



## Clinical trial results:

### **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**

#### **Summary**

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2009-018141-20                   |
| Trial protocol           | ES DE SK CZ AT PT IT DK GR LV BG |
| Global end of trial date | 31 May 2014                      |

#### **Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 19 February 2016 |
| First version publication date | 22 July 2015     |

#### **Trial information**

##### **Trial identification**

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | IN0901INT |
|-----------------------|-----------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01130025 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | LEO Pharma A/S   |
| Sponsor organisation address | Industriparken 55, Ballerup, Denmark,  |
| Public contact               | Clinical Trial Disclosure Manager, LEO Pharma A/S, +45 44945888, ctr.disclosure@leo-pharma.com |
| Scientific contact           | Clinical Trial Disclosure Manager, LEO Pharma A/S, +45 44945888, ctr.disclosure@leo-pharma.com |

Notes:

##### **Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 31 May 2014 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 31 May 2014 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 31 May 2014 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the efficacy of Innohep® in preventing the recurrence of Venous Thromboembolism (VTE) in patients with active cancer who have had an acute Venous Thromboembolism (VTE) episode.

Protection of trial subjects:

Frequent visits and telephone contacts.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 30 August 2010 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 7            |
| Country: Number of subjects enrolled | Romania: 28            |
| Country: Number of subjects enrolled | Slovakia: 31           |
| Country: Number of subjects enrolled | Spain: 34              |
| Country: Number of subjects enrolled | Austria: 10            |
| Country: Number of subjects enrolled | Bulgaria: 20           |
| Country: Number of subjects enrolled | Czech Republic: 16     |
| Country: Number of subjects enrolled | Russian Federation: 32 |
| Country: Number of subjects enrolled | Poland: 5              |
| Country: Number of subjects enrolled | Serbia: 20             |
| Country: Number of subjects enrolled | Germany: 20            |
| Country: Number of subjects enrolled | Greece: 12             |
| Country: Number of subjects enrolled | Ukraine: 24            |
| Country: Number of subjects enrolled | Italy: 13              |
| Country: Number of subjects enrolled | Latvia: 14             |
| Country: Number of subjects enrolled | Argentina: 12          |
| Country: Number of subjects enrolled | South Africa: 30       |
| Country: Number of subjects enrolled | Brazil: 75             |
| Country: Number of subjects enrolled | Chile: 5               |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Guatemala: 7           |
| Country: Number of subjects enrolled | Mexico: 24             |
| Country: Number of subjects enrolled | Peru: 46               |
| Country: Number of subjects enrolled | Egypt: 43              |
| Country: Number of subjects enrolled | India: 148             |
| Country: Number of subjects enrolled | Jordan: 2              |
| Country: Number of subjects enrolled | Korea, Republic of: 73 |
| Country: Number of subjects enrolled | Lebanon: 29            |
| Country: Number of subjects enrolled | Saudi Arabia: 12       |
| Country: Number of subjects enrolled | Canada: 6              |
| Country: Number of subjects enrolled | Israel: 18             |
| Country: Number of subjects enrolled | Taiwan: 16             |
| Country: Number of subjects enrolled | Thailand: 68           |
| Worldwide total number of subjects   | 900                    |
| EEA total number of subjects         | 210                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 579 |
| From 65 to 84 years                       | 312 |
| 85 years and over                         | 9   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

There was a screening visit period of up to 72 hours prior to randomisation (-72 hrs to 0 hr). The screening visit included evaluation of eligibility criteria, objective diagnosis of venous thromboembolism (VTE), signed informed consent, and laboratory assessments.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | 6-month treatment period (overall period) |
| Is this the baseline period? | Yes                                       |
| Allocation method            | Randomised - controlled                   |
| Blinding used                | Not blinded                               |

Blinding implementation details:

This was an open-label trial. All efficacy endpoints (lower limb DVTs and PEs) and major safety endpoints (bleeding events, HIT events, and causes of death) were adjudicated blindly by the independent adjudication committee (IAC)

### Arms

|  |  |
|--|--|
| Are arms mutually exclusive?           | Yes  |
| <b>Arm title</b>                       | Innohep®                                     |
| Arm description: -                     |  |
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Innohep® (tinzaparin sodium)                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Innohep® (tinzaparin sodium) 20,000 anti-Xa IU/mL was dispensed in syringes of 0.5 mL, 0.7 mL, and 0.9 mL. The dose was 175 anti-Xa IU/kg body weight once daily by s.c. injection. The duration of the treatment was 6 months (180 calendar days).

|  |                   |
|--|-------------------|
| <b>Arm title</b>                       | Warfarin          |
| Arm description: -                     |                   |
| Arm type                               | Active comparator |
| Investigational medicinal product name | Warfarin          |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Warfarin was dispensed as oral tablets of 1 mg, 3 mg, and 5 mg in combination with initial (5-10 days) overlapping s.c. treatment with innohep®. The dose was adjusted to maintain international normalised ratio (INR) target level 2-3.

