Clinical trial results:
Pentaerithrityl tetranitrate (PETN) for secondary prevention of intrauterine growth restriction (PETN Trial)

Summary

EudraCT number	2016-004396-51
Trial protocol	DE
Global end of trial date	07 February 2022

Results information

Result version number	v1 (current)
This version publication date	06 January 2024
First version publication date	06 January 2024

Trial information

Trial identification

Sponsor protocol code	ZKS_0021PETN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03669185
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trial Register (DRKS): DRKS-ID: DRKS00011374

Notes:

Sponsors

Sponsor organisation name	Friedrich-Schiller-Universität Jena
Sponsor organisation address	Am Klinikum 1, Jena, Germany, 07747
Public contact	Project Manager, Jena University Hospital, Center for Clinical Studies, ZKS@med.uni-jena.de
Scientific contact	sponsor represented, Jena University Hospital, Department for Obstetrics, Petn@med.uni-jena.de

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 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2022
Global end of trial reached?	Yes
Global end of trial date	07 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial investigates the efficacy and safety of PETN to reduce the incidence of intrauterine growth restriction, perinatal death and accompanied preterm delivery in women with insufficient placental development and uterine perfusion identified by pathological uterine artery Doppler at 19+0 to 22+6 weeks of gestation.

Protection of trial subjects:

The application of the intervention (investigational drug/matching placebo, two tablets per day) is very similar to the one usually applied in clinical routine. Study specific measures were limited to additional laboratory parameter during inclusion procedere and data collection.

Background therapy: -

Evidence for comparator:

matching placebo used

Actual start date of recruitment	30 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 317
Worldwide total number of subjects	317
EEA total number of subjects	317

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)	317
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

317 female pregnant patients were recruited from 15th Aug 2017 to 27th Mar 2021.

Pre-assignment

Screening details:

A total of 688 patients were presented for study inclusion at the study centers, of which 154 patients did not meet one or more inclusion criteria during the study center examination, 204 patients did not consent to study participation, and 16 patients were excluded for other reasons. A total of 317 patients were included.

Period 1

Period 1 title	treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum arm

Arm description:

patients in verum arm took 2 times daily of one tablet each Pentalong® 50 mg

Arm type	Experimental
Investigational medicinal product name	Pentalong® 50mg
Investigational medicinal product code	
Other name	PETN
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of one tablet twice daily (total of 100 mg PETN).

Arm title	placebo arm

Arm description:

Patients in the placebo arm took one tablet each of placebo 2 times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of one tablet twice daily.

Number of subjects in period 1	Verum arm	placebo arm
Started	155	162
Completed	155	162

Period 2	
Period 2 title	Follow up 12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Verum arm

Arm description:
patients in verum arm took 2 times daily of one tablet each Pentalong® 50 mg

Arm type	Experimental
Investigational medicinal product name	Pentalong® 50mg
Investigational medicinal product code	
Other name	PETN
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Oral intake of one tablet twice daily (total of 100 mg PETN).

Arm title	placebo arm

Arm description:
Patients in the placebo arm took one tablet each of placebo 2 times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Oral intake of one tablet twice daily.

Number of subjects in period 2	Verum arm	placebo arm
Started	155	162
Completed	155	162

Baseline characteristics

Reporting groups	
Reporting group title	treatment period

Reporting group description:

Pregnant women (singleton pregnancy) aged 18 years and older with available pathologic uterine Doppler indices in the uterine arteries (left and right) at 19+0 SSW to 22+6 SSW (mean PI (left and right) must exceed a mean of 1.6 or at least the 95% percentile according to Gomez (Gomez 2008)) who gave written informed consent for study participation were included.

Reporting group values	treatment period	Total	
Number of subjects	317	317	
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	34		
full range (min-max)	18 to 44	-	
Gender categorical Units: Subjects			
Female	317	317	
Male	0	0	

End points

End points reporting groups	
Reporting group title	Verum arm
Reporting group description: patients in verum arm took 2 times daily of one tablet each Pentalong® 50 mg	
Reporting group title	placebo arm
Reporting group description: Patients in the placebo arm took one tablet each of placebo 2 times daily	
Reporting group title	Verum arm
Reporting group description: patients in verum arm took 2 times daily of one tablet each Pentalong® 50 mg	
Reporting group title	placebo arm
Reporting group description: Patients in the placebo arm took one tablet each of placebo 2 times daily	

Primary: combined perinatal death and/or development of FGR	
End point title	combined perinatal death and/or development of FGR
End point description:	
End point type	Primary
End point timeframe: from randomization to 7 days after birth	

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	62	71		
no	89	85		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.17

Secondary: perinatal death

End point title	perinatal death
End point description:	

End point type	Secondary
End point timeframe:	
from randomization to 7 days after birth	

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	5	7		
no	146	149		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	placebo arm v Verum arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	2.27

Secondary: Birthweight below third percentile and/or perinatal death and/or placental abruption

