Clinical trial results:
Safety and efficay of 0.2% propranolol eye drops in newborns with retinopathy of prematurity: a pilot study

Summary

EudraCT number	2014-005472-29
Trial protocol	IT
Global end of trial date	20 April 2018

Results information

Result version number	v1 (current)
This version publication date	21 November 2021
First version publication date	21 November 2021

Trial information

Trial identification

Sponsor protocol code	DROP-ROP-0.2%

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02504944
WHO universal trial number (UTN)	-
Other trial identifiers	na: na

Notes:

Sponsors

Sponsor organisation name	AZIENDA OSPEDALIERO UNIVERSITARIA MEYER
Sponsor organisation address	VIALE PIERACCINI 24, FIRENZE, Italy, 50139
Public contact	CLINICAL TRIAL OFFICE, AZIENDA OSPEDALIERO UNIVERSITARIA MEYER, 0039 0555662425, clinicaltrialoffice@meyer.it
Scientific contact	CLINICAL TRIAL OFFICE, AZIENDA OSPEDALIERO UNIVERSITARIA MEYER, 0039 0555662425, clinicaltrialoffice@meyer.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	07 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2018
Global end of trial reached?	Yes
Global end of trial date	20 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and efficacy of 0.2% propranolol eye drops to stop the progression of classic retinopathy of prematury (ROP) stage 1 towards stage 2 plus or stage 3 plus, therefore avoiding interventions such as laser therapy or anti-VEGF therapy.

Protection of trial subjects:

No specific risks were expected for trial subjects, therefore no specific protection measures were put in place for trial subjects.

Background therapy:

No background treatments are used in the trial for the specific condition (retinopathy of prematury, ROP). Otherwise, patients will be treated according to clinical practice for other clinical conditions, if any.

Evidence for comparator:

No active comparator or placebo were used in the trial.

Actual start date of recruitment	15 August 2015
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: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	98
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 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Preterm newborns delivered at gestational age ranging from 23 to 32 weeks and admitted to Italian neonatal intensive care units (NICU) participating to the study were considered for recruitment. Recruitment period began in August 2015 and lasted two years.

Pre-assignment

Screening details:

According to clinical practice and international guideline, preterm newborns delivered at gestational age ranging from 23 to 32 weeks undergone to ophtalmological screening for ROP evaluation. During this screening patients were evaluated for enrollment.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm

Arm description:

This is a single arm study.
This study was planned according to the Simon optimal two-stage design for phase II clinical trials. Therefore, the study analysis plan required 37 participants to be enrolled in Stage 1, with <6 participants meeting failure criteria in Stage 1 before Stage 2 was conducted. If Stage 1 criteria was not met, the study would be terminated for lack of efficacy. If <6 participants met Stage 1 failure criteria, additional participants would be enrolled in Stage 2. A total of <13 failures of the 96 total participants (in both Stages) would indicate sufficient promise to warrant further investigation. 96 patients was the initial calculated sample size.

Arm type	Experimental
Investigational medicinal product name	Propranolol 0.2% eye-drops
Investigational medicinal product code	Propranolol
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Newborns received three micro-drops of 6 µL (12 µg propranolol per micro-drop) in each eye, applied with a micropipette, every 6h. After each administration, the nasolacrimal duct was carefully compressed for 30 sec to decrease the drug absorption through the conjunctival and nasal vessels. Treatment was continued until retinal vascularization was complete, but for no longer than 90 days.

Number of subjects in period 1	Single arm
Started	98
Completed	97
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall period
Reporting group description:	
Number of overall enrolled patients	

Reporting group values	Overall period	Total	
Number of subjects	98	98	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	98	98	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Gestational age, weeks, mean ± SD			
Units: weeks			
arithmetic mean	26.7		
standard deviation	± 2.0	-	
Gender categorical Units: Subjects			
Female	50	50	
Male	48	48	
Cesarean delivery Units: Subjects			
Cesarean delivery	72	72	
Other	26	26	
Stained amniotic fluid Units: Subjects			
Stained amniotic fluid	7	7	
Other	91	91	
Apgar Score, 1 min Units: minute			
median	5		
full range (min-max)	1 to 9	-	
Apgar Score, 5 min Units: minute			
median	8		
full range (min-max)	4 to 10	-	
Post menstrual age Units: week			

arithmetic mean	34.2		
standard deviation	± 2.3	-	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

This is a single arm study.
This study was planned according to the Simon optimal two-stage design for phase II clinical trials. Therefore, the study analysis plan required 37 participants to be enrolled in Stage 1, with <6 participants meeting failure criteria in Stage 1 before Stage 2 was conducted. If Stage 1 criteria was not met, the study would be terminated for lack of efficacy. If <6 participants met Stage 1 failure criteria, additional participants would be enrolled in Stage 2. A total of <13 failures of the 96 total participants (in both Stages) would indicate sufficient promise to warrant further investigation. 96 patients was the initial calculated sample size.

Primary: Number of infants who progress from ROP Stage 1 to Stage 2 or 3

End point title	Number of infants who progress from ROP Stage 1 to Stage 2 or 3[1]

End point description:

Number of infants who progress from ROP Stage 1 in zone II or III, without plus, to Stage 2 with plus or Stage 3 with plus.

End point type	Primary

End point timeframe:

From the begin to the end of treatment

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: This study was planned according to the Simon optimal two stage design for phase II clinical trials. The study analysis plan required 37 participants to be enrolled in Stage 1. If <6 participants met Stage 1 failure criteria, 59 additional participants would be enrolled in Stage 2. A total of <13 failures of the 96 total participants (in both Stages) would indicate sufficient promise to warrant further investigation. No further statistical analysis were expected.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Number of patients	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Study period

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Single arm

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse event related to propranolol were reported.

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 98 (4.08%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Retinal haemorrhage	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bilateral papillary pallor	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lens opacities	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal failure	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Infections and infestations			
Viral sepsis	Additional description: Not related to study drug		
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)		

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/28709412

http://www.ncbi.nlm.nih.gov/pubmed/31134171