TB-402-004	Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) After Total Knee Replacement Surgery: A Dose-Escalating, Multicentre, Randomised, Active-Controlled Open-Label Study	TB-402

Summary of study results

Name of Sponsor/Company ThromboGenics N.V.
Investigational Drug TB-402; 15 mL (10 mg/mL solution)
Title of Study Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) After Total Knee Replacement Surgery: A Dose-Escalating, Multicentre, Randomised, Active-Controlled Open-Label Study
Participating countries Bulgaria, Israel, Latvia, Poland, Romania, Russia and Ukraine
Publications Verhamme P, Tangelder M, Verhaeghe R, Ageno W, Glazer S, Prins M, Jacquemin M, Büller H. Single intravenous administration of TB-402 for the prophylaxis of venous thromboembolism after total knee replacement: a dose-escalating, randomized, controlled trial. *J Thromb Haemost*. 2011 Apr; 9(4):664-671
Study period Date first patient enrolled: 18 Feb 2009 Date last patient completed: 22 Jan 2010
Phase of development Phase 2
Objectives The objective of this study was to evaluate the safety and efficacy of a single administration of TB-402 for the prevention of VTE in patients undergoing knee replacement surgery
Methodology This was a phase II, dose-escalating, multicentre, prospective, randomised, active-controlled open-label trial to investigate the safety and efficacy of three different dose regimens of TB-402 administered as a single intravenous (IV) bolus 18 to 24 hours post-knee replacement surgery, compared with standard Low Molecular Weight Heparin (LMWH) prophylaxis. The trial investigated four treatment arms (0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg TB-402 or 40 mg/day enoxaparin). The planned sample size was 300 patients (75 per treatment arm). The treatment regimens were to be evaluated in three sequential, ascending-dose cohorts of 100 patients each in a 3:1 ratio between TB-402 and enoxaparin. Cohort 1: 0.3 mg/kg single IV infusion or enoxaparin* Cohort 2: 0.6 mg/kg single IV infusion or enoxaparin* Cohort 3: 1.2 mg/kg single IV infusion or enoxaparin* *Enoxaparin 40 mg/day subcutaneous (SC) injection for at least 10 days post-surgery
Number of patients In total 316 patients were randomised, 236 received TB-402 and 79 received enoxaparin • TB-402 0.3 mg/kg: 75 patients • TB-402 0.6 mg/kg: 75 patients • TB-402 1.2 mg/kg: 87 patients • Enoxaparin Cohort 1: 26 patients • Enoxaparin Cohort 2: 25 patients • Enoxaparin Cohort 3: 28 patients One patient was randomised to the TB-402 0.6 mg/kg cohort, but actually received 1.26 mg/kg. One patient randomised to the TB-402 1.2 mg/kg cohort was withdrawn prior to receiving study drug, due to post-operative bleeding prior to receiving study drug, and was not included in the Safety Analysis Set.

TB-402-004	Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) After Total Knee Replacement Surgery: A Dose-Escalating, Multicentre, Randomised, Active-Controlled Open-Label Study	TB-402

Diagnosis and main criteria for inclusion

The study population included patients between 18 and 80 years old, who were to undergo total knee replacement surgery.

Test product, dose and mode of administration

TB-402: Cohort 1, 0.3 mg/kg; Cohort 2, 1.2 mg/kg. Single IV infusion

Reference therapy, dose and mode of administration

Enoxaparin, 40 mg/day SC injection.

Duration of treatment

Patients randomised to TB-402 received one IV infusion of study drug over approximately 15 minutes.
Patients randomised to enoxaparin received daily treatment for up to 10 days.
For each patient, the study lasted up to 114 days: screening period up to 14 days prior to surgery and two follow-up visits at 35 (± 7) and 90 (± 10) days post-surgery.

Criteria for evaluation

Efficacy
The primary efficacy variable was the composite of the occurrence of asymptomatic deep vein thrombosis (DVT) as detected by bilateral venography and symptomatic VTE, i.e. DVT or fatal or non-fatal pulmonary embolism (PE), from randomisation to hospital discharge (Day 7 to 11).
Secondary efficacy variables were: major VTE (proximal DVT, PE, VTE-related death) at hospital discharge and objectively confirmed major VTE at 1 month and at the end of the study.

Safety
The primary safety endpoint for this study was the occurrence of total bleeding defined as major and/or clinically relevant non-major bleeding events, from randomisation until the end of the study.
The following secondary safety endpoints were also assessed: incidence of major bleeding events, incidence of clinically significant non-major bleeding events, incidence of minor bleeding events, incidence of all causes of mortality, incidence of adverse events (AEs); changes in vital signs from pre-infusion to post-infusion (for TB-402 cohorts only) and from screening to each post-randomisation visit where vital signs were collected and End of Study; changes in clinical laboratory parameters from screening to post-infusion Month 1, post-infusion Month 3 and End of Study; immunogenicity.
In addition, changes in pharmacodynamic (PD) parameters (assessed locally) from pre-infusion Day 1 to post-infusion Day 1 (for TB-402 cohorts only) and post-infusion Day 2, as well as from screening to pre-infusion Day 1, post-infusion Day 1 (TB-402 cohorts only), post-infusion Day 2 and hospital discharge Day 7-11; and immunogenicity.
VTE and bleeding were centrally adjudicated by a committee blinded for the allocated treatment.

Pharmacokinetics/Pharmacodynamics
A PK/PD sub-study was performed at selected sites, to develop a more detailed understanding of the PK (TB-402 levels) and PD of TB-402 (prothrombin time [PT], activated partial thromboplastin time [aPTT], factor VIII [FVIII]).

Statistical methods:

Efficacy analysis
The primary efficacy analysis was a non-inferiority analysis of the Per Protocol Set (PPS), comprising all patients on study treatment, with evaluable venograms and without major protocol deviations.
The one-sided 90% confidence interval (CI) was calculated for the difference between the proportion of patients experiencing an event in the combined enoxaparin group and the pooled second and third cohorts of TB-402 (0.6 mg/kg and 1.2 mg/kg groups). Non-inferiority was concluded if the upper limit of this CI for the difference in proportions was less than 15%. If non-inferiority was concluded, the Fisher's exact test done to assess superiority in the full analysis set (FAS), comprising all patients who had at least one dose of study drug and who had an evaluable venogram.
The proportion and corresponding 95% CIs of patients experiencing the composite primary efficacy endpoint as well as the individual components and secondary endpoints was summarised by treatment group for each cohort separately as well as for the pooled cohorts.

TB-402-004	Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) After Total Knee Replacement Surgery: A Dose-Escalating, Multicentre, Randomised, Active-Controlled Open-Label Study	TB-402

Safety Analysis
All safety analyses were performed on the Safety Analysis Set population, defined as all patients who received at least one dose of study drug. The proportion and corresponding 95% CI of patients with major and clinically relevant non-major bleeding calculated for each cohort separately as well as for the combined enoxaparin group.

Summary of results

Efficacy
Based on the predefined assumptions, non-inferiority of the primary endpoint for the pooled TB-402 group (0.6 mg/kg and 1.2 mg/kg groups) versus the combined enoxaparin group was observed. The upper one-sided 90% CI of the difference in event rates of -6.3% was less than the non-inferiority margin of 15.0%. Additionally, the upper one-sided CI was less than 0%, suggesting superiority of the pooled TB-402 group compared with the combined enoxaparin group. Sensitivity analysis in the FAS population was consistent with this finding.
The proportion of patients experiencing an asymptomatic DVT and symptomatic VTE was significantly lower for the pooled TB-402 group (0.6 mg/kg and 1.2 mg/kg) (24%) compared with the combined enoxaparin group (39%). Also, when combining all TB-402 groups (0.3 mg/kg, 0.6 mg/kg and 1.2 mg/kg dose groups), the incidence of the primary endpoint was lower for TB-402 (21.6%) compared with enoxaparin (39%).
A dose-response relationship between TB-402 and incidence of asymptomatic DVT and symptomatic VTE was not observed. The lowest dose (0.3 mg/kg TB-402) was associated with the lowest primary outcome event rate (16.7%, versus 24.2% in the 0.6 mg/kg TB-402 and 24.1% in the 1.2 mg/kg TB-402 dose groups) and the absolute risk reductions versus enoxaparin were 23.1% for the 0.3 mg/kg TB-402 dose group 15.5% and 15.7% for the 0.6 and 1.2 mg/kg TB-402 dose groups, respectively.
This also indicates that a dose of 0.3 mg/kg TB-402 provides sufficient duration of anticoagulation after knee replacement surgery.
The results of the secondary endpoints analysis support that TB-402 is an effective anticoagulant drug. Few patients, six in total, experienced a major VTE from randomisation to the end of the study. No patient in this study experienced a PE event or fatal VTE. Individually, the TB-402 groups had lower numbers of patients experiencing secondary endpoints than was in the combined enoxaparin group.

Safety
The analysis of bleeding events adjudicated as major or clinically relevant non-major bleeding from randomisation to end of study showed a higher proportion of patients with bleeding events in the TB-402 1.2 mg/kg dose group (seven patients [8.0%]), followed by TB-402 0.6 mg/kg group (four patients [5.4%]). The proportion of patients reporting bleeding events was comparable between the lowest TB-402 dose group (0.3 mg/kg) and the combined enoxaparin groups: 4.0% and 3.8%, respectively. These findings suggest a dose response trend between TB-402 and bleeding risk. Earlier studies demonstrated a dose-anticoagulant duration relation, which was consistent with the present finding that bleeding occurred in the highest dose group up to 28 days after surgery, whereas at lower doses occurred up to nine days after surgery.

Adverse Events
Overall, 101 patients (32.1%) experienced a total of 156 TEAEs during the study. A higher percentage of patients in the combined TB-402 group experienced one or more TEAEs compared with the combined enoxaparin group (78/236, 33.1% vs. 23/79, 29.1%). There was a greater proportion of patients with TEAEs in the TB-402 1.2 mg/kg group (35/87, 40.2%) compared with the other two TB-402 dose groups (19/75, 25.3% in the TB-402 0.3 mg/kg group and 24/74, 32.4% in the TB-402 0.6 mg/kg group). Most TEAEs were mild or moderate in severity, with four patients (1.3%) experiencing a severe TEAE: two patients receiving TB-402 0.3 mg/kg, one patient receiving TB-402 1.2 mg/kg and one patient receiving enoxaparin.
Two patients died during the study, both in the TB-402 0.3 mg/kg group. Neither death was considered related to study drug. The deaths were both cardiac in nature (myocardial infarction and acute cardiac failure). In both cases the patients had underlying medical conditions.

TB-402-004	Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) After Total Knee Replacement Surgery: A Dose-Escalating, Multicentre, Randomised, Active-Controlled Open-Label Study	TB-402

Fifteen patients had ≥1 SAE during the study and the majority were considered unrelated to study drug. The only treatment-related SAEs were the five serious bleeding events.
No patients were withdrawn from the study due to a TEAE and no patients were discontinued from study medication because of a TEAE.
Six patients (1.9%) in total experienced treatment-related TEAEs. Five of these patients received TB-402 1.2 mg/kg.

Other Safety Evaluations
There were no clinically significant changes observed in haematology or biochemistry parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP) or pulse rate during the study.
Only one sample from the TB-402 groups, collected after 3 months' treatment, had an anti-TB-402 antibody titre at 2.24 IU, which was above the cut-off level. This patient was negative for TB-402 antibodies at screening and at the Month 1 visit and did not have a VTE.

PK/PD sub-study
The terminal elimination phase of TB-402 could not be adequately characterised for any patients at the lowest dose level (0.3 mg/kg) where TB-402 only remained quantifiable on to Day 7-11. The elimination phase was determined for 3/12 patients at the 0.6 mg/kg dose level and 8/22 patients at the 1.2 mg/kg dose level, where TB-402 was quantifiable up to Day 35. TB-402 had a terminal elimination half-life within the normal range, being approximately 14 days at the highest dose level.
Single IV administration of TB-402 resulted in a 23% to 40% lowering of FVIII:C at 2 hours after dosing on Day 1 compared to Day 1 (pre-dose TB-402), followed by recovery on Day 3 (48 hours post-dose TB-402) for the 0.3 to 1.2 mg/kg dose levels.
Single IV administration of TB-402 resulted in prolongation of aPTT of between 12% and 20% at 2 hours after dosing on Day 1 compared to Day 1 (pre-dose TB-402). Administration of TB-402 did not modify PT.
Administration of 40 mg/day enoxaparin SC resulted in slight increases in FVIII:C on Days 1 to 7-11, decreases in aPTT on Days 1 to 7-11, and slight increases in PT on Day 1 compared to screening.

CONCLUSION:

All doses of TB-402 were effective in preventing asymptomatic DVT and symptomatic VTE. Noninferiority, and superiority were demonstrated for the pooled TB-402 group (0.6 mg/kg and 1.2 mg/kg groups) compared to the combined enoxaparin group. Very few patients had a major VTE during the study and no patient in this study had a PE event or fatal VTE.
TB-402 administered as a single IV infusion appeared safe and well-tolerated. There was no clinically relevant difference in the number of AEs or bleeding AEs reported during the study. A higher proportion of patients had bleeding events in the TB-402 1.2 mg/kg group, compared with the other TB-402 dose groups and enoxaparin; this may be a result of prolonged duration of anticoagulation with this highest dose.