| <b>Number of subjects in period 1</b> | <b>Innohep®</b> | <b>Warfarin</b> |
|---------------------------------------|-----------------|-----------------|
| Started                               | 449             | 451             |
| Completed                             | 309             | 279             |
| Not completed                         | 140             | 172             |
| Consent withdrawn by subject          | 17              | 17              |
| Patient/physician preference          | 24              | 23              |
| Adverse event, non-fatal              | 24              | 22              |
| Protocol violation                    | 12              | 16              |
| Unable to obtain blood sample for INR | -               | 3               |
| Progressive cancer                    | 39              | 35              |
| Target INR not achieved               | -               | 18              |
| Lost to follow-up                     | 3               | 5               |
| Reason not specified                  | 4               | 3               |
| Contraindication for anticoagulation  | 17              | 30              |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Innohep® |
|-----------------------|----------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

|                       |          |
|-----------------------|----------|
| Reporting group title | Warfarin |
|-----------------------|----------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values                | Innohep® | Warfarin | Total |
|---------------------------------------|----------|----------|-------|
| Number of subjects                    | 449      | 451      | 900   |
| Age categorical<br>Units: Subjects    |          |          |       |
| Adults (18-64 years)                  | 280      | 299      | 579   |
| From 65-84 years                      | 165      | 147      | 312   |
| 85 years and over                     | 4        | 5        | 9     |
| Age continuous<br>Units: years        |          |          |       |
| arithmetic mean                       | 59.7     | 58.8     |       |
| full range (min-max)                  | 19 to 89 | 18 to 86 | -     |
| Gender categorical<br>Units: Subjects |          |          |       |
| Female                                | 262      | 273      | 535   |
| Male                                  | 187      | 178      | 365   |

## End points

### End points reporting groups

|                                |          |
|--------------------------------|----------|
| Reporting group title          | Innohep® |
| Reporting group description: - |          |
| Reporting group title          | Warfarin |
| Reporting group description: - |          |

### Primary: Efficacy Endpoint

|   |                   |
|---|-------------------|
| End point title   | Efficacy Endpoint |
| End point description:<br>The primary efficacy endpoint is a composite endpoint represented by the time in days from randomisation to the first occurrence of any of the following 5 objectively documented components: Symptomatic non-fatal deep vein thrombosis (DVT), symptomatic non-fatal pulmonary embolism (PE), fatal pulmonary embolism (PE), incidental proximal deep vein thrombosis (DVT) (popliteal vein or higher), incidental proximal pulmonary embolism (PE) (segmental arteries or larger). All recurrent VTE outcomes were adjudicated blindly by a independent adjudication committee. The estimated subdistribution hazard ratio (SHR) is presented as a measure of relative risk between the two treatment groups (innohep® versus warfarin) together with the 95% confidence interval (CI). |                   |
| End point type  | Primary           |
| End point timeframe:<br>All recurrent VTE outcomes occurring from the time of randomisation up until day 180 regardless of whether the patient was on or off IMP-treatment (including 24 hours after the last dose of IMP) were eligible for the primary efficacy analysis.   |                   |

| End point values                           | Innohep®            | Warfarin            |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                         | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                | 449                 | 451                 |  |  |
| Units: Subdistribution HR - point estimate |                     |                     |  |  |
| number (confidence interval 95%)           | 0.65 (0.41 to 1.03) | 0.65 (0.41 to 1.03) |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Primary efficacy analysis: Recurrent VTE |
| Statistical analysis description:<br>Competing Risk Regression of Recurrent VTE (Full analysis set 900 subjects): The competing risk regression analysis adjusting for region, tumour stratum, and history of VTE |  |
| Comparison groups   | Innohep® v Warfarin                      |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 900                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | = 0.068 <sup>[2]</sup>     |
| Method                                  | Wald's test                |

Notes:

[1] - Competing Risk Regression of Recurrent VTE - The test for no treatment effect

[2] - A reduction in recurrent VTE was seen in the innohep® treated patients versus the warfarin treated patients, but the primary endpoint did not meet the 5% significant level.

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Per protocol analysis: Recurrent VTE |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Per protocol analysis set (658 subjects): The competing risk regression analysis adjusting for region, tumour stratum, and history of VTE

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | Innohep® v Warfarin                |
| Number of subjects included in analysis | 900                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | = 0.048 <sup>[3]</sup>             |
| Method                                  | Competing risk regression analysis |
| Parameter estimate                      | Subdistribution hazard ratio       |
| Point estimate                          | 0.62                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 0.38                               |
| upper limit                             | 1                                  |

Notes:

[3] - The competing risk regression analysis, based on the PP analysis set and adjusting for region, tumour stratum, and history of VTE, resulted in an SHR of 0.62 (95% CI: 0.38-1.00) in favour of innohep®; very similar to the full analysis set analysis.

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Sensitivity Analysis: Recurrent VTE |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Sensitivity analysis: The stratified competing risk analyses of recurrent VTE including a combination of all stratification factors or 1 covariate at a time.

|   |                        |
|---|------------------------|
| Comparison groups                       | Innohep® v Warfarin    |
| Number of subjects included in analysis | 900                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.069 <sup>[4]</sup> |
| Method                                  | Gray's test            |

Notes:

[4] - The analyses resulted in p-values (range: 0.069-0.085) very similar to the p-value (p=0.068) for the primary analysis.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Stratified Competing Risk Analysis: Recurrent VTE |
|-----------------------------------|---|

Statistical analysis description:

Stratified competing risk analysis: A proportional hazards regression analysis (treating deaths other than fatal PEs as censored) was performed with treatment group, region, tumour stratum, and history of VTE as main effects

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Innohep® v Warfarin |
|-------------------|---------------------|



|   |  |
|---|--|
| Number of subjects included in analysis | 900                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.079 <sup>[5]</sup>                   |
| Method                                  | Proportional hazards regression analysis |
| Parameter estimate                      | Hazards ratio (innohep/warfarin)         |
| Point estimate                          | 0.66                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.42                                     |
| upper limit                             | 1.05                                     |

Notes:

[5] - The outcome of this sensitivity analysis showed very similar results to that of the primary efficacy analysis, supporting the robustness of these results.

## Secondary: Symptomatic non-fatal PE

|                 |                          |
|-----------------|--------------------------|
| End point title | Symptomatic non-fatal PE |
|-----------------|--------------------------|

End point description:

6 subjects (innohep®: 3; warfarin: 3) experienced a symptomatic PE whereof 5 were bilateral; 1 of the symptomatic PEs in the warfarin group was not a first event and was thus not counted in the efficacy analyses. 5 subjects with symptomatic PE (innohep®: 3; warfarin: 2) are counted in the efficacy analyses.

The 6-month incidence of recurrent symptomatic non-fatal PE was low, not allowing for a meaningful competing risk regression analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.

| End point values                       | Innohep®        | Warfarin        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                     | Reporting group | Reporting group |  |  |
| Number of subjects analysed            | 449             | 451             |  |  |
| Units: The 6-month incidence (percent) |                 |                 |  |  |
| number (not applicable)                | 0.7             | 0.4             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Fatal PE

|                 |          |
|-----------------|----------|
| End point title | Fatal PE |
|-----------------|----------|

End point description:

Adjudication of cause of death classified a death due to PE as: PE confirmed by autopsy; PE confirmed by objective testing/imaging; sudden and unexplained death, which could not be attributed to a documented cause and for which PE was the most probably cause.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.

| End point values                       | Innohep®        | Warfarin        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                     | Reporting group | Reporting group |  |  |
| Number of subjects analysed            | 449             | 451             |  |  |
| Units: The 6-month incidence (percent) |                 |                 |  |  |
| number (not applicable)                | 3.8             | 3.8             |  |  |

## Statistical analyses

| Statistical analysis title                             | Competing risk regression of fatal PE |
|--|---------------------------------------|
| Statistical analysis description:<br>full analysis set |                                       |
| Comparison groups                                      | Innohep® v Warfarin                   |
| Number of subjects included in analysis                | 900                                   |
| Analysis specification                                 | Pre-specified                         |
| Analysis type  | other <sup>[6]</sup>                  |
| P-value  | = 0.9 <sup>[7]</sup>                  |
| Method   | Competing risk regression analysis    |
| Parameter estimate                                     | Subdistribution hazard ratio          |
| Point estimate   | 0.96                                  |
| Confidence interval                                    |                                       |
| level  | 95 %                                  |
| sides  | 2-sided                               |
| lower limit  | 0.49                                  |
| upper limit  | 1.88                                  |

Notes:

[6] - 36 subjects (innohep®: 17; warfarin: 19) had a fatal PE whereof 2 in the warfarin group were not first events and thus not counted in the efficacy analyses. 34 fatal PEs (innohep®: 17; warfarin: 17) are counted in the efficacy analyses.

[7] - The 6-month incidence of fatal PE was identical in the treatment groups. None of the fatal PEs counted in the efficacy analyses were objectively confirmed.

## Secondary: Incidental proximal DVT (popliteal vein or higher)

| End point title   | Incidental proximal DVT (popliteal vein or higher) |
|---|--|
| End point description:<br>1 subject in the warfarin group experienced an incidental DVT, which is counted in the efficacy analyses. The 6-month incidence or recurrent incidental DVT was low with only 1 case occurring in the warfarin group, not allowing for a meaningful competing risk regression analysis. |  |
| End point type  | Secondary  |

End point timeframe:

The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.

| End point values             | Innohep®        | Warfarin        |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 449             | 451             |  |  |
| Units: The 6-month incidence |                 |                 |  |  |
| number (not applicable)      | 0               | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidental proximal PE (segmental arteries or larger)

|                 |   |
|-----------------|---|
| End point title | Incidental proximal PE (segmental arteries or larger) |
|-----------------|---|

End point description:

2 subjects (innohep®: 1; warfarin: 1) had an incidental proximal PE whereof 1 in the innohep® group was not a first event and thus not counted in the efficacy analyses. 1 incidental non-fatal PEs in the warfarin group is counted in the efficacy analyses. The 6-month incidence of recurrent incidental PE was low with only 1 case occurring in the warfarin group, not allowing for a meaningful competing risk regression analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.

| End point values             | Innohep®        | Warfarin        |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 449             | 451             |  |  |
| Units: The 6-month incidence |                 |                 |  |  |
| number (not applicable)      | 0               | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Any symptomatic DVT and/or PE, including fatal PE

|                 |   |
|-----------------|---|
| End point title | Any symptomatic DVT and/or PE, including fatal PE |
|-----------------|---|

End point description:

The composite endpoint of the 3 symptomatic components of the primary endpoint

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.

| End point values                       | Innohep®        | Warfarin        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                     | Reporting group | Reporting group |  |  |
| Number of subjects analysed            | 449             | 451             |  |  |
| Units: The 6-month incidence (percent) |                 |                 |  |  |
| number (not applicable)                | 6.9             | 9.5             |  |  |

## Statistical analyses

| Statistical analysis title  | Competing risk regression analysis |
|---|------------------------------------|
| Statistical analysis description:   |                                    |
| Competing risk regression analysis of the secondary efficacy analysis of symptomatic events (i.e. symptomatic DVTs plus symptomatic non-fatal PEs plus fatal PEs) adjusting for region, tumour stratum, and history of VTE. |                                    |
| Comparison groups   | Innohep® v Warfarin                |
| Number of subjects included in analysis   | 900                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other                              |
| P-value   | = 0.11 [8]                         |
| Method  | Competing risk regression analysis |
| Parameter estimate  | Subdistribution hazard ratio       |
| Point estimate  | 0.69                               |
| Confidence interval   |                                    |
| level   | 95 %                               |
| sides   | 2-sided                            |
| lower limit   | 0.43                               |
| upper limit   | 1.09                               |

Notes:

[8] - The result of the analysis was in favour of innohep®, but not at the 5% significance level.

## Secondary: Recurrent Symptomatic non-fatal DVT

| End point title   | Recurrent Symptomatic non-fatal DVT |
|---|-------------------------------------|
| End point description:  |                                     |
| 36 subjects (innohep®: 12; warfarin: 24) who experienced 41 symptomatic DVTs are counted in the efficacy analyses. 5 of the confirmed DVTs were bilateral events (innohep®: 2; warfarin: 3) and only count once in the efficacy analyses. |                                     |
| End point type  | Secondary                           |
| End point timeframe:  |                                     |
| The secondary endpoints are given as the time in days from randomisation to the first occurrence of the respective secondary endpoint.  |                                     |

| End point values                       | Innohep®        | Warfarin        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                     | Reporting group | Reporting group |  |  |
| Number of subjects analysed            | 449             | 451             |  |  |
| Units: The 6-month incidence (percent) |                 |                 |  |  |
| number (not applicable)                | 2.7             | 5.3             |  |  |

## Statistical analyses

|  |                                    |
|--|------------------------------------|
| <b>Statistical analysis title</b>  | Competing risk regression analysis |
| Statistical analysis description:<br>Competing risk regression analysis of symptomatic non-fatal DVT adjusting for region, tumor stratum, and history of VTE |                                    |
| Comparison groups  | Innohep® v Warfarin                |
| Number of subjects included in analysis  | 900                                |
| Analysis specification   | Pre-specified                      |
| Analysis type  | other                              |
| P-value  | = 0.038 [9]                        |
| Method   | Risk regression analysis           |
| Parameter estimate   | Subdistribution hazard ratio       |
| Point estimate   | 0.48                               |
| Confidence interval  |                                    |
| level  | 95 %                               |
| sides  | 2-sided                            |
| lower limit  | 0.24                               |
| upper limit  | 0.96                               |

Notes:

[9] - The result of the analysis was statistically in favour of innohep®

## Secondary: Overall bleeding events

|   |                         |
|---|-------------------------|
| End point title   | Overall bleeding events |
| End point description:<br>Bleeding events were sent to the central adjudication committee for blinded adjudication. Bleeding was defined in accordance with the International Society of Thrombosis and Haemostasis (ISTH). Major bleeding criteria were defined as any event meeting any one or more of the following: bleeding with a fall in haemoglobin of >2 g/dL; bleeding requiring a transfusion of >2 units of red cells or whole blood; bleeding in a critical location, i.e. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial; bleeding causing death.<br>All non-major bleeding events (i.e. bleeding events that did not meet the criteria for major bleeding above) that required any medical or surgical intervention, including unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of IMP were classified as "clinically relevant non-major bleeding". |                         |
| End point type  | Secondary               |
| End point timeframe:<br>From the first dose of IMP and included in the analysis up to 24 hours following the last administration of IMP (i.e. more than 5 x the half-life of innohep®)  |                         |

| <b>End point values</b>                     | Innohep®        | Warfarin        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 449             | 451             |  |  |
| Units: Overall bleeding incidence (percent) |                 |                 |  |  |
| number (not applicable)                     | 25.4            | 24.4            |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Trivial bleeding        |
|---|-------------------------|
| Comparison groups                       | Innohep® v Warfarin     |
| Number of subjects included in analysis | 900                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.063 <sup>[10]</sup> |
| Method                                  | Chi-squared             |

