Clinical trial results:
Pilot study to investigate the clinical effect of orally inhaled AP301 on treatment of primary graft dysfunction (PGD) in mechanically ventilated patients after primary lung transplantation

Summary

EudraCT number	2013-000716-21
Trial protocol	AT
Global end of trial date	18 March 2015

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	AP301-III-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Apeptico GmbH
Sponsor organisation address	Mariahilfer Straße 136, Vienna, Austria, 1150
Public contact	Head of Company, Apeptico Forschung und Entwicklung GmbH, 0043 6641432919, b.fischer@apeptico.com
Scientific contact	Head of Company, Apeptico Forschung und Entwicklung GmbH, 0043 6641432919, b.fischer@apeptico.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	02 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2015
Global end of trial reached?	Yes
Global end of trial date	18 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to assess the clinical effect of orally inhaled AP301 on treatment of primary graft dysfunction (PGD) according to ISHLT (International Society for Heart and Lung Transplantation) criteria in patients after primary LuTX in comparison to placebo.

Secondary Objectives were to

-evaluate recipients mortality at 30 days after transplantation (%)
-duration of intubation
-requirement of mechanical ventilation
-length of ICU stay
-incidence of acute rejections
-freedom of chronic lung allograft dysfunction
-graft survival within 30 days
-local and systematic safety and tolerability of AP 301

Protection of trial subjects:

To guarantee the highest possible protection of subjects, safety measures were put in place throughout Screening, Treatment and Follow up. Withdrawal rules including safety endpoints were defined carefully. Specific safety measures concerned :

Administration of AP301
AP301 or any other ingredients of the IMP can potentially cause hypersensitivity reactions, including serious anaphylactic/anaphylactoid reactions . Local ICU staff had proven expertise in rapid diagnoses and treatment of these disease patterns. The Staff was advised to withdraw any subject, who showes corresponding symptoms immediately from this study. Resuscitation measures including airway management, administration of large volumes of intravenous fluids and 1:1000 adrenalin solution for i.m. injection were all time and without delay enforceable at ICU.
The subject's protection from dose dependent side effects had crucial importance.For the subject’s safety, selection oft he administered dose was based on prior scientific evidence about pharmacokinetics- and dynamics of AP301 and influencing factors of the nebulizing process. Prior to site initiation, all site staff had received hands- on training regarding the dosage regimen and handling of the nebulizer unit.

Medical and Safety Assessment
During screening, Inclusion/Exclusion criteria, medical history, physical examination, vital signs and pregnancy test (if applicable) were evaluated. During treatment, vital signs were assessed daily. On EOT visit, physical examination was repeated. Monitoring of ventilation parameters and evaluation of PGD score, CXR and EVLW was carried out daily during treatment in accordance to national LuTX guidelines. Special Safety Assessment including Hematology, Clinical Chemistry and blood gasses was carried out daily during screening and treatment. As many patients were multimorbid,the need for change in comitant medication was frequently evaluated and, if necessary, conducted by qualified staff

Background therapy:

As this study has been performed with ICU patients under severe health conditions, a high number of different concomitant medications have been administered. Apart from cancer Therapy (chemotherapy or biological), any other medically indicated medications were allowed, including immunsupressive therapies. Modifications of concomitant treatment during the clinical investigation were allowed as necessary and were documented in the patients record by staff with proven qualification.

Evidence for comparator:

Treatment of PGD is supportive and in severe cases may include lung-protective ventilation strategies , inhaled nitric oxide and temporary ECMO support.Retransplantation represents a last resort (Fuehner, Grer, Welte&Gottlieb, 2012)
In cases of established PGD, NO-therapy seems to be useful for improving gas exchange it. Nevertheless, there are currently no studies supporting its use for ventilatory or survival benefit. Regarding prophylactic inhaled NO there are currently no randomised controlled studies that demonstrate a reduction in morbidity(time to extubation, length of ICU stay or hospital stay and mortality (Tavare& Tsakok, 2011)
If compared to other investigational medicinal products, AP301 represents a new molecular type and new concept for prevention and treatment of pulmonary permeability edema and prevention of ischemia - reperfusion injury. The test compound- for the first time - represents a molecule that directly improves alveolar fluid clearance and that restores the endothelial barrier function of the micro-capillary and alveolar tissue.AP301 is expected to therapeutically treat primary graft dysfunction by reducing leakage fluids from capillaries in the lungs, by activating alveolar edema clearance and by restoring the endothelial barrier function.
The therapeutic potential of AP301 in PGD has been demonstrated in preclinical studies in rats (Hemacher et al, 2010). In another preclinical transplantation study in pigs at the department of Thoracic Surgery of the Medical department of the Medical University of Vienna, it was demonstrated that inhalative application of nebulized AP301 during an extracorporal mode simulating LUTX to severely pre-damaged donor lungs significantly improved the gas exchange compared to placebo treatment(Aigner et al, 2013).Also, the therapeutic potential of AP301 to treat pulmonary permeability edema has been highlighted in Critical Care medicine (Matthay, 2008) and Vascular Pharmacology

Actual start date of recruitment	20 June 2013
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	Austria: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Start date: 20.6.2013
Trial country: Austria
Planned number of subjects: 20
Actual number of subjects enrolled: 20
The subjects were recruited from the AKH 's waiting list for primary single or double LuTX

Pre-assignment

Screening details:

Study screening procedures included the following: Inclusion/Exclusion criteria, demographic data, physical examination, vital signs, medical history and concomitant diseases, clinical laboratory tests and pregnancy test for females.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	20

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AP301

Arm description:

Subjects randomized to AP301 administration

Arm type	Experimental
Investigational medicinal product name	AP301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

The IMP was reconstituted in water for injection to a final concentration of 25mg/ml.After randomization patients received 5ml of the study drug according to treatment allocation via endotracheal nebulisation every 12 hours for a maximum of 7 days using an Aerob Solo nebulizer (Aerogen, Galway, Ireland).This equates to a nebulizer filling dose of 125 mg AP301 peptide. This filling dose corresponds with an orally delivered dose of 87,6 mg AP301.
The timepoints for inhalations were 9.00 a.m. (+/-60 min) and 9.00 p.m. (+/-60 min).After diagnosis of PGD , study drug was administered immediately, if the interval for next regularly scheduled time point for administration would have exceeded more than three hours.

Arm title	PLACEBO

Arm description:

Subjects randomized to Placebo administration

Arm type	Placebo

Investigational medicinal product name	0.9% Na-Cl Solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Inhalation use

Dosage and administration details:

5 ml nebulizer filling dose was inhaled after endotracheally nebulization via device (Aeroneb® solo nebulizing system) every 12 hours for a total of 7 days or till day of extubation.

Number of subjects in period 1	AP301	PLACEBO
Started	10	10
IMP adm. till extubation	10	10
First administration of IMP	10	10
Completed	10	10

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AP301

Arm description:

Patients who had received AP301 in period 1

Arm type	Experimental
Investigational medicinal product name	AP301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

The IMP was reconstituted in water for injection to a final concentration of 25mg/ml.After randomization patients received 5ml of the study drug according to treatment allocation via endotracheal nebulisation every 12 hours for a maximum of 7 days using an Aerob Solo nebulizer (Aerogen, Galway, Ireland).This equates to a nebulizer filling dose of 125 mg AP301 peptide. This filling dose corresponds with an orally delivered dose of 87,6 mg AP301.
The timepoints for inhalations were 9.00 a.m. (+/-60 min) and 9.00 p.m. (+/-60 min).After diagnosis of PGD , study drug was administered immediately, if the interval for next regularly scheduled time point for administration would have exceeded more than three hours.

Arm title	PLACEBO

Arm description:

Patients who had received Placebo in period 1

Arm type	Placebo
Investigational medicinal product name	0.9% Na-Cl Solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Inhalation use

Dosage and administration details:

Same dosage as IMP applied, 5ml NaCl solution for inhalation prepared

Number of subjects in period 2	AP301	PLACEBO
Started	10	10
Interview 30 days after Transplantation	10	10
Completed	10	10

Baseline characteristics

Reporting groups	
Reporting group title	AP301
Reporting group description:	
Subjects randomized to AP301 administration	
Reporting group title	PLACEBO
Reporting group description:	
Subjects randomized to Placebo administration	

Reporting group values	AP301	PLACEBO	Total
Number of subjects	10	10	20
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)	10	10	20
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.8	53.9	
standard deviation	± 13.02	± 5.67	-
Gender categorical Units: Subjects			
Female	4	5	9
Male	6	5	11
Ethnic Origin Units: Subjects			
caucasian	10	10	20
others	0	0	0
Clinical examination, abnormal findings (in addition to pulmonary findings) Units: Subjects			
Cardiovascular	6	4	10
Abdomen	1	0	1
HEENT	1	1	2
Neck	0	0	0
Neuro	0	1	1
Psych	1	1	2
Skeletal	1	3	4

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This set includes subjects who where randomized and reveived at least one dose study drug

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

This set comprises all subjects who received study drug and did not viloate the protocol in a way that might affect the evaluation of the effect of the study drugs on the primary objective,i.e., without major protocol violations

Reporting group values	ITT	PP	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
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)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female	9	9	
Male	11	11	
Ethnic Origin Units: Subjects			
caucasian	20	20	
others	0	0	
Clinical examination, abnormal findings (in addition to pulmonary findings) Units: Subjects			
Cardiovascular	10	10	
Abdomen	1	1	
HEENT	2	2	
Neck	0	0	
Neuro	1	1	
Psych	2	2	
Skeletal	4	4	

End points

End points reporting groups

Reporting group title	AP301
Reporting group description:	
Subjects randomized to AP301 administration	
Reporting group title	PLACEBO
Reporting group description:	
Subjects randomized to Placebo administration	
Reporting group title	AP301
Reporting group description:	
Patients who had received AP301 in period 1	
Reporting group title	PLACEBO
Reporting group description:	
Patients who had received Placebo in period 1	
Subject analysis set title	ITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This set includes subjects who where randomized and reveived at least one dose study drug	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
This set comprises all subjects who received study drug and did not viloate the protocol in a way that might affect the evaluation of the effect of the study drugs on the primary objective,i.e., without major protocol violations	

Primary: Change in Arterial blood oxygen tension (paO2)

End point title	Change in Arterial blood oxygen tension (paO2)
End point description:	
PaO2 was assessed once daily during treatment period. It has been assessed using BGA measured on FiO2 =1.0 (=100%) and PEEP=5 for at least 10 minutes while still on mechanical ventilation.For the main comparison of the primary effiacy variable, means of the individual LOCF-PaO2between baseline and treatment day 3 were calculated.	
End point type	Primary
End point timeframe:	
change of PAO2 between T0 (= time of PGD diagnosis) and day 3.	

End point values	AP301	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mmHg				
arithmetic mean (standard deviation)	365.61 (± 90.94)	335.2 (± 42.27)		

Statistical analyses

Statistical analysis title	Statistical comparison of PaO2 data
Comparison groups	PLACEBO v AP301
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 1-sided

Statistical analysis title	Statistical comparison of PaO2 data
Comparison groups	AP301 v PLACEBO
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.049 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - no hypothesis tested and the power of 10 patients per group would only be 0.6.

Secondary: Duration of intubation within 30 days after enrolment

End point title	Duration of intubation within 30 days after enrolment

End point description:

End point type	Secondary

End point timeframe:

Day of enrolment till day 30 after transplantation

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: days				
arithmetic mean (standard deviation)	2 (± 0.82)	3.7 (± 1.95)	2 (± 0.82)	3.7 (± 1.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Recipient mortality 30 days after transplantation

End point title	Recipient mortality 30 days after transplantation

End point description:

death rate in the study population within 30 days after transplantation

End point type	Secondary

End point timeframe:
Day 30 after transplantation

End point values	AP301	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percent				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Oxygenation index once daily until end of treatment or until extubation

End point title	Oxygenation index once daily until end of treatment or until extubation

End point description:
As few data after day 3 was available,only values till this day were put into consideration

End point type	Secondary

End point timeframe:
day of enrolment till day 3

End point values	AP301	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: arbitrary units				
arithmetic mean (standard deviation)				
day1	5.8 (± 3.36)	7.5 (± 2.92)		
day2	2.56 (± 0.73)	3 (± 0.47)		
day3	2 (± 0)	2.78 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement of mechanical ventilation within 30 days after enrolment

End point title	Requirement of mechanical ventilation within 30 days after enrolment

End point description:

End point type	Secondary

End point timeframe:
Within 30 days after enrolment

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: days				
arithmetic mean (standard deviation)	2 (± 0.82)	3.7 (± 1.95)	2 (± 0.82)	3.7 (± 1.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of acute rejection

End point title	Incidence of acute rejection

End point description:
Percentage of subjects diagnosed with acute transplant rejection

End point type	Secondary

End point timeframe:
Day of enrolment till follow-up interview

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: percent				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Freedom of chronic lung allograft dysfunction (CLAD)

End point title	Freedom of chronic lung allograft dysfunction (CLAD)

End point description:
Percentage of subjects not diagnosed with chronic lung allograft dysfunction (CLAD)

End point type	Secondary

End point timeframe:
Day of enrolment till follow up interview

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: percent				
number (not applicable)	100	100	100	100

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival within 30 days

End point title	Graft survival within 30 days

End point description:

Percentage of patients that have a functioning transplant at the end the given time period

End point type	Secondary

End point timeframe:

Day of enrolment till follow -up Interview

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: percent				
number (not applicable)	100	100	100	100

Statistical analyses

No statistical analyses for this end point

Secondary: Length of ICU stay within 30 days after enrolment

End point title	Length of ICU stay within 30 days after enrolment

End point description:

End point type	Secondary

End point timeframe:

Treatment and Follow Up

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: days				
arithmetic mean (standard deviation)	7.5 (± 3.14)	10.8 (± 8.65)	7.5 (± 3.14)	10.8 (± 8.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival within 30 days

End point title	Overall survival within 30 days

End point description:

percentage of patients that are alive at the end of the given time period

End point type	Secondary

End point timeframe:

Day 30 after transplantation

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: percent				
number (not applicable)	100	100	100	100

Statistical analyses

No statistical analyses for this end point

Secondary: EVLW (measured with PiCCO technique)measured twice daily within 60 to 120 minutes after study drug administration until end of treatment

End point title	EVLW (measured with PiCCO technique)measured twice daily within 60 to 120 minutes after study drug administration until end of treatment

End point description:

End point type	Secondary

End point timeframe:

daily during treatment period

End point values	AP301	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ml /KG				
arithmetic mean (standard deviation)				
Measurement baseline	13.88 (± 5.28)	16 (± 6.29)		
Measurement 1	13.33 (± 6.5)	13.43 (± 2.44)		
Measurement 2	11 (± 3.11)	11.88 (± 6.92)		
Measurement 3	9.9 (± 3.68)	10 (± 2.79)		
Measurement 4	9 (± 3.12)	8.7 (± 1.7)		
Measurement 5	8.2 (± 0.84)	8.7 (± 2.21)		
Measurement 6	7.75 (± 1.71)	7.88 (± 2.9)		
Measurement 7	8 (± 1.41)	9 (± 3.92)		
Measurement 8	0 (± 0)	7.8 (± 3.56)		
Measurement 9	0 (± 0)	8 (± 2.55)		
Measurement 10	0 (± 0)	7.8 (± 2.59)		
Measurement 11	0 (± 0)	7.5 (± 2.38)		
Measurement 12	0 (± 0)	9.5 (± 2.12)		
Measurement 13	0 (± 0)	8 (± 0.71)		
Measurement 14	0 (± 0)	8 (± 1.41)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Local and systematic safety and tolerability of AP301

End point title	Local and systematic safety and tolerability of AP301

End point description:

End point type	Other pre-specified

End point timeframe:

Treatment and Follow Up

End point values	AP301	PLACEBO	AP301	PLACEBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: percent				
number (not applicable)				
Safety evaluation	100	100	100	100

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: treatment period and follow period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Ap301 group
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Ap301 group	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (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	Ap301 group	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Total Atelektasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hematome right lower lobe			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Respiratory Acidosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Increasing BUN and creatinin level			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Increased creatinine level			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

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