



## Clinical trial results:

### Efficacy of thalidomide in the treatment of severe recurrent epistaxis in hereditary hemorrhagic telangiectasia (HHT)

#### Summary

EudraCT number	2011-004096-36
Trial protocol	IT
Global end of trial date	11 October 2016

#### Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

#### Trial information

##### Trial identification

Sponsor protocol code	THALI-HHT
-----------------------	-----------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01485224
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Fondazione IRCCS Policlinico San Matteo
Sponsor organisation address	Viale Golgi 19, Pavia, Italy, 27100
Public contact	Struttura di Medicina Generale III, Fondazione IRCCS Policlinico San Matteo, 0039 0382 502169, r.invernizzi@smatteo.pv.it
Scientific contact	Struttura di Medicina Generale III, Fondazione IRCCS Policlinico San Matteo, 0039 0382 502169, r.invernizzi@smatteo.pv.it

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	15 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2016
Global end of trial reached?	Yes
Global end of trial date	11 October 2016
Was the trial ended prematurely?	No

Notes:

---

**General information about the trial**

---

Main objective of the trial:

To assess the clinical effects of thalidomide therapy on the severity of epistaxis in subjects with HHT who are refractory to standard therapies.

Protection of trial subjects:

This study was conducted in agreement with the Declaration of Helsinki, which provides the greatest protection of the patient. The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice) (EMA 2006).

The protocol and the informed consent were approved by the local Ethics Committee. Any amendment of the protocol and/or consent form has been approved by the Ethics Committee.

The name of the patient was not recorded on case report forms. A sequential identification number was attributed to each patient registered in the trial. This number identified the patient and had to be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters) and date of birth were also reported on the case report forms.

Prior to entering the study, patients were informed of the aims of the study, the nature of the study drug and the study procedures, the possible adverse events, the strict confidentiality of their data, but that their medical records could be reviewed for trial purposes by authorized individuals other than their treating physician.

It was emphasized that the participation was voluntary and that the patient was allowed to refuse further participation in the protocol whenever he/she wanted. This would not prejudice the patient's subsequent care. Documented informed consent was obtained for all patients included in the study before they were registered. The written informed consent form was signed and personally dated by the patient or by the patient's legally acceptable representative and by the investigator.

The Investigator agreed, by signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

---

**Population of trial subjects**

---

**Subjects enrolled per country**

---

Country: Number of subjects enrolled	Italy: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

<b>Subjects enrolled per age group</b>	
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)	11
From 65 to 84 years	20
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients with a diagnosis of HHT and with severe recurrent epistaxis refractory to mini-invasive surgical procedures were included in an open label, phase II, prospective, non-randomized, single-centre study. Patients were enrolled from 1 December 2011 to 28 February 2014.

### Pre-assignment

Screening details:

Patients were included after checking inclusion/non-inclusion criteria.

### Pre-assignment period milestones

Number of subjects started	31
Number of subjects completed	31

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Thalidomide
-----------	-------------

Arm description:

This study was an open-label, phase 2, dose-finding, single-group, non-randomised, single-centre study. All eligible patients received thalidomide.

Arm type	Experimental
Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Eligible patients received thalidomide at a starting dose of 50 mg/day by mouth at bedtime for four weeks. In the event of no response, thalidomide dosage was progressively increased by 50 mg/day every four weeks until complete or partial response, to a maximum expected dose of 200 mg/day. Then, treatment was continued as follows: eight additional weeks after the achievement of complete response, 16 additional weeks after the achievement of partial response, 24 weeks in case of no response. A maximum dose of 100 mg/day was used in patients older than 74 years. The duration of the induction treatment was then from 12 to 28 weeks, depending on the effective dose for response achievement.

Number of subjects in period 1	Thalidomide
Started	31
Completed	30
Not completed	1
Surgical treatment	1



## Baseline characteristics

### Reporting groups

Reporting group title	Overall study
-----------------------	---------------

Reporting group description:

Thirty-one patients, 20 male and 11 female, median age 64 years, have been enrolled. They had previously been treated with many surgical procedures; in all cases there was also skin involvement, in 25 cases involvement of the gastro-intestinal tract, lung or liver. Various types of mutations were observed in either ACVRL gene (23 cases) or ENG gene (3 cases); there were also duplications, insertions and deletion. Women of childbearing potential agreed to follow acceptable birth control methods to avoid conception throughout the study, to have negative serum pregnancy test obtained within 48 hours prior to the first dose of thalidomide, and to declare intention to undergo pregnancy tests periodically while on the study medication; males with female partner of childbearing potential had to agree to use an effective method of contraception throughout the study.

Reporting group values	Overall study	Total	
Number of subjects	31	31	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	64		
full range (min-max)	44 to 84	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	20	20	

## End points

### End points reporting groups

Reporting group title	Thalidomide
Reporting group description:	
This study was an open-label, phase 2, dose-finding, single-group, non-randomised, single-centre study. All eligible patients received thalidomide.	

### Primary: Efficacy of thalidomide

End point title	Efficacy of thalidomide <sup>[1]</sup>
End point description:	
The primary end point was computed as percentage of patients showing a reduction to grade 1-2 at least in one of the epistaxis parameters (frequency, intensity, duration). The difference between baseline scores and frequency, intensity, and duration scores evaluated at each time point during treatment was computed. If any of these was more than zero, the patient was considered as responder. A complete responder was defined as a patient with all three epistaxis scores equal zero. Reduction in the severity of any bleeding parameter less than complete response did represent partial response. Both complete and partial response had to be maintained for at least four weeks. Failure to achieve at least a partial response was defined as no response, whereas relapse after complete or partial response was defined as the regression from complete response to any other degree of response or return from partial response to pretreatment severity of bleeding parameters.	
End point type	Primary
End point timeframe:	
Each 4-week period. After response achievement, patients were treated for 8 to 16 additional weeks. The duration of the induction treatment was then from 12 to 28 weeks, depending on the effective dose for response achievement.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: We calculated the primary endpoint as the number and percentage of patients showing a reduction of at least one grade in one of the epistaxis parameters. The system does not allow for statistical analysis for studies with a single treatment arm.

<b>End point values</b>	Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: number and percent of patient				
complete response	3			
partial response	28			
no response	0			

<b>Attachments (see zip file)</b>	Change in patient epistaxis parameters with time/Response to
-----------------------------------	--

### Statistical analyses

No statistical analyses for this end point

### Secondary: need for blood transfusions

End point title	need for blood transfusions
-----------------	-----------------------------

End point description:

Thalidomide treatment removed or greatly reduced the need for transfusions with a maximum decrease of 1.77 (95% CI 0.70-2.84) transfused red blood cell units per month. Twenty (87%, 95% CI 66-97) of the 23 patients who were dependent on transfusions became transfusion independent.

End point type	Secondary
----------------	-----------

End point timeframe:

The mean number of blood transfusions was calculated during the study period together with a Poisson 95% CI, and the change in the number of transfused units per month was analysed with a repeated measures negative binomial regression model.

End point values	Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: number of red blood cells transfused				
arithmetic mean (standard deviation)				
Baseline	1.47 (± 1.79)			
Thalidomide 4 weeks	1.13 (± 1.75)			
Thalidomide 8 weeks	0.58 (± 1.18)			
Thalidomide 12 weeks	0.52 (± 1.18)			
Thalidomide 16 weeks	0.57 (± 1.10)			
Thalidomide 20 weeks	0.25 (± 0.70)			
Thalidomide 24 weeks	0.57 (± 0.98)			
Thalidomide 28 weeks	0.00 (± 0.00)			

Attachments (see zip file)	Transfusion need with time/ugt-wks.pdf
----------------------------	--

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to response and minimum dose of the drug that reduces bleeding

End point title	Time to response and minimum dose of the drug that reduces bleeding
-----------------	---

End point description:

Twenty-five patients (81%) obtained remission with 50 mg/day of thalidomide, after 4 weeks, five (16.1%) with 100 mg/day following 8 weeks, and one (3.2%) with 150 mg/day after 12 weeks of treatment. Time to response was associated with dose of thalidomide.

End point type	Secondary
----------------	-----------

End point timeframe:

The number and percent of responders at 4, 8, 12, 16, 20, 24 and 28 weeks and binomial 95% CI was computed. The minimum dose of the drug that reduces bleeding was summarized as number and percent of patients for each dosage (50, 100, 150 and 200 mg)



<b>End point values</b>	Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Number and percent of patients				
Thalidomide 4 weeks (50 mg)	25			
Thalidomide 8 weeks (100 mg)	5			
Thalidomide 12 weeks (150 mg)	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to relapse

End point title	Time to relapse
-----------------	-----------------

End point description:

Relapse-free survival was described and plotted with the Kaplan Meier method. Thirty patients completed the treatment. A patient, who achieved partial remission after eight weeks of treatment at a dose of 100 mg/day thalidomide, noticed progressive worsening of epistaxis in the following weeks and underwent surgical treatment. An 80-year-old male patient suddenly died a month after the end of treatment for unknown reasons. A relationship with therapy could not be completely excluded, although no side effects had been recorded during treatment. At a median follow-up of 14.1 months after the end of therapy, 8 (27.59%) patients maintained remission, whereas 21 patients (72.41%) relapsed with a median relapse-free survival of 7.0 months (95% CI 6.1-9.6). We detected no association between clinical features (age, sex, epistaxis severity) and time to response, response duration or toxicity.

End point type	Secondary
----------------	-----------

End point timeframe:

The observation began at the date of therapy termination and stopped at the date of relapse for patients relapsing or at the end of the study follow-up otherwise

<b>End point values</b>	Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	7.0 (6.1 to 9.6)			

<b>Attachments (see zip file)</b>	Relapse-free survival after the end of treatment/relapse.pdf
-----------------------------------	--

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hb levels

End point title	Hb levels
-----------------	-----------

End point description:

Treatment significantly increased patients' hemoglobin concentrations (p=0.00011), with a maximum

increase of 2.27 g/dL (95% CI 1.13-33.42).

End point type	Secondary
----------------	-----------

End point timeframe:

The mean Hb level (SD) was computed at each 4-week period. The difference between baseline and end-of-treatment Hb levels were compared with the paired Student t test. A regression model for repeated measures was fitted to describe changes over time.

<b>End point values</b>	Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: g/dL				
arithmetic mean (standard deviation)				
Baseline	8.23 (± 1.80)			
Thalidomide 4 weeks	9.94 (± 2.18)			
Thalidomide 8 weeks	9.93 (± 1.78)			
Thalidomide 12 weeks	9.90 (± 2.16)			
Thalidomide 16 weeks	10.51 (± 2.48)			
Thalidomide 20 weeks	10.50 (± 2.71)			
Thalidomide 24 weeks	10.85 (± 2.06)			
Thalidomide 28 weeks	14.40 (± 0.00)			

<b>Attachments (see zip file)</b>	Hb concentrations with time/Hb wks (1).pdf
-----------------------------------	--

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

We assessed toxic effects every 4 weeks during treatment. The number (%) of adverse events for each grade of toxicity was tabulated for each system at each time point

Adverse event reporting additional description:

Patients had only non-serious, grade 1, adverse effects during treatment, the most common of which were constipation and drowsiness. Thalidomide did not need to be discontinued for any patient

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

### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

### Reporting groups

Reporting group title	Thalidomide 4 weeks
-----------------------	---------------------

Reporting group description:

This study was an open-label, phase 2, dose-finding, single-group, non-randomised, single-centre study. All eligible patients received thalidomide.

Reporting group title	Thalidomide 8 weeks
-----------------------	---------------------

Reporting group description: -

Reporting group title	Thalidomide 12 weeks
-----------------------	----------------------

Reporting group description: -

Reporting group title	Thalidomide 16 weeks
-----------------------	----------------------

Reporting group description: -

Reporting group title	Thalidomide 20 weeks
-----------------------	----------------------

Reporting group description: -

Reporting group title	Thalidomide 24 weeks
-----------------------	----------------------

Reporting group description: -

Reporting group title	Thalidomide 28 weeks
-----------------------	----------------------

Reporting group description: -

Serious adverse events	Thalidomide 4 weeks	Thalidomide 8 weeks	Thalidomide 12 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Thalidomide 16 weeks	Thalidomide 20 weeks	Thalidomide 24 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Thalidomide 28 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	Thalidomide 4 weeks	Thalidomide 8 weeks	Thalidomide 12 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 31 (54.84%)	24 / 31 (77.42%)	27 / 31 (87.10%)
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 31 (9.68%)	4 / 31 (12.90%)	5 / 31 (16.13%)
occurrences (all)	4	5	7
Drowsiness			
subjects affected / exposed	2 / 31 (6.45%)	5 / 31 (16.13%)	6 / 31 (19.35%)
occurrences (all)	4	8	7
Peripheral neuropathy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	2 / 31 (6.45%)
occurrences (all)	0	3	3
Peripheral oedema			

subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	5 / 31 (16.13%) 5	7 / 31 (22.58%) 7
Blood and lymphatic system disorders Leucopenia subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	1 / 31 (3.23%) 1	1 / 31 (3.23%) 1
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	9 / 31 (29.03%) 9  0 / 31 (0.00%) 0	15 / 31 (48.39%) 15  1 / 31 (3.23%) 3	19 / 31 (61.29%) 19  0 / 31 (0.00%) 0
Endocrine disorders Increase in TSH subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	3 / 31 (9.68%) 3	4 / 31 (12.90%) 4

<b>Non-serious adverse events</b>	Thalidomide 16 weeks	Thalidomide 20 weeks	Thalidomide 24 weeks
Total subjects affected by non-serious adverse events subjects affected / exposed	27 / 30 (90.00%)	26 / 28 (92.86%)	7 / 7 (100.00%)
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 28 (3.57%) 1	1 / 7 (14.29%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Drowsiness subjects affected / exposed occurrences (all)  Peripheral neuropathy subjects affected / exposed occurrences (all)  Depression	5 / 30 (16.67%) 7  6 / 30 (20.00%) 8  2 / 30 (6.67%) 2	5 / 28 (17.86%) 5  6 / 28 (21.43%) 8  3 / 28 (10.71%) 3	1 / 7 (14.29%) 1  1 / 7 (14.29%) 1  1 / 7 (14.29%) 1

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 28 (3.57%) 1	0 / 7 (0.00%) 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 30 (10.00%)	3 / 28 (10.71%)	3 / 7 (42.86%)
occurrences (all)	3	4	4
Peripheral oedema			
subjects affected / exposed	8 / 30 (26.67%)	7 / 28 (25.00%)	0 / 7 (0.00%)
occurrences (all)	8	7	0
Blood and lymphatic system disorders			
Leucopenia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 28 (7.14%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	21 / 30 (70.00%)	20 / 28 (71.43%)	4 / 7 (57.14%)
occurrences (all)	21	20	4
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Increase in TSH			
subjects affected / exposed	4 / 30 (13.33%)	5 / 28 (17.86%)	1 / 7 (14.29%)
occurrences (all)	4	5	1

<b>Non-serious adverse events</b>	Thalidomide 28 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Drowsiness			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Peripheral neuropathy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Peripheral oedema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Leucopenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Increase in TSH			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### 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/26686256>