SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities Volume:	(For National Authority Use only)
Name of Investigational Product/ Finished Product, if available: **innohep®** 20,000 IU/ml Heparin LEO 25,000 IU/ml		
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Title of study/Protocol Code Number:

Safety profile of **innohep®** versus subcutaneous unfractionated heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis/IN 0401 INT

Centre details:

Multicentre study conducted in 10 different European countries. The total number of recruiting sites were 109 (Denmark: 0; Belgium: 5; France: 50; Germany: 13; Spain: 18; Serbia: 9; Croatia: 3; Romania: 10; Poland: 1; Czech Republic: 0).

Publication references:

- Leizorovicz A. Tinzaparin compared to unfractionated Heparin for initial treatment of deep vein thrombosis in very elderly patients with renal insufficiency – the IRIS trial. Oral presentation at ASH 2008. http://ash.confex.com/ash/2008/webprogram/Paper4719.html
- Safety profile of **innohep®** versus subcutaneous unfractionated Heparin in elderly patients with impaired renal function treated for acute deep vein thrombosis. The IRIS study Steering Committee. (Corresponding Author: Dr. Alain Leizorovicz). *To be submitted.*

Study period details:	Phase of development:
First patient enrolled: 24-DEC-2005 Last patient visit: 26-MAY-2008.	III/IV (Phase IV in countries where **innohep®** is registered).

Objectives:

The primary objective of this study was to compare the safety of **innohep®** and unfractionated Heparin in terms of Clinically Relevant Bleedings (CRBs) in elderly patients with impaired renal function for initial treatment of acute deep vein thrombosis (DVT).

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Secondary objectives were to verify that **innohep®** in elderly patients with impaired renal function is effective in terms of prevention of recurrences of venous thromboembolism (VTE) and to evaluate other safety endpoints under parallel treatment with **innohep®** or Heparin and oral anticoagulant (OAC).

Study methodology:

The study was a prospective, international, multicentre, randomised, controlled, open study. Eligible patients were randomised to treatment with either **innohep®** or Heparin, stratified by renal function (creatinine clearance ≤ 30 ml/min and creatinine clearance > 30 ml/min) ensuring balance of renal impairment between the two treatment groups. About 25% of the patients were to be randomised to the severe renal impairment stratum. During the 90 +/-5 days follow-up period there were 12 contacts/visits scheduled. Safety data reviews were planned after enrolment of 50, 200, 500 and 650 patients and additionally, an interim analysis was planned after completion of 350 patients.

Interim analysis:

The planned 350-patient interim analysis (i.e. when 350 patients had completed 90 +/-5 days) identified a higher mortality in the **innohep®** arm compared to the Heparin arm. Therefore, the Data Monitoring Committee (DMC) recommended that the study was prematurely stopped and LEO halted the study immediately. At time of closure the mechanisms behind the findings were not completely clear and enrolment of more patients was considered futile by the DMC. The recruitment was immediately stopped but all patients who were enrolled and had completed the SC period continued the study according to the protocol. When the total enrolled population had been followed up to day 90 there were 537 evaluable patients. For details, please see Safety Results below.

Number of patients enrolled and analysed:

The study was planned to enrol between a minimum of 650 patients and a maximum of 900 patients. Recruitment was to be stopped if, and when, a total of 120 patients with a CRB prior to day 90 +/-5 were enrolled. At the premature closure of the study 541 patients were enrolled of whom 539 patients were randomised. Two patients withdrew consent before any

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trial medication was given, thus the full analysis set comprised 537 patients; 269 patients in the **innohep®** group and 268 patients in the Heparin group. A total of 64 CRBs were observed prior to day 90 +/- 5.

