TB-402-006	Single Intravenous Administration Of Tb-402 For The Prophylaxis Of Venous Thromboembolic Events (Vte) After Total Hip Replacement Surgery: A Phase 2b, Multicentre, Randomised, Active-Controlled, Double Blind, Double Dummy, Parallel Group Study	TB-402

Summary of study results

Name of Sponsor/Company: ThromboGenics N.V.
Investigational Drug TB-402; 4.1mL (10mg/mL solution)
Title of Study: Single Intravenous Administration of TB-402 for the Prophylaxis of Venous Thromboembolic Events (VTE) after Total Hip Replacement Surgery: A Phase 2b, Multicentre, Randomised, Active-Controlled, Double Blind, Double Dummy, Parallel Group Study
Study centres: In total, 39 centres were activated and 36 centres randomised patients: Austria (4 centres), Belgium (1 centre), Bulgaria (5 centres), Hungary (3 centres), Latvia (4 centres), Netherlands (1 centre), Poland (5 centres), Russia (7 centres) and Ukraine (6 centres)
Publications (reference): None
Studied period (years): Date first subject enrolled: 13 April 2011 Date last subject completed: 07 Mar 2012
Phase of development: Phase 2b
Objectives: The primary objective of this study was to evaluate the safety and efficacy of two doses of TB-402 administered as a single intravenous infusion for the prevention of venous thromboembolic events in subjects undergoing total hip replacement surgery
Methodology: This was a phase 2b, multicentre, randomised, active-controlled, double-blind, double-dummy, parallel group study to investigate the safety and efficacy of two different doses of TB-402 in subjects undergoing total hip replacement (THR) surgery as compared with rivaroxaban. In the two weeks before the planned surgery, subjects were screened to determine whether they met the inclusion and exclusion criteria. On the day before surgery (pre-operative day -1), inclusion/exclusion criteria were re-checked and, if still eligible for enrolment, subjects were randomised in a 1:1:1 ratio to

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one of the following treatments:
n total 632 subjects were randomised. Of these 632 randomised subjects, 10 subjects did not receive study drug. The remaining 622 subjects were each allocated to one of the three groups as follows: • TB-402 25mg: 207 subjects • TB-402 50mg: 208 subjects • Rivaroxaban 10mg: 207 subjects
Diagnosis and main criteria for inclusion: The study population included male or female subjects aged ≥ 18 years old scheduled for elective THR surgery
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 / placebo:** was supplied in matching glass vials. The vials with active TB-402 contained 4.1mL of a 10mg/mL solution of TB-402. The vials with TB-402 placebo contained 4.1mL of TB-402 placebo. Investigational product from 2 BioInvent batches of active TB-402 and 2 BioInvent batches of TB-402 placebo was used in this study, as follows. Active TB-402 TB-402 placebo A single post-operative infusion (25 mg TB-402, or 50 mg TB-402, or TB-402 placebo) was to be administered 2 to 4 hours (or in case of inadequate haemostasis, up to 4 to 8 hours) after wound closure. The infusion was administered over an approximately 10-minute period.
Duration of treatment: For each subject, the study lasted up to 114 days, including a screening period up to 14 days prior to surgery, follow-up visits at post-operative days 35 and 70, and a telephone visit at post-operative day 90±10 days.
Reference therapy, dose and mode of administration, batch number: Rivaroxaban / placebo was supplied in matching capsules inside matching blisters. The blister cards with active rivaroxaban contained 7 capsules of 10mg rivaroxaban per blister. The blister cards with rivaroxaban placebo contained 7 capsules of rivaroxaban placebo per blister; both were packaged 5 blister packs per carton. Rivaroxaban / placebo was administered orally as a capsule once a day for 35 days. The first capsule of rivaroxaban / placebo was to be taken 6 to 10 hours after wound closure.
Criteria for evaluation:

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Efficacy:

The primary efficacy outcome was the composite of the occurrence of asymptomatic deep vein thrombosis (DVT) as detected by bilateral venography and symptomatic venous thromboembolic events (VTE), i.e. DVT or fatal or non-fatal pulmonary embolism (PE), from randomisation to post-operative day 35, inclusive.

Secondary efficacy outcomes were objectively confirmed major VTE (proximal DVT, symptomatic DVT, PE, or VTE-related death from randomisation to post-operative day 35, inclusive; total DVT from randomisation to post-operative day 35, inclusive; proximal DVT from randomisation to post-operative day 35, inclusive; and distal DVT from randomisation to post-operative day 35, inclusive; PE from randomisation to post-operative day 35, inclusive; VTE-related death from randomisation to post-operative day 35, inclusive; objectively confirmed major VTE from randomisation to post-operative day 70, inclusive; symptomatic VTE from randomisation up to post-operative day 35 inclusive (Modified ITT Set); and symptomatic VTE from randomisation up to post-operative day 70 inclusive (Modified ITT Set).

Safety:

The principal safety outcome was major bleeding or clinically relevant non-major bleeding from randomisation to post-operative day 35, inclusive.

The following other safety outcomes were assessed: Major bleeding from randomisation to post-operative day 70, inclusive; clinically relevant non-major bleeding from randomisation to post-operative day 70, inclusive; surgical wound bleeding (other than major surgical wound bleeding) from randomisation to post-operative day 35, inclusive; arterial thromboembolic events (e.g. myocardial infarction, stroke, systemic arterial embolic events) from randomisation to post-operative day 70, inclusive; all-cause death; adverse events (AEs); changes in safety parameters over time: changes in vital signs, changes in laboratory parameters; and immunogenicity (anti-TB-402 antibody titres).

Pharmacokinetics/Pharmacodynamics:

A Pharmacokinetic / Pharmacodynamic (PK / PD) sub-study was performed, in which 301 subjects were randomized according to a separate PK / PD randomization scheme, at sites which had agreed to participation in the PK / PD sub-study.

The PK / PD sub-study was performed to develop a more detailed understanding of the pharmacokinetics (TB-402 levels) and pharmacodynamics (Factor VIII Activity, Factor VIII Protein Level, thrombin generation, Factor VIIa and Von Willebrand Factor Antigen) of TB-402.

Statistical methods:

Efficacy analysis:

The primary efficacy outcome was the composite of the occurrence of asymptomatic DVT as detected by bilateral venography and symptomatic VTE, i.e. DVT or fatal or non-fatal PE, from randomisation up to post-operative day 35, inclusive.

The proportion and 95% confidence interval (CI) of subjects experiencing a primary efficacy outcome were summarised by treatment group. The 95% CIs were calculated using the Wilson score method.

Both absolute risk differences and relative risks with corresponding two-sided 95% CIs were calculated for the proportion of subjects experiencing the primary efficacy outcome in each TB-402 group, as well as for the pooled TB-402 groups, compared to the rivaroxaban group. For the absolute risk difference, the 95% CI was calculated according to the Newcombe-Wilson method.

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The number and percentage of the composite and individual components of the primary outcome were summarised for the Modified Intention-to-Treat (mITT) set (all patients who received at least one dose of study drug and also had an evaluable VTE assessment with regards to the primary efficacy outcome), as well as the Per Protocol Set (PPS) (all patients without major protocol deviations warranting exclusion from PPS), based on the OAC adjudication. The corresponding results, as assessed by the site, were listed and summarised in a similar manner.

Safety Analysis:

All safety analyses were performed on the Safety Analysis Set (SAS), defined as all subjects who received at least one dose of study drug (TB-402 or rivaroxaban) after THR surgery.

The principal safety outcome was the incidence of major or clinically relevant non-major bleeding events, from randomisation up to post-operative day 35, inclusive. The proportion of subjects with a bleeding event in each TB-402 group and pooled TB-402 groups was calculated and compared with the rivaroxaban group, using two-sided 95% CIs. Absolute risk differences and relative risks were presented with their corresponding 95% CI.

The secondary safety outcomes were summarised in a similar manner.

EFFICACY RESULTS:

Primary Outcome

The primary efficacy outcome (total VTE events) from randomisation to post-operative day 35, inclusive, occurred in 10 patients (5.3%) treated with TB-402 25mg; in 10 patients (5.2%) treated with TB-402 50mg; and in 9 patients (4.7%) treated with rivaroxaban. The absolute between-treatment risk differences for the comparison of pooled TB-402 groups and the rivaroxaban group is 0.6% (95% CI -4.2%, 4.3%), indicating no significant treatment difference for the primary efficacy outcome.

Secondary Outcomes

No subjects in any treatment group experienced symptomatic VTEs or VTE related death.

Only six major VTEs occurred, and these were all asymptomatic proximal DVTs.

In summary, there were no notable differences for any between-treatment comparisons for the primary efficacy outcome, or for any of the secondary efficacy outcomes.

SAFETY RESULTS:

Adjudicated Major Bleeding or Clinically Relevant Non-Major Bleeding Events

- An analysis of the composite outcome of adjudicated major bleeding or clinically relevant non-major bleeding events for the SAS shows that the two TB-402-treated groups each had a higher proportion of subjects experiencing the combined bleeding outcome compared to rivaroxaban-treated subjects (TB-402 25mg group: 5.8%; TB-402 50mg group: 7.2%; and rivaroxaban: 1.4%; absolute between-treatment risk difference between the pooled TB-402 groups and the rivaroxaban group was 5.1% [95% CI of 1.3% to 8.2%]).
- When rivaroxaban was compared to each of the TB-402 groups separately, the absolute risk differences were also statistically significant in favour of rivaroxaban.
- All bleeding events occurred prior to day 35, therefore the results for bleeding outcome measures to post-operative day 70 and conclusions are identical to those until day 35.

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Surgical Wound Bleeding (other than Major Surgical Wound Bleeding) from Randomisation to Post-Operative Day 35, Inclusive

- An analysis of surgical wound bleeding events from randomisation to post-operative day 35, inclusive, for the SAS shows that the two TB-402-treated groups each had a higher proportion of subjects experiencing this bleeding event compared to rivaroxaban-treated subjects (TB-402 25mg group: 9.2%; TB-402 50mg group: 11.5%; and rivaroxaban: 4.3%; absolute risk difference between the pooled TB-402 groups and the rivaroxaban group was 6.0% [95% CI: 1.2% to 10.1%]).

Adverse Events

- Only treatment-emergent AEs were collected in this study.
- Overall, 293 subjects (47.1%) experienced a total of 564 AEs during the study.
- About the same proportion of subjects in each of the two TB-402 groups experienced at least one AE (101 subjects in the TB-402 25mg group [48.8%] compared with 105 subjects [50.5%] in the TB-402 50mg group). In the rivaroxaban group 87 subjects (42.0%) experienced one or more AEs.
- The proportions of subjects whose AE was considered treatment related was about twice as high in the TB-402 groups combined compared to the rivaroxaban group (54 subjects [13.0%] vs. 14 subjects [6.8%]).
- The majority of AEs were either mild or moderate in severity (TB-402 pooled groups: 191 subjects [92.7%] compared to the rivaroxaban group: 80 subjects [92.0%]).
- Post-operative anaemia was the most common AE, which occurred in 57 subjects (13.7%) in the pooled TB-402 groups and in 12 subjects (5.8%) in the rivaroxaban group.
- The proportion of subjects with an AE considered to be serious was more than twice as high in the TB-402 groups combined compared to the rivaroxaban group (19 subjects [4.6%] *vs.* 4 subjects [1.9%]).
- Five subjects discontinued the study drug due to an AE in the TB-402 groups (1 in the 25mg group, and 4 in the 50mg group), compared to no subjects in the rivaroxaban group.
- No subject in any of the treatment groups withdrew from the study due to an AE.
- One subject in the TB-402 25mg group (Subject 53003, myocardial infarction), and one subject in the rivaroxaban group (Subject 88036, alcohol poisoning) experienced a serious AE that resulted in death, but neither death was considered to be related to study drug.
- One subject (53003, TB-402 25mg group) was confirmed by OAC adjudication to have experienced a thromboembolic event (myocardial infarction); this AE had a fatal outcome.

Other Safety Evaluations

- All treatment groups experienced a decrease in mean haemoglobin between the pre-operative day and post-operative day 7; the decrease was smaller in the rivaroxaban group (-33.25g/L) compared to the pooled TB-402 treatment groups (-43.63g/L). The rivaroxaban group also showed fewer subjects with

a low haemoglobin value at post-operative day 7 (158/207; 76.3%) than the TB-402 treatment groups combined (357/415; 86.0%).

- All treatment groups experienced an increase in mean platelet count between the pre-operative day and post-operative day 7; the increase was smaller in the rivaroxaban group (86.2 x 10^9/L) compared to the pooled TB-402 treatment groups (106.4 x 10^9/L). The rivaroxaban group also showed fewer subjects with above normal platelet counts at post-operative day 7 (56/207; 27.1%) than the TB-402 treatment groups combined (149/415; 35.9%).
- All treatment groups experienced a slight decrease in mean serum creatinine between the pre-operative day and post-operative day 7; the mean decrease ranged from a low of -6.7mg/dL in the TB-402 25mg group, to a high of -8.27mg/dL in the TB-402 50mg group.
- All treatment groups experienced a slight increase in mean creatinine clearance between the pre-operative day and post-operative day 7; the mean increase ranged from a low of 10.65mL/min in the rivaroxaban group, to a high of 12.74mL/min in the TB-402 50mg group.
- The two TB-402 treatment groups combined experienced an increase in total bilirubin between the pre-operative day and post-operative day 7 (+5.1µmol/L); in contrast, there was no increase in the rivaroxaban group in this period (+0.71 µmol/L). Subjects in the pooled TB-402 treated groups were also more likely to show a shift from normal on the pre-operative day to high on post-operative day 7 (46/415, 11.1%) compared to the rivaroxaban treated group (3/207, 1.4%).
- All treatment groups experienced an increase in mean aspartate aminotransferase (AST) between the pre-operative day and post-operative day 7; the mean change in AST was smaller in the rivaroxaban group (+7.5IU/L) compared to the Pooled TB-402 treatment groups (+10.3IU/L). There was no difference between the TB-402-treated subjects and those treated with rivaroxaban in regard to the number of subjects experiencing a shift to high AST.
- All treatment groups experienced an increase in mean alanine aminotransferase (ALT) between the pre-operative day and post-operative day 7; the mean change in ALT was slightly smaller in the rivaroxaban group (+12.9IU/L) compared to the pooled TB-402 treatment groups (+14.5IU/L).
- All treatment groups experienced an increase in mean gamma-glutamyltransferase (GGT) between the pre-operative day and post-operative day 7; the mean change in GGT ranged from a low of 18.5IU/L in TB-402 25mg group, to a high of 23.6IU/L in the TB-402 50mg group.
- Mean activated partial thromboplastin time (aPTT) values were essentially unchanged from the pre-operative day throughout the study in all treatment groups.
- All treatment groups experienced a ≥7-fold increase in D-dimer from the pre-operative day to the day of surgery, post-surgery. The administration of a TB-402 infusion following surgery had no discernable effect on the pharmacodynamics of D-dimer following major surgery.
- All treatment groups experienced a ≥2-fold increase in Fragment 1+2 (F1+2) values from the pre-operative day to the day of surgery, post-surgery but before infusion. The administration of a TB-402 infusion following surgery had no discernable effect on the pharmacodynamics of F1+2 immediately

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following major surgery. However, shift table analysis of later time points suggested the existence of a possible delay in the return to normal F1+2 levels related to TB-402 administration following major surgery, or that continuing rivaroxaban administration suppressed a day 7 rise in F1+2 that might ordinarily be seen following major surgery.

- No immunogenicity against TB-402 infusion developed during the study.

Safety Conclusions

- TB-402 administered as a single IV infusion appeared safe and well-tolerated.
- The composite outcome of adjudicated major bleeding or clinically relevant non-major bleeding events for the Safety Analysis Set showed a treatment effect favouring rivaroxaban-treated subjects.
- Surgical wound bleeding events from randomisation to post-operative day 35 inclusive for the Safety Analysis Set showed a treatment effect favouring rivaroxaban-treated subjects.
- Individual components and other bleeding outcome events (Major Bleeding Events, Clinically Relevant Non-Major Bleeding Events, and Minor Bleeding Events, each considered separately) also showed a trend favouring the rivaroxaban-treated subjects.

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PK / PD Sub-Study

A total of 301 subjects were randomised into the PK/PD substudy, however 2 subjects received no study drug and did not continue in the study. The remaining 299 subjects were each allocated to one of the three groups as follows: TB-402 25mg: n=100; TB-402 50mg: n=99 and rivaroxaban: n=100. The proportion of male subjects in the TB-402 25mg group (45%) was slightly higher than in the other groups (39% in the TB-402 50mg group and 38% in the rivaroxaban group), otherwise baseline characteristics were well balanced and comparable to the overall study population.

Pharmacokinetic Results

Summary of Pharmacokinetic Parameters for TB-402 Following Single IV Doses

Parameter (geometric mean [CV%])	**TB-402 25mg**	**N**	**TB-402 50mg**	**N**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	260261 (67.1)	99	788815 (51.0)	99
C_{max} (ng/mL)	5595 (51.5)	100	11499 (36.8)	99
t_{max} [a] (h)	2.33 (2.0-47.8)	99	2.42 (2.08-7.33)	99
$t_{½}$ [a] (h)	94.6 (16.6-646)	77	229 (22.7-756)	87
CL (mL/min)	1.40 (57.1)	77	0.923 (51.3)	87
V_{ss} (L)	8.03 (42.4)	77	12.2 (31.3)	87

[a] Median (min-max)

Source: Section 16.1.13

Maximum concentrations of TB-402 were estimated at a medium time (t-max) of just over two hours in both dose groups. The median half-life of the 25mg dose was 94.6 hours, or four days, and 229 hours, or 9.5 days for the 50mg dose.

Functional TB-402 serum concentrations measured after infusion for TB-402 50mg were, in the first week, at least twice as high at all measured times as those measured after infusion of TB-402 25mg, and three times as high at day 14. The lower limit of quantification of TB-402 was reached at day 35 in both dose groups. Thus, TB-402 was circulating for 14 to 34 days, and likely longer with 50mg than with 25mg.

Pharmacodynamic Results

Both single IV doses of TB-402 caused mean FVIII levels to decrease transiently, for approximately 24 hours, as measured with the one-stage assay, and for up to 48 hours as measured by the chromogenic assay. The median % change of FVIII:c from just prior to infusion with the one-stage / chromogenic assay was -30% / -49.3%, -23.4% / -47.9% and -0,8% / -1.2% at two to three, six to eight, and 24 hours after 25mg infusion; and -28.9% / -47.1%, -21.3% / -44.3% and +2.8% / -14.7% at two to three, six to eight, and 24 hours after 50mg infusion.

The arrhythmic mean Endogenous Thrombin Potential (ETP) increased after surgery from two to three hours after infusion until at least 14 days following the TB-402 25mg infusion, and 35 days following the TB-402 50mg infusion. The median percent change of ETP from the day before surgery varied from -4.2% to -31.9% after infusion of TB-402 25mg and from -5.1% to -42% after infusion of TB-402 50mg. Rivaroxaban resulted in a decrease of ETP from 24 hours after TB-402 placebo infusion until day 35,

with median percent change from pre-operative baseline ranging from -5.5% to -18.3%.

CONCLUSION:

- Evaluation of the primary efficacy outcome (total VTE from randomisation to post-operative day 35 inclusive) showed no notable treatment difference. Similarly, the five secondary efficacy outcomes for which at least one subject experienced that outcome also showed no notable between-treatment differences.
- Bleeding events were more common in subjects treated with TB-402 compared to those treated with rivaroxaban. Based upon absolute and relative risk differences and the associated 95% CIs, statistically significant risk differences favouring rivaroxaban were noted for the principal safety outcome (major bleeding or clinically relevant non-major bleeding event) and for surgical wound bleeding (other than major surgical wound bleeding). Other categories of bleeding events were also more common in the TB-402-treated groups.
- Post-operative anaemia was the most commonly occurring AE in all treatment groups and in the study population overall; post-operative anaemia occurred more frequently in Pooled TB-402 groups compared to the rivaroxaban group.
- TB-402 was well-tolerated and there appeared to be no dose-effect between the groups receiving 25mg and 50mg infusions with respect to bleeding events or other safety evaluations.

Date of the report:

07 Mar 2013

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