End point title	Birthweight below third percentile and/or perinatal death

	and/or placental abruption

End point description:

End point type	Secondary

End point timeframe:
from randomization to 7 days after birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	38	41		
no	113	115		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.41

Secondary: Birthweight <10th percentile

End point title	Birthweight <10th percentile

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	61	69		
no	90	87		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.19

Secondary: Birthweight <5th percentile

End point title	Birthweight <5th percentile

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	38	41		
no	113	115		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.41

Secondary: Birthweight <3rd percentile	
End point title	Birthweight <3rd percentile
End point description:	
End point type	Secondary
End point timeframe:	
at birth	

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	32	35		
no	119	121		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.46

Secondary: FGR and birth before 30 weeks

End point title	FGR and birth before 30 weeks
End point description:	
End point type	Secondary
End point timeframe:	
at birthy	

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	10	13		
no	141	143		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.78

Secondary: FGR and birth before 34 weeks

End point title	FGR and birth before 34 weeks

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	18	23		
no	133	133		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.45

Secondary: preterm delivery before 37 weeks

End point title	preterm delivery before 37 weeks

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	57	81		
no	94	75		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.94

Secondary: preterm delivery before 34 weeks

End point title	preterm delivery before 34 weeks

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	39	49		
no	112	107		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.18

Secondary: stay at intensive care unit	
End point title	stay at intensive care unit
End point description:	
End point type	Secondary
End point timeframe:	
from birth to admission	

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	63	80		
no	88	76		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.03

Secondary: Combined neonatal outcome

End point title	Combined neonatal outcome

End point description:

Combined outcome of need of ventilation, occurence of intraventricular hemorrhage III - IV or necrotized enterocolitis requiring surgery

End point type	Secondary

End point timeframe:

birth to admission

End point values	Verum arm	placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	156		
Units: subjects				
yes	45	53		
no	106	103		

Statistical analyses

Statistical analysis title	relative risk
Comparison groups	Verum arm v placebo arm
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.2

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From treatment start to 12 months follow-up	
Adverse event reporting additional description:	
Adverse adverse were collected for mother, child (unborn) and mother and child together	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Verum arm
Reporting group description:	
patients in verum arm took 2 times daily of one tablet each Pentalong® 50 mg	
Reporting group title	placebo arm
Reporting group description:	
Patients in the placebo arm took one tablet each of placebo 2 times daily	

Serious adverse events	Verum arm	placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 155 (39.35%)	87 / 162 (53.70%)	
number of deaths (all causes)	5	9	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
HELLP syndrome	Additional description: Serious adverse events affected both mother and child		
subjects affected / exposed	7 / 155 (4.52%)	9 / 162 (5.56%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental insufficiency	Additional description: Serious adverse events affected both mother and child		
subjects affected / exposed	25 / 155 (16.13%)	30 / 162 (18.52%)	
occurrences causally related to treatment / all	0 / 25	0 / 30	
deaths causally related to treatment / all	0 / 5	0 / 6	
Pre-eclampsia	Additional description: Serious adverse events affected both mother and child		
subjects affected / exposed	14 / 155 (9.03%)	23 / 162 (14.20%)	
occurrences causally related to treatment / all	0 / 14	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			

subjects affected / exposed	10 / 155 (6.45%)	20 / 162 (12.35%)	
occurrences causally related to treatment / all	0 / 10	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Verum arm	placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 155 (40.65%)	88 / 162 (54.32%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 155 (9.68%)	16 / 162 (9.88%)	
occurrences (all)	17	25	
Headache			
subjects affected / exposed	43 / 155 (27.74%)	41 / 162 (25.31%)	
occurrences (all)	107	63	
Pregnancy, puerperium and perinatal conditions			
Gestational hypertension			
subjects affected / exposed	2 / 155 (1.29%)	12 / 162 (7.41%)	
occurrences (all)	2	12	
HELLP syndrome			
subjects affected / exposed	7 / 155 (4.52%)	9 / 162 (5.56%)	
occurrences (all)	7	9	
Placental insufficiency			
subjects affected / exposed	25 / 155 (16.13%)	31 / 162 (19.14%)	
occurrences (all)	26	31	
Pre-eclampsia			
subjects affected / exposed	14 / 155 (9.03%)	23 / 162 (14.20%)	
occurrences (all)	14	23	
Premature labour			
subjects affected / exposed	11 / 155 (7.10%)	20 / 162 (12.35%)	
occurrences (all)	11	20	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	13 / 155 (8.39%)	13 / 162 (8.02%)	
occurrences (all)	28	20	

Diarrhoea subjects affected / exposed occurrences (all)	11 / 155 (7.10%) 21	8 / 162 (4.94%) 11	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	25 / 155 (16.13%) 28	19 / 162 (11.73%) 25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2018	Extension of recruitment period Specifying the termination criteria Concretization of the statistical methods
09 December 2019	Extension of recruitment period
15 March 2021	Correction of secundary outcome (Writing error)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported