PASS Information

Title	Assessment of the effectiveness of risk minimisation measures set up for new safety information of Efient® a multinational survey among physicians to evaluate their knowledge and consideration of the new safety information of prasugrel in France, Germany, Sweden, and the Netherlands
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Date of last version	NA
EU PAS Register No:	ENCEPP/SDPP/6355
Active substance	Prasugrel (ATC code : B01AC22)
Medicinal product(s):	Prasugrel (Efient)
Marketing authorisation holder(s)	Eli Lilly and Company (Lilly)
Joint PASS	No
Research question and objectives	The research question is whether the new safety information included in the additional risk minimisation measures (Direct Healthcare Professional Communication (DHPC), international congress and journal publication) were effective in: • educating Healthcare Professionals (HCPs) about the increased bleeding risk when pre-treating with a loading dose of Efient® (prasugrel) prior to diagnostic coronary angiography in UA/NSTEMI patients, and • influencing their consideration of this risk when prescribing a loading dose of Efient® (prasugrel). **Primary objective**: to evaluate the proportion of targeted physicians who are knowledgeable of the new safety information for prasugrel. **Secondary objective**: to evaluate whether the physicians will consider the safety information when prescribing prasugrel.
Country(-ies) of study	France, Germany, Sweden, and the Netherlands
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2. List of Abbreviations

Term	Definition
ACS	acute coronary syndrome
AE	adverse event
ASOCS	Association des Sociétés d'étude de l'Opinion et du Comportement dans le domaine de la Santé (Association of Opinion and Behaviour in health field research companies)
DHPC	direct healthcare professional communication
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology
EphMRA	European Pharmaceutical Marketing Research Association
ESC	European Society of Cardiology
ESOMAR	European Society for Opinion and Market Research (German association)
EU	European Union
HCP	healthcare professional
MAH	marketing authorisation holder
NSTEMI	non-ST segment elevation myocardial infarction
PAS	postauthorisation study
PASS	postauthorisation safety study
PCI	percutaneous coronary intervention
PSUR	periodic safety update report
RMM	risk minimization measures
RMP	risk minimization plan
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
STEMI	ST segment elevation myocardial infarction
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UA	unstable angina

3. Responsible parties

Sponsor:

Eli Lilly and Company (Lilly)

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Subcontractor:

IMS Health, Real world evidence solutions (RWES) and Medical Radar divisions

Dr. Massoud Toussi: Principal, Medical Director, IMS RWES, France

4. Abstract

4.1. Rationale and background

Efient® (prasugrel) is an oral antiplatelet drug, coprescribed with acetylsalicylic acid (ASA), indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (ACS), including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), or ST segment elevation myocardial infarction (STEMI) (Montalescot et al. 2013), undergoing primary or delayed percutaneous coronary intervention (PCI) (EMA 2013). Efient® (prasugrel) was approved in 2009, both in the United States and in Europe.

The ACCOAST clinical trial showed that NSTEMI patients who received 2 loading doses of 30 mg, the first at the time of diagnosis and with a median of 4 hours (up to 48 hours) before PCI and the second at the time of PCI, had an increased risk of major and minor bleedings. The pretreatment has no additional benefit on prevention of new ischemic events in these patients (Montalescot et al. 2013). Therefore, in UA/NSTEMI-ACS patients undergoing PCI within 48 hours of hospitalization, a single 60-mg loading dose should be given at the time of PCI in order to minimise the potential risk for increased bleeding. This new safety information and the clinical trial results were published in the New England Journal of Medicine (Montalescot et al. 2011) and presented at the European Society of Cardiology (ESC) Congress (Montalescot 2013) both in September 2013.

These 2 risk minimisation measures (RMM) were implemented as part of the Efient® (prasugrel) risk management plan (RMP). The new safety information was added in an updated version of the Summary of Products Characteristics (SmPC), and prescribers and other healthcare providers were informed via Direct Healthcare Professional Communication (DHPC) distributed in December 2013 in the countries where the drug was marketed. The DHPC was the third RMM that provided this new safety information to physicians.

The MAH will track and report implementation of the RMM in the appropriate regulatory submission document. This postauthorisation safety study (PASS) will serve to evaluate the process and outcome indicators to assess that physicians received the new safety information, understood it and will consider this information when prescribing prasugrel.

4.2. Research question and objectives

The research question is whether the new safety information included in the risk minimisation measures (DHPC, international congress, and journal publication) were effective in:

- educating HCPs about the increased bleeding risk when pretreating with a loading dose of Efient® (prasugrel) prior to diagnostic coronary angiography in UA/NSTEMI patients, and
- influencing their consideration of this risk when prescribing a loading dose of Efient® (prasugrel).

Primary objective: to evaluate the proportion of targeted physicians who are knowledgeable of the new safety information of prasugrel.

Secondary objective: to evaluate whether the physicians will consider the safety information when prescribing Efient® (prasugrel).

4.3. Study design

This physician survey is cross-sectional, noninterventional, and multinational.

The survey will be conducted through a web questionnaire among prescribers and potential prescribers of Efient® (prasugrel), in a hospital setting, in 4 European countries (France, Germany, Sweden, and the Netherlands).

4.4. Population

Inclusion criteria:

- Physicians, prescribers, or potential prescribers, of Efient® (prasugrel),
- Specialists of any of those targeted for the DHPC:
    - cardiologists in all countries
    - physicians working in emergency departments, according to country specificities (cardiologists, emergency physicians, and physicians working in first aid)

Exclusion criteria:

- Physicians who do not treat patients or who may have a conflict of interest (that is, physicians employed by regulatory bodies, pharmaceutical industries, and so on)
- Physicians who do not know Efient® (prasugrel)

4.5. Variables

The collected information will include: demographics, type of practice, awareness and knowledge about the new safety information on Efient® (prasugrel), routes of communication, and the intention of the physician to consider the new safety information.

The endpoint of interest is the proportion of appropriate answers to the questions regarding the new safety information of use of Efient® (prasugrel) (see the questionnaire in Annex 3), as described in the DHPC and the updated SmPC.

The endpoints will be assessed overall, by country, and among subgroups of specialties.

4.6. Data sources

The survey will be conducted among physicians from the 2 following data sources:

- Lilly's lists of physicians who were targeted for the DHPC
- IMS Medical Radar reference files

4.7. Study size

The sample size calculation is based on the survey objective, that is, to evaluate prescribers and potential prescriber knowledge concerning the new safety information of use of Efient® (prasugrel) as described in the DHPC and the updated SmPC.

As there is no evidence supporting the expected proportion of physicians who will be knowledgeable about the new safety information about Efient® (prasugrel), the worst case hypothesis will assume a proportion of 50% (conservative assumption). For a confidence interval of 95% and a precision of 5%, a total of 384 analysable physicians web questionnaires will be needed for the overall sample, which will be divided into country sample sizes according to the distribution of eligible physicians in each country.

4.8. Data analysis

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

Results will be presented overall and at country level per physician's specialty.

Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, Q1, Q3, minimum, and maximum. No missing data will be replaced. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals of 95% will be calculated when relevant.