Diagnosis and main criteria for patient selection:

The main inclusion criterion was symptomatic and objectively confirmed VTE (lower limb DVT or pulmonary embolism (PE)) with mandatory presence of objectively confirmed treatment-requiring DVT. All included patients were to have reduced renal function; for patients ≥75 years the creatinine clearance was to be ≤60 ml/min, and for patients ≥70 years the creatinine clearance was to be ≤30 ml/min.
All included patients had to provide a signed and dated informed consent before any trial-related activity was carried out.

Investigational product, dose, method of administration, lot numbers:

innohep® 175 anti-Xa IU/kg was administered subcutaneously (SC) once daily.
Lot numbers: 05 228 61, 05 228 62, 05 228 63, 07 053 61, 07 053 62, 07 053 63, 07 181 61, 07 181 62 and 07 181 63

Reference product, dose, method of administration, lot numbers:

Heparin was given as intravenous (IV) bolus injection of 50 IU /kg followed by a total dose of 400 to 600 IU/kg/day divided into two SC injections daily. The subsequent doses of Heparin were titrated based on the activated Partial Thromboplastin Time [aPTT] to achieve an aPTT ratio between 1.5 and 2.5, or according to local laboratory recommendations.
Lot numbers: A7613 and DA3979

Duration of treatment:

Treatment with **innohep®** and Heparin was initiated on day 1 and was to be given until INR was between 2.0 and 3.0 for two consecutive days (i.e. when adequate anticoagulation with OAC had been achieved) and for at least 5 days. Treatment with OAC treatment was initiated between day 1 and day 3 or when appropriate according to the investigator. Treatment with OAC was to be continued until at least day 90 +/-5.

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Criteria for evaluation

Efficacy :

Recurrence of VTE prior to day 90 +/-5 was a secondary response criterion. Any suspected recurrence of symptomatic VTE was adjudicated by an independent Critical Event Committee (CEC) blinded to treatment allocation.

Safety:

The primary response criterion of this study was to compare the safety of **innohep®** and Heparin in terms of CRBs prior to day 90 +/- 5. Major or minor bleedings prior to day 90 +/- 5 constituted secondary response criteria. All bleedings were adjudicated and classified by the CEC. The tertiary endpoints (CRBs during SC anticoagulant treatment, heparin induced thrombocytopenia (HIT) temporally related to SC anticoagulant treatment and death of any cause prior to day 90 +/- 5) were also blindly adjudicated by the CEC.

Statistical methodology:

A comparison was made of the percentage of patients with CRBs prior to day 90 +/-5 between treatment groups using a confidence interval (CI) approach. For the final analysis, the upper limit of the Mantel-Haenszel adjusted 95.2% two-sided CI of the relative risk was to be compared to 1 (adjusted for renal impairment strata: severe or moderate). If superiority was not achieved the following non-inferiority margins were to be used: 1.3 in terms of relative risk if the frequency of CRBs was > 10% and 2.5% in terms of absolute risk if the frequency of CRBs was <10 %. The percentage of patients with CRBs prior to day 12 +/-2 was to be compared between the treatment groups in the same way but a non-inferiority margin of 1.5 in terms of relative risk was to be used for the day 12 +/-2 comparison.

Summary – Conclusions

Baseline characteristics:

Creatinine clearance was balanced between the two treatment groups at baseline (mean: 39.9 ml/min in the **innohep®** group vs. 39.8 ml/min in the Heparin group) with 26.0% of the randomised patients in the **innohep®** group and 25.2% in the Heparin group having a creatinine clearance ≤30 ml/min.

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The mean age was 82.9 years in the **innohep®** group vs. 82.6 years in the Heparin group but more patients in the **innohep®** group than in the Heparin group were aged ≥90 years (14.5% vs. 12.2%). For patients with severe renal impairment, the mean age was higher in the **innohep®** group (85.9 years) than in the Heparin group (83.5 years) and the proportion of patients aged ≥90 years differed more than for the full population (30.0% in the **innohep®** group vs. 22.1% in the Heparin group). Of all randomised patients, 36.0% were males and 64.0% were females. However, in the severe renal insufficiency stratum, there were more males in the **innohep®** group (31.4%) compared to the Heparin group (16.2%). Among patients aged ≥ 90 years there were also more males in the **innohep®** group (23.1% vs. 6.1%).

