Summary of study results

Sponsor ThromboGenics Ltd., Ireland
Investigational drug Microplasmin
Title of study An Open Label Clinical Trial of Microplasmin Administered via the Trellis-8 Infusion System for the Treatment of Acute Iliofemoral Deep Vein Thrombosis
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Participating Countries Ireland
Publication None at the time of this report
Studied period Mar 2007 – Jul 2008
Phase of development Phase IIa
Objectives To evaluate the safety and efficacy of microplasmin administration using the Trellis-8 Infusion System in patients with acute iliofemoral DVT.
Methodology This study was a Phase IIa, open label, single centre, single-arm interventional study investigating Treatment Success using the Trellis-8 Infusion System to deliver an infusion dose of microplasmin (20mg or 40 mg dependent on trellis treatment length) over a 10 minute period. Laboratory samples for microplasmin and microplasmin/ alpha-2 anti-plasmin (AAP) complex and a coagulation panel were taken immediately after infusion and 4 hours post procedure. The coagulation panel was repeated 48 hours post procedure. Seven days post procedure PT (INR) was analyzed. Thirty days post procedure PT (INR) and microplasmin antibody levels were analyzed. Clinical follow-up occurred at 48 hours post infusion and 7 and 30 days following the procedure. Clinical follow-up included a physical exam of the treated leg, leg circumference measurements, CEAP/Venous Clinical Severity Score, assessment of patency using Venous Duplex Ultrasonography and completion of the EVOLVE Symptoms Severity Scale. To monitor and ensure patient safety, the Study Safety Committee continually reviewed adverse events, adverse Drug reactions and Serious Adverse Events.
Number of patients The planned sample size for this study was approximately 15 patients. The study was terminated early after the inclusion of seven patients.

Main Criteria for Inclusion

1. Patient is at least 18 years old.
2. Patient has clinical manifestations (i.e. symptoms and/or signs) of acute DVT of the lower extremity
3. Duration of leg symptoms ≤ 14 days of presentation.
4. Ultrasound confirmation of venous thrombus located in the iliac and/or femoral vein, with or without popliteal vein involvement
5. Obstructed vessel calibre can accommodate an 8FR System, from insertion site to target segment.
6. Women of child-bearing potential must have a negative pregnancy test prior to enrollment and be using a reliable form of contraception.

Study treatment

A microplasmin dose of 20 or 40mg in 10ml (depending on treatment length of Trellis-8 Infusion System used) was infused in the targeted thrombosed vein over 5 minute period.
No more than 3 treatments runs were administered in each of the targeted thrombosed venous segments and a total cumulative dose of 120mg was permitted per patient. Additional treatment runs with other thrombolytics were prohibited.

Investigational Drug, Dose and Mode of Administration

Microplasmin
20mg (in 10 ml) with Trellis-8 15cm Treatment Length
40mg (in 10 ml) with Trellis-8 30cm Treatment Length

Duration of treatment

The individual duration of study treatment was 5 minutes followed by a 30-day follow-up observation period without administration of study drug

Reference therapy, dose and mode of administration

Not applicable

Endpoints for evaluation

Safety
The safety evaluation was based on the occurrence of intracranial haemorrhage, major bleeding and bleeding other than major, pulmonary embolism, stroke, allergic reactions, serious and non-serious adverse events, abnormal results for immunology -and laboratory findings for complement activation markers.
In the context of this study, major bleeding was defined as any bleeding event resulting in death; any retroperitoneal hemorrhage; overt bleeding associated with a need for transfusion of 2 or more units of blood or which required surgical intervention; overt bleeding associated with a decrease from baseline in hemoglobin of at least 2.0 g/dL; clinical intracranial haemorrhage

Efficacy
The primary efficacy end point was based on venography results showing a ≤ 25% residual thrombus AND flow is present following administration of microplasmin before any adjunctive manoeuvres to address underlying disease or residual thrombus.
The secondary efficacy endpoints were based on the proportion of patients, and venographic results, achieving lysis of > 95%, 50 – 95% and < 50% following administration of microplasmin and any additional adjunctive manoeuvres.
Additional secondary efficacy endpoints for limb patency and clinical outcomes were assessed at 48 hours, Day 7 and Day 30 post procedure and compared to baseline.
Patency of target limb was based upon an improved (e.g. decreased) Duplex Limb Thrombus Score as compared to baseline score, with all vessel segments on the duplex ultrasound having a Grade 1 or 0 (modified Porter scale).
Clinical Outcomes were based on leg circumference measurements, CEAP/Venous Clinical Severity Score and EVOLVE Symptom Severity Scale and changes at each visit from baseline.
Time to reintervention for treatment of thrombus in a previously treated vessel segment of treated limb was measured from the time of procedure until the end of the assessment period.

Statistical methods

Since only seven patients were included in this study, a formal statistical analysis was not preformed. In accordance with Section 5.4 of the protocol, the Sponsor prematurely terminated the study as a result of a decision not to pursue with the vascular indication.

Summary of results

Efficacy

Seven patients (5 female and 2 male), aged between 33 and 82 years entered the study. Only five of the patients completed the 30 day follow-up per protocol.

The results are summarized from individual data listings.

Baseline venography procedures were conducted for all patients, except one. The results indicate that a ≤ 25% residual thrombus and flow were present for all patients following administration of microplasmin via the Trelis-8 infusion system. For one of these patients the ≤ 25% was only achieved after adjunctive manoeuvres. Three of the six patients achieved lysis of >95% with the remaining three achieving 50-95%.

The five patients completing the 30 day follow-up reported at the end of the study on the EVOLVE Symptom Severity Scale that overall leg symptoms were much less when compared to the time of DVT diagnosis.

Improvements in clinical outcomes were assessed from the CEAP/Venous Clinical Severity Score. Two patients did not show any improved clinical signs after the 30 day follow-up. One patient did not present with any visual or palpable signs of venous disease and there was no change reported at the end of the study. Two patients presented with oedemas at the baseline visit showed no clinical signs at the end of their respective follow-up periods.

Patency of target limb was observed in all five patients completing the 30 day follow-up with all vessel segments having a Grade 1 or 0 based on a duplex ultrasound.

There were no reinterventions for treatment of thrombus for any patient completing the 30 day follow-up period.

Safety

Three patients experienced a total of 4 Adverse Events (AEs), two of which were Serious Adverse Events (SAEs).

Of the SAEs, one pulmonary embolus was reported as remotely related to study treatment and one pulmonary artery thrombosis was reported as unrelated and resulted in patient death on the same date. On further review this event was upgraded to possibly related and was therefore reported to the appropriate authorities as a Suspected Unexpected Serious Adverse Reaction (SUSAR) .

Antibody to microplasmin was measured before and 30 days after study treatment. In one patient, only the baseline titer was available. One patient had an increase in titer levels from 20 Titer-1 to 80 Titer-1 at the end of the 30-day follow-up. One patient had half (160 Titter¹ to 80 Titer-1) the microplasmin antibodies at the end of the 30 day follow-up. The remaining three patients showed no change at the end of the study from baseline levels of 10 Titer-1.

Total Complement (CH50) and C3 and C4 were analyzed at baseline to determine the effects of microplasmin on the complementary pathway in the event that any patient experienced any allergic signs or symptoms. As no patients displayed these symptoms, no additional analysis of complement activation markers was performed for any patient during the follow-up period.

Conclusions

Based on the venography results from 5 patients that completed the 30 day follow-up period, it can be concluded that target vessel segment treated for all five patients resulted in a ≤ 25% residual thrombus and flow presence, following administration of microplasmin via the Trellis-8 Infusion System.

The secondary endpoints and additional efficacy parameters of grade of lysis, limb patency and target limb intervention were also achieved for patients completing the study.

Microplasmin was well tolerated by all administered the treatment. One serious adverse event of pulmonary embolism was reported as remotely related to treatment and no allergic reactions