Division: Worldwide Development

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Information Type: Worldwide Epidemiology Study Protocol Amendment

Title:	Physician Adherence to Fondaparinux Prescribing Information for Patients with Superficial Vein Thrombosis (SVT) of the Lower Limbs

Compound Number: GSK576428

Development Phase: IV

Effective Date: 10th July 2013

Description: Evaluate physician adherence to the fondaparinux prescribing information for the treatment of patients with confirmed, isolated superficial vein thrombosis (SVT) of the lower limbs.

Subject: Fondaparinux, Arixtra, superficial vein thrombosis

Author(s): Abell, Jill; Quentzel, Steven; Barker, Tara; Norry, Elliott; Worsfold, Andrew; Updated by Stirnadel-Farrant, Heide; Quentzel, Steven; Galwey, Nicholas; Spera, Patricia; Desai, Mona; Barker, Tara; Worsfold, Andrew. Second update by Stirnadel-Farrant, Heide; Quentzel, Steven, Irwin, Joseph, Smith Fiona.

REVISED CHRONOLOGY

DNG #	Date	
NA	4th May 2012	Original
2012N152424_00	20th Nov 2012	Amendment No.1: Power calculations and milestones updated
2012N152424_01	10th July 2013	Amendment Minor changes including additional details relating to renal impairment in the CRF and feasibility questionnaire.

SPONSOR SIGNATORY:

[redacted] **Date**

Director, Worldwide Epidemiology

[redacted] **Date**

TA Director, Worldwide Epidemiology

[redacted] **Date**

Acting Head. Worldwide Epidemiology

SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

Required Standard Wording:

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:

_____

_____ _____

Investigator Signature Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ARW	Adelphi Real World
CALISTO	Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report Form
CUS	Compression Ultrasound Imaging
DUS	Duplex Ultrasound Imaging
DVT	Deep Vein Thrombosis
EC	Ethics Committees
EMA	European Medicines Agency
EU	European Union
GEE	Generalised Estimating Equations
GP	General Practitioner
GSK	GlaxoSmithKline
IRB	Institutional Review Board
LOC	Local Operating Companies
NSTEMI	Non-ST segment Elevation Myocardial Infarction
PE	Pulmonary Embolism
POST	Prospective Observational Superficial Thrombophlebitis
SAS	Statistical Analysis Software
SAP	Statistical Analysis Plan
STEMI	ST segment Elevation Myocardial Infarction
SVT	Superficial Vein Thrombosis
UA	Unstable Angina
VTE	Venous Thromboembolism
WWEpi	World Wide Epidemiology

Note: throughout this protocol, SVT is used as an abbreviation solely for superficial vein thrombosis

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
ARIXTRA	

PROTOCOL SUMMARY

Rationale

Fondaparinux is an anticoagulant used in the prevention and treatment of thromboembolic disease. It has recently been approved in the European Union (EU) for the treatment of patients with isolated superficial vein thrombosis (SVT), i.e. without concomitant deep vein thrombosis (DVT), of the lower limbs. As part of EU approval, GlaxoSmithKline (GSK) committed to evaluate physicians' adherence to fondaparinux prescribing information regarding proper diagnosis and dosing for the treatment of SVT. This includes demonstration that physicians are prescribing fondaparinux at the recommended dose (2.5mg, or 1.5mg in patients with renal impairment), especially given the extended duration of treatment and the higher risk of bleeding which may result if the higher DVT treatment doses are used in this patient population. In addition, the study will assess whether physicians have performed a compression ultrasound (CUS), or other diagnostic imaging procedures, in order to rule out concomitant DVT, which should be treated with a higher dose (5mg, 7.5mg, 10mg).

Objective(s)

The primary objective is to evaluate physicians' adherence to fondaparinux prescribing information for the treatment of patients with SVT without concomitant DVT.

Study Design

The study is designed as a non-interventional, retrospective chart review of patients prescribed fondaparinux to treat their SVT. The study will be conducted in several EU countries. Potential investigators who have experience in the treatment of patients with SVT will be randomly identified and may include angiologists, phlebologists, vascular surgeons, etc. At each participating site, medical charts for patients with SVT treated with fondaparinux will be identified and data relating to fondaparinux dosing, use of

CUS (or other diagnostic imaging procedure) and details of the SVT will be collected. Data collection will not begin until at least six months following availability and reimbursement of the product at the particular site. This delay should be sufficient to allow fondaparinux to be adopted into routine practice and to be prescribed to a sufficient number of patients per physician.

Study Endpoints/Assessments

The primary outcome measure will be the percentage of patients for whom both an ultrasound (or other objective measure) was performed in order to rule out concomitant DVT prior to patients commencing fondaparinux therapy and who were prescribed the recommended dose (2.5mg, or 1.5mg) of fondaparinux. This will be evaluated overall and per country.

1. INTRODUCTION

1.1. Background

Superficial vein thrombosis (SVT), also termed superficial thrombophlebitis, is considered to be a common disease, even though incidence rates have not been properly assessed [1]. SVT has been reported to occur in an estimated 3-11% of the general population, associated with a higher prevalence in women, and in patients with a mean age of 60 years [2]. It is most often found in the veins of the lower limbs, but has also been reported in many other locations [2]. SVT is known to present with pain, erythema and swelling around a superficial vein that feels like a cord on palpation [2].

The main risk factors for SVT include age, varicose veins, postoperative states, pregnancy, active malignancies, immobilisation, hormone replacement therapy, auto-immune diseases, use of oral contraceptives, obesity, prolonged flights and a history of previous venous thromboembolism (VTE) [2, 3]. SVT diagnosis is based principally on clinical assessment, but the use of duplex ultrasound imaging (DUS) has enabled accurate detection of the extent and progress of the condition [2]. Treatment options available for SVT include ambulation, surgery, elastic stockings, anti-inflammatory agents and anticoagulants [2, 3].

Although once considered to be a relatively benign condition, SVT may be associated with concomitant deep vein thrombosis (DVT) and pulmonary embolism (PE). In the POST study, concomitant DVT and/or symptomatic PE was present in approximately 25% of SVT patients [4]. Patients with SVT but without concomitant DVT/PE (ie isolated SVT) are at high risk of thromboembolic complications including recurrent disease and thrombus extension into the deep veins that may lead to DVT and potentially PE. In the POST study, 8.3% of patients with isolated SVT experienced at least one symptomatic thromboembolic complication during the 3 months following diagnosis, these included 2.8% with symptomatic DVT and 0.5% with PE [4].

The anticoagulant fondaparinux (ARIXTRA™) is approved in the European Union (EU) for the prevention of VTE, in the initial treatment of acute DVT and PE, and in the treatment of acute coronary syndromes: unstable angina (UA),

non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). As of Sept 2010, fondaparinux is also approved for the treatment of adults with acute symptomatic spontaneous SVT of the lower limbs without concomitant DVT. Approval was supported by the phase III study 'Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo' (CALISTO) [5]. Patients with isolated SVT randomised to 2.5mg fondaparinux once daily for 45 days had a significantly lower risk of venous thromboembolic complications of SVT at the end of treatment, compared to those receiving placebo (relative risk reduction 85% [95%CI: 74%, 92%], p<0.001).

1.2. Rationale

Fondaparinux is an anticoagulant used in the prevention and treatment of thromboembolic disease. It has recently been approved in the European Union (EU) for the treatment of patients with isolated SVT, i.e. without concomitant DVT, of the lower limbs. As part of EU approval, GlaxoSmithKline (GSK) committed to evaluate physicians' adherence to fondaparinux prescribing information regarding proper diagnosis and dosing for the treatment of SVT. This includes demonstration that physicians are prescribing fondaparinux at the recommended dose (2.5mg, or 1.5mg in patients with renal impairment), especially given the extended duration of treatment and the higher risk of bleeding which may result if the higher DVT treatment doses are used in this patient population. In addition, the study will assess whether physicians have performed a compression ultrasound (CUS), or other diagnostic imaging procedures, in order to rule out concomitant DVT, which should be treated with a higher dose (5mg, 7.5mg, 10mg).

2. OBJECTIVE

The primary objective is to evaluate physicians' adherence to fondaparinux prescribing information for the treatment of patients with SVT of the lower limbs without concomitant DVT.

The primary endpoint of the study is the proportion of patients with isolated SVT of the lower limbs treated with fondaparinux, for whom the prescribing information was followed (i.e., an ultrasound, or other diagnostic imaging procedure, was performed in order to rule out concomitant DVT prior to patients commencing fondaparinux therapy and the correct dose of fondaparinux [either 2.5 or 1.5mg] was prescribed).

Based on the availability of data, as identified in the feasibility phase of this study, a sensitivity analysis of the primary endpoint will be conducted, incorporating the length of the thrombus (>5 cm) and/or its distance from the sapheno-femoral junction (>3 cm).

Secondary endpoints of the study include:

- The proportion of patients with SVT of the lower limbs treated with fondaparinux, for whom an ultrasound, or other diagnostic imaging procedure, was performed in order to rule out concomitant DVT prior to patients commencing fondaparinux therapy
- The proportion of patients with SVT of the lower limbs treated with fondaparinux, for whom either 2.5mg or 1.5mg fondaparinux was prescribed.

Pending the availability of the data as identified from the feasibility study, the following will also be included as secondary endpoints of the study:

- The proportion of patients with SVT of the lower limbs treated with fondaparinux, for whom the length of thrombus was measured (<5 cm being non-adherence)

- The proportion of patients with SVT of the lower limbs treated with fondaparinux, for whom the distance from the sapheno-femoral junction was recorded (<3 cm being non-adherence).

3. STUDY POPULATION

3.1. Selection of Sites

A geographically representative sample of sites in each country will be targeted for recruitment; sites responsible for managing relatively few patients (<2 patients per month) will be excluded. Reasons for non-eligibility will be documented.

Each recruited site will have one or more physicians who routinely manage SVT patients and who make decisions regarding prescribed treatment for those patients.

3.2. Sampling Strategy for Site Recruitment

The aim of the sampling strategy will be to recruit sites and site investigators that reflect routine treatment practice in their respective countries.

A master list of potential sites will be prepared for each country, based on practice information known to ARW and its local fieldwork partners, and with additional input as required from GSK local operating companies. Sites will be stratified by geographic region and, in addition, according to resident population densities within those regions.

Sites will be sampled such that good geographical representation is achieved within each country and that the number of site investigators recruited is proportionate to the treated patient population served in each geographical region. Thus, a region with twice the estimated patient population of another will be anticipated to provide a greater number of sites and/or site investigators.

3.3. Patient inclusion and exclusion criteria

3.3.1. Inclusion Criteria

(1) Diagnosis of SVT

(2) Prescribed fondaparinux for the treatment of SVT

(3) Age 18 years or older.

3.3.2. Exclusion Criteria

(1) Patients should not have been involved in any clinical trial that could influence SVT treatment during the observational period (i.e. the retrospective period during which data is recorded).

4. STUDY DESIGN

The study is a non-interventional, retrospective chart review of patients prescribed fondaparinux to treat their SVT. The study will be conducted in several EU countries. Qualified medical record abstractors will be identified at each site and specifically trained on the data collection required for the study.

It is essential that the study design and objective does not influence physician practice for treating those patients being included in the study. Consequently, the study will not begin recruitment until at least six months following availability and reimbursement of the product at the particular site. This delay should be sufficient to allow fondaparinux to be adopted into routine practice at each recruited site and to be prescribed to a sufficient number of patients per physician. Sites may be identified during this time period, however, recruitment will only begin after the six months have passed and a sufficient number of patients have accrued.

The site abstractor(s) will complete a short paper-based case report form (CRF) on the first consecutive ‘n’ SVT patients prescribed with fondaparinux by each physician practising at the site starting one month after the availability and reimbursement of fondaparinux, and who meet the other study inclusion criteria It is assumed that each site will have more than one physician who can provide patients for inclusion in the study. Thus, it is envisaged that one

physician will take the role of the site lead investigator, who would be the main point of contact during the study and would be responsible for coordinating site activities (e.g. assisting with EC submissions, data collection, etc.).

The lead investigator of each site will be fully briefed on the study objectives, methodology and data requirements prior to data collection.

Sites will track abstracted records by an identification log kept at the site to ensure that records can be re-accessed in the case of an outstanding query or audit. This information will not be entered into the database or retained by the sponsor. Consecutive records which fulfil the inclusion criteria are desired; however, if it is not possible to identify the date and dose of fondaparinux prescribed to eligible SVT patients in the source records, then these patient(s) may be excluded from the study.

The exclusion of any consecutive records will also be tracked.

4.1. Site Identification

A simple survey containing a series of queries will be completed by those sites identified on the master list for each country to determine their eligibility to participate in the study.

The queries within the survey will include the following:

- Site details (such as overall number of patients)
- Number of DVT/SVT patients treated at each site
- Types and number of physicians/specialists who are managing such patients
- Diagnostic criteria employed (such as physical assessment; imaging techniques, other blood tests)
- Diagnostic tools/capabilities within each site.

The survey will not contain any indications of overall objective of the study.

Eligible sites will be stratified by geographical region and between 18 and 36 sites that are representative of each country’s population distribution will be

randomly selected and invited to complete a feasibility study as a pre-cursor to being finally selected for recruitment into the study.

4.2. Feasibility Study

A feasibility study will be conducted in those randomly selected eligible sites to determine the availability of select data components within the medical chart. The feasibility study will comprise a simple questionnaire which will contain the variables of interest as a check list. Physicians who could act as the lead investigator at each eligible site will be asked to review the medical charts of those SVT patients meeting the criteria for the study, to determine the variables/data of interest that are routinely available for each patient. The patient charts to be reviewed will be representative of those treated by each physician within each site. Additionally, the number of patient charts to be reviewed will be equivalent to the number of eligible patients a site may have available for the main study (within the upper limits set out in the main study protocol).

The variables of interest will include as follows:

- Age
- Gender
- Renal status
- Presence/absence of concomitant DVT
- Length of thrombus
- Distance from sapheno-femoral junction
- Diagnostic procedures performed (e.g. ultrasound or other objective tests)
- Prescribed fondaparinux dose and duration.

This questionnaire will not contain any indication with regards to the overall objective of the study.

Between 12 and 18 eligible sites, proportionate to the country's population and representative of the country's main geographical regions, successfully completing the feasibility study will be invited to progress to the main study.

4.3. Outcome

The primary outcome measure will be the proportion of patients for whom **both** an ultrasound (or other diagnostic imaging procedure), was performed in order to rule out concomitant DVT prior to patients commencing fondaparinux therapy **and** that the correct dose of fondaparinux (2.5mg or 1.5mg) was prescribed (i.e. adherence to fondaparinux prescribing information – see Appendix 9.1). This will be evaluated overall and in each country.

A sensitivity analysis of the primary outcome will be conducted incorporating the length of the thrombus (>5 cm) and/or its distance from the sapheno-femoral junction (>3 cm), pending the availability of the data.

Secondary outcomes will evaluate the proportion of patients prescribed the correct dose of fondaparinux, as well as those who had an ultrasound (or other diagnostic imaging procedure) performed to rule out concomitant DVT. In addition, when available, the proportion of patients having a thrombus >5 cm and a distance from the sapheno-femoral junction of at least 3 cm will be estimated.

Similar to the primary outcome, these will also be evaluated overall and in each country.

Please note that patient outcome data following fondaparinux prescription will not be collected.

4.4. Data Collection

Prior to the start of data collection, the lead investigator of each participating site will have received the Study Protocol and a copy of the CRF for reference. Once the study protocol has been approved by the relevant regulatory body and ethics committee (if applicable) in each country and contracts are

finalised, an initiation telephone call will be organised with the lead investigator in each participating site.

All CRFs received will be tracked and logged on a central database before being processed by Adelphi Real World (ARW) Data Management teams. Sites will regularly be followed-up in order to facilitate the data collection process.

The following data (but not limited to) will be collected by the site abstractors onto CRFs:

- Patient demographics
- Relevant medical history
- Diagnostic procedures performed
- SVT characteristics
- Initial fondaparinux dose, administration frequency and duration of treatment (planned/actual if known). If a dose other than 2.5mg is prescribed/administered, the rationale for this will be requested
- Absence/presence of DVT and relevant details
- Renal Function.

4.5. Validation Procedures

To ensure the validity of the results, it is necessary that the data collected are of good quality. Any missing data will be sought from, and the accuracy of the records will be checked with the respective site/investigator. Once completed case report forms are received by Adelphi, there begins a process of 'logic checks' with identification of, and raising of queries, and query resolution at site level. The resolved queries will then be checked again before being entered into the data base.

5. SAMPLE SIZE AND POWER/PRECISION CALCULATIONS

5.1. Sample Size Calculations

As the primary objective of the study is to obtain an estimate of physician adherence to the fondaparinux prescribing information for SVT, overall and per country, a methodology that takes into consideration the study design, i.e. patients nested within each physician and within each site, has been identified. This explicitly recognises the fact that the prescribing for different patients consulting the same physician is unlikely to be independent and will be correlated (the amount of correlation represented by the intra-class correlation coefficient). It is assumed that prescribing for patients consulting different physicians and sites is independent.

For any given total patient sample size, the higher the ratio of the number of participant physicians to the number of patients each physician recruits, the greater the power achieved. The design of the study intends to allow sites some flexibility (in order to ensure site participation) in the number of physicians and number of patients each may recruit. This flexibility is described in Table 2 below with minimum and target numbers defined. Upper limits in terms of the maximum permissible number of patients per physician and the maximum permissible number of physicians per site are also stated.

Table 2: Enrolment – Minimum, Target and Upper Limits Defined

	Enrolment		
	Target	**Minimum**	**Upper limit**
Physicians per country	30*	19	30*
Patients per physician	7	7	10
Patients per country	210*	133	210*
Physicians per site	2	1	5
Patients per site	14	7	20
Sites per country	15*	10	15*
Countries	4	4	4
Total No. Patients	**840**	**532**	**840**

** Average across all countries*

The patient sample calculations were based on using the technique described by Emrich and Piedmonte [6] contained within the R statistical package "mvtBinaryEP" [7]. Correlated binary data for a specific user-entered intra-class correlation coefficient could be generated.

Monte Carlo simulations generating such correlated binary data (of the specified intra-class correlation, of the specified sample size, N, and assuming an underlying population probability of adherence of 0.8) were performed. For each simulated data set a Generalised Estimating Equation, GEE, containing a constant term was applied and the 95% confidence interval around the computed average percent adherence prediction was calculated. An indicator variable was created for each simulated data set which took the value 1 if the lower 95% confidence interval just described was above 60% and took the value 0 otherwise. The mean value of this indicator variable was then calculated across all simulation runs and represents the power of achieving a lower bound greater than 60% (given an assumed adherence rate of 80% and a specified intra-class correlation) from the stated sample size/mix.

Table 3 below demonstrates how the power can vary for the same patient sample size of 210 by varying the intra-class correlation and/or the mix of number of physicians and patients managed per physician. The higher the intra-class coefficient the greater the benefit from increasing the number of physicians selected and decreasing the number of patients managed per physician to generate the same total patient base. With this in mind it has also been decided that no one physician should provide more than ten patients to the study (see appendix 9.4).

Table 3: Power Calculations for Minimum and Target Physician Numbers with varying intra-class correlations

	Intra-class correlation	Power
Scenario 1 (210 patients)	0.1	0.998
30 physicians, 7 patients each	0.2	0.974
total 210 patients	0.25	0.963
	0.3	0.937
Scenario 2 (210 patients)	0.1	0.994
21 physicians, 10 patients each	0.2	0.950
total 210 patients	0.25	0.916
	0.3	0.874
Scenario 3 (180 patients)	0.1	0.981
18 physicians, 10 patients each	0.2	0.900
total 180 patients	0.25	0.854
	0.3	0.807
Scenario 4 (Minimum sample)	0.1	0.964
19 physicians, 7 patients each	0.2	0.891

total 133 patients	0.25	0.846
	0.3	0.804

The power results achieved for the scenarios in Table 3 show that the minimum sample required to still achieve a power ≥0.8 can be achieved by recruiting 10 sites (9 sites with 2 physicians per site and 1 site with 1 physician) with each physician reporting on 7 patients, resulting in a total of 133 patients. It is therefore thought acceptable to implement the targeting scheme with lower limits imposed as detailed in Table 3 ('Minimum sample'). Analysing all four countries will increase the sample size to 840 (4x210; best case scenario) or to 532 (4x133; worst case scenario) and will clearly improve the power beyond that of a single country. Therefore the power for all four countries will exceed 0.8.

5.2. Planned Analyses

All statistical analyses will be conducted in Statistical Analysis Software (SAS) v9.1 or later. The proportion of patients treated according to the prescribing information for fondaparinux (the adherence rate) will be estimated using generalized estimating equations (GEEs).

5.2.1. Primary Analyses

Adherence estimates with confidence intervals will be derived using generalised estimating equations (GEE) overall and for each country [8]. The GEE will explicitly take into account the nesting of patients, per physician, within a medical practice.

Adherence in the current study will be defined as performing CUS, or other diagnostic imaging procedure, in order to rule out concomitant DVT prior to patients commencing fondaparinux therapy **and** ensuring that the recommended dose of fondaparinux is prescribed.

A sensitivity analysis will be conducted incorporating the length of the thrombus and the distance of the thrombus from the sapheno-femoral junction into the primary endpoint if the data is available.

5.2.2. Secondary Analyses

Further analyses will investigate the four secondary endpoints, namely performing CUS or other diagnostic imaging procedure, prescribing of the recommended dose and the length of thrombus and the distance of the thrombus from the sapheno-femoral junction. The same methodology as applied to the primary analyses will be utilised here. Adherence estimates will be calculated overall and per country.

6. STUDY LIMITATIONS

The study objective focuses on evaluating physician adherence to fondaparinux prescribing information; that ultrasound is conducted prior to prescribing fondaparinux, and that the correct dose is administered.

The study involves the retrospective review of patient charts and it is acknowledged that certain additional information may not be available for all patients included in the study, for example:

- the rationale for prescribing a dose other than 2.5mg may not always have been recorded
- the planned and/or actual treatment duration may not be known
- patient non-adherence will not be known.

Note, as it is not the objective of this study to evaluate treatment outcomes, patient follow up will not be conducted as part of the study.

7. STUDY MANAGEMENT

7.1. Ethical Approval and subject confidentiality

ARW will work with the appropriate ethics committees and regulatory bodies to gain approval for the study in each of the planned countries.

7.2. Subject Confidentiality

CRFs will be stored and information entered into a secure database within the UK. All data will be collected, handled and processed in accordance with the UK Data Protection Act (1998). Each study site will be assigned a unique code and, likewise, each patient record collected will also be uniquely coded. No data that could identify the patient (for example, name and date of birth) will be collected and all data will be kept completely confidential. Aggregated data will be uploaded onto a secure (password-protected) database, where it will be held for the duration of the study. The database will then be passed to the Sponsor who will keep the data in accordance with legal and company data retention laws, as well as company specific data protection laws.

All information collected will be securely archived and kept for a maximum of 3 years after study completion.

7.3. Reporting of Adverse Drug Events

The present study does not require collection of any patient outcome or adverse event data following fondaparinux prescription. However any serious adverse events explicitly attributed to GSK products which are identified should be reported to the GSK's Central Safety Department within 24 hours of identification. Site investigators will be trained on GSK's reporting procedure, should the need arise during the study.

7.4. Study Milestones

EMA/CHMP Approval	October 2011
GSK Approval	April 2012
Site Identification & Assessment	April 2011 – December 2012
Feasibility Study & Review*	August 2012 – March 2013 Dependent upon launch date in each study country

Site Recruitment & EC Submissions*:	September 2012 – June 2013 Dependent upon outcome of feasibility review and launch date in each study country
First Patient Included*:	January 2013 – July 2013 (Country dependent)
Last Patient Included*:	February 2013 – August 2013 (Country dependent)
Country Analyses Completion*:	March 2013 – September 2013
Global Analyses and Report Completion*:	December 2013

***still pending**

7.5. Study Advisory Committee

Role

It is envisaged that the Study Advisory Committee will be comprised of a study representative (primary investigator) from each country and, if needed, a non-investigator expert. The role of the committee will include:

- Leading regulatory/ ethical procedures in each country (i.e. ECs, informed consent, etc.)
- Advising on physician selection and recruitment in each country (if required)
- Contributing to the development of any associated publications once the study is complete.

7.6. Study Reporting and Publications

All data, results and intellectual property rights in the data and results derived from the study will be the property of the Sponsor (GSK), who may utilise the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

The Sponsor's policy is to seek publication of all study results including this

proposed study. Each investigator, whilst free to utilise data derived from the study for scientific purposes, will be asked to discuss any publication with the Sponsor prior to release and obtain written consent of the Sponsor on the intended publication. The Sponsor recognises the right of the investigator to publish the results upon completion of the study. However, the investigator will be asked to send a draft manuscript of the publication or abstract to the Sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the Sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

7.7. Resourcing Needs

ARW (external to WWEpi) will be managing the study on behalf of GSK, including study set-up, physician recruitment, facilitating EC and regulatory submissions, contracting and data collection. Analyses and reporting will also be conducted by ARW.

8. REFERENCES

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9. APPENDICES

9.1 Fondaparinux prescribing information

PRESCRIBING INFORMATION FOR USE IN PATIENTS WITH SVT

Treatment of superficial-vein thrombosis

The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Patients eligible for fondaparinux 2.5 mg treatment should have acute, symptomatic, isolated, spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long and documented by ultrasonographic investigation or other objective methods. Treatment should be initiated as soon as possible following diagnosis and after exclusion of concomitant DVT or superficial-vein thrombosis within 3 cm from the sapheno-femoral junction. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications. Patients could be recommended to self-inject the product when they are judged willing and able to do so. Physicians should provide clear instructions for self-injection.

Special populations

Renal impairment

- *Treatment of superficial-vein thrombosis* - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min. The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min. No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min). The safety and efficacy of 1.5 mg has not been studied.

Hepatic impairment

- *Treatment of superficial-vein thrombosis* - The safety and efficacy of fondaparinux in patients with severe hepatic impairment has not been studied, therefore fondaparinux is not recommended for use in these patients.

Low body weight

- *Treatment of superficial-vein thrombosis* - The safety and efficacy of fondaparinux in patients with body weight less than 50 kg has not been studied**,** therefore fondaparinux is not recommended for use in these patients.

9.1 Site Assessment Survey

SVT – Physician Prescribing Study

Site assessment survey

Good morning/afternoon, I am calling from _____, a market research organisation specialising in healthcare.

We are currently looking to recruit centres for a study relating to the treatment of patients with Superficial Vein Thrombosis (SVT) and I would be grateful if you could answer some questions to establish whether your centre is one that we wish to include in the study.

Would you be willing to answer these preliminary questions?

☐ Yes ☐ No

If 'No', thank and close – record as a 'refused contact'.

_____

1a.	Where do you <u>mainly</u> practice?	□ Hospital □ Office □ GP clinic/surgery □ Other (_____)
1b.	If 'hospital', how would you describe the type of hospital?	□ Teaching/University hospital □ Regional general hospital □ Local general hospital □ Other (_____)
1c.	And if 'hospital', what is the name of the Department you work in?	_____
2.	Does your clinical setting have routine access to diagnostic imaging facilities	□ Yes
3.	What is your primary specialty?	□ Angiologist □ Radiologist □ Angio-surgeon □ Vascular surgeon □ General surgeon □ Internal medicine physician □ Phlebologist

		□ General practitioner □ Emergency Room physician □ Other (_____)
4a.	Do you personally diagnose and treat patients with SVT and/or DVT?	□ Yes □ No
4b.	If 'no', would they be treated by someone else in your clinical setting or by someone else in a different clinical setting?	□ Same setting (specify who: _____) □ Different setting (specify which setting: _____) **THANK AND CLOSE**
5a.	Including yourself, how many physicians in your setting will diagnose and treat patients with SVT?	_____
5b.	How many patients are currently being managed in your setting who have isolated SVT and how many have SVT with concomitant DVT?	_____ isolated SVT _____ SVT with concomitant DVT
6.	What proportion of these patients is treated with fondaparinux?	_____% isolated SVT _____% SVT with concomitant DVT
7.	In a typical month, how many patients would your department diagnose with: a. Isolated SVT b. SVT with concomitant DVT	_____ isolated SVT _____ SVT with concomitant DVT
8a.	In what proportion of patients would you use the following procedures to diagnose SVT: a. Physical examination b. Laboratory tests c. Imaging procedures	_____% physical examination _____% laboratory tests _____% imaging procedures
8b.	In those patients for whom imaging is performed, would the details and results of diagnostic imaging be	□ Yes, imaging details □ Yes, imaging results □ No

	routinely recorded in the patient's record?	
9.	Following diagnosis, after what period of time would you normally follow up with an SVT patient?	_____ □ days *or* □ weeks

Thank you! Would you be interested in taking part in an observational, non-interventional study looking at the treatment of patients with SVT? The study will require each participating site to provide simple information on up to 14 patients meeting certain criteria from a representative sample of physicians within your practice setting.

If you are interested in the study, we will contact you again shortly with further information.

If 'Yes', please record full contact details:

Name: _____

Institution: _____

Address: _____

Address: _____

Telephone: _____

City: _____

Facsimilie: _____

If 'No': Can I please ask why you do not want to participate?

[INTERVIEWER: ALL ANSWERS SHOULD BE SPONTANEOUS. DO NOT READ OUT LIST BELOW]

TOO BUSY	1	
STUDY DOES NOT INTEREST DOCTOR	2	
ETHICAL CONCERNS	3	
ETHICAL RESTRICTIONS FROM PRACTICE/HOSPITAL	4	
DOES NOT WANT TO INVOLVE OWN PATIENTS	5	
OTHER	7	**THANK AND CLOSE**
[RESPONSE TO Q3b – REFERRED TO ANOTHER SETTING	6]	

9.2 Feasibility Questionnaire

To: Adelphi Real World (f.a.o. SVT Study Manager)
Fax: 0044 1625 575853

The following details were available in the records of up to 14 patients recently diagnosed with SVT within my practice setting who were prescribed with fondaparinux as a treatment for their SVT:
(Please ✓ each box <u>only</u> if that information was available in the patient's record)

	Case record number													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Gender	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Concomitant conditions	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Evidence of renal disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Serum creatinine	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Creatinine clearance /GFR	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diagnostic imaging details	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diagnostic test results	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Length of thrombus	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Distance from sapheno-femoral junction	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presence/absence of DVT	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fondaparinux:														
Prescribed dos	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prescribed duration	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Signature: _____

First name: _____ Last name: _____

Position: _____

Hospital/Institution: _____

City: _____ Country: _____

9.3 Case Report Form

OFFICE USE ONLY	
Doctor Number	Patient Number

Superficial Vein Thrombosis (SVT): Case Record Form

Today's date: _____ / _____ / _____ (dd/mm/yyyy)

Date patient first presented with symptoms: _____ / _____ / _____ (dd/mm/yyyy)

Date patient diagnosed: _____ / _____ / _____ (dd/mm/yyyy)

Fondaparinux prescribing

Date fondaparinux first prescribed: _____ / _____ / _____ (dd/mm/yyyy)

Fondaparinux dose initially prescribed: _____ mg

Planned duration of fondaparinux treatment: _____ ☐ days ☐ weeks (please ✓ if days or weeks)

Diagnosis

Was SVT confirmed through imaging? ☐ Yes ☐ No

If yes, what diagnostic imaging, was performed on this patient?

☐ Ultrasound ☐ Venography ☐ CT Scan ☐ MRI

☐ Other (specify: _____)

If 'No', please state how SVT was confirmed: _____

If imaging was not performed, please state why: _____

Please state location of the SVT: ☐ Left lower limb ☐ Right lower limb

Please state position of the SVT: ☐ Great saphenous ☐ Lesser saphenous

☐ Tributary ☐ Other (_____)

Please state length of the SVT: ____ · ____ cm ☐ Not recorded

Please state diameter of the SVT: ____ · ____ cm ☐ Not recorded

Please state distance from sapheno-femoral junction ____ · ____ cm ☐ Not recorded

Was DVT diagnosed? ☐ Yes ☐ No ☐ Imaging not performed

Was symptomatic PE diagnosed? ☐ Yes ☐ No

OFFICE USE ONLY	
Doctor Number	Patient Number

Superficial Vein Thrombosis (SVT): Case Record Form

Patient demographics

Age: _____ years
Weight: _____ Kg
Gender ☐ Female ☐ Male

Patient history

Is there documented evidence that this patient has renal impairment?:

☐ Yes ☐ No ☐ Do not know

If Yes, ☐ Mild ☐ Moderate ☐ Severe ☐ Do not know

Serum Creatinine result: _____µm/L

☐ Not assessed

Date last calculated _____ / _____ / _____

Creatinine Clearance result: _____ml/min

☐ Not assessed

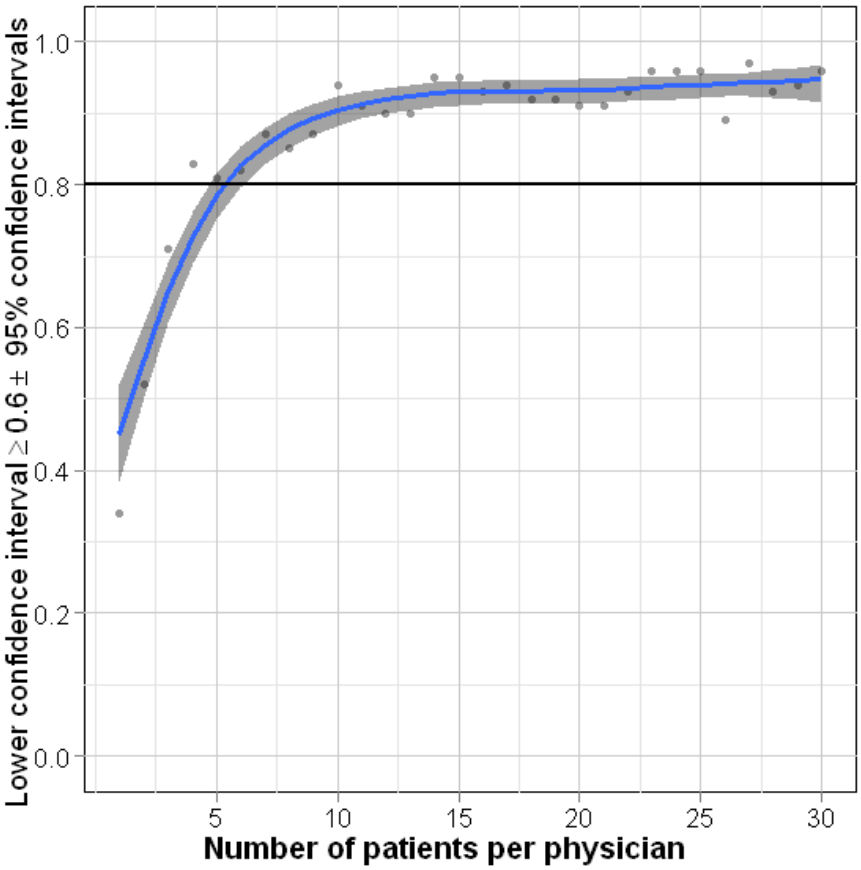
Date last calculated _____ / _____ / _____

Has this patient been previously treated for DVT, PE and/or SVT?

☐ DVT ☐ PE ☐ SVT

9.4 Further Power Calculations

Figure 3 - Graph Showing Power to Observe A Lower 95% Confidence Interval When 18 Physicians are Recruited in a Country with Varying Number of Patients Per Physician With an Intraclass Correlation of 0.2 and a Population Probability of Success of 0.8.



Dots represent the proportion of times the lower confidence interval was ≥ 0.6 adherence for 100 simulated data sets. From Figure 3 it is clear that there is little to be gained from recruiting beyond ten patients per physician in the scenario above.

9.5 Protocol Amendment

This 20th November 2012 version of the protocol had two main amendments incorporated:

a. The present status for fondaparinux as a treatment for SVT across Europe, depending on several factors such as reimbursement or local prescription practices, means that it has been only possible to identify four countries to deploy the described study. As a consequence, the scope of the study described in this protocol has been amended to focus on four countries instead of five. In order to maintain the same patient sample (840 patients in total), the protocol now describes the recruitment of an average of fifteen sites per country, with a higher number of physicians overall per country.

b. The study timeline in the present version of the protocol has been updated to reflect the additional time associated with defining and implementing the requested feasibility study, identifying and agreeing the final selection of countries.

The milestones in section 7.4 have been updated to reflect the remaining study timeline.

This latest version of the protocol amendment addresses the uncertainty on the specificity of renal information after completion of feasibility in Germany, Slovenia and Greece. This led to the inclusion of a row ‘serum creatinine’ in the feasibility CRF and also the extension of the first question in the patient history section to include severity of renal function.