Baseline characteristics which in the literature have been found to be risk factors for VTE (malignancy, leg paralysis, chronic respiratory failure, cardiac insufficiency and infectious disease) are in many cases also predictors of death. These comorbidities as well as immobilisation were all overrepresented in the **innohep®** group at baseline. The differences between the treatment groups with regard to these comorbidities were more pronounced in patients aged above 90 years than for the full randomised population.

A total of 429 (79.6%) of the randomised patients had a confirmed diagnosis of DVT alone (81.4% in the **innohep®** group vs. 77.8% in the Heparin group) and 109 patients (20.2%) had a confirmed diagnosis of both DVT and PE (18.2% in the **innohep®** group vs. 22.2% in the Heparin group). In the severe renal impairment stratum, proximal DVT was present in 90.0% of the patients in the **innohep®** group vs. 85.3% in the Heparin group.

Efficacy results:

This prematurely stopped study was primarily a safety study and the only efficacy parameter was a secondary response criterion; recurrence of VTE prior to day 90 +/-5. Risk factors for VTE were overrepresented in the **innohep®** group compared to the Heparin group (please

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see baseline characteristics above).

According to the blinded assessment by the CEC, 16/269 patients (6.0%) in the **innohep®** group vs. 9/268 patients (3.4%) in the Heparin group experienced possible recurrence of VTE. The relative risk of experiencing a recurrence of VTE prior to day 90 +/-5 in the **innohep®** group vs. the Heparin group was 1.77 (95% CI: 0.79 – 3.92); p = 0.157.

Seven of 16 patients in the **innohep®** group had confirmed recurrent VTE vs. 3 of 9 patients in the Heparin group. In the **innohep®** group, 9 patients had non-confirmed recurrent VTE (1 death assessed as probably/possibly due to PE and 8 deaths assessed as "unknown cause of death, PE cannot be ruled out"). In the Heparin group, 6 patients had non-confirmed recurrent VTE (1 death assessed as probably/possibly due to PE and 5 deaths assessed as "unknown cause of death, PE cannot be ruled out").

Recurrence of VTE was more commonly reported in the stratum of severe renal impairment both in the **innohep®** group (8.6% in the severe stratum vs. 5.0% in the moderate stratum) and in the Heparin group (4.4% in the severe stratum vs. 3.0% in the moderate stratum).

Three confirmed recurrences of VTE in the **innohep®** group vs. one in the Heparin group occurred during SC treatment. No death, in which PE was a contributing cause or could not be ruled out, occurred during SC treatment.

Safety results:

The exposure to SC treatment was similar in the treatment groups with a mean exposure of 7.9 days in the **innohep®** group vs. 7.5 in the Heparin group. The number of days the OAC was taken concomitantly with SC treatment was also similar between the treatment groups (mean: 6.8 days in the **innohep®** group vs. 6.4 days in the Heparin group) without major differences between the two renal impairment strata. The average daily dose of **innohep®** was 174.1 IU/kg (SD: 13.8 IU/kg) and the average daily dose of Heparin was 326.9 IU/kg

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(SD: 80.7 IU/kg).

Forty-eight patients died during the 90 +/-5 days of the study, 31 (11.5%) in the **innohep®** group vs. 17 (6.3%) in the Heparin group. The unadjusted relative risk of dying in the **innohep®** group vs. the Heparin group was 1.82 (95% CI: 1.03 – 3.20) with a p-value of 0.035. The difference in mortality between the treatment groups tended to be more pronounced, without being statistically significant, in the severe renal impairment stratum in which 16 patients (22.9%) in the **innohep®** group and 6 patients (8.8%) in the Heparin group died as well as in patients aged ≥90 years (12 deaths [30.7%] in the **innohep®** group vs. 3 deaths [9.4%] in the Heparin group).

One patient in each treatment group died during SC treatment. The divergence between the treatment groups in term of frequency of deaths did not start to occur until approximately 3 weeks after the stop of the SC treatment with **innohep®**/Heparin, i.e. during OAC treatment only. Two patients in the **innohep®** group vs. none of the patients in the Heparin group were reported to have fatal outcomes from a bleeding event. As assessed by the CEC, one patient in each group died due to a PE.

A multiple regression analysis showed that treatment group was not statistically significantly related to death when adjusted to baseline characteristics (p = 0.283) and showed that six parameters were highly significantly correlated to death. These included ongoing malignancy (p <0.001), infectious disease (p = 0.005), age ≥90 years (p = 0.005), cardiac insufficiency (p = 0.009), severe renal impairment (p = 0.011) and leg paralysis (p=0.033). All of these six identified risk factors for death (except for renal impairment which was balanced by design) were more common in the **innohep®** group than in the Heparin group (**innohep®** vs. Heparin), full analysis set:

- ongoing malignancy (20 patients vs. 12);

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- infectious disease (30 patients vs. 15);
- age ≥90 years (39 patients vs. 32);
- cardiac insufficiency (62 patients vs. 51);
- leg paralysis (10 patients vs. 5).

A total of 19 patients in the **innohep®** group and 4 patients in the Heparin group had three or more of the 6 identified mortality risk factors. This difference (15 patients) could seem irrelevant with regard to the total population of 537 patients but this difference greatly impacts on the total number of deaths as mortality for patients with three or more mortality risk factors was 43.5% (10 of 23 patients).

The proportion of patients experiencing a CRB up to day 90 +/-5 (primary response criterion) was identical in the two treatment groups (11.9% in each treatment group). The relative risk of experiencing a CRB in the **innohep®** group vs. the Heparin group was 0.99 (95.2% CI: 0.63 – 1.57). Although the relative risk was 0.99, non-inferiority could not be claimed because the upper limit of the 95.2% CI of the relative risk was above 1.3 in this prematurely stopped study. During the 12 +/- 2 first days the proportion of patients experiencing a CRB was also identical (7.1% in each treatment group; RR = 0.99; 95.2% CI: 0.54 – 1.84). A CRB during SC treatment was experienced by 6.7% of the patients in the **innohep®** group vs. 5.6% in the Heparin group (RR = 1.20; 95% CI: 0.62 – 2.32). In both treatment groups, the rates of CRBs were higher in the severe renal impairment stratum than in the moderate stratum (**innohep®** group: 15.7% in the severe stratum vs. 10.6% in the moderate stratum; Heparin group: 20.6% in the severe stratum vs. 9.0% in the moderate stratum). Likewise, in both treatment groups, the rates of CRBs were higher in in patients aged ≥ 90 years than in patients < 90 years.

Major bleeding was experienced by 4.5% of the patients in the **innohep®** group vs. 3.7% in the Heparin group (RR: 1.19; 95% CI: 0.52 – 2.70). Minor bleedings up to day 90 +/-5 were

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observed in 18.2% of the patients in the **innohep®** group vs. 16.0% in the Heparin group (RR: 1.13; 95% CI: 0.78 – 1.64). In both treatment groups, the rates of both major and minor bleedings were higher in the severe renal impairment stratum than in the moderate stratum. In both treatment groups skin/subcutaneous haematomas, ecchymosis or bruising not related to injection site were the most frequent types of bleedings.

One patient in the **innohep®** group and two patients in the Heparin group developed HIT during the SC treatment period. The HIT in the **innohep®** group occurred during treatment with another LMWH, 18 days after treatment with **innohep®** was discontinued. The relative risk of developing HIT in the **innohep®** group vs. the Heparin group was 0.50 (95% CI: 0.05 – 5.46) with a p-value of 0.624.

A total of 551 adverse events (AEs) were reported in the **innohep®** group vs. 537 AEs in the Heparin group (p = 0.329). In both treatment groups, the majority of the AEs were within the MedDRA SOCs of “gastrointestinal disorders”, “infections and infestations” and “general disorders and administration site disorders”.

The percentage of patients experiencing any adverse drug reaction (ADR) was 16.3% in the **innohep®** group vs. 22.3% in the Heparin group (RR = 0.73; 95% CI: 0.51 – 1.04). Of the 65 ADRs in the **innohep®** group, 7.7% were of severe intensity and 18.5% were of moderate intensity. In the Heparin group, 8.9% of the 79 ADRs were of severe intensity and 24.1% were of moderate intensity.

The percentage of patients experiencing any serious AE (SAE) was 23.3% in the **innohep®** group vs. 19.7% in the Heparin group (RR = 1.18; 95% CI: 0.86 – 1.64; p = 0.307).

More patients in the **innohep®** group than in the heparin group reported SAEs within the

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MedDRA SOCs "investigations", "vascular disorders" and "neoplasms".

When looking at malignancies, 32 patients in the **innohep®** group vs. 16 patients in the Heparin group had either ongoing malignancy at baseline, or had any malignant neoplasm reported as an (S)AE without having any reported malignancy at baseline.

In accordance with the protocol definitions, the preliminary analysis of the sub-study of anti-Xa activity showed no accumulation of **innohep®**.

Conclusion:

The study was prematurely stopped as the planned 350-patient interim analysis identified a higher mortality in the **innohep®** arm compared to the Heparin arm. Forty-eight patients died during the 90 +/-5 days of the study, 31 (11.5%) in the **innohep®** group vs. 17 (6.3%) in the Heparin group (i.e., the absolute difference in mortality was 14 patients). Baseline characteristics which are well known predictors for mortality and VTE were found to be overrepresented in the **innohep®** group. The difference in mortality rate could be explained by imbalances in baseline characteristics. A multiple regression analysis showed that treatment group was not statistically significantly related to death when adjusted to baseline characteristics, but six other parameters were statistically significantly correlated to death. These included ongoing malignancy, infectious disease, age ≥90 years, cardiac insufficiency, severe renal impairment and leg paralysis.

Since the significant difference in mortality was found from an unplanned analysis of an interim sample and since the treatment groups were found to differ with respect to the presence of important baseline characteristics, the p-value should be interpreted with caution and only regarded as descriptive. Results from interim analyses are subject to fluctuations when they are repeated and this is exemplified by the fact that the difference in mortality rate between the two treatment groups narrowed (from 7.9% to 5.2%) from the time of the interim analysis to the time of the full analysis.

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Authorities and clinicians have raised concerns that the elderly with renal impairment should be treated with great caution due to the potential risk of overdosing LMWH with the resultant risk of bleeding. Investigating the safety of full weight-based, unadjusted treatment doses of **innohep®** was the main reason for performing this study. The data from the study, although underpowered, do not suggest any difference with regard to bleedings and the preliminary analysis of the sub-study of anti-Xa activity showed no accumulation of **innohep®**. Furthermore, usually when death is caused by bleeding it is readily apparent. It is reasonably clear from this study that the difference in mortality rates can not be explained by overdosage with **innohep®**.

In conclusion, it is not rational to recommend decreased dose of this LMWH, **innohep®**, in this patient population based on this study. Overall, both treatments were well tolerated. None of the safety data indicate that a full, weight-based, unadjusted, dose of **innohep®** is an inappropriate treatment in patients with acute VTE, aged ≥70 years with renal impairment. No definite conclusions should be drawn from this study as the treatment groups were imbalanced with respect to important baseline characteristics and the study was underpowered due to premature termination.

Report date:

09-MAR-2009