • Cegedim Strategic Data Longitudinal Patient Database (CSD-LPD) in France • National Health Databases in Denmark • Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK)		
Subjects and study size, including dropouts:	*The study population* included new users of dabigatran etexilate in the study period. *New users* were defined as those patients who initiated treatment with dabigatran etexilate during the study period and who had not used it during the previous year. The *index date* was defined as the date on which each identified new user received the first prescription (*index prescription*) for dabigatran etexilate. Patients who received a new prescription of dabigatran etexilate were required to meet the following criteria, as ascertained from each of the data sources: have at least 1 year of enrolment in the electronic data source and had not been prescribed dabigatran etexilate during the 1-year period prior to the index date. A minimum of 1 year prior to the index date was considered the "baseline period."		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
	The estimated study size for each country-specific data source was approximately 5,000 new users of dabigatran etexilate. The study period for France covered the time period since approval of the SPAF indication in 01 August 2011 to 30 June 2014. New users were identified from panels of cardiologists and general practitioners (GPs). Because there is no possibility to link patients across panels, all the results were stratified by panel. The study period for Denmark covered the time period since approval of the SPAF indication in 01 August 2011 to 30 November 2013. The study period for the UK covered the time period since approval of the SPAF indication in 01 August 2011 to 30 August 2015.		
Variables and data sources:	The main outcome, which is the primary outcome of the study, was the proportion of potential off-label use estimated among new users of dabigatran etexilate in each of the data sources. No additional secondary outcomes were defined. No interim analyses were planned or conducted. New users were characterised at the index prescription, including comorbidities and comedications. In France, this characterisation was stratified according to the type of physician that had issued the prescription (cardiologist or GP). The definition of off-label use of oral dabigatran etexilate was based on use for a disease or medical condition other than the labelled indications, as described and documented in the data source used in the respective countries, taking into account the changes in the label within the study period. For the French, Danish, and UK components of this study, the approved label indications until June 2014 (prevention of venous thromboembolism [VTE] after hip or knee surgery and prevention of stroke and systemic embolism in atrial fibrillation) were applied to define the on-label group. For the prevention of stroke/systemic embolism in atrial fibrillation specifically, the list of risk factors to be considered was modified in December 2013, and this was taken into account in France and the UK to define off-label use from that time forward.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

A new indication for treatment of DVT and PE and secondary prevention of recurrent DVT and PE in adults has been in place since 03 June 2014. For the French study component and the CPRD, no patients with an index date during June 2014 had this indication recorded.

Diagnoses associated with potential off-label use of dabigatran were identified with algorithms and used as proxies to identify potential clinical indications. ICD-10 codes[1] and codes from the specific dictionaries in place in each data source were used in creating the algorithms.

Definitions and levels of on-label and off-label use

Two levels of on-label use were investigated to determine the potential off-label groups:

- The first level included a broad definition of on-label use based on the main code(s) for the approved clinical indications, e.g., atrial fibrillation.
- The second level, as a subset of the first level, is a more restrictive definition of on-label use that excluded patients that may have had conditions for which the medication is not indicated, e.g., valvular heart disease or low-risk patients with non-valvular atrial fibrillation, based on the information included in the database.

In a third level, the dose strength of the index prescription and duration of use were used to further classify on- and off-label use according to recommendations for the labelled indications, including use in special populations.

Contraindications

The proportion of new users of dabigatran etexilate with contraindications applicable at the time of the index date was described.

1 ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
Results:	*France (CSD-LPD)* During the study period (August 2011 through June 2014), we identified 1,706 new users of dabigatran etexilate from the cardiologist panel and 2,813 from the GP panel. The mean age (SD) was 75.5 (10.0) years and 74.0 (10.4) years, respectively. There were more men than women in the cardiologist panel (825 men [57.9%], 599 women [42.1%]) and in the GP panel (1,541 men [54.8%], 1,272 women [45.2%]). Among new users of dabigatran etexilate, the diagnosis of atrial fibrillation was present in the electronic records in 76% of the cardiologist group and 65% of the GP group. Atrial fibrillation was classified as non-valvular among 74% (cardiologist) and 64% (GP) of the total new dabigatran etexilate users. None (cardiologist) and 1% (GP) of new dabigatran etexilate users had a recorded diagnosis of hip or knee replacement. No patients with an index date during June 2014 had a recorded indication of VTE treatment/secondary prevention. Among patients whose first prescription was written by a cardiologist, the prevalence of potential off-label use was estimated to be 24.1% (95% confidence interval [CI], 22.1%-26.1%) using the broad definition and 37.5% (95% CI, 35.2%-39.8%) using the restrictive definition. For GPs, the prevalence of potential off-label use was estimated to be 34.0% (95% CI, 32.3%-35.8%) with the broad definition and 44.1% (95% CI, 42.2%-45.9%) with the restrictive definition. All new users were adults aged 18 years or older. Therefore, no paediatric patients were identified as using dabigatran etexilate off-label. Under the broad definition, among potential off-label users, the most frequently recorded diagnoses associated with the potential off-label use of dabigatran etexilate were atrial flutter (11.9%, cardiologist panel; 6.6%, GP panel) and other arrhythmias or cardioversion (18.0%, cardiologist panel; 27.6%, GP panel). In 36.7% (cardiologist group) and 38.9% (GP group) of the potential off-label users, no diagnoses potentially related to the indication of anticoagulant treatment could be identified.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

Denmark (National Health Databases)

During the study period (August 2011 through November 2013), we identified 28,619 new users of dabigatran etexilate. The mean (SD) age was 71.8 (10.9) years, and there were more men (15,052 [52.6%]) than women (13,567 [47.4%]).

Among new users of dabigatran etexilate, the diagnosis of atrial fibrillation was present in 59%, and 57% were classified as having non-valvular atrial fibrillation (97% of those with a diagnosis of atrial fibrillation). Overall, 24% of new users had a recorded diagnosis of hip or knee replacement.

The estimated prevalence of potential off-label use was 17.1% (95% CI, 16.6%-17.5%) using the broad definition and 29.1% (95% CI, 28.4%-29.7%) using the restrictive definition. Three paediatric patients with dabigatran etexilate prescriptions were identified.

The most frequently recorded diagnoses associated with potential off-label use of dabigatran etexilate were general prophylaxis/treatment of thrombus in any site (16.3%), anticoagulation for heart valve replacement or stent (10.5%), and stroke and transient ischaemic attack (TIA) (7.8%); whereas only 0.1% of potential off-label users had a recorded diagnosis of atrial flutter without atrial fibrillation. In a majority of cases of potential off-label use (52.6%), no potential indication for the use of dabigatran etexilate could be identified.

UK (CPRD)

During the study period (August 2011 through August 2015) we identified 3,435 new users of dabigatran etexilate (2,150 linkable to Hospital Episode Statistics [HES] [62.6%] and 1,285 not linkable to HES [37.4%]). The overall mean (SD) age was 73.7 (11.3) years, and there was a higher proportion of men (1,926 [56.1%]) than women (1,509 [43.9%]).

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

Among new users of dabigatran etexilate, the diagnosis of atrial fibrillation was present in the records of 87% of the new users (88.3% in HES-linkable patients, 83.5% in non-linkable patients). Atrial fibrillation was classified as non-valvular among 84% of new users (84.6% in HES-linkable patients, 81.9% in non-linkable patients). Overall, 4% of new users had a recorded diagnosis of hip or knee replacement (5.0% in the HES-linkable group, 3.5% in the non-linkable group), and 1.2% had a recorded indication of VTE treatment/secondary prevention starting in July 2014 (1.0% in HES-linkable patients, 1.5% in non-linkable patients). Additional (post hoc) analyses confirmed that no patients with an index date during June 2014 had a recorded indication of VTE treatment/secondary prevention.

Under the broad definition, the estimated prevalence of potential off-label use was 7.9% (95% CI, 7.0%-8.8%) overall, 5.7% (95% CI, 4.7%-6.7%) in HES-linkable patients, and 11.5% (95% CI, 9.8%-13.4%) in non-linkable patients. Under the restrictive definition, the estimated prevalence of potential off-label use was 20.5% (95% CI, 19.1%-21.9%) overall, 17.4% (95% CI, 15.8%-19.1%) in HES-linkable patients, and 25.6% (95% CI, 23.2%-28.1%) in non-linkable patients. Only one paediatric patient with a dabigatran etexilate prescription was identified.

Overall, the most frequently recorded diagnoses associated with the potential off-label use of the drug were general prophylaxis/treatment of thrombus in any site (16.3%), stroke and TIA (16.3%), and treatment/secondary prevention of VTE (8.5%), whereas only 3% of potential off-label users had a recorded diagnosis of atrial flutter without atrial fibrillation. In 47% of cases, no potential indication for the use of dabigatran etexilate could be identified.

Pooled analyses

Per the protocol, the results were combined in a pooled, random-effects model. The combined estimated prevalence of potential off-label use of dabigatran etexilate was 18.2% (95% CI, 8.9%-27.5%) under the broad definition and 30.3% (95% CI, 21.1%-39.6%) under the restrictive definition. However, heterogeneity across studies was very high ($I^2 \approx 100\%$ for all analyses), suggesting that the pooled results should be interpreted with caution.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
Discussion:	*Study design* The study used health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to differential reporting of prescriptions or impacts of contacts with patients and health care professionals. Studies evaluating data already collected may be the most efficient and accurate way to assess potential off-label use. However, it must be acknowledged that underrecording or misclassification of clinical indications and risk factors is a potential issue for all data sources. It is important to consider that any prevalence estimation of potential off-label use is highly dependent on the databases and the sources and completeness of information. Therefore, for this type of research (evaluating potential off-label use), very detailed information on clinical conditions is of utmost importance. The sources of information for clinical conditions were highly variable across countries/data sources, and this is likely to have been the major driver of the different prevalences between study populations. Also, prescriptions in the hospital setting that are not continued after discharge are not captured in any of the data sources. Since this was a cross-sectional study, the capture of follow-up prescriptions for dabigatran etexilate or other comedications of interest based on the observation period of 90 (or 120) days after index date was very limited. The following sections contain more details regarding the different analyses. *France (CSD-LPD)* Limitations Lack of linkage. Individual patients in each panel cannot be linked, and duplicate patients cannot be identified. Limited information available. Diagnosis and procedural codes for hospital episodes are not available in this data source. Also, physicians record only conditions that concern their day-to-day medical practice. Regarding indications for prescriptions, only diagnoses made by physicians within the same panel are available, so the indication information for some patients may be missing. As a result, off-label use might have been overestimated.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
	Finally, prescriptions available in the medical record are only those issued for each patient by the physician in the panel. Comedications taken by the patient and prescribed by other physicians in a different panel or outside the panels are not recorded. Potential for indication and other data to be incorrectly recorded in the data sources. Recording the indication (diagnosis) for each prescribed treatment is mandatory in the Cegedim software, but there may be errors, and the physician is free to enter (or not) any other associated diagnosis (according to an in-house thesaurus list). Potential for incomplete/missing data. No individual patient identifiers are available in CSD-LPD. Therefore, physicians cannot be reached to provide information for missing data. The diagnosis of atrial fibrillation was present in the records for 75.9% of the cardiologist group and 64.9% of the GP group. Although algorithms based on diagnoses, procedures, and treatments were developed, some indications might have not been identified due to unrecorded information. The 11% difference across the two panels is reassuring about the appropriateness of using information collected from cardiologists in addition to GPs, as they provide complementary information. However, duplicate patients are possible because some of the prescriptions might have been initiated by the cardiologist, with follow-up prescriptions issued by the GP. Recording of information was likely differential across panels, with cardiovascular conditions more frequently recorded by cardiologists but other chronic conditions more likely recorded by general practitioners. Only a few patients with hip or knee replacement were identified. Because of the characteristics of the panels, this indication was probably not well captured in CSD-LPD. As highlighted above, among the conditions frequently associated with potential off-label use, 12% (cardiologist group) and 7% (GP group) had a diagnosis of atrial flutter. These findings need to be interpreted with caution when considering these patients to constitute potential off-label users because many of these patients may have had atrial fibrillation combined with atrial flutter, or some initially labelled as “atrial flutter” may have converted into atrial fibrillation at some point. Also, a number of patients with atrial fibrillation might have been coded as “cardioversion” in CSD-LPD. Thus, it is possible that a non-negligible proportion of these patients		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

were actually on-label users, at least under the broad definition.

Denmark (National Health Databases)

Limitations

- Diagnosis and procedural codes are available for hospital episodes and for hospital-ambulatory care episodes. However, data on clinical conditions that are managed mainly by primary care physicians are likely to have been missed, potentially overestimating off-label use.
- The potential for incomplete/missing data exists. The national registers in Denmark do not capture clinical data in detail. Most of the information corresponds to diagnosis or procedural codes and data on drugs.
- Recording of the indication is not available in the registers, and indication can be derived only by using proxies (diagnosis and procedural codes and medications). This may have resulted in the potential misclassification/underdetection of some treatment indications.
- No data available on prescribed daily dose or length of supply from the Danish National Prescription Registry.

In Denmark, the prevalence of potential off-label use of dabigatran etexilate using the broad definition was 17.0%. Generally, a limitation of the algorithm used in the Danish component is the fact that it relies on hospital diagnoses in order to identify on-label indications. While it can be assumed that this captures all patients undergoing a hip or knee replacement procedure in the Danish registers, the same may not be the case for patients with atrial fibrillation due to three potential factors:

Lack of data from the primary care sector. For patients with atrial fibrillation who are treated only in the primary care sector, the indication would not be captured by the Danish registries.

Delay of registration of the atrial fibrillation diagnosis in the secondary sector (e.g., patients who initiaited treatment in the primary care sector and only afterwards were referred to the hospital)

Coding errors/omission leading to no recorded atrial fibrillation diagnosis despite the patient presenting to the hospital with this condition

All of these factors may have led to overestimation of off-label use.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

UK (CPRD)

Limitations

- HES linkage was not available for a significant proportion of patients in the CPRD (37.4%).
- Prescriptions for dabigatran etexilate issued in the hospital setting or by specialists are not captured.
- Potential for indication and other data to be incorrectly recorded in the data sources. There is no process within the CPRD software that checks whether a diagnosis is correctly linked to a prescription. Therefore, misclassification/underrecording cannot be ruled out.
- Potential for incomplete/missing data. The recording by GPs of relevant clinical data and tests generated during hospital admissions may be poor. This is particularly relevant among patients not linkable to HES.
- Use of Read codes, which includes thousands of codes. Some relevant codes may have not been captured by the final algorithms.

The UK component showed the lowest prevalence of potential off-label use under both definitions. Because CPRD includes detailed primary care information, it is likely to have led to the accurate detection of atrial fibrillation cases. Consistent with this, the prevalence of atrial fibrillation in CPRD was the highest of the three components. Because CPRD also included hospital diagnostic information in a large portion of patients (63% were linkable to HES), it may have had a higher sensitivity for the detection of *acute* dabigatran etexilate indications (hip or knee replacement surgery) than purely primary care databases. Consistent with this, the lowest prevalence of potential off-label use was estimated among HES-linkable CPRD patients. The estimates of on-label and off-label use derived from CPRD are likely to be based on the most complete patient history information, and therefore be the most accurate, particularly those for HES-linkable patients.

Pooled analyses

The very high heterogeneity observed across studies and partially quantified by the I^2 statistic suggests that the focus should be on the results in each of the individual study populations rather than on the pooled

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**

estimates.

Potential off-label indications for dabigatran etexilate

The clinical diagnoses most frequently associated with the potential off-label use of dabigatran etexilate varied across study populations. In CSD-LPD (France), a large portion of potential off-label users had recorded diagnoses of atrial flutter and other arrhythmias/cardioversion, but in CPRD and Denmark the frequency of those diagnoses was marginal, with the main potential off-label uses of the drug being prophylaxis/treatment of thrombotic processes and stroke/TIA. These differences may be the consequence of differences in coding practices, as well as in the data available in each of the data sources.

Clinical profile of potential on-label and off-label users of dabigatran etexilate

Differences between potential on-label and off-label users in the frequency of recorded clinical features varied slightly across the three study populations. The differences were more marked in CPRD and more subtle in CSD-LPD.

Conclusion

In all countries, atrial fibrillation was the most frequently recorded potential indication among new users of dabigatran etexilate. The prevalence of recorded hip or knee replacement surgery varied markedly across populations, probably as a consequence of differences in the sources of data used. Under a broad definition of on-label use, estimates of potential off-label use of dabigatran etexilate ranged from 5.7% in HES-linkable patients in CPRD (UK) to 34% in the French CSD-LPD general practitioner panel. Under a more restrictive definition, potential off-label use ranged from 17.4% in HES-linkable patients in CPRD (UK) to 44.1% in the French CSD-LPD general practitioner panel. Differences in the clinical profiles of potential on-label and off-label new users of dabigatran etexilate, as well as in the distribution of conditions associated with potential off-label use, varied across populations.

It is important to keep in mind the inherent limitations of each of the data sources when interpreting the results, most of which may have led to some overestimation of off-label use of dabigatran etexilate—particularly in CSD-LPD. The high proportion of potential off-label users in which no

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
	reason for use of anticoagulant therapy could be identified suggests under-recording of clinical indications in many patients. In this context, because dabigatran etexilate may be used for the treatment of both *acute* and *chronic* conditions (such as after hip or knee replacement surgery and atrial fibrillation, respectively), CPRD is likely to provide the most accurate estimates of potential off-label use of the drug, particularly among patients with HES-linkable data. On the other hand, for France and Denmark, the data need to be interpreted cautiously because of the limited information available. These databases would be strengthened for this type of research if data for hospital episodes (in France) or for primary care episodes (in Denmark) were available. Due to the limitations in the availability of some of the data, both the broad and restrictive definitions of on-label and off-label use should be considered to better understand the potential off-label use of the drug in clinical practice. The marketing authorisation holder informs that it has committed to continue to distribute and further improve the distribution of the educational materials (Prescriber Guide (PG) and Patient Alert Card (PAC)) in European countries in which Pradaxa is marketed as a result of a study evaluating the effectiveness of this risk minimization measure which was completed in February 2016. The educational material, a risk minimization measure imposed by EMA together with the SPAF approval in August 2011, consists of one prescriber guide per indication (DVT/PE and SPAF prescriber guides as one document and the pVTEp prescriber guide as a separate document), a patient alert card applying to all indications, a communication plan applying to all indications, and the SmPC applying to all indications. Specifically, the distribution of the PG and PAC to the health care providers is believed to support that Pradaxa is appropriately prescribed and used in accordance with the approved indications and labelling.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim		
Names and affiliations of principal	[redacted], RTI Health Solutions (RTI-HS) [redacted] RTI-HS [redacted] RTI-HS		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa ®			
Name of active ingredient: Dabigatran etexilate (ATC: B01AE07)			
Report date: 15 December 2016	**Study number:** 1160.144	**Version/Revision:** 1.0	**Version/Revision date:**
investigators:	[redacted] RTI-HS [redacted] RTI-HS [redacted] CSD-LPD, France [redacted] CSD-LPD, France [redacted] University of Southern Denmark (SDU), Denmark [redacted] SDU, Denmark [redacted] SDU, Denmark		