Calculations will first be performed on raw data, per specialty. Then, they will be weighted according to the real proportion of targeted physicians in each country in order to accurately reflect the population the survey seeks to measure.

Possible occurrence of a selection bias will be assessed by comparison of the distributions of available characteristics (for example, region, age, gender, type of practice, and specialty) between the physicians who answered the questionnaire and those who did not want to or were not reachable.

4.9. Milestones

- Fieldwork - Start of data collection: approximately 01 July 2014
- Fieldwork - End of data collection: approximately 01 September 2014
- Final study report: approximately 30 November 2014

5. Amendments and updates

None.

6. Milestones

Milestones	Planned date
Start of data collection	01 July 2014
End of data collection	01 September 2014
<Registration in the EU PAS register> [EU PASS Only]	23 April 2014
Final report of study results	30 November 2014

7. Rationale and background

Efient® (prasugrel) is an oral antiplatelet drug, coprescribed with ASA, indicated for the prevention of atherothrombotic events in adult patients with ACS, including UA, NSTEMI, or STEMI (Montalescot et al. 2013), undergoing primary or delayed PCI (EMA 2013). Efient® was approved in 2009, both in the United States and in Europe.

At the time of the ACCOAST study, the posology for Efient® was: Efient® (prasugrel) treatment is initiated as a 60-mg single oral loading dose and then continued at 10 mg orally once daily. Patients taking prasugrel should also take ASA (75 to 325 mg daily). This drug may be administered with or without food and is available in 5 and 10 mg tablets (EMA 2013).

The ACCOAST clinical trial showed that NSTEMI patients who were pretreated with a loading dose of 30 mg, on a median of 4 hours before PCI followed by an additional dose of 30 mg at the time of PCI, had an increased risk of major and minor bleedings. In these patients, there was no additional benefit in prevention of ischemic events compared to a loading dose administered at time of PCI (Montalescot et al. 2011). Thus, to minimise the potential risk for increased bleeding in UA/NSTEMI-ACS patients, a single loading dose should be given at the time of PCI. The posology of the SmPC was modified to reflect this new timing of administration.

This new safety information and the clinical trial results were published in the New England Journal of Medicine (Montalescot et al. 2011) and presented at ESC Congress (Montalescot 2013) both in September 2013. These 2 RMM were implemented as part of the Efient® (prasugrel) RMP. The new safety information was added in an updated version of the SmPC, and prescribers and other healthcare providers were informed via a DHPC distributed in December 2013 in the countries where the drug was marketed. The DHPC was the third RMM that provided this new safety information to physicians.

The MAH will track and report implementation of the risk minimisation elements in the appropriate regulatory submission document for example, the periodic safety update report (PSUR). This PASS will serve to evaluate the process and outcome indicators to ensure that physicians received the new safety information, understood it, and will consider this information when prescribing prasugrel.

7.1. Rationale for country selection

The selection of the countries to be involved in the survey was based upon meeting all of the following criteria:

- countries where Efient® (prasugrel) is registered and marketed
- countries where observational or market research data show evidence of treatment with Efient® (prasugrel) before PCI
- sufficient Efient® (prasugrel) market share to achieve an adequate physicians sample in the country

Among European countries, 4 have been selected for this survey: France, Germany, Sweden, and the Netherlands.

7.2. Rationale for the selection of specialties

Lilly sent the DHPC letters to physician specialties most likely to prescribe Efient® (prasugrel).

The survey will be conducted among specialists who were targeted for the DHPC.

The specialties per country are the following:

- France: cardiologists and emergency physicians
- Germany: cardiologists, cardiology and emergency physicians, medical doctors with experience in emergency medicine (any specialty)
- Sweden: cardiologists,
- The Netherlands: cardiologists and physicians working in first aid

8. Research question and objectives

The research question is whether the new safety information included in the risk minimisation measures (DHPC, international congress, and journal publication) were effective in:

- Increasing the knowledge of HCPs about the increased bleeding risk when treating with a loading dose of Efient® (prasugrel) prior to diagnostic coronary angiography in UA/NSTEMI patients

  and

- Influencing their consideration of this risk when prescribing a loading dose of Efient® (prasugrel)

Primary objective: to evaluate the proportion of targeted physicians for the DHPC who are knowledgeable of the new safety information for prasugrel.

Secondary objective: to evaluate the proportion of physicians who intend to consider the safety information when prescribing Efient® (prasugrel).

9. Research methods

9.1. Study design

Cross-sectional, noninterventional, and multinational physician survey.

9.2. Setting

The survey will be conducted through a web questionnaire among prescribers, or potential prescribers, of Efient® (prasugrel) in a hospital setting in 4 European countries (France, Germany, Sweden, and the Netherlands).

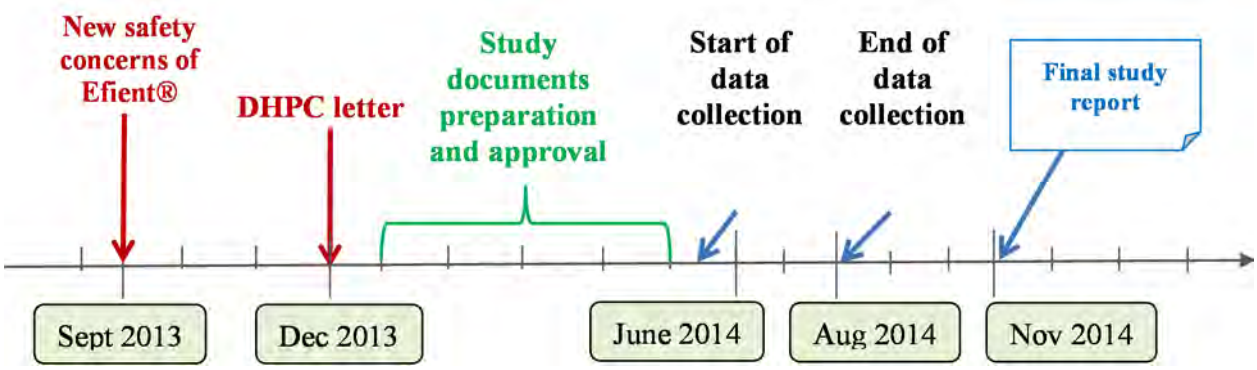


Figure 9.1. Study scheme and main timelines.

9.2.1. Inclusion criteria

The survey will be conducted among physicians meeting the following inclusion criteria:

- Prescribers, or potential prescribers, of Efient® (prasugrel)
- A specialist of any of those targeted for the DHPC, namely
  - in France: cardiologists and emergency physicians (excluding anaesthesiology-recovery physicians)
  - in Germany: cardiologists, cardiology and emergency physicians, medical doctors with experience in emergency medicine (any specialty)
  - in Sweden: cardiologists
  - in The Netherlands: cardiologists and physicians working in first aid

9.2.2. Exclusion criteria

Retired and inactive physicians will be deleted from the contact lists before randomisation whenever evidence is available to identify them.

