Clinical trial results:
Proof of concept study in male and female intensive care patients to investigate the clinical effect of repetitive orally inhaled doses of AP301 on alveolar liquid clearance in acute lung injury

Summary

EudraCT number	2012-001863-64
Trial protocol	AT
Global end of trial date	11 August 2014

Results information

Result version number	v2 (current)
This version publication date	26 March 2016
First version publication date	09 August 2015
Version creation reason	• Correction of full data set according to EudraCT requirement, study results have been reviewed again, no corrections needed.

Trial information

Trial identification

Sponsor protocol code	AP301-II-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01627613
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Apeptico GmbH
Sponsor organisation address	Mariahilfer Straße 136, Top 1.15, Vienna, Austria, 1060
Public contact	Doz. Dr. Bernhard Fischer, Apeptico Forschung und Entwicklung GmbH, 0043 6641432919, b.fischer@apeptico.com
Scientific contact	Doz. Dr. Bernhard Fischer, 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	11 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2014
Global end of trial reached?	Yes
Global end of trial date	11 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of orally inhaled AP301 on alveolar liquid clearance in ALI patients with the purpose to assess the treatment associated changes of extravascular lung water (EVLW) within 7 days of treatment.

Protection of trial subjects:

Patients have been treated according to standard of care to minimize any pain and suffering in connection to their initial disease/condition leading to ICU admission and development of ALI.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2012
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	33
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

To be eligible, subjects had to be mechanically ventilated adult male and female patients at AKH, Vienna, Austria, with an onset of the ALI within the last 48 hours, present with a paO2/FiO2 ratio ≤300 mmHg, bilateral pulmonary infiltrates in the frontal chest X-ray, have absence of cardiac failure, and an EVLWI ≥8ml/kg PBW.

Pre-assignment

Screening details:

Demographic data , vital signs the medical history as well as concomitant medication has been documented. Blood gases, clinical chemistry and hematology were determined. The following scores were obtained: GOCA, SOFA, EVLW and lung injury scores were measured. Hemodyn. parameters were analyzed. For childbearing women, pregnancy test was performed

Period 1

Period 1 title	Overall study participation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

In this arm, patientes received the IMP.

Arm type	Experimental
Investigational medicinal product name	AP-301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

After patients met inclusion criteria, in study group I orally delivered doses of 87.6 mg AP301 (dose per subject, 5 ml nebuliser filling dose) were inhaled every 12 hours (± 30 min), for a total of 7 days. 87,6 mg AP301 are based on 125 mg nebuliser filling dose.
This dose level is well below the highest dose level used in the phase I study. It represents a dose level corresponding to the most effective dose levels used in pharmacologic studies.
To enable oral inhalation, reconstituted AP301 in WFI wasconverted into an inhalable aerosol by the Aeroneb Solo medicinal device. The Aeroneb Solo medicinal device is a product of Aerogen, Galway, Ireland and is a commercially available liquid nebuliser.

Arm title	Placebo

Arm description:

in this arm, patients received Placebo treatment without active substance

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

After patients meet inclusion criteria, in study group II Placebo solution (0.9% physiologic NaCl, / 5 ml nebuliser filling dose) was inhaled every 12 hours (± 30 min), for a total of 7 days.

To enable oral inhalation, reconstituted AP301 in WFI was converted into an inhalable aerosol by the Aeroneb Solo medicinal device. The Aeroneb Solo medicinal device is a product of Aerogen, Galway, Ireland and is a commercially available liquid nebuliser.

Number of subjects in period 1	Treatment	Placebo
Started	20	20
Completed	14	16
Not completed	6	4
Adverse event, serious fatal	6	4

Baseline characteristics

Reporting groups

Reporting group title	Overall study participation

Reporting group description: -

Reporting group values	Overall study participation	Total	
Number of subjects	40	40	
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)	33	33	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	48.88		
standard deviation	± 16.04	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	26	26	

Subject analysis sets

Subject analysis set title	AP-301
Subject analysis set type	Full analysis

Subject analysis set description:

Here, all patients received the IMP, AP-301

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

In this arm, patients received Placebo treatment

Reporting group values	AP-301	Placebo	
Number of subjects	19	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)	14	18	
From 65-84 years	5	2	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	47.55	50.2	
standard deviation	± 17.39	± 14.91	
Gender categorical			
Units: Subjects			
Female	5	8	
Male	14	12	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
In this arm, patientes received the IMP.	
Reporting group title	Placebo
Reporting group description:	
in this arm, patients received Placebo treatment without active substance	
Subject analysis set title	AP-301
Subject analysis set type	Full analysis
Subject analysis set description:	
Here, all patients received the IMP, AP-301	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
In this arm, patients received Placebo treatment	

Primary: EVLWI

End point title	EVLWI
End point description:	
EVLW stands for extravascular lung water, and upon damage of the alveolar capillary barrier the infiltration of water into the lung can happen (Hypermeability Oedema).	
End point type	Primary
End point timeframe:	
Within the treatment period of seven days	

End point values	Treatment	Placebo	AP-301	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	19	20
Units: ml/PBW				
number (not applicable)	1.94	0.65	1.94	0.65

Statistical analyses

Statistical analysis title	Statistical Analysis of AP-301-II
Comparison groups	AP-301 v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - This has been a pilot study to evaluate the effect of AP-301 on the reduction of EVLW in ICU patients

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Twenty eight days after inclusion of study subjects	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Treatment
Reporting group description: In this arm, patients received the IMP.	
Reporting group title	Placebo
Reporting group description: in this arm, patients received Placebo treatment without active substance	

Serious adverse events	Treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	5 / 20 (25.00%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	5 / 20 (25.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 1	
Nervous system disorders			
Intracranial bleeding			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Acute abdomen			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory insufficiency			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxaemia/hypoxia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
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: 5 %

Non-serious adverse events	Treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 20 (60.00%)	12 / 20 (60.00%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	4	
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	4 / 20 (20.00%)	6 / 20 (30.00%)	
occurrences (all)	5	8	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	6 / 20 (30.00%)	7 / 20 (35.00%)	
occurrences (all)	11	9	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 20 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	

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