



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
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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 Olímpic Nº 6, 2ª Planta, Parc Mediterrani de la Tecnologia, 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 $\mu\text{g/mL}$
- 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
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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
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Reporting group description:

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Reporting group title	Control
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Reporting group description:

Saline solution

Primary: Hemostasis

End point title	Hemostasis
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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
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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
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Statistical analyses

Statistical analysis title	Kaplan-Meier curves
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	TT-173
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Reporting group description:

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- Administration route: topical. It was directly applied on the donor site after skin graft harvest
- Batch number: 9100411003

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