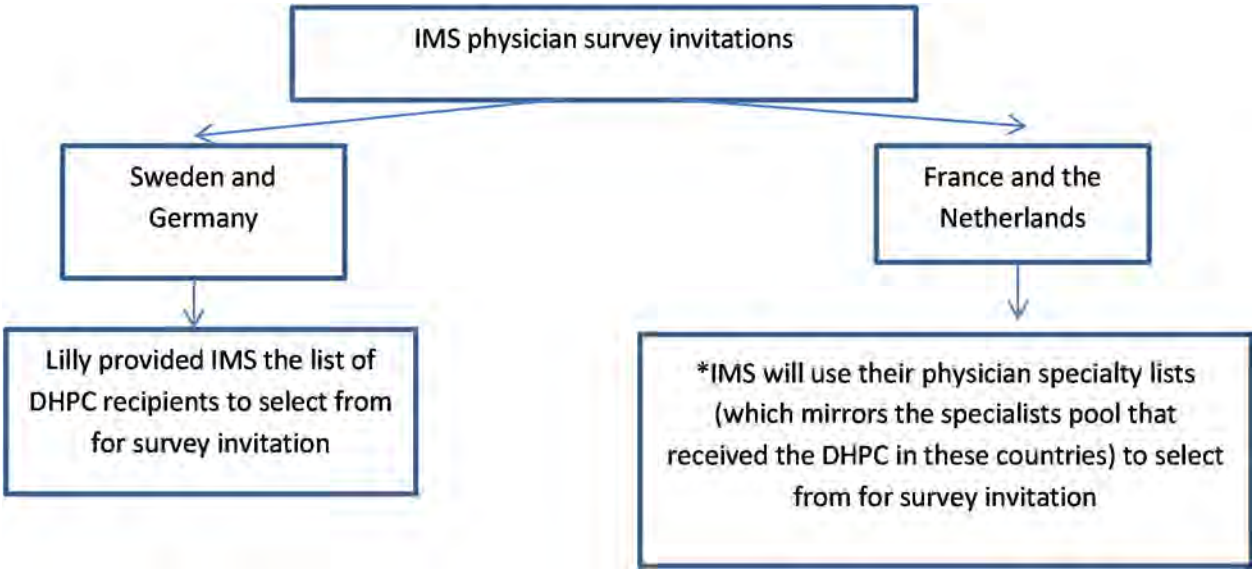
The following exclusion criteria will be checked at the beginning of the web questionnaire:

- physicians who do not treat patients or who may have a conflict of interest (that is, physicians employed by regulatory bodies, pharmaceutical industries, and so on)
- physicians who do not know Efient® (prasugrel)

9.2.3. Sampling plan

The statistical unit in this survey is the physician. For each selected country, the sample survey combines 2 data sources:

- Lilly's lists of physicians who were targeted for the DHPC
- IMS Medical Radar's reference lists of specialists



* The IMS list has the potential to include a small number of physicians who did not receive the DHPC if they were added to IMS list of specialists after distribution of DHPC in December 2013.

These lists will be restricted to the target specialists population, that is, selected specialists who are currently active (not retired) in 2014 at the time of the survey. The use of IMS Medical Radar's lists is needed for France and the Netherlands because Lilly cannot transfer the lists to IMS due to local data protection laws.

As per the overall sample size defined in Section 9.5 and the number of selected countries and specialities, physicians will be stratified only by country and specialty. The use of other criteria such as region, age, and gender of prescriber is less relevant than country and specialty, because such additional criteria may not be available in all countries or not be a determinant as important as country or specialty. The use of more strata would have needed a larger sample size.

A random stratified sampling method will be applied. As a first step, all lists will be merged, and then the eligible physicians will be divided into homogeneous groups, called strata, which

are mutually exclusive (a physician can only belong to one stratum). This stratification will be done based on the following criteria:

- country: 4 possibilities
- specialty: 1 (in Sweden) to 2 (in the other countries) possibilities depending on the considered country

Thus, 3 x 2 + 1 = 7 strata will be formed.

Table 9.1. Strata definitions

Stratum ID	Country	Specialty
1	France	Cardiologists
2	France	Emergency physicians (excluding anaesthesiology-recovery physicians)
3	Germany	Cardiologists, cardiology
4	Germany	Emergency physicians, medical doctors with experience in emergency medicine (any specialty)
5	Sweden	Cardiologists
6	The Netherlands	Cardiologists
7	The Netherlands	Physicians working in first aid

The physicians' allocation to a stratum is explained in Section 9.5.

9.3. Variables

The collected information from each physician will include demographics, type of practice, awareness and knowledge about the content of the new safety warning on Efient® (prasugrel), the sources of communication, and the intention of the physician to consider the new safety warning.

The endpoint of interest is the proportion of correct answers to the questions regarding new safety information and recommendations of use of Efient® (prasugrel) as described in the DHPC, in international congress(es), and in a publication in an internationally read journal (see the questionnaire in Annex 3).

The proportions of appropriate answers will be expressed among physicians with complete web questionnaires. The endpoints will be assessed overall, by country, and among subgroups of physicians based on their specialty.

9.4. Data sources

In this survey, data sources are the following:

- Lilly's lists of physicians
- IMS Medical Radar reference files

From these data sources, a sample of physicians who will participate in the survey and answer the web questionnaire will be identified. The questionnaire completion on the web is estimated to take between 10 and 15 minutes. It will be developed along with the protocol in English.

After an initial approval, it will be tested among a number of physicians (generally 5 to 6 and until there are no new comments) for the appropriateness of medical terms, its comprehensibility, and consistency. The local translated version of the questionnaire will also be tested using the back and forth method to make sure that the translation is correct.

9.5. Study size

The sample size formula, based on the normal approximation to the binomial distribution, for calculating the number of subjects required for a proportion is the following:

$$n = \frac{P \cdot (1-P) \cdot (Z_{1-\alpha/2})^2}{e^2},$$

where P is the expected proportion, e is one-half the desired width of the confidence interval, and $Z_{1-\alpha/2}$ is the standard normal Z value corresponding to a cumulative probability of $1 - \alpha/2$.

As the proportion of physicians informed of the new safety information and recommendations for use of Efient® (prasugrel) is not known in advance and there is no evidence supporting the expected proportion, the worst case hypothesis will be assumed considering that 50% of physicians will be knowledgeable about the new safety concerns. This assumption yields the largest sample size. Considering this hypothesis and in order to achieve a confidence interval of 95% with a half-width of 5%, a total of 384 analysable physician questionnaires will be needed for the overall sample.

Based on estimates and experience of IMS Medical Radar from the previous surveys, about 10% to 15% of physicians will not complete the questionnaire. Taking into account these respondents without analysable questionnaires, the overall sample size must be increased. Thus, 442 participating physicians would be required to reach 384 analysable questionnaires (physicians who respond to questions regarding their knowledge on the new safety concerns of Efient® [prasugrel]).

This overall sample size can be further divided into country sample sizes based on the observed distribution of eligible physicians in each country. However, to ensure the robustness of statistical calculations at country level, the sample size in each country should not be lower than 40 physicians if only 1 specialty is targeted, and not lower than 80 (40*2) physicians if 2 specialties are targeted.

