



## Clinical trial results:

### **Efficacy and safety of topical administration of timolol maleate 0.5% solution in the treatment of Child Proliferative Hemangioma Early Stage Surface. Randomized Controlled Study**

#### **Summary**

EudraCT number	2013-005199-17
Trial protocol	ES
Global end of trial date	09 January 2017

#### **Results information**

Result version number	v1 (current)
This version publication date	02 July 2021
First version publication date	02 July 2021
Summary attachment (see zip file)	summary (SUMMARY.pdf)

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	IIBSP-TIM-2013-156
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02731287
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau - IIB Sant Pau
Sponsor organisation address	Sant Quintí 77-79, Barcelona, Spain, 08041
Public contact	Enrique Peña, Institut de Recerca HSCSP, 34 935537636, epenag@santpau.cat
Scientific contact	Enrique Peña, Institut de Recerca HSCSP, 34 935537636, epenag@santpau.cat

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	26 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2017
Global end of trial reached?	Yes
Global end of trial date	09 January 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of timolol maleate 0.5% solution in the treatment of infantile hemangiomas surface during the early proliferative stage.

Protection of trial subjects:

This study has been organized in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines and national regulations.

The study protocol has been reviewed by an Ethics Committee, whose task is to verify that the necessary requirements for the protection of the nursing baby and her rights have been met. The Ethics Committee issued a favorable opinion before the start of the study.

The study protocol has been sent to the health authorities and they have authorized it.

The doctor treating has been informed of the nursing baby's participation in this clinical trial. Likewise, they will be given a patient file with the contact details of the sponsor / researcher, the study drug and the indication.

The sponsor of the study has an insurance policy that complies with current legislation and compensation will be granted in the event of deterioration of health or injury that may occur in relation to the infant's participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2014
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	Spain: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	70

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

## Subject disposition

### Recruitment

Recruitment details:

Seventy patients were included in this study. Thirty-three patients were randomly distributed in the treatment group (timolol) and 37 patients were distributed in the same way in the placebo group. In the timolol group, 22 patients completed the 36th week follow-up and in the placebo group just 25 patients.

### Pre-assignment

Screening details:

- Growth / ulceration of the lesion. Change to propranolol (n = 7)
- Parents notice lack of effectiveness and want to do off-label treatment (n = 3)
- Loss of follow-up / Refusal to finish the study (n = 12)
- Fail screening (n=1)

### Pre-assignment period milestones

Number of subjects started	70
Number of subjects completed	70

### Period 1

Period 1 title	Week 0
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

The protocol has been designed as a double-blind, placebo-controlled study. The assignment of treatments will be done blindly. The package and label product's look similar. Researchers and parents or legal guardians doesn't know what product patients receive during the study.

Participants have been randomized with a 1: 1 ratio. Randomization has been managed by an independent randomization team carried out by the Department of Pharmacy (HSCSP)

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Timolol group

Arm description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Experimental
Investigational medicinal product name	Timolol maleate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

<b>Arm title</b>	Placebo group
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Arm description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Placebo
Investigational medicinal product name	Saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

Number of subjects in period 1	Timolol group	Placebo group
Started	33	37
Completed	33	37

## Period 2

Period 2 title	Week 12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

## Arms

Are arms mutually exclusive?	Yes
Arm title	Timolol group

Arm description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Experimental
Investigational medicinal product name	Timolol maleate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

Arm title	Placebo group
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Arm description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Placebo
Investigational medicinal product name	Saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

Number of subjects in period 2	Timolol group	Placebo group
Started	33	37
Completed	29	31
Not completed	4	6
Lack of efficacy	4	6

### Period 3

Period 3 title	Week 24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Timolol group

Arm description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Experimental
Investigational medicinal product name	Timolol maleate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

<b>Arm title</b>	Placebo group
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Arm description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Placebo
Investigational medicinal product name	Saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

<b>Number of subjects in period 3</b>	Timolol group	Placebo group
Started	29	31
Completed	29	31

#### **Period 4**

Period 4 title	Week 36
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

#### **Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Timolol group

Arm description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Experimental
Investigational medicinal product name	Timolol maleate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

<b>Arm title</b>	Placebo group
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Arm description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Arm type	Placebo
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Investigational medicinal product name	Saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Dosage: 2 drops / 12 hours

<b>Number of subjects in period 4</b>	Timolol group	Placebo group
Started	29	31
Completed	22	25
Not completed	7	6
Consent withdrawn by subject	2	-
Error inclusion	-	1
Lost to follow-up	5	5



## Baseline characteristics

### Reporting groups

Reporting group title	Timolol group
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Reporting group description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Reporting group title	Placebo group
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Reporting group description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Reporting group values	Timolol group	Placebo group	Total
Number of subjects	33	37	70
Age categorical			
Units: Subjects			
Newborns (0-27 days)	0	4	4
Infants and toddlers (28 days-23 months)	33	33	66
Gender categorical			
Units: Subjects			
Female	29	27	56
Male	4	10	14

