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:

Subjects enrolled per age group

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
Arm title	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).

Arm title	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:

Wafarin 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.

Number of subjects in period 1	Innohep®	Warfarin
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 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 Units: years			
arithmetic mean	59.7	58.8	
full range (min-max)	19 to 89	18 to 86	-
Gender categorical 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:

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:

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:

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[1]
P-value	= 0.068 [2]
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.

Statistical analysis title	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 [3]
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.

Statistical analysis title	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 [4]
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.

Statistical analysis title	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 [5]
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:	
full analysis set	
Comparison groups	Innohep® v Warfarin
Number of subjects included in analysis	900
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.9 [7]
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:

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 warfaring 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

Statistical analysis title	Competing risk regression analysis

Statistical analysis description:

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:

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.
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:

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®)

End point values	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

Statistical analysis title	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 [10]
Method	Chi-squared

Notes:

[10] - Test for no treatment effect

Statistical analysis title	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 [11]
Method	Chi-squared

Notes:

[11] - Test for no treatment effect

Statistical analysis title	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 [12]
Method	Chi-squared

Notes:

[12] - Test for no treatment effect

Secondary: Major bleeding events

End point title	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 througout the trial, starting from the first dose of IMP and included in the analysis up to 24 hours (i.e. more thatn 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 [13]
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

Statistical analysis title	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 [14]
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[15]
P-value	= 0.801 [16]
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 VTA as well as any previous VTE(s). Consequently, the Baseline Villalta score does not reflect the presence of 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 inEQ-5D Utility index

End point title	Health-related Quality of Life (QoL) by Change inEQ-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.

End point values	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 %

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