# Clinical trial results:
# A Phase II, randomized, controlled, double blind study to evaluate the haemostatic efficacy and safety of TT-173 applied in the donor site of patients undergoing skin graft.

## Summary

| | |
|---|---|
| EudraCT number | 2013-002784-25 |
| Trial protocol | ES |
| Global end of trial date | 20 July 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 February 2020 |
| First version publication date | 19 February 2020 |
| Summary attachment (see zip file) | EHTIC study: Evaluation of a new hemostatic agent based on tissue factor in skin grafting procedures (ehtic.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | THO-IM_01-CT |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02012569 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Thrombotargets Europe |
| Sponsor organisation address | Avda Canal Olimpic Nº 6, 2ª Planta, Parc Mediterrani de la Tecnología, Castelldefels, Spain, 08860 |
| Public contact | Director de Desarrollo de Producto, Thrombotargets Europe, +34 936642040NA, jesusmurat@thrombotargets.com |
| Scientific contact | Director de Desarrollo de Producto , Thrombotargets Europe, 635579689 936642040NA, jesusmurat@thrombotargets.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 20 July 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the haemostatic efficacy of TT-173 when applied in the donor site of patients undergoing skin graft.

Protection of trial subjects:

Safety variables
AEs were collected from the signature of the ICF until the end of the follow-up period of the study. For this purpose, all the AEs that occurred from the product administration were recorded, as well as their characteristics: start date, intensity (mild, moderate, severe, life-threatening, death related to adverse event), causality relationship with the study drug (likely, possible, unrelated), action taken for the study drug, end date and outcome of the AE (resolved, resolved with sequelae, not resolved, fatal and unknown), serious (yes/no) and/or unexpected.
Data of hemogram, coagulation parameters and biochemistry were collected at all study visits.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 November 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 1 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 78 |
| Worldwide total number of subjects | 78 |
| EEA total number of subjects | 78 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---|---|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 70 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study consisted of a recruitment period of 12 months with a screening period after signing the informed consent form, 1 intervention visit (day 0) and a follow-up period of 1 month in which 5 visits were done.

### Pre-assignment

Screening details:

1. Subjects who signed informed consent
2. Subjects who were going to receive a skin graft
3. Subjects of either gender, aged ≥ 18 years at the time of consent
4. Subjects with a skin lesion by burn, trauma or other cause affecting less than 30% of body surface
5. Subjects with a platelet count not suggesting any pathology

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Investigators, sponsor, patients and other study staff did not have access to the treatment identity. Only have access to the treatment identity the personnel responsible for preparing the treatment solutions from the site's pharmacy or other designated unblinded personnel. The final appearance of TT-173 and saline solutions was similar.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | TT-173 |

Arm description:

The experimental drug was TT-173, a topical haemostatic that contains recombinant human Tissue Factor (rhTF) anchored to the membrane vesicles derived from yeast and phosphatidylserine to enhance product activity. TT-73 was supplied by Thrombotargets Europe S.L.

- Active Ingredient: TT-173
- INN: not applicable
- Thrombotargets code: TT-173
- Concentration: 37 µg/mL
- Total dose: 148 µg
- Pharmaceutical form: Lyophilized powder for suspension
- Administration route: topical. It was directly applied on the donor site after skin graft harvest
- Batch number: 9100411003

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | TT-173 |
| Investigational medicinal product code | TT-173 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for epilesional solution |
| Routes of administration | Topical use |

Dosage and administration details:

- Pharmaceutical form: Lyophilized powder for suspension
- Administration route: topical. It was directly applied on the donor site after skin graft harvest.

| | |
|---|---|
| **Arm title** | Control |

Arm description:

Saline solution

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Saline solution |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Cutaneous use, Local use |

Dosage and administration details:

The first 1 mL dose was applied on the donor site just after the skin graft obtention. The second, third and fourth 1 mL doses were applied, at 1 minute intervals, after 1, 2 and 3 minutes had elapsed since the first dose.

| **Number of subjects in period 1** | TT-173 | Control |
|---|---|---|
| Started | 43 | 35 |
| Completed | 38 | 33 |
| Not completed | 5 | 2 |
| Consent withdrawn by subject | 2 | 2 |
| Not fulfilling eligibility criteria | 3 | - |

## Baseline characteristics

## End points

### End points reporting groups

| Reporting group title | TT-173 |
|---|---|

Reporting group description:

The experimental drug was TT-173, a topical haemostatic that contains recombinant human Tissue Factor (rhTF) anchored to the membrane vesicles derived from yeast and phosphatidylserine to enhance product activity. TT-73 was supplied by Thrombotargets Europe S.L.

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- Batch number: 9100411003

| Reporting group title | Control |
|---|---|

Reporting group description:

Saline solution

### Primary: Hemostasis

| End point title | Hemostasis |
|---|---|

End point description:

To analyze the bleeding duration, a survival analysis by means of a Kaplan-Meier model, stratified by the treatment group, was carried-out. The Kaplan-Meier curves, the median with the corresponding 95% confidence interval and the HR are shown. Comparison between treatments was analyzed by means of Log-Rank test.
A bilateral risk of =5% was fixed for all analyses performed, and a signification level of 95% (alpha=0.05) has been considered.
All analyses were performed by using the SAS version 9.3 statistical package.

| End point type | Primary |
|---|---|

End point timeframe:

Bleeding duration

| End point values | TT-173 | Control | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 33 | | |
| Units: minutes | 43 | 35 | | |

| Attachments (see zip file) | Analysis of Efficacy.pdf |
|---|---|

### Statistical analyses

| Statistical analysis title | Kaplan-Meier curves |
|---|---|

Statistical analysis description:

To analyze the bleeding duration, a survival analysis by means of a Kaplan-Meier model, stratified by the treatment group, was carried-out. The Kaplan-Meier curves, the median with the corresponding 95% confidence interval and the HR are shown. Comparison between treatments was analyzed by means of Log-Rank test.
A bilateral risk of =5% was fixed for all analyses performed, and a signification level of 95% (alpha=0.05) has been considered.
All analyses were performed by using the SAS

| | |
|---|---|
| Comparison groups | TT-173 v Control |
| Number of subjects included in analysis | 71 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Logrank |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |
| Dispersion value | 0.05 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the signature of the ICF until the end of the follow-up period of the study. 35 ± 5 days.

Adverse event reporting additional description:

For this purpose, all the AEs that occurred from the product administration were recorded, as well as their characteristics: start date, intensity, causality relationship with the study drug, action taken for the study drug, end date and outcome of the AE, serious (yes/no) and/or unexpected.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | TT-173 |

Reporting group description:

The experimental drug was TT-173, a topical haemostatic that contains recombinant human Tissue Factor (rhTF) anchored to the membrane vesicles derived from yeast and phosphatidylserine to enhance product activity. TT-73 was supplied by Thrombotargets Europe S.L.

- Active Ingredient: TT-173
- INN: not applicable
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- Batch number: 9100411003

| | |
|---|---|
| Reporting group title | Control |

Reporting group description:

Placebo (Saline solution)

| Serious adverse events | TT-173 | Control | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 33 (6.06%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| dizziness | Additional description: 2 subjects treated with placebo who suffered grade 3 (severe) AEs, consisting in dizziness and headache respectively. Both grade 3 AEs were unrelated to the study treatment and resolved. | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 33 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 33 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | TT-173 | Control | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 38 (63.16%) | 26 / 33 (78.79%) | |
| Injury, poisoning and procedural complications | | | |
| Wound complication | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 4 / 33 (12.12%) | |
| occurrences (all) | 3 | 4 | |
| Procedural pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 33 (9.09%) | |
| occurrences (all) | 3 | 3 | |
| Incision site pruritus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 33 (9.09%) | |
| occurrences (all) | 0 | 3 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 33 (6.06%) | |
| occurrences (all) | 0 | 2 | |
| Wound secretion | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 33 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vascular disorders | | | |
| Phlebitis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 33 (6.06%) | |
| occurrences (all) | 2 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 33 (3.03%) | |
| occurrences (all) | 4 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 14 / 38 (36.84%) | 5 / 33 (15.15%) | |
| occurrences (all) | 14 | 5 | |
| Pain | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | 9 / 33 (27.27%) | |
| occurrences (all) | 10 | 9 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | 8 / 33 (24.24%) | |
| occurrences (all) | 7 | 8 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 1 / 33 (3.03%) | |
| occurrences (all) | 5 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 33 (3.03%) | |
| occurrences (all) | 4 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 33 (6.06%) | |
| occurrences (all) | 2 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 4 / 33 (12.12%) | |
| occurrences (all) | 8 | 4 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 3 / 33 (9.09%) | |
| occurrences (all) | 1 | 3 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 33 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 33 (0.00%) | |
| occurrences (all) | 2 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 28 March 2014 | There was one protocol relevant amendment, amendment 1 (28-Mar-2014), resulting in protocol v2.0. The main changes were:<br>• The inclusion criterion 4 was modified to allow the enrollment of subjects with skin lesions affecting less than 30% of the body surface. Previously subjects with skin lesions affecting less than 20% of the body surface were eligible.<br>• The exclusion criterion 3 was modified to exclude subjects with skin lesions affecting more than 30% of the body surface. Previously there were excluded subjects with more than 20% of the body surface affected by skin lesions<br>• The exclusion criterion 7 was modified to further define which systemic diseases or adverse reactions would not be allowed. Thus, the criterion was expanded from subjects with uncontrolled diabetes, severe hypertension or serious systemic disease to subjects with uncontrolled diabetes with retinopathy or peripheral vasculopathy, severe hypertension or serious systemic disease would not be enrolled. Subjects with brief decompensations associated to stress induced by lesions or surgery could be included.<br>• The screening period was increased from 2 days (-2 days to day 0) to 4 days (-4 days to day 0) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/28126447