Single intravenous administration of TB-402 for the prophylaxis of VTE after total knee replacement surgery

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Background

TB-402 acts as a partial Factor VIII (FVIII) inhibitor. It is a human IgG4 antibody that *in vitro* exerts a plateau inhibition of FVIII activity even when TB-402 is in large excess over FVIII.
The long half-life of this human monoclonal antibody allows for a prolonged antithrombotic effect following a single administration. Increasing the dose is expected to prolong its pharmacodynamic effect. The antithrombotic efficacy of TB-402 has been demonstrated in preclinical thrombosis models [1-3].

Objectives

The aims of this study were to evaluate the efficacy and safety of a single intravenous administration of TB-402 for the prevention of VTE in patients undergoing total knee replacement (TKR).

Patients

This was a phase II, multicenter, dose-escalating, randomized, enoxaparin-controlled open-label study. Men and women aged ≥ 18 and ≤ 80 years, undergoing primary elective TKR surgery and willing and able to comply with the study procedures were included.
All patients received enoxaparin 40 mg pre-operatively and were randomly assigned post-operatively in a sequential cohort design to receive one of three doses of TB-402 (0.3 mg/kg, 0.6 mg/kg or 1.2 mg/kg) or enoxaparin 40mg (3:1 TB-402 to enoxaparin, n=75 per group). TB-402 was administered as an intravenous bolus 18 to 24 hours after TKR. Enoxaparin 40mg q24h was administered for at least 10 days.

The primary efficacy outcome was the composite of asymptomatic DVT as detected by bilateral venography and symptomatic VTE by Day 7–11. The primary safety outcome was the incidence of major bleeding and clinically relevant non-major bleeding (CRNMB) from randomisation until the end of the study at 3 months.
All outcomes were adjudicated by a blinded independent central adjudication committee.

Results

316 patients were randomized.
Total VTE was lower in each of the TB-402 groups compared to the enoxaparin group: 16.7% (9.8-26.9), 23.9% (15.3-35.3), 24.1%(16.0-34.5) and 39.0%(28.8-50.1) for TB-402 0.3mg/kg, 0.6mg/kg, 1.2mg/kg and enoxaparin, respectively (p=0.003 for TB-402 0.3 mg/kg vs enoxaparin) (Table 2).
A comparison of the pooled TB-402 groups versus the enoxaparin group demonstrated a reduction in the incidence of the primary efficacy outcome [47/218; 22%(95%CI:17–28) vs 30/77; 39%(95%CI:29–50) p<0.05].

Major or clinically relevant non-major bleeding was observed in 3/75(4.0%), 4/74(5.4%), 7/87(8.0%) and 3/79(3.8%) patients for TB-402 0.3mg/kg, 0.6mg/kg, 1.2mg/kg and enoxaparin, respectively.
The drug was well-tolerated. Two deaths occurred during the study, both were considered unrelated to the study drug.

	TB-402 0.3 mg/kg N = 75	TB-402 0.6 mg/kg N = 74	TB-402 1.2 mg/kg N = 87	Enoxaparin 40 mg N = 79	Total All Groups N = 315
Age (years) Mean (SD)	64.6 (7.2)	65.2 (7.4)	65.5 (9.3)	63.8 (8.6)	64.8 (8.2)
Male n (%)	16 (21.3)	26 (35.1)	15 (17.2)	12 (15.2)	69 (21.9)
BMI (kg/m²), Mean (SD)	31.10 (4.438)	29.87 (4.205)	30.50 (4.802)	30.11 (4.781)	30.40 (4.577)

Table 1: Demographics

Table 2: Efficacy and Safety

			TB-402 0.3 mg/kg	TB-402 0.6 mg/kg	TB-402 1.2 mg/kg	Enoxaparin 40 mg
Efficacy			N= 72	N= 67	N=79	N=77
	Total VTE	n (%) [95 C.I.]	12 (16.7%) [9.8-26.9]	16 (23.9%) [15.3-35.3]	19 (24.1%) [16.0-34.5]	30 (39.0%) [28.8-50.1]
	Major VTE	n (%)	1 (1.4%)	0 (0%)	1 (1.3%)	3 (3.9%)
Safety			N= 75	N= 74	N=87	N=79
	Major Bleeding	n (%)	0 (0%)	1 (1.4%)	4 (4.6%)	0 (0%)
	CRNMB	n (%)	3 (4.0%)	3 (4.1%)	3 (3.4%)	3 (3.8%)

Conclusions

In this phase II trial, TB-402 demonstrated superior antithrombotic activity as compared to enoxaparin 40mg. There was no statistically significant difference in major bleeding and CRNMB between the treatment groups. Major bleeding and CRNMB was similar in patients randomized to enoxaparin 40mg or to TB-402 0.3mg/kg or 0.6mg/kg.
Single administration of TB-402 warrants further investigation as a thromboprophylactic agent , even for an extended duration beyond 2 weeks.

References

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