Notes:

[10] - Test for no treatment effect

| <b>Statistical analysis title</b>       | Clinically relevant non-major bleeding |
|---|--|
| Comparison groups                       | Innohep® v Warfarin                    |
| Number of subjects included in analysis | 900                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.051 <sup>[11]</sup>                |
| Method                                  | Chi-squared                            |

Notes:

[11] - Test for no treatment effect

| <b>Statistical analysis title</b>       | Any non-trivial bleeding events |
|---|---------------------------------|
| Comparison groups                       | Innohep® v Warfarin             |
| Number of subjects included in analysis | 900                             |
| Analysis specification                  | Post-hoc                        |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.101 <sup>[12]</sup>         |
| Method                                  | Chi-squared                     |

Notes:

[12] - Test for no treatment effect

## Secondary: Major bleeding events

| <b>End point title</b> | Major bleeding events |
|------------------------|-----------------------|
|------------------------|-----------------------|

End point description:

Bleeding events were sent to the central adjudication committee for blinded adjudication. Bleeding was defined in accordance with the International Society of Thrombosis and Haemostasis (ISTH). Major bleeding criteria were defined as any event meeting any one or more of the following: bleeding with a fall in haemoglobin of >2 g/dL; bleeding requiring a transfusion of >2 units of red cells or whole blood; bleeding in a critical location, i.e. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial; bleeding causing death.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Bleeding events were recorded throughout the trial, starting from the first dose of IMP and included in the analysis up to 24 hours (i.e. more than 5 x the half-life of innohep®) following the last administration of IMP. |           |

| End point values                                | Innohep®        | Warfarin        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                              | Reporting group | Reporting group |  |  |
| Number of subjects analysed                     | 449             | 451             |  |  |
| Units: Major bleeding event incidence (percent) |                 |                 |  |  |
| number (not applicable)                         | 2.7             | 2.4             |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | Major bleeding          |
| Comparison groups                       | Innohep® v Warfarin     |
| Number of subjects included in analysis | 900                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.824 <sup>[13]</sup> |
| Method                                  | Chi-squared             |

Notes:

[13] - Test for no treatment effect

### Secondary: Heparin-induced Thrombocytopenia (HIT)

|                 |  |
|-----------------|--|
| End point title | Heparin-induced Thrombocytopenia (HIT) |
|-----------------|--|

End point description:

The diagnosis of heparin-induced thrombocytopenia (HIT) reported as AEs required both clinical and laboratory diagnostic confirmation that was consistent with standard practice including the use of the Warkentin 4T score. The IMP treatment was permanently discontinued if HIT was confirmed. Laboratory analyses performed for confirmation of HIT were performed locally and had to be confirmed at the central laboratory. The subject was treated according to the site practice and followed up. All cases of HIT occurring up to 1 month after the last dose of IMP were sent to the blinded independent adjudication committee (IAC) for adjudication.

No statistical analyses for this end point (as there were no confirmed events).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The period from the first dose of IMP up to 1 month after the last dose of IMP.

| End point values                          | Innohep®        | Warfarin        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 449             | 451             |  |  |
| Units: Incidence of occurrences (percent) |                 |                 |  |  |
| number (not applicable)                   | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall mortality

|                 |                   |
|-----------------|-------------------|
| End point title | Overall mortality |
|-----------------|-------------------|

End point description:

The time to death (overall mortality) up to and including Day 180 was assessed in a proportional hazards model including treatment group and the 3 stratification factors as main effects. The hazard ratio and associated 95% CI is presented. The test for no treatment effect was conducted as a Wald's test within this model. All deaths were adjudicated and cause of death was classified in the following way: 1) due to PE, 2) due to cancer progression, 3) due to bleeding or due to 4) other specific cause (as specified by the IAC)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The overall mortality status on Day 180

| End point values            | Innohep®        | Warfarin        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 449             | 451             |  |  |
| Units: number of subjects   |                 |                 |  |  |
| number (not applicable)     | 150             | 138             |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Proportional hazards regression overall mortality |
| Comparison groups                       | Innohep® v Warfarin                               |
| Number of subjects included in analysis | 900   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other   |
| P-value                                 | = 0.536 <sup>[14]</sup>                           |
| Method                                  | Wald's test                                       |
| Parameter estimate                      | Hazard ratio (HR)                                 |
| Point estimate                          | 1.08  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.85    |
| upper limit         | 1.36    |

Notes:

[14] - The numbers indicate that there was no difference in mortality rate across the 6 months trial period

### Secondary: Thromboses other than objectively confirmed VTE

|                 |   |
|-----------------|---|
| End point title | Thromboses other than objectively confirmed VTE |
|-----------------|---|

End point description:

Other objectively confirmed thromboses, i.e. other than objectively confirmed VTE, were collected throughout the trial and included e.g. upper limb DVT, incidental subsegmental PE, portal or renal vein thrombosis, as well as arterial thrombosis, e.g. myocardial infarction (MI), stroke, or systemic embolic events.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The period from the first dose of IMP until day 180 regardless of whether the patient was on or off IMP treatment (including 24 hours after the last dose of IMP).

| End point values            | Innohep®        | Warfarin        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 449             | 451             |  |  |
| Units: number of events     |                 |                 |  |  |
| number (not applicable)     | 9               | 13              |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Chi-square test for no treatment effect |
| Comparison groups                       | Innohep® v Warfarin                     |
| Number of subjects included in analysis | 900                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[15]</sup>             |
| P-value                                 | = 0.801 <sup>[16]</sup>                 |
| Method                                  | Chi-squared                             |

Notes:

[15] - Test for no treatment effect

[16] - Test for no treatment effect

### Secondary: Significant abnormal vital signs

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Significant abnormal vital signs |
|-----------------|----------------------------------|

End point description:

Vital signs include: systolic and diastolic blood pressure and heart rate. If an investigator found a vital sign to be of clinical significance, this was to be reported as an AE.

In a population of subjects with cancer, and in addition different cancer diagnoses and stages, the vital signs are likely to fluctuate due to the underlying disease. Hence, analyses were made for change from Baseline to End of Treatment, only. The results from these analyses did not give reason to perform any further analyses.

Two AEs associated with vital signs were reported in the innohep® group; blood pressure increased and blood pressure fluctuation – both were mild and not related to treatment.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Vital signs were assessed at all visits, except at Visit 3 (Week 2) and Visit 10 (Month 7) |           |

| End point values             | Innohep®        | Warfarin        |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 449             | 451             |  |  |
| Units: Number of occurrences |                 |                 |  |  |
| number (not applicable)      | 2               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Elevated liver enzymes

|                 |                        |
|-----------------|------------------------|
| End point title | Elevated liver enzymes |
|-----------------|------------------------|

End point description:

In a population of subjects with cancer, and in addition with different cancer diagnoses and stages, the values of liver enzymes are likely to fluctuate due to the underlying disease and treatment regimens. Hence, analyses were made of change from Baseline to End of Treatment, only. The results from these analyses did not give reason to perform any further analyses.

If an investigator found a laboratory result to be of clinical significance, this was to be reported as an AE.

No subject discontinued treatment due to liver enzyme elevation.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Clinical laboratory safety parameters were assessed every month |           |

| End point values                                | Innohep®        | Warfarin        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                              | Reporting group | Reporting group |  |  |
| Number of subjects analysed                     | 449             | 451             |  |  |
| Units: No. of subjects with events (in percent) |                 |                 |  |  |
| number (not applicable)                         | 2.4             | 1.1             |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Post-thrombotic Syndrome (PTS)

|                 |                                |
|-----------------|--------------------------------|
| End point title | Post-thrombotic Syndrome (PTS) |
|-----------------|--------------------------------|

End point description:

The development and severity of post-thrombotic syndrome (PTS) were analysed using the Villalta scale. PTS was assessed after diagnosis of the initial VTE at Baseline; therefore, the Baseline Villalta score reflects signs and symptoms of both the initial VTE as well as any previous VTE(s). Consequently, the Baseline Villalta score does not reflect the presence or absence of PTS.

The villalta scores are given for the completers. The total mean Villalta score declined (improved) in both groups during the trial. At End of Treatment, 398 subjects in the innohep® group and 409 in the warfarin group had no or mild PTS, whereas 15 and 18 subjects had moderate PTS, and 17 versus 9 had severe PTS, respectively.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first dose of IMP until completion of the 30-day follow-up visit for subjects who completed treatment

| End point values            | Innohep®        | Warfarin        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 449             | 451             |  |  |
| Units: Villalta score       |                 |                 |  |  |
| number (not applicable)     | 1.3             | 1.2             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related Quality of Life (QoL) by Change in EQ-5D Utility index

|                 |   |
|-----------------|---|
| End point title | Health-related Quality of Life (QoL) by Change in EQ-5D Utility index |
|-----------------|---|

End point description:

The EQ-5D is a brief questionnaire designed to measure health status. The 5-item descriptive portion addresses 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with respondents indicating 1 of 3 possible responses for each dimension.

The second portion, EQ VAS, is a single item (0 to 100) visual analogue scale (VAS), on which 0 corresponds to 'the worst health you can imagine' and 100 corresponds to 'the best health you can imagine'. The VAS is used to report overall health status and offers a simple method for obtaining a self-rating of current health status.

Overall, the health status levels were similar between the treatment groups both at Visit 1 and End of Treatment.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The health related QoL was assessed at Baseline, at all monthly visits, at the End of Treatment Visit and at the Post-Treatment Follow-Up Visit.

| End point values                     | Innohep®        | Warfarin        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 449             | 451             |  |  |
| Units: Change inEQ-5D Utility Index  |                 |                 |  |  |
| arithmetic mean (standard deviation) | 0.07 (± 0.34)   | 0.06 (± 0.35)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Blood Transfusions

|   |                              |
|---|------------------------------|
| End point title   | Number of Blood Transfusions |
| End point description:  |                              |
| Percentage of subjects with blood transfusion   |                              |
| End point type  | Secondary                    |
| End point timeframe:  |                              |
| From the first dose of IMP and up to 30 days following the last administration of IMP |                              |

| End point values            | Innohep®        | Warfarin        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 449             | 451             |  |  |
| Units: Percentage           |                 |                 |  |  |
| number (not applicable)     | 25.8            | 31.5            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: All adverse events including serious adverse events

|  |   |
|--|---|
| End point title  | All adverse events including serious adverse events |
| End point description:   |   |
| Percentage of subjects with adverse events including serious adverse events  |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| The period from the first dose of IMP up to 24 hours after the last dose of IMP. Serious adverse events were collected up to 30 days following the last dose of IMP. |   |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Innohep®        | Warfarin        |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 449             | 451             |  |  |
| Units: Percentage           |                 |                 |  |  |
| number (not applicable)     | 87.5            | 85.4            |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period from the first dose of IMP up to 24 hours after the last dose of IMP. Serious-adverse events were collected up to 30 days following the last dose of IMP.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Innohep® |
|-----------------------|----------|

Reporting group description: -

|                       |          |
|-----------------------|----------|
| Reporting group title | Warfarin |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events  | Innohep®           | Warfarin           |  |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed   | 221 / 449 (49.22%) | 195 / 451 (43.24%) |  |
| number of deaths (all causes)                                       | 159                | 147                |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Malignant neoplasm progression                                      |                    |                    |  |
| alternative assessment type: Non-systematic                         |                    |                    |  |
| subjects affected / exposed   | 77 / 449 (17.15%)  | 39 / 451 (8.65%)   |  |
| occurrences causally related to treatment / all                     | 0 / 77             | 0 / 41             |  |
| deaths causally related to treatment / all                          | 0 / 64             | 0 / 33             |  |
| Investigations  |                    |                    |  |
| International normalized ratio increased                            |                    |                    |  |
| alternative assessment type: Non-systematic                         |                    |                    |  |
| subjects affected / exposed   | 0 / 449 (0.00%)    | 18 / 451 (3.99%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 10 / 20            |  |
| deaths causally related to treatment / all                          | 0 / 0              | 1 / 1              |  |
| Vascular disorders  |                    |                    |  |
| Deep vein thrombosis  |                    |                    |  |
| alternative assessment type: Non-systematic                         |                    |                    |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 7 / 449 (1.56%)  | 16 / 451 (3.55%) |  |
| occurrences causally related to treatment / all      | 0 / 7            | 2 / 16           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders                 |                  |                  |  |
| Anaemia  |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |
| subjects affected / exposed                          | 10 / 449 (2.23%) | 8 / 451 (1.77%)  |  |
| occurrences causally related to treatment / all      | 1 / 11           | 1 / 11           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Neutropenia  |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |
| subjects affected / exposed                          | 8 / 449 (1.78%)  | 7 / 451 (1.55%)  |  |
| occurrences causally related to treatment / all      | 0 / 9            | 0 / 7            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Febrile Neutropenia                                  |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |
| subjects affected / exposed                          | 10 / 449 (2.23%) | 3 / 451 (0.67%)  |  |
| occurrences causally related to treatment / all      | 0 / 11           | 0 / 4            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                     |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |
| subjects affected / exposed                          | 3 / 449 (0.67%)  | 7 / 451 (1.55%)  |  |
| occurrences causally related to treatment / all      | 0 / 5            | 0 / 9            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Pyrexia  |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |
| subjects affected / exposed                          | 5 / 449 (1.11%)  | 4 / 451 (0.89%)  |  |
| occurrences causally related to treatment / all      | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                           |                  |                  |  |
| Rectal haemorrhage                                   |                  |                  |  |
| alternative assessment type: Non-systematic          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 449 (1.34%)  | 6 / 451 (1.33%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 1 / 6            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |
| subjects affected / exposed                     | 5 / 449 (1.11%)  | 6 / 451 (1.33%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Pneumonia                                       |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |
| subjects affected / exposed                     | 12 / 449 (2.67%) | 10 / 451 (2.22%) |  |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2            |  |
| Pulmonary embolism                              |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |
| subjects affected / exposed                     | 3 / 449 (0.67%)  | 7 / 451 (1.55%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 1 / 5            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Haematuria                                      |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |
| subjects affected / exposed                     | 5 / 449 (1.11%)  | 7 / 451 (1.55%)  |  |
| occurrences causally related to treatment / all | 1 / 5            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Urinary tract infection                         |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |
| subjects affected / exposed                     | 7 / 449 (1.56%)  | 4 / 451 (0.89%)  |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| alternative assessment type: Non-systematic     |                  |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 8 / 449 (1.78%) | 2 / 451 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 5           | 0 / 1           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Innohep®           | Warfarin           |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 358 / 449 (79.73%) | 364 / 451 (80.71%) |  |
| Investigations  |                    |                    |  |
| International normalised ratio increased              |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 0 / 449 (0.00%)    | 146 / 451 (32.37%) |  |
| occurrences (all)                                     | 0                  | 263                |  |
| Blood and lymphatic system disorders                  |                    |                    |  |
| Anaemia   |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 49 / 449 (10.91%)  | 59 / 451 (13.08%)  |  |
| occurrences (all)                                     | 65                 | 73                 |  |
| Neutropenia   |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 24 / 449 (5.35%)   | 30 / 451 (6.65%)   |  |
| occurrences (all)                                     | 35                 | 40                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| pyrexia   |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 27 / 449 (6.01%)   | 42 / 451 (9.31%)   |  |
| occurrences (all)                                     | 34                 | 60                 |  |
| Asthenia  |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |
| subjects affected / exposed                           | 26 / 449 (5.79%)   | 24 / 451 (5.32%)   |  |
| occurrences (all)                                     | 28                 | 25                 |  |
| Oedema peripheral                                     |                    |                    |  |
| alternative assessment type: Non-systematic           |                    |                    |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 19 / 449 (4.23%)  | 24 / 451 (5.32%)  |  |
| occurrences (all)                               | 24                | 25                |  |
| Gastrointestinal disorders                      |                   |                   |  |
| Nausea  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 52 / 449 (11.58%) | 51 / 451 (11.31%) |  |
| occurrences (all)                               | 62                | 72                |  |
| Vomiting  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 40 / 449 (8.91%)  | 42 / 451 (9.31%)  |  |
| occurrences (all)                               | 62                | 48                |  |
| Constipation                                    |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 36 / 449 (8.02%)  | 45 / 451 (9.98%)  |  |
| occurrences (all)                               | 47                | 53                |  |
| Diarrhoea                                       |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 41 / 449 (9.13%)  | 33 / 451 (7.32%)  |  |
| occurrences (all)                               | 53                | 47                |  |
| Abdominal pain                                  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 29 / 449 (6.46%)  | 21 / 451 (4.66%)  |  |
| occurrences (all)                               | 35                | 23                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cough   |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 27 / 449 (6.01%)  | 30 / 451 (6.65%)  |  |
| occurrences (all)                               | 30                | 34                |  |
| Dyspnoea  |                   |                   |  |
| alternative assessment type: Non-systematic     |                   |                   |  |
| subjects affected / exposed                     | 24 / 449 (5.35%)  | 26 / 451 (5.76%)  |  |
| occurrences (all)                               | 27                | 33                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |

|   |                        |                        |  |
|---|------------------------|------------------------|--|
| Pain in extremity<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 21 / 449 (4.68%)<br>29 | 26 / 451 (5.76%)<br>31 |  |
| Back pain<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 26 / 449 (5.79%)<br>28 | 22 / 451 (4.88%)<br>27 |  |
| Infections and infestations<br>Urinary tract infection<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 25 / 449 (5.57%)<br>34 | 20 / 451 (4.43%)<br>23 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 39 / 449 (8.69%)<br>46 | 34 / 451 (7.54%)<br>37 |  |
| Hypokalaemia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 19 / 449 (4.23%)<br>21 | 23 / 451 (5.10%)<br>24 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 21 June 2010     | Before the inclusion of the first subject, the number of subject to be randomized was reduced from 1000 to 900 subjects, 450 in each treatment group. This was based on a time-to-event approach replacing the more conservative approach based on Fisher's exact test. The overall power of the trial of 90%, the assumptions of a 6-month event rate of 12.6% in the control group, and a 50% reduction in the innohep® group remained unchanged. |
| 24 February 2011 | Time points of assessments (outcome events) were clarified in several sections to give better guidance to investigators and site staff.<br>The amendment clarified that post treatment-emergent AEs/SAEs covered only new SAEs and SAEs with worsening of intensity within 30 days after the last dose of IMP, while AEs with onset more than 24 hours after the last dose of IMP were not to be collected.   |
| 07 July 2011     | Taro Pharmaceuticals UK Ltd and Crescent Pharma UK Ltd, were added as alternative suppliers of warfarin to be used only if the supplier Goldshield Marevan was unable to provide new stocks of their warfarin product. It was added to the protocol that INR was to be closely monitored if a subject in the warfarin group switched warfarin product during the treatment period.  |
| 06 October 2011  | Change of CRO responsible for the conduct of the trial from PRA International Ltd (PRA) to INC Research (INC), and change in planned number of sites and participating countries from 180 sites in 25 countries to approximately 230 sites in approximately 30 countries.   |
| 30 January 2012  | Updates were made with regard to regions due to inclusion of additional countries: the region "Canada" was changed to "North America", "Asia Pacific" was changed to "Asia", and "South Africa" was changed to "Africa". Israel and India were omitted as separate regions.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported