Statistical Analysis Plan Update
including Blind Review

Efficacy and Safety of Long-Term (6 Months) Innohep®
Treatment Versus Anticoagulation with a Vitamin K Antagonist (Warfarin)
for the Treatment of Acute Venous Thromboembolism in Cancer Patients /
IN 0901 INT

A Phase 3 Study of Subcutaneous Innohep® 20,000 anti-Xa IU/ml for the Treatment of
VTE in Cancer Patients

Multi-National, Multi-Centre, 6-Month, Randomised, Controlled, Open-Label Study with
Blinded Adjudication

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to
protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential
information.
Summary data are included but data on individual study subjects, including data listings, are removed. This may result in
page numbers not being consecutively numbered.
Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient
and Scientific Review Board.
Appendices to the clinical study report are omitted.
Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR
ANONYMISATION OF CLINICAL TRIAL DATA

LEO Pharma A/S
Biostatistics

Trial IN 0901 INT
SAPU Date 11-JUL-2014
EudraCT Number: 2009-018141-20
1 Statistical Analysis Plan Update Approval

1.1 Approval Statement

On behalf of LEO, the Head of Biostatistics and the Head of Clinical Development and Safety, are authorised to approve the Statistical Analysis Plan Update.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan Update using electronic signatures as presented on the last page of this document.
2 Statistical Analysis Plan Update Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan Update is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice and E9: Statistical Principles for Clinical Trials).
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CIF</td>
<td>Cumulative incidence functions</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FSFV</td>
<td>First subject first visit</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>INR</td>
<td>International normalised ratio</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive voice response system</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PTS</td>
<td>Post-thrombotic syndrome</td>
</tr>
<tr>
<td>SAPU</td>
<td>Statistical Analysis Plan Update</td>
</tr>
<tr>
<td>SDV</td>
<td>Source data verify</td>
</tr>
<tr>
<td>SMQ</td>
<td>Standardised MedDRA Queries</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>TTR</td>
<td>Time in therapeutic range</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
</tbody>
</table>
4 Statistical Analysis Plan Update Authors

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5 Introduction

The statistical analysis will be performed as outlined in the Consolidated Clinical Study Protocol, including amendments. This Statistical Analysis Plan Update (SAPU), prepared before receiving the results from the adjudication committee (i.e. blinded to the primary and secondary endpoints in the trial), but after blind review of the other data, contains a more technical and detailed elaboration of some points in the statistical analysis described in the Consolidated Clinical Study Protocol. Minor deviations from the planned data presentation and analysis are accounted for and changes/omissions are justified. Furthermore, the analysis sets, which are to be used for the statistical analysis, are presented. The SAPU was written based on a blind review of the data present in the clinical database on 18-Jun-2014. Only little outstanding data is expected to be entered after this date but the principles to handle all data are stated in the following.

There have been several amendments to the Clinical Study Protocol but only the first two protocol amendments are relevant to the statistical reporting of the trial.

In the first protocol amendment, which was implemented prior to the first subject first visit (FSFV), dated 21-Jun-2010, the sample size was reduced from 1000 to 900 patients. In the amendment, the sample size is calculated using a time-to-event approach, which is in line
with the protocol-stated analysis of the primary endpoint. The method results in the reduction in sample size and replaces the more conservative approach based on Fisher’s exact test described in version 1.0 of the Clinical Study Protocol. The overall power of the trial of 90% and the assumptions of a 6-month event rate of 12.6% in the control group and a 50% reduction in the innohep® group remain unchanged.

In the second protocol amendment, dated 24-Feb-2011, the visit window for the End of Treatment visit, Visit 9 (Day 180), was corrected from ±7 to +7 in order to ensure availability of the overall mortality status on Day 180. Some investigators have, however, discontinued subjects, regarded as completers of treatment, according to the ±7 day window and hence for consistency Day 173 is used as the cut-off in the definition of a completer.

6 Trial Analysis Sets
The analysis sets are determined based on the criteria defined in the Consolidated Clinical Study Protocol.

The number of subjects who attended each visit is shown in Figure 1. The reasons for withdrawal from trial as stated by the investigators are indicated on the flowchart. In each box the number of subjects attending the visit is stated with the sum in brackets indicating how many of these attended a regular visit and how many attended an off-treatment telephone visit. To the right of each box is indicated how many subjects are still followed in the trial and of these the number of subjects followed off-treatment. The term ‘withdrew consent’ covers the subject voluntary withdrawal from the trial, including off-treatment telephone contacts, which they can chose at any time during the trial and for any reason.
Figure 1: Visit attendance

<table>
<thead>
<tr>
<th>Screening visit</th>
<th>Number of subjects attending</th>
<th>Primary reason for withdrawal from trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>900</td>
<td>7</td>
</tr>
<tr>
<td>Visit 2</td>
<td>851</td>
<td>22</td>
</tr>
<tr>
<td>Visit 3</td>
<td>813</td>
<td>43</td>
</tr>
<tr>
<td>Visit 4</td>
<td>736</td>
<td>88</td>
</tr>
<tr>
<td>Visit 5</td>
<td>666</td>
<td>72</td>
</tr>
<tr>
<td>Visit 6</td>
<td>587</td>
<td>63</td>
</tr>
<tr>
<td>Visit 7</td>
<td>547</td>
<td>41</td>
</tr>
<tr>
<td>Visit 8</td>
<td>518</td>
<td>30</td>
</tr>
<tr>
<td>Visit 9</td>
<td>528</td>
<td>22</td>
</tr>
<tr>
<td>Completes 180 days in trial</td>
<td>512</td>
<td></td>
</tr>
<tr>
<td>30 Day Follow-up</td>
<td>525</td>
<td>22</td>
</tr>
</tbody>
</table>

- 3 death
- 4 withdrew consent
- 893 in trial (1 off treatment)
- 12 death
- 8 withdrew consent
- 2 other reason(s)
- 871 in trial (8 off treatment)
- 32 death
- 1 lost to follow-up
- 8 withdrew consent
- 2 other reason(s)
- 828 in trial (31 off treatment)
- 73 death
- 1 lost to follow-up
- 10 withdrew consent
- 4 other reason(s)
- 740 in trial (55 off treatment)
- 52 death
- 5 lost to follow-up
- 8 withdrew consent
- 7 other reason(s)
- 668 in trial (69 off treatment)
- 51 death
- 1 lost to follow-up
- 8 withdrew consent
- 3 other reason(s)
- 605 in trial (79 off treatment)
- 30 death
- 3 lost to follow-up
- 7 withdrew consent
- 1 other reason(s)
- 564 in trial (86 off treatment)
- 18 death
- 3 lost to follow-up
- 6 withdrew consent
- 1 other
- 2 completed
- 534 in trial (98 off treatment)
- 7 death
- 15 completed
- 525 in trial (98 off treatment)
- 16 death
- 7 lost to follow-up
- 5 withdrew consent
- 4 other
6.1 Enrolled/Randomised Subjects

In a randomised clinical trial, all subjects randomised form the basis for defining the analysis sets for safety and efficacy evaluations and for baseline descriptions. A total of 914 subjects signed an informed consent and were randomised in the IVRS (Interactive Voice Response System). However, 14 of these subjects were randomised in error and should have been treated as screen failures. They did not meet the requirements of the trial in-/exclusion criteria and were discovered and withdrawn prior to receiving any investigational product (IP). The reasons for withdrawal are listed below and are judged not to present any risk of bias of the trial results.

<table>
<thead>
<tr>
<th>Site</th>
<th>Patient</th>
<th>Country</th>
<th>Reason for failing inclusion/exclusion criteria</th>
<th>Inc/Exc Criteria Not Met</th>
<th>Comment</th>
</tr>
</thead>
</table>

The 900 remaining subjects comprise the set of randomised subjects included in the baseline descriptions and form the basis for the other analysis sets defined in the following sections. When referring to randomised subjects in the following, only the 900 subjects are considered.

6.2 Full Analysis Set

All 900 randomised subjects are included in the full analysis set and analysed for efficacy.

6.3 Safety Analysis Set

All 900 randomised subjects were dispensed IP and are hence included in the safety analysis set and analysed for safety.
Since, no subjects were dispensed the wrong type of IP all subjects are analysed for safety according to the allocated treatment group.

### 6.4 Per Protocol Analysis Set

All 900 subjects in the full analysis set were dispensed trial IP and provide efficacy data following start of treatment.

One subject participated in another clinical trial at the same time and is therefore excluded from the per protocol analysis set.

24 subjects did not meet the disease-defining inclusion criteria; had no histology or other proof of active cancer; had either no VTE at baseline or had a thrombosis not fulfilling the inclusion criteria and were excluded from the per protocol analysis set.

Two subjects took prohibited medication known to have a potential impact on VTE recurrence concomitantly with the trial IP for ≥14 days and are hence excluded from the per protocol analysis set. All concomitant medications within the ATC3 group ‘B01A’ were considered by the medical expert but only a few were deemed to have an impact on VTE recurrence. In case the prohibited medication was taken during a planned temporary treatment discontinuation the subject was not excluded from the per protocol analysis set.

12 subjects had a temporary treatment discontinuation lasting more than 3 weeks and are hence excluded from the per protocol analysis set. Subjects discontinuing treatment permanently more than 3 weeks prior to death, recurrent event or 180 days after randomisation will be excluded from the per protocol analysis set. These subjects cannot be given by subject ID here but will be specified further in the CSR.

Two sites were closed due to non-compliance issues. 24 subjects were randomised at these sites. The subjects were not followed by the site staff as prescribed by the protocol, but their data was entered and source data verified (SDV) and the data were considered reliable. These subjects are hence not excluded from the per protocol analysis set.

No subjects were excluded from the per protocol analysis set due to deviations from the visit windows; these were not deemed to have an impact on the efficacy endpoints.
The total number of subjects in the per protocol analysis set will depend on the outcome of the trial (occurrence of VTE recurrence, blinded at data review) and can therefore, not be specified in the SAPU. The per protocol analysis set will be analysed for efficacy.

All major protocol deviations including those not leading to exclusion from the per protocol analysis set are presented in a listing by subject ID and summarised in a table by deviation type.

### 6.5 Treatment-specific Exposure Analysis Sets

The subjects in the safety analysis set who were allocated to the warfarin treatment group comprise the warfarin exposure analysis set. This analysis set is used to present exposure and compliance data relevant for the warfarin-treated subjects, only.

The subjects in the safety analysis set who were allocated to the innohep® treatment group comprise the innohep® exposure analysis set. This analysis set is used to present exposure and compliance data relevant for the innohep®-treated subjects, only.

### 7 Statistical Analysis

The statistical analysis will be performed as described in the Consolidated Clinical Study Protocol. Where additional analyses are planned, or further details are needed, these are specified in the following sections.

#### 7.1 Baseline Considerations

Subjects were randomised 1:1 to the two treatment groups within the 3 strata – Region (Western Europe, Eastern Europe, Americas, Asia), History of VTE (yes, no), and Tumour stratum (known distant metastasis, no distant metastasis, haematological malignancy).

The region variable used in tabulations and analyses comprise the geographical regions included in the stratified randomisation. The country allocation to regions is as follows:

**Western Europe:** Austria, Canada, Germany, Greece, Israel, Italy, Portugal, South Africa, and Spain.

**Eastern Europe:** Bulgaria, Czech Republic, Latvia, Poland, Romania, Russia, Serbia, Slovakia, and Ukraine.

**Americas:** Argentina, Brazil, Chile, Guatemala, Mexico, and Peru.

**Asia:** Egypt, India, Jordan, South Korea, Lebanon, Saudi Arabia, Taiwan, and Thailand.
163 subjects (18%) were discovered after randomisation during Source data verification (SDV) to have been randomised according to a wrong stratum. These subjects will be analysed according to their actual stratum, representing their true baseline risk.

7.1.1 Subject Disposition

To assess the performance of the stratified randomisation, the subject disposition to the 24 strata will be summarised. Subjects were expected to remain in the trial up to and including Day 180, even if they discontinued treatment prior to Day 180 and irrespective of the 30-day safety follow-up after their last day of dosing. For that reason, both the subject-reported reason for discontinuing treatment and the reason for leaving the trial as recorded by the investigator will be summarised by treatment group.

A subject is regarded as a completer of the trial if he/she either dies or meets an endpoint up to and including Day 180 + 24 hours after the last dose of IP, or if he/she is treated up to and including day 173 not having died, or met an endpoint up to and including Day 180 + 24 hours after the last dose of IP. To illustrate this, a separate table will be produced giving the number and the percentage of subjects in these categories by treatment group. A 7-day visit window for the Day 180 visit explains the choice of day 173 as the cut-off for a subject to have completed treatment.

7.1.2 Demographics and Baseline Characteristics

Descriptive statistics of demographics and baseline characteristics will be presented as planned in the Consolidated Clinical Study Protocol and is repeated below with more detail.

All demographics (age, age category, sex, race, ethnicity, body weight at Baseline, body mass index [BMI] at Baseline, and BMI category at Baseline) will be presented for each treatment group. All but the age categories will be presented by region. Only age and BMI categories will be presented by the two other stratification factors, tumour stratum and history of VTE. Only the BMI and the BMI categories will be presented by country.

The baseline characteristics (category of renal clearance, tumour stratum, primary site of cancer, initial VTE, history of VTE, and ECOG measured prior to the VTE episode) will all be presented for each treatment group by region.

Cancer stage and best response to cancer treatment were collected but not planned in the clinical study protocol. This information is only listed.

The medical/surgical history at baseline and the concomitant diagnoses at baseline will be presented by MedDRA primary system organ class for each treatment group.
7.1.3 Prior and Concomitant Medication

Prior and concomitant medication will be presented by ATC classification as planned in the Consolidated Clinical Study Protocol. The therapeutic anticoagulant treatment taken during the screening period will be tabulated separately by ATC category. Chemotherapy and whether or not the subject received radiotherapy during the trial will be tabulated separately.

7.1.4 Extent of IP Exposure and Compliance

The duration of exposure to IP will be presented as planned in the Consolidated Clinical Study Protocol together with an additional table summarising the duration of temporary treatment discontinuations. For subjects in the warfarin exposure analysis set, the duration of the initial innohep® treatment will be tabulated overall and by region.

The duration of exposure will be summarised by region and by tumour stratum.

The exposure categories (<10, 10-29, 30-59, 60-89, 90-119, 120-149 150-179, >=180 days) will be tabulated. The category ‘<10 days’ was added in the SAPU as it is used for safety reporting in the Risk Management Plan.

For the innohep® exposure analysis set, the average daily dose per kg bodyweight prescribed by the investigator will be summarised in IU/kg. For the warfarin exposure analysis set, the average daily dose prescribed by the investigator will be summarised in mg.

Due to many missing or incomplete subject diaries, the date of the first dose in all exposure calculations will be taken to be the subject date of randomisation. This introduces a small chance of inflating the subject exposure by one day but as this is done equally for all subjects it is judged not to introduce any bias to the trial.

As a measure of treatment compliance, the number of dosing days recorded in the diaries divided by the treatment duration from the first dosing date to the last dosing date will be summarised as the number of subjects who are 100%, 75-99%, 50-74%, 25-49% and <25% compliant. Subjects with some or all diary data missing will be presented in a separate category.

The number of temporary treatment discontinuations of more than 3 weeks consecutive duration will be tabulated and the actual length of these discontinuations will be summarised for each treatment group. Some subjects have a temporary treatment discontinuation recorded with no resume date. These are treated like permanent stop of treatment and will not be part of the tabulations. The temporary treatment discontinuations are all listed by subject including those with no resumed date.
For the warfarin exposure analysis set, the percentage time in therapeutic range (TTR) of the international normalised ratio (INR) values is calculated as a measure of treatment compliance. The TTR will be presented by region and the percentage time below (INR<2), within (INR between 2 and 3), and above (INR >3) range will be presented overall. The TTR is calculated according to the Rosendaal method (Rosendaal FR et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69:236-239) using linear interpolation between INR values.

To calculate a valid TTR, the following rules will be adhered to:

- The TTR is calculated from Day 7 up to and including Day 180 or End of Treatment, whichever occurs first. Days 1 to 6 are regarded as an adjustment period.
- The TTR is not calculated for subjects with less than 2 INR values after Day 7.
- Subjects who never reach the therapeutic target interval after Day 7 have a TTR of zero.
- For subjects with an unknown date of the last dose, the last available INR value is used as the last reference point for the TTR.
- Temporary treatment interruptions of more than 5 days duration with a medical justification are accounted for by subtracting the relevant period plus an additional 7 days for re-adjustment from the TTR calculations.

7.2 Analysis of Efficacy

The analysis of efficacy will be analysed and presented for the full analysis set as planned in the Consolidated Clinical Study Protocol. A supportive analysis of the primary efficacy endpoint will be performed for the per protocol analysis set.

As described in section 7.1 some subjects were randomised according to the wrong strata by mistake. For completeness, the primary analysis will also be performed with the originally entered stratification variables to assess any impact on the outcome.

7.2.1 Primary Efficacy Criterion

The primary efficacy analysis will be performed as described in the Consolidated Clinical Study Protocol as a time to event analysis accounting for competing risks. The event of interest is the first recurrent event confirmed by adjudication. A recurrent event is defined as experiencing one of the following 5 objectively documented components:
1. symptomatic non-fatal DVTs
2. symptomatic non-fatal PEs
3. fatal PE
4. incidental proximal DVT (popliteal vein or higher)
5. incidental proximal PE (segmental arteries or larger)

The competing risks in the primary analysis are deaths other than fatal PEs.

The regression model described by Fine and Grey (Jason P. Fine & J. Grey (1999) A Proportional Hazards Model for the subdistribution of a Competing Risk, Journal of the American Statistical Association, 94:446, 496-509) is used to model the cumulative incidence functions (CIF) for the two treatment groups (assuming proportionality) in the presence of competing risks and adjusted for the stratification factors. The strata region, tumour stratum, and history of VTE are included in the model as main effects as is the treatment allocation. The test for no treatment effect will be conducted as a Wald’s test within this model.

As a sensitivity analysis of the primary analysis, the model described by Grey (J. Grey (1988) A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing risk, The annals of Statistics, Vol. 16, No. 3, 1141-1154) is used. The CIFs for the two treatment groups in the presence of competing risks stratified by the product of the 3 stratification factors (24 levels) will be modeled, if possible, due to the potential sparseness of events within strata. Grey’s stratified test for no treatment effect within this model will be presented.

In addition, Grey’s stratified test for no difference in treatment effect, will be performed including each stratum separately in the statistical model, to assess the robustness of the primary analysis.

The CIFs by stratum and treatment group will be presented graphically to assess the underlying assumption of proportionality in the primary analysis.

A proportional hazards regression analysis treating deaths other than fatal PEs as censored will be performed with treatment group, region, tumour stratum, and history of VTE as main effects.

**7.2.2 Secondary Efficacy Endpoints**

The 6 secondary efficacy endpoints defined in the Consolidated Clinical Study Protocol are given as the time in days from randomisation to the first occurrence of
• the 5 individual components of the composite primary efficacy endpoint

• any symptomatic DVT and/or PE, including fatal PE

In case of a subject experiencing more than one type of event, it is only the type and time of the first event that counts in the definition of the secondary endpoints. In case of a subject experiencing more than one type of event on the same day, it is the event of interest that is counted first. Only events confirmed by adjudication will be included.

To examine the consistency of the results between the different components of the primary endpoint, the time to the first occurrence of each of the primary endpoint components or the end of the trial period, whichever occurs first, will be analysed separately. All 6 secondary endpoints will be analysed and presented as described for the primary efficacy endpoint. For each time-to-event analysis, the components not defined as the event of interest will be considered a competing risk. Hoechbergs method will be used to correct for multiplicity.

7.3 Analysis of Safety

The analysis of safety will be analysed and presented as planned in the Consolidated Clinical Study Protocol.

7.3.1 Overall Mortality

The time to death (Overall mortality) up to and including Day 180 will be assessed in a proportional hazards model including treatment group and the 3 stratification factors as main effects. Their hazard ratios and associated 95% confidence intervals will be presented. The test for no treatment effect will be conducted as a Wald’s test within this model.

Kaplan-Meier estimates for the two treatment groups stratified by the product of the 3 stratification factors (24 levels) will be presented, if possible, due to the potential sparseness of events within strata. A stratified log-rank test for no treatment effect within the proportional hazards model will be conducted.

In addition, a stratified log-rank test for no difference in treatment effect, will be performed for each stratum separately to assess the robustness of the analysis of mortality.

The Kaplan-Meier curves by stratum and treatment group will be presented graphically to assess the underlying assumption of proportionality.

The 180 day mortality for the two treatment groups will be estimated by the Kaplan-Meier estimate at 180 days and presented together with their 95% confidence limits.
The overall mortality status on Day 180 will be summarised by treatment group.

Every effort was made to follow up on subjects who discontinued the trial prior to Day 180 with respect to mortality status on Day 180. Some subjects were followed up long time after they discontinued the trial and if they had died their date of death was recorded even though it was long after the reporting period for the CSR. Deaths occurring more than 217 days after randomisation will only appear in the Overall Mortality subject data listing. In summary, 18 subjects provided information on overall mortality after having discontinued the trial.

7.3.2 Bleeding Event Data

All bleeding events occurring up to and including 24 hours after the last dose of IP will be presented as planned in the Consolidated Clinical Study Protocol.

For subjects in the warfarin exposure analysis set, the number of major bleeding events will be presented by INR category, where the INR category is defined as having an INR value below 2, between 2 and 3, or above 3 just prior to the bleeding episode. “Just prior to the bleeding episode” will be defined as the last INR value measured in the 14-day period leading up to the bleeding event. In case the subject has no INR values in this period, the INR category will be displayed separately as missing.

7.3.3 Thromboses other than Objectively Confirmed VTE

Thromboses other than objectively confirmed VTEs will be presented as planned in the Consolidated Clinical Study Protocol. Thromboses other than objectively confirmed VTEs are defined as treatment-emergent AEs or SAEs within the SMQs (standardised MedDRA queries) ‘Embolic and thrombotic events’, ‘Embolic and thrombotic events, arterial’, ‘Embolic and thrombotic events, venous’, and ‘Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous’ that have not been confirmed by adjudication to be a primary outcome event.

7.3.4 Adverse Events

Adverse events will be presented as planned in the Consolidated Clinical Study Protocol by MedDRA system organ class and/or preferred term. AE tables will be sorted by overall frequency.

According to the eCRF completion guidelines, AEs that increase in intensity after onset will only be reported as a new AE if it becomes serious. In that case, an SAE will be created with the onset date being the date of worsening. For this reason, the treatment-emergent AEs/SAEs will be defined as any AE or SAE with onset after the first dose of IP. The pre-treatment
emergent AEs/SAEs and the post-treatment emergent SAEs will be tabulated separately by system organ class and preferred term. All other AE/SAE tabulations will be for the treatment-emergent AEs/SAEs only.

In case of an incomplete onset date or an unknown date of the last dose the AE/SAE will be treated as treatment-emergent.

Additional tables displaying only the most common AEs (>1% of subject in any treatment group) by system organ class and/or preferred term will be presented overall and by causality and intensity, respectively. The most common related adverse events (>1% of subjects in any treatment group) will be displayed by system organ class, preferred term, and intensity. The most common adverse events (>5% of subjects in any treatment group) will be displayed by preferred term.

Osteoporosis is an AE of special interest and will be listed separately. It is defined as AEs within the SMQ ‘osteoporosis/osteopenia’.

Serious allergic reactions are AEs of special interest and will be listed separately. They are defined as AEs within the SMQs ‘Severe cutaneous adverse reactions (narrow)’, ‘Anaphylactic reaction (narrow)’, ‘Anaphylactic/anaphylactoid shock conditions (narrow)’, and ‘Angioedema (narrow)’.

Hyperkalaemia is an AE of special interest and will be listed separately. It is defined as AEs within the Low Level Term ‘Hyperkalaemia’ or ‘Hypoaldosteronism’ according to the MedDRA code.

All reported cases of overdose will be listed separately as those AEs with a preferred term of ‘Overdose’ or ‘Accidental overdose’.

7.3.5 Vital Signs and BMI

Vital signs will be presented not by visit as planned in the Consolidated Clinical Study Protocol but as change from Baseline to End of Treatment. Weight and BMI will be presented as change or shift from Baseline to Visit 8 where the last measurement of weight is performed.

7.3.6 Laboratory Data

The laboratory data will be presented as planned in the Consolidated Clinical Study Protocol.

For laboratory values, the last available value taken prior to the date of randomisation is used as the baseline value for each parameter. The tabulations and listings will represent the
centrally analysed data with the exception of INR values analysed locally throughout the trial as part of the monitoring of warfarin subjects, and, the screening values of aPTT, platelets and creatinine clearance analysed locally for assessment of in-/exclusion criteria eligibility.

In cases when central lab analysis could not be performed and the medical monitor requested that the local lab was entered in the database as a record of the monitoring of the subject, these data will not be tabulated or listed, but are kept in the database.

In general, the last observation will be carried forward unless only the baseline assessment is present.

Laboratory values outside of reference ranges will be flagged in the listings and the number of subjects with values outside the reference range will be presented by laboratory parameter for each treatment group for all central laboratory values. Laboratory values found to be of clinical significance by the Investigator were reported as AEs within the system organ class 'Investigations’ and are listed.

In case of more than one reference range per laboratory parameter the data will be presented by reference range.

All adjudicated cases of suspected HIT events are listed. If more than 5 cases of HIT are confirmed in the trial, these will be tabulated by treatment group.

### 7.3.7 Analyses accounting for the safety reporting period

For each subject, the safety reporting period of treatment emergent adverse events is from the date of randomisation to the date of last dose plus 24 hours. To account for a potential difference in the aggregate safety reporting period between the treatment groups, the number of major bleeding events in each group will be presented both overall and per 100 subject-treatment years. A subject-treatment year is defined as the number of days from the date of randomisation to the date of last dose or Day 180, whichever comes first, divided by 365.25.

In addition, the number of adverse events, the number of related adverse events, and the number of serious adverse events (SAEs) in each group will be presented both overall and per 100 subject-treatment years. The number of SAEs per region will also be presented overall and by 100 subject-treatment years.
7.3.8 Exploratory Analyses of Risk Factors and coagulation factors

The exploratory analyses of risk factors for recurrent VTE and major bleeding events will be performed as detailed below, including the assessed coagulation factors (D-Dimer, tissue factor, soluble P-selectin, factor VIII, and CRP).

Biomarker sampling was not approved by the local IEC and therefore not performed in Guatemala (7 subjects), at site [removed] in India (0 subjects), and site [removed] in South Africa (8 subjects). Nor was biomarker sampling performed in Jordan (2 subjects) and Brazil (75 subjects) as regulatory approval was not received. Hence, in total 808 subjects should provide information on the coagulation factors and are included in the tabulations and exploratory analysis of these.

A range of risk factors for VTE and bleeding were collected in the trial. The main risk factors for VTE (region, tumour stratum, and history of VTE) were stratified for at randomisation and are accounted for in the primary analysis. The occurrence of all risk factors for both VTE and bleeding will be summarised at baseline.

All risk factors for VTE listed in the Consolidated Clinical Study Protocol were recorded as a risk if present at baseline. However, some of the risk factor values could change during the course of the trial up until Day 180 or the occurrence of an event, whichever comes first. These post baseline risk factors related to disease diagnoses, concomitant treatments, or treatment courses, are summarised together with the pre-specified risk factors.

To explore the relationship between recurrent VTE and the different risk factors the model used for the primary analysis will be applied extended by including separately each of the risk factors. Risk factor values that change during the trial will be included as time dependent covariates. For each risk factor the hazard ratio and corresponding 95% CI will be presented.

The relationship between major bleeding events and the different risk factors will be analysed as described for recurrent VTEs.

In addition, the incidence rates of recurrent VTE and major bleeding events, respectively, will be presented by quartiles of coagulation factors at Baseline. The incidence rates of recurrent VTE will further be presented by quartiles of coagulation factors at the End of Treatment and by change in quartiles from Baseline to End of Treatment (increase, no change, decrease). Missing values will be presented in a separate category.

The Ottawa score and the Khorana score for prediction of VTE recurrence risk will be calculated and subjects will be categorised to be of low, intermediate, or high risk of VTE.
recurrence according to these scores. The number of recurrent VTEs will be summarised by
the categorised scores. The definitions of the different scores are given below.

The calculation of the Ottawa score is defined as the sum of the following points (den Exter
PL, Kooiman J, Huisman MV. Validation of the Ottawa prognostic score for the prediction of
Haemost. 2013 May;11(5):998-1000):

+1 point for being a woman
+1 point for lung cancer
+1 point for prior VTE
-1 point for breast cancer
-1 point for localised cancer without metastasis (stages 1 and 2 for solid tumours)

The Ottawa risk score is defined as high if the score is ≥1, intermediate if the score is 0, and
low if the score is ≤ -1.

The calculation of the Khorana score is defined as the sum of the following points (Khorana
AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a
15;111(10):4902-7):

+2 points for very high risk site of cancer (stomach, pancreas)
+1 point for high risk site of cancer (lung, lymphoma, gynaecologic, bladder, testicular)
+1 point for pre-chemotherapy platelet count ≥350 x 10^9/L
+1 point for haemoglobin level <100 g/L or use of red cell growth factors
+1 point for pre-chemotherapy leukocyte count >11 x 10^9/L
+1 point for BMI ≥35 kg/m^2

The Khorana risk score is defined as high if the score is ≥3, intermediate if the score is 1 to 2,
and low if the score is 0.

7.3.9 Post-Thrombotic Syndrome

The post-thrombotic syndrome (PTS) will be summarised by the total Villalta score as defined
in the Consolidated Clinical Study Protocol. PTS will be summarised at Baseline and by visit
and by the PTS categories (no PTS/mild, moderate, severe) at Baseline and as change from
Baseline to End of Treatment. The last available assessment prior to the End of Treatment
visit will be used for subjects with no data at the End of Treatment visit.
7.4 Other Assessments

7.4.1 Health-related Quality of Life

The health-related quality of life data measured by EQ-5D will be presented, as described in the Consolidated Clinical Study Protocol, at Baseline and as change from Baseline to End of Treatment using descriptive statistics. The last available assessment prior to the End of Treatment visit will be used for subjects with no data at the End of Treatment visit. The EQ-5D general health state VAS score and the EQ-5D utility index will be presented by visit for observed cases. All observed values will be displayed in listings.

For comparability between results from different countries, the same value index set will be used for all countries when calculating the utility index. With a multi-country trial it is sub-optimal to choose only one value index set as no one set will be the correct one. The European index value set is used here as can be requested from the EuroQol homepage (http://www.euroqol.org).

7.4.2 Healthcare Resource Utilisation

None of the analyses related to costs of healthcare utilisation are included in the Clinical Study Report, the data related to costs are not collected as part of the trial and will be gathered and reported separately. The data related to healthcare resource utilization presented by region in the Clinical Study Report (CSR) include the number of blood transfusions and the length of the initial hospitalisation.

7.5 General Principles

7.5.1 Pooling of Trial Sites

No analysis is done at site level and hence no pooling of trial sites is needed. No analysis is done at country level either.

7.5.2 Handling of Drop-outs and Missing Values

There are no missing data for the primary and secondary efficacy analyses. A subject is counted as censored at the time of withdrawal from trial if no recurrent event has been experienced and confirmed or any competing risk has occurred. The stratification variables in the model have no missing data.

Every effort was made to follow up on subjects who discontinued the trial prior to Day 180 with respect to mortality status on Day 180 and occurrence of recurrent events.
For the presentation of laboratory, biomarkers, PTS, and quality of life data, the summaries will be done on observed data. Changes from Baseline to End of Treatment will use the last observed value prior to the End of Treatment, should this value be missing. In case only the baseline value is present in the database, no carrying forward will be performed and the change will be missing for this subject. In a few instances laboratory values could not be measured below or above a certain value. For these the cut-off value was imputed.

For incomplete dates where duration is calculated, the first day of the month and/or first month of the year is imputed. 12 subjects have not a recorded date of last dose and for these the last date of drug dispensed will be imputed as their date of the last dose. 5 of these subjects have only had drug dispensed at Visit 1 and for these subjects the duration of exposure will be 1 day.

Based on the many missing diary data values, the date of randomisation is used as the date of first dose for all subjects.

The following rules are adhered to for other variables presented in the CSR: for the categorical variables the number of missing data will be displayed as a separate category. For numerical variables the summaries will be based on observed cases only.

For further details, see the individual sections above.

### 7.6 Interim Analysis

An interim analysis was planned in the protocol to be performed after 450 subjects (50%) had completed the trial or early withdrawn. This was achieved on 06-Apr-2013. Based on the time needed for data entry, data cleaning, the adjudication process, and performance and evaluation of the interim analysis, it was estimated that the result of the interim analysis would be available mid August 2013. Based on the recruitment rates in April 2013, there would have been 885 randomised subjects in the trial in August 2013 comprising 98% of the total 900 subjects. On this ground, it was decided not to perform the interim analysis in accordance with the criteria stated in the Consolidated Clinical Study Protocol.
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**IN 0901 INT Statistical Analysis Plan Update**

**Electronic Signatures**

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

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