## End points

### End points reporting groups

Reporting group title	Timolol group
Reporting group description: Timolol maleate 0.5% solution (ophthalmic eye drops) Dosage: 2 drops / 12 hours Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Placebo group
Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Timolol group
Reporting group description: Timolol maleate 0.5% solution (ophthalmic eye drops) Dosage: 2 drops / 12 hours Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
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Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Timolol group
Reporting group description: Timolol maleate 0.5% solution (ophthalmic eye drops) Dosage: 2 drops / 12 hours Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Placebo group
Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Timolol group
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Reporting group title	Placebo group
Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
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Reporting group title	Placebo group
Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Timolol group
Reporting group description: Timolol maleate 0.5% solution (ophthalmic eye drops) Dosage: 2 drops / 12 hours Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Reporting group title	Placebo group
Reporting group description: Saline solution (ophthalmic eye drops) Dosage: 2 drops c / 12 hrs Route of administration: topical Pharmaceutical form: ophthalmic eye drops	
Subject analysis set title	Efficacy evaluation
Subject analysis set type	Intention-to-treat
Subject analysis set description: Qualitative evaluation of Childish Hemangioma (CH): -Color intensity -Surface component -Hemangioma resolution compared to baseline	

-Evolution of the resolution of the hemangioma compared to the previous visit  
 -Evaluation of the hemangioma compared to the baseline

## Primary: Resolution of Childish Hemangioma (CH)

End point title	Resolution of Childish Hemangioma (CH)
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End point description:

The primary endpoint (complete /almost complete or not) will be evaluated comparing the qualitative characteristics of the CH pictures took between the 24 week and the basal visit. Success rates will be based on centralized independent qualitative assessments, that will be described in the complete set of analyzes by treatment group and time of evaluation (W12 and W24).

End point type	Primary
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End point timeframe:

the 24th week

End point values	Timolol group	Placebo group	Timolol group	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	37	29	31
Units: percent				
number (not applicable)				
complete/almost complete	33	37	29	31
not complete	0	0	29	31

## Statistical analyses

Statistical analysis title	Resolution comparative
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Statistical analysis description:

This analysis will allow to know if there is a statistic difference between Timolol and Placebo group.

Comparison groups	Placebo group v Timolol group
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Number of subjects included in analysis	60
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Analysis specification	Post-hoc
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Analysis type	equivalence
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P-value	< 0.05
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Method	Fisher exact
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Parameter estimate	Odds ratio (OR)
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Confidence interval

level	95 %
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sides	1-sided
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## Secondary: Size of CH

End point title	Size of CH
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End point description:

Evaluations will be made regarding the volume and thickness of HI in weeks 2, 4, 8, 12, 24 and 36. The data obtained will be expressed in percentages (%). The average of both measurements will be taken into account to determine the evolution of the HI with respect to the treatment and the evaluation time, using the Wilcoxon test. Any value of  $P < 0.05$  will be considered significant.

End point type	Secondary
End point timeframe:	
Weeks: 12,24	

End point values	Timolol group	Placebo group	Timolol group	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	24	22	35
Units: Subjects				
flat	15	10	15	14
slight elevation	4	10	3	8
Moderate elevation	2	3	2	2
Marked elevation	2	1	2	1

Attachments (see zip file)	Size of CH/Size of CH.pdf
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### Statistical analyses

Statistical analysis title	Evolution of CH between treatment and time of eval
Comparison groups	Timolol group v Placebo group
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

After drug administration and during the 36 weeks of follow-up.

Adverse event reporting additional description:

treatment group, patient code, sex and age, term notified by the investigator, preferred term, starting day based on the date of the first administration of the study treatment, duration, measure taken in relation to the administration of the treatment of the study, use of a corrective treatment, outcome and relationship with the treatment

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Timolol group
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Reporting group description:

Timolol maleate 0.5% solution (ophthalmic eye drops)

Dosage: 2 drops / 12 hours

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Reporting group title	Placebo group
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Reporting group description:

Saline solution (ophthalmic eye drops)

Dosage: 2 drops c / 12 hrs

Route of administration: topical

Pharmaceutical form: ophthalmic eye drops

Serious adverse events	Timolol group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	0 / 37 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Timolol group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	8 / 37 (21.62%)	
Respiratory, thoracic and mediastinal disorders			
Bronchiolitis			
subjects affected / exposed	1 / 33 (3.03%)	4 / 37 (10.81%)	
occurrences (all)	1	4	

Skin and subcutaneous tissue disorders			
Xerosis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Ulcerated haemangioma			
subjects affected / exposed	0 / 33 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Infected dermal cyst			
subjects affected / exposed	0 / 33 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Dermatitis atopic			
subjects affected / exposed	1 / 33 (3.03%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Dermatitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 37 (0.00%)	
occurrences (all)	2	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2015	The amendment was done for including a new investigative site (Hospital Virgen de la Macarena- Virgen del Rocío en Sevilla) changing the protocol bversion ( V5.0) and the ICF (V3.0)

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported