A first-in-man, phase I, dose escalation study of TB-403, a monoclonal antibody directed against PlGF, in healthy male subjects

Rikke Riisbro[1], Leonard Larsson[2], Lena Winstedt[2], Titti Niskanen[2], Steve Pakola[3], Jean-Marie Stassen[3], Ulrik Lassen[4] and Steven Glazer[2].
[1]Cyncron Clinical Research Unit, Copenhagen/Birkerød, Denmark, [2]BioInvent International AB, Lund, Sweden, [3]ThromboGenics, Leuven, Belgium, [4]Rigshospitalet, Copenhagen, Denmark.

Background

Solid tumor growth requires new blood vessel formation (angiogenesis). Inhibition of angiogenesis as a therapeutic strategy in oncology has been validated by treatments that block vascular endothelial growth factor (VEGF) or its receptors, such as bevacizumab (Avastin®), which is an anti-VEGF antibody that prolongs survival in colorectal, lung and other cancer patients in combination with chemotherapy. However, since not all tumors are sensitive to VEGF blockade and resistance mechanisms to VEGF therapies can develop, inhibition of additional targets may be necessary in order to control tumor growth and achieve better clinical effects.

PlGF is a member of the VEGF family that is usually found only in very low levels under normal physiological conditions, but is up-regulated in almost all major malignant diseases. PlGF expression has shown to correlate with tumor stages and patient survival in breast cancer, colorectal cancer, gastric cancer, NSCLC and renal cell carcinoma [1-4].

Pre-clinical data support a role for PlGF in tumor angiogenesis, and demonstrate that blocking PlGF can inhibit tumor growth. In mouse tumor models, treatment with an anti-murine PlGF antibody resulted in anti-tumor activity [5]. Anti-PlGF was shown to inhibit tumor growth and metastasis of syngeneic subcutaneous B16 melanoma and orthotopic Panc02 pancreas tumor models.

TB-403 is a humanized IgG1 monoclonal antibody directed against PlGF that has anti-tumor activity in xenograft models of cancer and a benign preclinical toxicology profile. Based on this, TB-403 is being developed for the treatment of multiple advanced cancer indications.

Primary objectives

- To investigate the safety and tolerability of a single dose of TB-403 administered intravenously to healthy male subjects

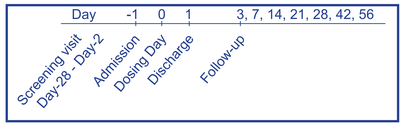
Secondary objectives

- To determine the pharmacokinetics of TB-403 after a single intravenous dose

Contact:
BioInvent International AB
Sölvegatan 41
SE-223 70 Lund
Sweden
www.bioinvent.com

Study Design

- Single-dose escalation in 16 healthy male subjects
- Single, intravenous infusion over 60 min
- Three dose groups: 0.3, 1.25 and 5 mg/kg
- Starting dose 0.3 = 1/10th of MABEL
- Placebo-controlled: 2+2, 4+2 and 4+2
- Safety monitored up to Day 56
- DMC review of adverse events, safety laboratory results, ECG and vital signs measurements up to Day 7 prior to dose escalation



Schematic Presentation of Trial Design

Dose group	Placebo	0.30 (mg/kg)	1.25 (mg/kg)	5.00 (mg/kg)
1	2	2		
2	2		4	
3	2			4

The MABEL was used in the determination of the starting dose and was calculated using data from *in vivo* xenograft tumour models, which were used for the pharmacology studies of effect on tumour growth. The MABEL in these studies was 3 mg/kg, which had no significant inhibitory effect on tumour growth. Applying a safety factor of 10 to the MABEL, the starting dose has been selected at 0.3 mg/kg for the first dose level.

References

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4. Zhang L, Chen J, Ke *et al.* Expression of placenta growth factor (PlGF) in non-small cell lung cancer (NSCLC) and the clinical and prognostic significance. World J Surg Oncol 2005;3:68-80
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Results

Table 1: Summary of the Total Adverse Events in Healthy Subjects

Number of Adverse Events	Placebo N=6	0.3 mg/kg N=2	1.25 mg/kg N=4	5.0 mg/kg N=4
All Adverse Events	**11**	**4**	**4**	**8**
Ear & Labyrinth Disorders:				
- Ear Pain	-	-	-	2
Gastrointestinal Disorders:				
- Abdominal Pain	1	-	-	-
- Dyspepsia	-	1	-	-
- Toothache	-	-	1	-
- Vomiting	-	1	-	-
General Disorders & Administration Site Conditions:				
- Puncture Site Hemorrhage	1	-	-	-
Infections & Infestations:				
- Herpes Simplex	-	-	-	1
- Nasopharyngitis	4	1	1	1
Injury, Poisoning & Procedural Complications:				
- Hand Fracture	-	-	-	1
- Joint Sprain	2	-	-	-
Musculoskeletal & Connective Tissue Disorders:				
- Back Pain	1	-	-	-
- Neck Pain	1	1	-	-
Nervous System Disorders:				
- Headache	1	-	2	1
Reproductive System Disorders:				
- Epididymitis	-	-	-	1
Respiratory, Thoracic & Mediastinal Disorders:				
- Pharyngolaryngeal Pain	-	-	-	1

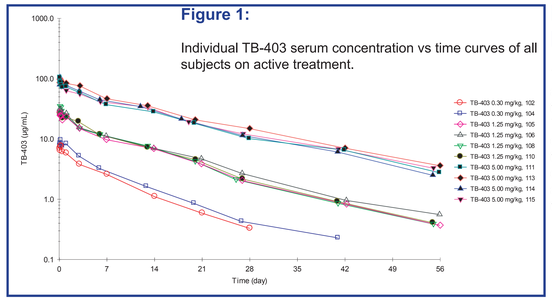

Figure 1:

Individual TB-403 serum concentration vs time curves of all subjects on active treatment.

Pharmacokinetic Results

The blood concentration data obtained allowed for an accurate estimation of the pharmacokinetic properties of TB-403 determined by non-compartmental analysis. The mean terminal half-life ranged from 8 to 13 days. The exposure of TB-403 appeared to be dose-proportional in terms of both Cmax and AUC.

Table 2: Mean Pharmacokinetic Parameters

Parameter	0.3 mg/kg	1.25 mg/kg	5.0 mg/kg
Cmax (µg/mL)	8.670	30.37	100.6
AUC (Day*µg/mL)	62.8	276	1200
AUC_t (Day*µg/mL)	59.6	269	1140
Tmax (h)	5.00	2.28	1.78
T½el (Day)	8.05	10.1	13.1
CL (mL/Day/kg)	4.90	4.55	4.18
Vz (mL/kg)	55.5	65.8	79.3

Table 3: AEs - moderate or severe - or not recovered at the time of database closure

Dose Group	Preferred term	Severity	Relationship	TEAE	Outcome
0.3 mg/kg	Nasopharyngitis	Severe	Unlikely	Yes	Recovered
	Neck pain	Moderate	Unrelated	Yes	Recovered
1.25 mg/kg	Headache	Moderate	Unrelated	Yes	Recovered
	Nasopharyngitis	Moderate	Unrelated	Yes	Recovered
	Toothache	Moderate	Unrelated	Yes	Recovered
5.0 mg/kg	Epididymitis	Severe	Unrelated	Yes	Recovering
	Nasopharyngitis	Moderate	Unrelated	No	Recovered
	Hand fracture	Moderate	Unrelated	Yes	Recovering
Placebo	Nasopharyngitis	Severe	Unrelated	Yes	Recovered
	Joint sprain	Mild	Unrelated	Yes	Recovering
	Nasopharyngitis	Moderate	Unrelated	Yes	Recovered
	Neck pain	Moderate	Unrelated	Yes	Recovered
	Back pain	Mild	Unrelated	Yes	Recovering

Demographics and other baseline characteristics

All subjects were Caucasians. The age range was 22-46 years, weight 63.1-114.5 kg and BMI 20.4-31.4 kg/m².

Safety Results

Thirty-two adverse events were recorded of which 27 were treatment emergent adverse events (TEAE).

Five placebo treated subjects experienced 11 TEAE.
Two subjects treated with TB-403 0.3 mg/kg experienced 4 TEAE.
Two subjects treated with TB-403 1.25 mg/kg experienced 4 TEAE.
Four subjects treated with TB-403 5.0 mg/kg experienced 8 TEAE.

Twenty-two of the events were considered not related or unlikely related to study drug. The majority of TEAEs were mild (16), 8 were moderate and 3 were severe.

There were no serious adverse events in the study and none of the events led to death or withdrawal. The most frequently reported adverse events (MedDRA Preferred Term) were nasopharyngitis, headache, neck pain and joint pain.
No changes observed for the primary endpoint i.e. for laboratory safety testing, vital signs or ECG gave rise to any concern. No other results from safety or tolerance assessments i.e. physical examination, body weight, concomitant medication, gave rise to any concern. There were no apparent differences between the three dose levels or active treatment compared to placebo.

Conclusion

- TB-403 was safely administered to healthy male subjects in this study as an intravenous infusion in the dose range of 0.3 mg/kg to 5 mg/kg.
- The safe administration of TB-403 allowed a higher initial safe start dose level in a subsequent study in cancer patients.

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