Clinical trial results:
Evaluation of phage therapy for the treatment of Pseudomonas aeruginosa wound infections in burned patients (Phase I-II clinical trial)

Summary

EudraCT number	2014-000714-65
Trial protocol	BE
Global end of trial date	16 January 2017

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	PHAGOBURN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02116010
WHO universal trial number (UTN)	-
Other trial identifiers	Pherecydes Pharma: PP

Notes:

Sponsors

Sponsor organisation name	Pherecydes Pharma
Sponsor organisation address	Campus Biocitech, ROMAINVILLE, France, 93230
Public contact	Guy-Charles Fanneau de La Horie, Pherecydes Pharma, +33 184861613, gc.delahorie@pherecydes-pharma.com
Scientific contact	Guy-Charles Fanneau de La Horie, Pherecydes Pharma, +33 184861613, gc.delahorie@pherecydes-pharma.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	27 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2017
Global end of trial reached?	Yes
Global end of trial date	16 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of PHAGOBURN study is to assess the efficacy and safety of topical applications of PP1131 bacteriophage cocktail, targeting P. aeruginosa infected third degree wounds in hospitalized patients, in comparison to silver sulfadiazine treatment.

Protection of trial subjects:

use of antibiotics

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 20
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	17
From 65 to 84 years	7
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

No specific screening visit is planned since swabs are routinely performed for each hospitalized burned patients in the participating centers.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PP1131

Arm description:

anti P aeruginosa PP1131 cocktail

Arm type	Experimental
Investigational medicinal product name	PP1131 anti P aeruginosa Phage cocktail
Investigational medicinal product code	PP1131
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Topical use

Dosage and administration details:

An Algosteril® plaque of 200 cm² is saturated with 20 ml of 106 PFU/ml phage cocktail solution.

Investigational medicinal product name	PP1131 anti P aeruginosa Phage cocktail
Investigational medicinal product code	PP1131
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Topical

Dosage and administration details:

An Algosteril® plaque of 200 cm² is saturated with 20 ml of 106 PFU/ml phage cocktail solution.
The phage saturated Algosteril® plaques are directly placed on the treatment area. A hydrophobic dressing as Jelonet ® type covers the treatment area.
Sterile gauze covers the primary dressing. A band like Velpeau ® closes the dressing.

Arm title	Silver Sulfadiazine

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Silver sulfadiazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical

Dosage and administration details:

Silver Sulfadiazine® is directly placed on the treatment area. The layer must be thick (several millimeters) covered by a gauze saturated with Silver sulfadiazine ® cream. A band like Velpeau ® closes the dressing.

Number of subjects in period 1	PP1131	Silver Sulfadiazine
Started	13	13
Completed	10	9
Not completed	3	4
Consent withdrawn by subject	1	-
Drug supplies	1	-
Adverse event, non-fatal	-	1
transfer to re-habilitation center	1	-
Transfer to rehabilitation center	-	1
transfer to a conventionnal care unit	-	1
fully cured	-	1

Baseline characteristics

Reporting groups	
Reporting group title	PP1131
Reporting group description: anti P aeruginosa PP1131 cocktail	
Reporting group title	Silver Sulfadiazine
Reporting group description: -	

Reporting group values	PP1131	Silver Sulfadiazine	Total
Number of subjects	13	13	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
adults	13	13	26
Age continuous Units: years			
arithmetic mean	57.0	45.8	
standard deviation	± 21.1	± 20.6	-
Gender categorical Units: Subjects			
Female	5	6	11
Male	8	7	15

End points

End points reporting groups	
Reporting group title	PP1131
Reporting group description: anti P aeruginosa PP1131 cocktail	
Reporting group title	Silver Sulfadiazine
Reporting group description: -	

Primary: time necessary for a persistent reduction of bacterial burden	
End point title	time necessary for a persistent reduction of bacterial burden
End point description: The primary endpoint is the time necessary for a persistent reduction of bacterial burden (for Pseudomonas aeruginosa as appropriate) of at least two quadrants (semi-quantitative technique of the four quadrants) or persistent bacteria eradication relative to D0.	
End point type	Primary
End point timeframe: Time from D0 until 7 days.	

End point values	PP1131	Silver Sulfadiazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: time in hours and days	12	13		

Statistical analyses

Statistical analysis title	Statistical analysis Primary Endpoint

Statistical analysis description:

The primary endpoint was the time required for a persistent reduction in a semi-quantitative bacterial burden (Pseudomonas aeruginosa) of two quadrants or more or persistent bacteria eradication relative to D0.
In case of multiple mono-bacterial infected wounds, the semi-quantitative bacterial burden used to evaluate the primary endpoint was defined as the highest semi-quantitative bacterial burden of all samples collected at the same visit.

Comparison groups	PP1131 v Silver Sulfadiazine
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.018
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.79
Variability estimate	Standard deviation

Notes:

[1] - Ordinal and continuous data were presented overall and by treatment arm, in the form of descriptive statistics as the number of patients, mean, standard deviation, minimum, median and maximum.
Categorical data were presented overall and by treatment arm using contingency tables with absolute and relative frequencies.
Baseline was defined as the last measurement prior to first study drug administration.

Secondary: Rate of patients with bacterial burden reduction

End point title	Rate of patients with bacterial burden reduction

End point description:

End point type	Secondary

End point timeframe:

The time required for a persistent reduction in semi-quantitative bacterial burden (for Pseudomonas aeruginosa) of two quadrants or more or persistent bacteria eradication relative to D0.

End point values	PP1131	Silver Sulfadiazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: patients number				
number (not applicable)	12	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: D0 to D21	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	PP1131
Reporting group description: -	
Reporting group title	Silver Sulfadiazine
Reporting group description: -	

Serious adverse events	PP1131	Silver Sulfadiazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	4 / 13 (30.77%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteriama fatal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Superinfection			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 13 (0.00%)	3 / 13 (23.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
pseudomonas infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
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: 0.05 %

Non-serious adverse events	PP1131	Silver Sulfadiazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	7 / 13 (53.85%)	
Investigations			
oxygene saturation decrease			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
post procedural haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vascular disorders			
chock haemorrhagic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	2	
Impaired healing			

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
pancythopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Haemorrhage urinary tract			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
bacteremia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Skin graft infection			

subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
facial infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	The first one submitted on December 22nd 2015, recommended including day 14 after treatment as a day for wound microbiological swabbing, in addition to the seven other days of infected burn wound swabbing already mentioned in the genuine protocol (D0 to D6).
31 May 2016	In the second amendment of May 31st, 2016, in view of the difficult recruitment of patients with E. coli infections, the sponsor and the coordinator decided to drop the clinical evaluation of PP0121 and both corresponding arms were closed. Furthermore, the possibility to recruit patients with a basal colonization level of bacteria belonging to other species than P. aeruginosa was authorized (basal level was set up at at maximum of 101 CFU/ml or one quadrant). Finally, in agreement with a recommendation of the DSMB (meeting of March 2016), it was decided to practice a SOFA evaluation before including patients in the remaining two arms (P. aeruginosa infections) , with the purpose to reduce the risk to recruit patients in severe condition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 January 2017	Decision of DSMB following insufficient efficacy	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30292481