Lilly's files or detailed counts, IMS Medical radar reference files, as well as official resources are used to estimate the relative weights of eligible HCPs that vary from country to country: from 6.2% for Sweden to 44.1% for France (see Table 9.2). With an overall sample of N=384 analysable questionnaires, the compliance with this distribution leads to 169 physicians for France, 155 for Germany, and below the acceptable thresholds for Sweden (24) and the Netherlands (36).

Table 9.2. Distribution of the DHPC letters sent to eligible HCPs by country

	France	Germany	Sweden	The Netherlands	Overall
Physicians targeted for DHPC*	12,136 Cardiologists, emergency and recovery physicians and hospital pharmacies	14,733 Cardiologists, cardiology and emergency physicians, medical doctors with experience in emergency medicine (any specialty) and hospital pharmacies	956 Cardiologists	2000 Cardiologists, physicians working in first aid, and hospital pharmacists	29,825
Number of distributed letters among targeted specialties**	6,818	6,255	956	1,430	15,459
Associated weight of each country	*44.1%*	*40.5%*	*6.2%*	*9.3%*	*100%*
Components:					
Cardiologists n (vertical %)	3,246 [1] (47.6%)	4,000 [3] (63.9%)	956 [5] (100%)	*1,210* [6] (84.6%)	
Emergency physicians n (vertical %)	3,572 [2] (52.4%)	2,255 [4] (36.1%)		*220* [7] (15.4%)	

* Source: Lilly

** Mixed sources depending on the country and the specialty - see details provided for each component

[1] Cardiologists working in a hospital setting - Source: Ecosanté Drees RPPS (Répertoire partagé des professionnels de santé) http://www.ecosante.fr/index2.php?base=DEPA&langh=FRA&langs=FRA&sessionid and IMS Medical Radar reference file

[2] Emergency physicians working in emergency units excluding anaesthesiology-recovery physicians - Source: CEGEDIM counts for Lilly France

[3] Cardiologists as a sub-specialty of General internal Medicine (9,025) - Source: European Society of Cardiology http://www.escardio.org/communities/councils/ccp/associations/Pages/Germany.aspx

[4] Anaesthesiologists as the most relevant specialty of emergency physicians, medical doctors with experience in emergency medicine among the Lilly's list with regards to knowledge of Efient® (prasugrel) – Source: Lilly

[5] Cardiologists - Source: Lilly

[6] Cardiologists - Source: Lilly

[7] Physicians working in first aid - Source: Lilly

As a consequence, by setting a minimum number of 40 physicians for Sweden where only 1 specialty is targeted, and a fixed number of 80 physicians for the Netherlands which relative weight is twice higher (2 specialties targeted), an imbalanced sample is obtained. The rest of the sample (384-40-80 = 264) is then allocated to France and Germany proportionally to their weights (calculated on the restrictive scope of France + Germany, that is, respectively 52.2% and 47.8%): 138 physicians for France and 126 for Germany. The assumption of 15% of incomplete questionnaires leads to the following number of participating physicians needed per country: 158 for France, 145 for Germany, 46 for Sweden, and 92 for the Netherlands.

Table 9.3. Sample size by country

	France	Germany	Sweden	The Netherlands	Overall
Number of participating physicians required	158	145	46	92	442
Number of participating physicians with complete analysable questionnaire expected	138	126	40	80	384
*Associated weight of each country**	*35.9%*	*32.9%*	*10.4%*	*20.8%*	*100%*

** The country-distributions of the 'Number of participating physicians required' and the 'Number of participating physicians with complete analysable questionnaire expected' are the same, since the second one is deducted from the first one through the application of a 15% inflation rate due to physicians who will not complete the questionnaire.*

As the relative weight of each country in the sampling plan is different from its real relative weight in the target lists (Table 9.3: line 'associated weight' which differs from that of Table 9.2), the extrapolation of the raw survey results to the overall target population would not be relevant. A sample adjustment will be applied: the survey results will be weighted to reflect the real proportion of countries, so that the survey results can be extended to the overall target population. Both unweighted (raw data) and weighted results will be presented in the report. To correct for oversampling of Sweden and the Netherlands and undersampling of France and Germany, a weight variable will be applied to each statistical unit (that is, the analysable physician) during calculation of results. This variable will indicate how many unit(s) (in the population of interest) an observation will count in a statistical procedure. Its value will change per country. Weights will be normalized so that the sum of the weights for the dataset will be equal to the sample size.

At each country level, the sample size will be further divided into the selected specialties, proportionally to their relative weight within the targeted population (Table 9.4 vertical %).

Table 9.4. Sample size by country and per specialty

n (vertical % per country)	France	Germany	Sweden	The Netherlands	Overall
Number of participating physicians required	158 (100%)	145 (100%)	46 (100%)	92 (100%)	442
Cardiologists	75 (47.6%)	93 (63.9%)	46 (100%)	*69 (75%)**	
Emergency physicians	83 (52.4%)	52 (36.1%)	NA	*23 (25%)**	
Number of participating physicians with complete analysable questionnaire expected	138 (100%)	126 (100%)	40 (100%)	80 (100%)	384
Cardiologists	66 (47.6%)	80 (63.9%)	40 (100%)	*60 (75%)**	
Emergency physicians	72 (52.4%)	46 (36.1%)	NA	*20 (25%)**	

NA: Not applicable

* Minor distortion compared to the vertical % of table 9.5-1 (+/- 10 points)

For the Netherlands, the application of the real proportion of emergency physicians (80*15.4%) leads to 12 physicians expected with analysable questionnaires only. Thus a distortion of the estimated proportions will be applied in order to provide a sufficient number of 40 emergency physicians. Note that the threshold of 40 may be difficult to achieve due to the few emergency physicians in the available list (220), and a usual expectable response rate of 10% to this kind of web survey. In the event that this goal would not be reached, then additional cardiologists will be recruited to compensate and preserve the sample size at the country level.

In order to fill-in each stratum of the sample survey from Lilly's files and/or the IMS Medical Radar reference files, an independent sample will be selected per stratum through a simple random sampling without replacement.

In each specific stratum, physicians will be contacted according to the order of draw in this stratum. If a physician does not want to participate in the survey, the next one in order of draw will be contacted, and so on until the required number of physicians is met. If the target for a stratum is not achieved after the end of the initial list, an additional randomly sampled list will be prepared and the physicians contacted until the goal is reached or no names are left in that stratum. If both the Lilly list and IMS Medical Radar file have been exhausted in any particular stratum, a strategy will be determined to adjust the sample size within stratum with associated weighting.

It is to be noted that this sample is calculated to be representative as a whole, not per country or specialty. Thus the subgroup analyses will not guarantee the same confidence intervals as the whole sample.

9.6. Data management

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IMS Medical Radar and IMS Real World Evidence Solutions.

Collected data will be entered and stored in a database specific to the survey and the country. Then, a study database will be created by merging of databases of each country.

Data will be checked in terms of consistency before data analysis:

- removal of duplicates (if required)
- data labelling and data formatting
- range and consistency checks for each variable to identify potential non admissible values
- cross-check the consistency of data for related variables (if feasible)

The study database will be locked once validated.

9.6.1. Data collection

The data collection period will last 5 to 6 weeks in 2014, and will be conducted in parallel in the 4 countries.

The survey will be conducted by IMS Medical Radar, a division of IMS Health specialized in the conduct of phone and web surveys for more than 20 years. IMS Medical Radar will create a

web-based instance survey. The lists of physicians will be loaded into separate databases for the management of the survey.

As described previously, physicians will be randomly contacted by phone or email by IMS Medical Radar according to their stratum. Their recruitment will be done as follows:

- IMS Medical Radar will contact the physicians to invite them to participate in the survey (physicians will be called or sent mails/emails). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. If they agree to participate in the survey, they will receive a link to access the survey and instructions for completion of the web questionnaire.
- A reminder will be sent by email after 1 week if the questionnaire is not completed, and sent to IMS Medical Radar.
- A reminder by phone will be conducted after 1.5 weeks if the target is not achieved in the stratum.
- Another reminder via email to the physicians will be sent after 2 weeks.

In some cases, the recruitment will be followed-up by phone, if necessary, to achieve the target in a specific stratum.

A physician will be considered as contacted if he/she has

- refused to participate
- been contacted at least 3 times and up to 5 times
- been sent the survey, completed it, and sent it back to IMS Medical Radar

Moreover, a physician will be considered as unreachable if he/she has been contacted between 3 and 5 times without any answer.

For each physician of the sample survey file, the number of times he/she has been contacted and the date and time of web questionnaire completion will be recorded. The operation of recruiting for each stratum will be stopped when the target is reached. If both the Lilly list and IMS file have been exhausted in any particular stratum, the recruitment of this stratum will be prematurely ended and a strategy will be determined to adjust the sample size within stratum with associated weighting.

Approaches for increasing the response rate:

Physicians are increasingly contacted to participate in web or phone surveys. Their overall response rate of participation remains low according to international studies (Kellerman and Herold 2001; Holbrook et al. 2007). Holbrook and colleagues (2007) showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey. VanGeest and colleagues (2007) conducted a systematic review of 66 published reports on efforts to perform for improving response rates. Two general strategies were explored: incentives-based and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician response rates while

nonmonetary incentives were much less effective. These measures include the use of a short questionnaire and questionnaires personalized and approved by professional associations.

In order to increase the response rate, several actions will be applied to this survey:

1) A compensation fee is proposed to physicians for their participation in the survey.
2) All physicians will be sent an email or contacted by experienced operators of IMS Medical Radar with extensive experience in conducting health related surveys.
3) Each physician will be emailed or called up to 3 to 5 times before being considered as "not reachable," and reminders will be sent by email if IMS Medical Radar does not receive the web questionnaire.

9.7. Data analysis

9.7.1. General statistical considerations

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

Statistical results of the 4 countries will be presented in the same report overall, by country, and per physician's specialty.

Table 9.5. Mock table to implement in the statistical and study reports

	Question n°1…		
Country	**Cardiologists**	**Emergency physicians**	**All**
France	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Germany	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Netherlands	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sweden	(N=xx)	NA	(N=xx)
answer 1	xx (xx.x%)	-	xx (xx.x%)
answer 2	xx (xx.x%)	-	xx (xx.x%)
answer 3	xx (xx.x%)	-	xx (xx.x%)
Overall - unweighted results	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - weighted results	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Table structure may be adjusted in the final study report.

Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Categorical variables will be described as the total number and relative percentage per category. These will be the percentage per category.

Confidence intervals of 95% will be calculated when relevant.

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, there will be a line "Overall – unweighted results" that will show only the results observed on the overall sample. It will not reflect the countries' universe because this sample is not proportional to the size of Lilly's lists or IMS Medical Radar reference files in each country.

In a second step, the results will be weighted according to the real proportion of physicians in each country in order to accurately reflect the population that the survey seeks to measure.

Within each country, the results will be reported according to the prescribers' specialty (selected specialists) that are distributed proportionally to their weight within Lilly or IMS reference lists.

9.7.2. Analysis of nonparticipation or refusal to participate

As often required by authorities, the different cases of total no-response will be analysed.

The following cases will be distinguished:

- Targeted physicians: Physicians reached to whom an email or mail has been sent, or have been called.
- Contacted physicians: Physicians who have been reached out by phone or have opened their email (if the score is technically available in their country).
- Physicians who agreed to participate: Physicians willing to participate in the survey (for example, by phone or by clicking on the link provided in the recruitment email).
- Physicians with complete questionnaire: Physicians who actually completed the questionnaire until its end.

Participation in the survey will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = Physicians who agreed to participate/ contacted physicians
- Cooperation rate = Physicians with complete questionnaire / Physicians who agreed to participate
- Refusal rate = (contacted physicians-physicians who agreed to participate) / Physicians reached

9.7.3. Questionnaire analysis

The general statistical considerations described in Section 9.7.1 will be applied for quantitative and qualitative variables. The number of missing data will be indicated. Missing values are expected to be few and distributed at random. Because there is no applicable method

unanimously accepted, there will be no replacement or imputation of missing data (Sterne et al. 2009).

Confidence intervals of 95% will be calculated for endpoints.

Physicians' answers will be analysed by subgroups of physician's specialty per country and on the overall dataset.

9.8. Quality control

9.8.1. Approaches for validating the questionnaire

The questionnaire will be tested among a small number of physicians (usually 5 to 6) for the appropriateness of medical terms, its comprehensibility, and consistency. The local translated version of the questionnaire will also be tested using the back and forth method to make sure that the translation is correct.

9.8.2. Approaches for validating the results

The quality control for validating the results will be conducted at 5 levels:

1. At the IMS Medical Radar management level, any efforts will be undertaken to collect complete and valid data:
    - reliability and security of the web questionnaire interface will be verified for each country by a qualified webmaster
    - datasets definition and quality will be ensured and monitored internally by a qualified data manager. In the background of the web questionnaire, real-time checks on the answers provided by respondents will be developed. Indeed, nonadmissible answers (that is, incorrect or unusual values, outlying values) will be detected and alerted to the physician accordingly.
2. At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond data management process):
    - Distribution of each variable to count the number of missing values and to estimate the associated relative percentage
    - Identification and count of non-analysable questionnaires:
        - estimation of the percentage of physicians who do not know Efient® (prasugrel)
        - estimation of the percentage of physicians without complete questionnaire

    Any changes in the database will be tracked and documented. The country datasets will be stored in a dedicated database. Once data validated and quality checked, the database will be locked.
3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be

stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, and so on.

4. At the results level, a data review to ensure data integrity will be planned. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5. At the study level, all aspects of the study will be conducted following SOPs of IMS Real World Evidence Solutions and Medical Radar divisions. The study documents were approved by persons competent in medical and safety areas of IMS.

9.8.3. Safeguards, security, and traceability of calls

Call centre operators specialized in health surveys will be assigned to the project and trained on the methodology prior to the phone calls. Phone calls will be traced using the call management software. All aspects of the survey from protocol development to the reporting of the results are conducted following SOPs of IMS Real World Evidence Solutions and Medical Radar divisions. These SOPs can be consulted on site.

9.9. Limitations of the research methods

9.9.1. Possible selection bias due to voluntary participation

The selection bias of physicians participating in a survey is an inherent bias to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of HCPs (country and specialty) will be compared between participants and nonparticipants.

9.9.2. Limits inherent to web-surveys

In such surveys, the generalization and external validity of results is restricted to physicians who have an active email account and are willing (and able) to answer an online questionnaire. These physicians may not be fully representative of the whole targeted population (Wyatt 2000).

The questionnaire is constructed with general questions followed by specific ones including correct responses. As the physicians may understand the right answer in subsequent questions, it would not be possible for the physician to go back and edit his/her answers to the former questions.

Moreover, web surveys may promote social desirability bias that refers to the tendency of physicians to give socially desirable responses instead of choosing responses that reflect their actual knowledge or behaviour. For example, physicians can copy-paste responses found online rather than giving his/her own opinion (Wyatt 2000).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire tends to reduce this bias (Nederhof 1985).

Among nonresponse bias, targeted physicians may also have activated filters in their mail box in order to block spams and unsolicited emails. If they have set a very strict degree of message filtering, they will not even see the invitation to participate in the survey. Another critical situation could happen if potential respondents have multiple email addresses. If the email address used is not the primary address or if he/she does not check the email box frequently they will not receive the invitation in the recruitment period. That is one of the reasons why the physicians will be also contacted by phone in this study.

As the access to the web questionnaire interface will be strictly limited to invited participants with a single possibility to participate and a traceability system, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey in order to influence the results), unverified respondents (when there is no way to verify who responds) are not applicable.

9.9.3. Generalization of the survey results to the overall target population with adjustment

As the study design presents oversampling of 2 countries (Sweden and the Netherlands) and undersampling of the 2 others (France and Germany), the raw survey results will not be generalized to the overall target population except if a sample adjustment is applied. For more transparency and accuracy, both unweighted (raw data) and weighted results will be presented in the report. Because the IMS list may identify a limited number of physicians who had not received the DHPC (added to IMS specialist list after December 2013 DHPC mailing), the results may be affected.

9.10. Other aspects

None.

10. Protection of human subjects

10.1. Regulatory and ethics considerations

The survey will follow the regulatory and ethical requirements of each country as described below:

IMS will follow the European Pharmaceutical Market Research Association (EphMRA) and European Society for Opinion and Market Research (ESOMAR) guidelines for all countries.

Specific local requirements as follows:

- France:

  The LOI Bertrand ("Sunshine Act"), the law of 29 December 2011 on the reinforcement of the safety of medicines and health products (the "Act"), supplemented by a decree dated 21 May 2013 (the "Decree"), regarding transparency of the relations between healthcare companies and, notably, French-registered HCPs will be followed.

  The Act states that companies that manufacture, market, or provide health products or services in relation to health products intended for human use must disclose the existence of the agreements they enter with players in the health sector, as well as any benefits that they grant to the same persons (Nederhof 1985; LOI 2001).

- Germany:

  The German local ESOMAR guidelines (ESOMAR 2013). Moreover, a physician who works in a hospital needs to have his/her chief's approval to participate in the study.

  The sponsor of this study classifies the study as a prospective noninterventional safety study. In accordance with § 67 Section 6 Drug Law (AMG), the competent federal authority, National Association of Statutory Health Insurance Physicians (KBV), Central Federal Association of Health Insurance Funds, and the Association of Private Health Insurance, must be notified about this study.

  Pursuant to § 63f Section 4 AMG "he/she shall also provide information on the location, time, purpose and the protocol of study as well as the name and lifelong physician identification number of the participating doctors. In so far as participating doctors provide benefits that are reimbursed by the statutory health insurance, the type and amount of the compensation paid to them shall be communicated and a confirmation of the agreement with them submitted in the case of notifications pursuant to sentence 1." For details, please refer to the legal text of the AMG (esp. §§ 63 sec.4, 67 sec. 6 AMG) and the published notification details by the competent Authorities

  (GKV: http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/anwendungsbeobachtung/Arznei_AWB_Erlaeuterung_zum_Meldeformular_20130601.pdf)

- Sweden:

  No specific guidelines for this type of survey.

- The Netherlands:

  No specific guidelines for this type of survey.

10.2. Protection of human subjects

The survey is noninterventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential and only aggregated data will be communicated and analysed.

10.3. Physicians information

The HCPs participating in the survey will be informed about the nature of the transmitted data, targets of the investigation, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to participate in the study or to IMS keeping their data.

10.4. Physicians compensation

Physicians will be offered compensation in return to the time spent participating in this survey (which they may refuse). The time to complete the survey is estimated between 10 to 15 minutes.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, and which states:

“When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws.”

11. Management and reporting of adverse events/adverse reactions

Adverse Event Collection

Trained operators will record via the specific web survey database all adverse events (AEs) they become aware of that occurred in temporal association with Lilly drug(s) under evaluation as defined in this protocol.

The IMS Medical Radar AE electronic system will be used to record all identified AE in this project. The project name 13315 // Lilly Study Code: H7T-MC-B021 will be used in all AE reports and reconciliation form. All AE reports will be sent to: mailindata_gsmtindy@lilly.com.

Adverse events will be collected on an IMS Medical Radar AE/PC collection form and forwarded by fax or email to the sponsor within 24 hours of awareness. Additionally, the operators or other study personnel will record via IMS Medical Radar AE/PC collection form the following information for Lilly drug(s) under evaluation as defined in this protocol, regardless of whether there is an associated serious or nonserious AE:

1) Instruct investigators/study personnel to collect all AEs they become aware of and are in temporal association with Lilly drugs under evaluation in the study protocol.

2) Instruct investigators/study personnel to forward the following information for Lilly drugs under evaluation in the study protocol to Lilly if the investigator/study personnel become aware of it, regardless of whether an associated serious or non-serious AE exists:

    - pregnancy exposures
    - suspected transmission of infectious agent
    - breast-feeding exposures
    - overdoses
    - misuse
    - abuse
    - off-label use
    - medication error
    - lack of drug effect

3) Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plan for disseminating and communicating study results

The survey will be registered in European Union-Postauthorisation Study (EU-PAS) register (currently the ENCePP e-register of studies) by Lilly.

A final survey report will be written in English, using a Lilly template and following STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations in MS Word format (Vandenbroucke et al. 2007).

The final survey results will be communicated to EMA.

13. References

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Annex 1. List of standalone documents

No.	Document Reference No	Date	Title
1. Protocol	Version 1	May2014	Efient® (prasugrel) Risk Assessment Study: a physician survey on the knowledge of new safety information in four European countries
2. Questionnaire	Version 1	May2014	Efient® (prasugrel) Risk Assessment Study : a physician survey on the knowledge of new safety information in four European countries
3. DHPC	<No>	<Date>	<text>
4. SmPC	Smpc - Ema-combined-h984enannotated14TT13OP21Nov	21Nov2013	Summary of Product Characteristics

Annex 2. ENCePP Checklist for study protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Page 14
1.1.2 The objectives of the study?	☒	☐	☐	
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Page 15/16
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	Page 15/16
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☐	☐	☒	
2.2.2 Age and sex?	☐	☐	☒	
2.2.3 Country of origin?	☒	☐	☐	
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Page 16

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	Page 14
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	Page 15
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.4 Is sample size considered?	☒	☐	☐	Page 16
3.5 Is statistical power calculated?	☒	☐	☐	Page 18-21

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
4.1.3 Covariates?	☐	☐	☒	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	Page 19-20
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	Page 24
8.3 Are descriptive analyses included?	☒	☐	☐	Page 24
8.4 Are stratified analyses included?	☒	☐	☐	Page 25-26
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Page 26
9.2 Are methods of quality assurance described?	☒	☐	☐	Page 26
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☒	
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☐	☒	☐	
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☐	☒	☐	
9.5.3 Study completion?	☐	☒	☐	Page 11
9.5.4 Reporting? (i.e. interim reports, final study report)	☐	☒	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	
9.7 Are communication methods to disseminate results described?	☒	☐	☐	Page 32
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	Page 29
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Page 29
10.3 Have data protection requirements been described?	☒	☐	☐	Page 29

Comments:

Name of principle investigator: _____

Date: 27/05/

Signature: Signature on file

Annex 3. Additional information

Survey questionnaire

Recruitment (by phone)

Survey presentation and arguments

Good morning/good afternoon, I'm Mr. /Mrs. XXXXX from IMS Health, a company specialized in epidemiological and observational studies and surveys in the field of drug safety.

IMS Health is currently undertaking a Risk Minimisation assessment study among specialists in four European countries on behalf of Eli Lilly and Company. The survey will assess the knowledge of prescribing conditions of Efient® (prasugrel), a platelet aggregation inhibitor, used to prevent thrombotic events in patients with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI).

The aim of this survey is to assess the effectiveness of the recent product safety information provided to prescribers. The information collected will be used only for this survey purpose. The results obtained will be presented to regulatory agencies, mainly the European Medicines Agency (EMA), in aggregated form.

This survey will be conducted in an anonymous way and doesn't involve any promotional material. You will not be contacted for marketing purposes based on your answers to the survey. Neither the survey sponsor nor its contractors will sell or rent your information.

The questionnaire will take 10-15 minutes to complete. As appreciation for your time we will compensate you with *[to be adapted to the specialty, e.g. 30 Euros for Cardiologists]*. You may also choose not to accept the monetary compensation.

If you are interested please supply me with an email address so that I may send you more details about the study and your personal link to the survey.

Thank you,

IMS Health Medical Radar Team

Recruitment (by e-mail)

Survey presentation and arguments

Dear Dr…….

We, IMS Health, a company specialized in epidemiological and observational studies and surveys in the field of drug safety, are contacting you on behalf of Eli Lilly and Company.

We are conducting a Risk Minimisation assessment study among specialists in four European countries. The survey will assess the knowledge of prescribing conditions of Efient® (prasugrel), a platelet aggregation inhibitor, used to prevent thrombotic eventsin patients with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI).

The aim of this survey is to assess the effectiveness of the recent product safety information provided to prescribers. The information collected will be used only for this survey purpose, and we would appreciate your participation in this research survey. The results obtained will be presented to regulatory agencies, mainly the European Medicines Agency (EMA), in aggregated form.

This survey will be conducted in an anonymous way and doesn't involve any promotional material. You will not be contacted for marketing purposes based on your answers to the survey. Neither the survey sponsor nor its contractors will sell or rent your information.

The questionnaire will take 10-15 minutes to complete.

We offer you a compensation *[to be adapted to the specialty, e.g. 30 Euros for Cardiologists]* for the time you will dedicate to this survey. You may also choose not to accept the monetary compensation.

If you are interested to participate in this, please click on the link below:

http://URL

Kind regards,

IMS Health Medical Radar Team

Web questionnaire

Introduction and agreement

The aim of this survey is to assess the effectiveness of the recent product safety information on Efient® (Prasugrel), a platelet aggregation inhibitor, provided to prescribers. The information collected will be used only for this survey purpose, and we appreciate your participation in this research survey. The results obtained will be presented toregulatory agencies.

The following questionnaire will take 10-15 minutes to complete.

We offer you a compensation *[to be adapted to the specialty and country, e.g. 30 Euros for Cardiologists]*for the time you will dedicate to this survey. You may also choose not to accept the monetary compensation.

❒ Please check this box if you do not want to be paid.

Before starting the questionnaire, we have to ensure that you are eligible for this survey by asking the following questions:

S1. Are you currently employed or contracted by regulatory bodies (e.g. EMA or *[add the name of the local regulatory agency]*, Eli Lillyand Company, or Daiichi Sankyo, Inc.?

No ☐ *Continue*

Yes ☐ Thank you for your interest in participating in this survey, unfortunately you cannot proceed with the survey.

Kind regards,
IMS Health Medical Radar Team

S2 Do you know the platelet aggregation inhibitor Efient® (prasugrel)?

Yes ☐ *Continue*

No ☐ Thank you for your interest in participating in this survey. As this survey is targeted at physicians that know Efient® (prasugrel), unfortunately you cannot proceed with the survey.

Kind regards,
IMS Health Medical Radar Team

Disclaimer

Start of Interview:

Please be assured that this study will comply with all *[to be adapted to the COUNTRY, e.g. Swedish]* laws in protecting your personal data, and will be in accordance with the EphMRA Code of Conduct.Your answers will be treated in confidence. Data will be combined with those of other respondents, and results presented in an aggregated and anonymous format. They will remain confidential and will not be used other than for this research purposes, or disclosed to any third party without your approval. Your identity will not be revealed to the company sponsoring this research.

We remind you that you may at all times request a copy of your personal information, have it corrected and object to its processing by contacting *[agency contact details]*. You can withdraw from the survey at any time."

Text only in Sweden and the Netherlands:
We are asked to pass on to our client details of Adverse Events that are mentioned during the course of the questionnaire. Although, your answers will be treated in confidence, should an Adverse Event in a specific patient be identified we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities. Later in the interview you will be asked whether or not you are willing to waive the confidentiality given to you according to the pharmacovigilancerulesspecifically in relation to Adverse Events. The answers you gave during the course of the interview will continue to remain confidential.
Are you happy to proceed with this interview on this basis?

Yes ☐ *Continue*

No ☐ *Thank you and close*

Text only in DE:
We are asked to pass on to our client details of Adverse Events that are mentioned during the course of the questionnaire. Although,your answers will be treated in confidence, should an Adverse Event in a specific patient be identified we will need to report this even ifyou have already reported it to the manufacturer or the regulatory authority.Your details will remain confidential and not be passed to the manufacturer.

As per instructions of the Sponsor of this study, this study may be classified as a so-called non-interventional safety study.
In accordance with § 67 Section 6 Drug Law (AMG), the competent federal authority, National Association of Statutory Health Insurance Physicians (KBV), Central Federal Association of Health Insurance Funds and the Association of Private Health Insurance, must be notified about this study.
Pursuant to § 63f Section 4 AMG "he/she shall also provide information on the location, time, purpose and the protocol of study as well as the name and lifelong physician identification

number of the participating doctors. In so far as participating doctors provide benefits that are reimbursed by the statutory health insurance, the type and amount of the compensation paid to them shall be communicated and a confirmation of the agreement with them submitted in the case of notifications pursuant to sentence 1." For details, please refer to the legal text of the AMG (esp. §§ 63 sec.4, 67 sec. 6 AMG) and the published notification details by the competent authorities (e.g. GKV: http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/anwendungsbeobachtung/Arznei_AWB_Erlaeuterung_zum_Meldeformular_20130601.pdf).

I hereby expressly agree to participate in the study under all the aforementioned conditions.

Yes ☐ *Continue*

No ☐ *Thank you and close*

Text only in FR:
We are asked to pass on to our client details of Adverse Events that are mentioned during the course of the questionnaire. Although, your answers will be treated in confidence, should an Adverse Event in a specific patient be identified we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities. Later in the interview you will be asked whether or not you are willing to waive the confidentiality given to you according to the pharmacovigilancerulesspecifically in relation to Adverse Events. The answers you gave during the course of the interview will continue to remain confidential.
Are you happy to proceed with this interview on this basis?

Yes ☐ *Continue*

No ☐ *Thank you and close*

In compliance with the French law n°2011-2012 of December 29, 2011 and the French Decree n° 2013-414 of May 21, 2013, IMS will publish the existence of the convention related to the study ***[to fill with the name of the survey]***.

IMS will publish the following information, in accordance with the provision of articles L1453-1 and R1453-3 of French Public Health Code:

- Convention signatory's identity (first name; last name; work address; qualification; specialty; title; order inscription number or RPPS number)
- The date of signature of the convention;
- The object of the convention in accordance with secrets protecting by law (as trade secrets for example).

The publication aforementioned will be available on IMS' website: www.imshealth.com

IMS will also publish the possible benefits granted to you for the execution of the convention. Please note that, in compliance with the French Data Protection Act of January 6, 1978 you have a right of access to

and rectification of your personal information. This right can be exercised by mail at the following address: IMS HEALTH , Legal Department – Tour Ariane, 5-7 place de la Pyramide – 92088 La Défense - France or by email at dataprivacy@fr.imshealth.com.

As this publication is set forth by French Law, it is specified that you do not have a right of opposition to such publication.

Text to include if consent from physicians' employer is needed (only in DE to hospital physicians):
Are you satisfied that you do not need, or you have already obtained, any consent from your employer, organization, or professional association to participate in this research?

Yes *Continue*
No *To proceed with the interview please obtain the necessary consent from your employer, organization, or professional association. Thank you.*

Section 1: Demographics and practice information

Q1. What is your age category?

≤ 30 years old	( )
31-39 years old	( )
40-49 years old	( )
50-59 years old	( )
≥ 60 years old	( )

Data: single punch

Q2.What is your primary medical specialty?

Cardiology	( )
Interventional Cardiology	( )
Emergency Room Physician	( )
Other, please specify:……	( )

Data: single punch
Data: list of physicians' specialties should be adapted per country.

Q3. For how long have you been practicing medicine?

|__|__| years

OR since which date: |__|__|__|__|

Data: open numeric, years

Q4. Are you affiliated to an academic (teaching) hospital?

❒ Yes
❒ No

Data: single punch

Q5. Approximately how many unique patients presenting with acute coronary syndrome (ACS) do you treat/follow-up per month on average?

|__|__|__| ACS patients

Data: open numeric

Q6. Among these ACS patients, approximately how many present with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) per month on average?

|__|__|__| UA/NSTEMI patients

Data: open numeric
Data: number in Q6 cannot exceed number in Q5.

Q7. Have you ever prescribed Efient® (prasugrel) to any of your patients?

Yes	( ) *Go to Q8*
No	( ) *Go to Section 2*

Data: single punch

Q8. If yes, how many Efient® (prasugrel) prescriptions do you write in any given **3 months** for UA/NSTEMI patients undergoing percutaneous coronary intervention (PCI)?

Number of Efient® prescriptions per 3 months	
0	( )
1-5	( )
6-10	( )
>10	( )

Data: single punch

Section 2: Awareness of safety information related to Efient® (prasugrel)

Q1. Are you aware of the latest safety information regarding timing of the loading dose in patients undergoing PCI with Efient® (prasugrel) related to patients undergoing PCI?

Yes	( ) *Go to Q2*
Don't recall/unsure	( ) *Go to Q2*
No	( ) *Go to Q3*

Data: single punch

Q2. Which of the following sources have provided you the latest safety or risk information about Efient® in the past 12 months?

(Please select the answers that apply. Several answers are possible)

Information sources	
Direct Healthcare Professional Communication (DHPC) (a letter communicating important safety information on Efient®)	( )
Summary of Product Characteristics (Label)	( )
Publication in the New England Journal of Medicine (September 2013)	( )
Presentation at ESC congress (in September 2013)	( )
Don't know/ recall the source of information where I read/heard the new safety information on Efient®	( )
Other(s)	( ) *Go to Q2a*

Data: multi punch

Data: ask Q2a only if Other(s) has been answered in Q2, otherwise go to Q3.
(The question will only be opened for the physicians who ticked the box and not for the others).

Q2a. Please specify from which other sources you have had the latest safety or risk information about Efient® in the past 12 months::

(Please select the answers that apply. Several answers are possible)

'Other' information sources	
Eli Lilly and Company representative	( )
Other scientific publication	( )
Professional meeting, congress, symposia	( )
Colleagues or healthcare providers	( )
Press / Media	( )
National Health Authorities website	( )
Eli Lilly and Company website, or other websites	( )
Other(s), please specify: ……	( )

Data: multi punch

Q3. According to the current product label, when should the loading dose of Efient® 60mg be given?

>4 hours prior to PCI	( )
2-4 hours prior to PCI	( )
At the time of PCI	( )
Don't know/ recall	( )

Data: single punch
If they answered no in Q1 jump to section 3

Q4. Are you considering the latest safety warnings when you are giving a loading dose of Efient® (prasugrel) to UA/NSTEMI patients?

Yes	( ) *Go to section 3*
No	( ) *Go to Q5*

Data: single punch

Question for the physicians who answered 'No' at Q4.

Q5. If no, please indicate why you are not considering this the latest safety warning in your use of Efient® (prasugrel)?.

Please specify:……

Data: open text

Section 3: Management and reporting of adverse events / adverse reactions

End of interview (in France, Sweden and the Netherlands):
In the event of an Adverse Event/side effect being found during this survey, are you willing to waive the confidentiality given to you under the studies Codes of Conduct specifically in relation to that Adverse Event. You may in that case be re-contacted by the pharmaceutical company's Drug Safety department. Please note that if you consent to a follow-up of the Adverse Event, your name will not be linked in any way to your responses given during the survey, other than in relation to the Adverse Event. (yes/no tick box)

❒ Yes
❒ **No**

End of interview (only in Germany):
In the event of an Adverse Event/side effect being found during this survey, are you willing to be re-contacted by IMS specifically in relation to that Adverse Event. Please note that if you consent to a follow up of the Adverse Event, your details will remain confidential and you will not be linked in any way to your responses given during the survey. (yes/no tick box)

❒ Yes
❒ **No**

End of the survey

Thank you very much for your participation

Kind regards,
IMS Health Medical Radar Team