Clinical trial results:
A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group Study of AP30663 Given Intravenously for Cardioversion in Patients with Atrial Fibrillation

Summary

EudraCT number	2018-004445-17
Trial protocol	DK HU
Global end of trial date	23 January 2023

Results information

Result version number	v1 (current)
This version publication date	08 December 2023
First version publication date	08 December 2023

Trial information

Trial identification

Sponsor protocol code	AP30663-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04571385
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acesion Pharma
Sponsor organisation address	Ole Maaløes Vej 3 , Copenhagen N, Denmark, DK-2200
Public contact	Birgitte Vestbjerg, Acesion Pharma ApS, +45 20772575, bve@acesionpharma.com
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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	23 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate efficacy of AP30663 on the basis of the ability to convert atrial fibrillation (AF) following intravenous administration.

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki in compliance with International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2019
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	Denmark: 1
Country: Number of subjects enrolled	Hungary: 65
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	27
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 active sites in 2 countries (Denmark and Hungary) from 09 September 2019 to 23 January 2023.

Pre-assignment

Screening details:

A total of 66 subjects were enrolled, of which 63 subjects received the study treatment in 2 parts. Part 1 consists of Placebo and AP30663 (3 milligrams per kilogram [mg/kg]) and part 2 consist of Placebo and AP30663 (5 mg/kg). As per pre-specified analysis, pooled data for placebo arm of both Part 1 and 2 was analysed in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 and 2: Pooled Placebo

Arm description:

Subjects received a single intravenous (IV) infusion of AP30663-matched placebo for 30 minutes on Day 1 in both Part 1 and 2.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received AP30663-matched placebo in both Part 1 and 2.

Arm title	Part 1: AP30663 3mg/kg

Arm description:

Subjects received a single IV infusion of AP30663 3mg/kg for 30 minutes on Day 1 in Part 1.

Arm type	Experimental
Investigational medicinal product name	AP30663
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received AP30663 3mg/kg intravenous infusion in Part 1.

Arm title	Part 2: AP30663 5mg/kg

Arm description:

Subjects received a single IV infusion of AP30663 5mg/kg for 30 minutes on Day 1 in Part 2.

Arm type	Experimental

Investigational medicinal product name	AP30663
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received AP30663 5mg/kg intravenous infusion in Part 2.

Number of subjects in period 1[1]	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg
Started	26	15	22
Full Analysis Set (FAS)	25 [2]	12 [3]	22
Safety Set	26	15	22
Pharmacokinetic (PK) Set	0 [4]	15	22
Completed	26	15	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only treated subjects were considered for the baseline period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: FAS included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: FAS included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The PK Set included all subjects in the Safety Set who had at least one evaluable post-baseline drug concentration value.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 and 2: Pooled Placebo
Reporting group description:	
Subjects received a single intravenous (IV) infusion of AP30663-matched placebo for 30 minutes on Day 1 in both Part 1 and 2.	
Reporting group title	Part 1: AP30663 3mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 3mg/kg for 30 minutes on Day 1 in Part 1.	
Reporting group title	Part 2: AP30663 5mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 5mg/kg for 30 minutes on Day 1 in Part 2.	

Reporting group values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg
Number of subjects	26	15	22
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.3	65.4	65.5
standard deviation	± 9.23	± 8.48	± 10.38
Gender categorical Units: Subjects			
Female	8	3	7
Male	18	12	15
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	26	15	22
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	63		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	18		
Male	45		

Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	63		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Part 1 and 2: Pooled Placebo
Reporting group description:	
Subjects received a single intravenous (IV) infusion of AP30663-matched placebo for 30 minutes on Day 1 in both Part 1 and 2.	
Reporting group title	Part 1: AP30663 3mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 3mg/kg for 30 minutes on Day 1 in Part 1.	
Reporting group title	Part 2: AP30663 5mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 5mg/kg for 30 minutes on Day 1 in Part 2.	

Primary: Percentage of Subjects Who Converted From Atrial Fibrillation (AF) Within 90 Minutes From Start of Infusion and Subsequently Had no AF Recurrence Within 1 Minute of Conversion From AF

End point title	Percentage of Subjects Who Converted From Atrial Fibrillation (AF) Within 90 Minutes From Start of Infusion and Subsequently Had no AF Recurrence Within 1 Minute of Conversion From AF[1]
End point description:	
The 12-lead Holter monitoring equipment was used to monitor heart rate and its rhythm. Electrocardiogram (ECG) was performed in a standardized manner after the subject had rested in the semi-supine position for at least 5 minutes. Conversion from AF to normal sinus rhythm within 90 minutes from start of infusion was determined by the investigator and documented with a rhythm strip confirming conversion. Percentages were based on "number of subjects converted from atrial fibrillation and absence of recurrence of AF within 1 minute of conversion" divided by "total number of subjects" *100 in each treatment group. Analysis was performed based on Bayesian model. Full Analysis Set included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion.	
End point type	Primary
End point timeframe:	
Within 90 minutes from the start of infusion (Day 1)	

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: A Bayesian analysis was performed for this endpoint, however the results from this cannot be reported in the system.

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	12	22	
Units: Percentage of subjects				
number (not applicable)	0	41.7	54.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Conversion From Atrial Fibrillation From Start of Infusion

End point title	Time to Conversion From Atrial Fibrillation From Start of Infusion

End point description:

The 12-lead Holter monitoring equipment was used to monitor heart rate and its rhythm. ECG was performed in a standardized manner after the participant had rested in the semi-supine position for at least 5 minutes. Time to conversion (in minutes) was calculated by time of conversion or censoring minus time of start of infusion. Full Analysis Set included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion. Here, "number of subjects analysed" signifies those subjects were evaluable for this endpoints.

End point type	Secondary

End point timeframe:

From start of infusion (Day 1) up to Day 2

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	5	12	
Units: minutes				
median (full range (min-max))	(to)	42.0 (24 to 81)	35.0 (19 to 89)	

Notes:

[2] - No subjects had conversion from AF to normal rhythm in placebo arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Relapse of AF Within 5 Minutes (IRAF) After Pharmacological or Direct Current (DC) Cardioversion

End point title	Percentage of Subjects With Relapse of AF Within 5 Minutes (IRAF) After Pharmacological or Direct Current (DC) Cardioversion

End point description:

The 12-lead Holter monitoring equipment was used to monitor heart rate and its rhythm. ECG was performed in a standardized manner after the subjects had rested in the semi-supine position for at least 5 minutes. Subjects with relapse of AF within 5 minutes following pharmacological or DC cardioversion was presented by treatment and analyzed using a logistic regression model. Percentages were based on "number of subjects with relapse of AF within 5 minutes after Pharmacological or DC cardioversion" divided by "total number of subjects" *100 in each treatment group. Full Analysis Set included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion

End point type	Secondary

End point timeframe:

Within 5 minutes after cardioversion (Day 1)

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	12	22	
Units: Percentage of subjects				
number (not applicable)	4.0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sinus Rhythm (SR) at 3 Hours, 24 Hours and Day 30 After Start of Infusion

End point title	Percentage of Subjects With Sinus Rhythm (SR) at 3 Hours, 24 Hours and Day 30 After Start of Infusion

End point description:

The 12-lead Holter monitoring equipment was used to monitor heart rate and its rhythm. ECG was performed in a standardized manner that the subject had rested in the semi-supine position for at least 5 minutes. Percentage of subjects in SR was assessed from Holter ECGs at 3 hours, 24 hours and Day 30 after start of infusion. Percentages were based on "number of subjects in SR at 3 hours, 24 hours and Day 30 after start of infusion" divided by "total number of subjects" *100 in each treatment group. Full Analysis Set included all randomized subjects who were administered double-blind study treatment and had an evaluable AF conversion status within 90 minutes from the start of infusion. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies to subjects evaluable at given timepoints.

End point type	Secondary

End point timeframe:

At 3 hours, 24 hours and Day 30 after start of Infusion (Day 1)

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	11	21	
Units: Percentage of subjects				
number (not applicable)				
Sinus Rhythm at 3 hours (n= 25, 11, 21)	84.0	100.0	95.2	
Sinus Rhythm at 24 hours (n= 25, 11, 21)	76.0	100.0	100.0	
Sinus Rhythm at Day 30 (n= 25, 10, 21)	64.0	90.0	71.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

and Serious TEAEs

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. TEAEs are defined as any AE occurring or worsening on or after the first dose of study medication. A serious adverse event (SAE) is defined as any serious adverse event that, at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, significant medical events that may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed before. TEAEs include both serious and non-serious adverse events. Safety set included all randomized subjects who were administered double-blind study treatment. Subjects analysed according to the treatment

End point type	Secondary

End point timeframe:

From start of infusion (Day 1) up to follow-up (Day 35)

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	15	22	
Units: Subjects				
Subjects with TEAEs	13	4	11	
Subjects with Serious TEAEs	4	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Fridericia's Correction of QT Interval (ΔQTcF) Interval Data Over Time

End point title	Changes From Baseline in Fridericia's Correction of QT Interval (ΔQTcF) Interval Data Over Time

End point description:

QTcF was assessed based on 12-lead Holter monitoring equipment. Triplicate ECGs were extracted at the same time points as PK sampling and were read in a semi-automated manner by a blinded cardiologist. The subject rested in the semi-supine position for at least 5 minutes at ECG extraction timepoints. Change from baseline was estimated based on a linear mixed-effects model: ΔQTcF = Time + Treatment + Time*Treatment + Baseline QTcF. All randomized subjects who were administered double-blind study treatment and with measurements at baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTcF value. Subjects were analyzed according to the treatment received. Here, "n" signifies to subjects evaluable at given timepoints. Here, "99999" refers no subject is available at 2-hours post-dose sample.

End point type	Secondary

End point timeframe:

Baseline, 15 minutes, 45 minutes, 2 hours, 8 hours and 24 hours post-dose

End point values	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	15	22	
Units: millisecond				
least squares mean (standard error)				
Change at 15 minutes post-dose (n= 26, 15, 22)	1.9 (± 3.21)	11.7 (± 4.26)	21.2 (± 3.49)	
Change at 45 minutes post-dose (n= 26, 15, 21)	1.0 (± 3.21)	19.4 (± 4.26)	37.7 (± 3.53)	
Change at 2 hours post-dose (n= 14, 15, 0)	6.2 (± 3.93)	23.0 (± 4.26)	99999 (± 99999)	
Change at 8 hours post-dose (n= 24, 14, 20)	11.5 (± 3.29)	13.6 (± 4.34)	17.2 (± 3.59)	
Change at 24 hours post-dose (n= 16, 11, 10)	10.3 (± 3.74)	14.9 (± 4.67)	13.1 (± 4.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Peak Plasma Concentration (Cmax) of AP30663

End point title	Maximum Observed Peak Plasma Concentration (Cmax) of AP30663[3]

End point description:

Cmax was defined as the maximum observed peak plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve. Blood samples were collected at indicated timepoints. Pharmacokinetics (PK) was conducted using standard noncompartmental method. The PK Set included all subjects in the Safety Set who had at least one evaluable post-baseline drug concentration value.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	22		
Units: Micrograms per liter				
geometric mean (geometric coefficient of variation)	7606.065 (± 31.5)	10281.754 (± 30.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Peak Plasma Concentration (Tmax) of AP30663

End point title	Time to Reach Peak Plasma Concentration (Tmax) of

End point description:

Tmax was directly determined from concentration time data. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the Safety Set who had at least one evaluable post-baseline drug concentration value.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	22		
Units: hours				
median (full range (min-max))	0.4170 (0.250 to 0.500)	0.4170 (0.250 to 1.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half Life of (T1/2) of AP30663

End point title	Terminal Half Life of (T1/2) of AP30663[5]

End point description:

T1/2 was calculated as loge (2) per elimination rate constant (kel), where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the Safety Set who had at least one evaluable post-baseline drug concentration value. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: hours				
median (full range (min-max))	5.363 (2.60 to 8.39)	5.620 (4.35 to 8.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve From Pre-dose Concentration up to 30 Minutes (AUC0-0.5) of AP30663

End point title	Area Under the Concentration Time Curve From Pre-dose Concentration up to 30 Minutes (AUC0-0.5) of AP30663[6]

End point description:

AUC0-0.5 was defined as area under the concentration time curve from pre-dose concentration up to 30 minutes. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the safety set who had at least one evaluable post-baseline drug concentration value.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30 minutes post-infusion

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	22		
Units: Hours*micrograms per liter				
geometric mean (geometric coefficient of variation)	2568.175 (± 41.2)	3446.078 (± 79.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve up to the Last Measurable Concentration (AUC0-t) of AP30663

End point title	Area Under the Concentration Time Curve up to the Last Measurable Concentration (AUC0-t) of AP30663[7]

End point description:

AUC0-t was defined as area under the concentration-time curve from time zero to time of last measurable concentration. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the safety set who had at least one evaluable post-baseline drug concentration value.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	22		
Units: Hours*micrograms per liter				
geometric mean (geometric coefficient of variation)	19328.384 (± 44.0)	29587.109 (± 31.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Pre-dose (Zero) Through Concentration to Infinity (AUC0-inf) of AP30663

End point title	Area Under the Concentration-Time Curve From Pre-dose (Zero) Through Concentration to Infinity (AUC0-inf) of AP30663[8]

End point description:

AUC0-inf was defined as area under the concentration time curve from pre-dose through concentration to infinity (extrapolated), calculated as AUC0-t + Ct/Kel, where Ct is the last observed non-zero concentration. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the safety set who had at least one evaluable post-baseline drug concentration value. Here, "number of subjects analysed" signifies those subjects were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: Hours*micrograms per liter				
geometric mean (geometric coefficient of variation)	21623.095 (± 43.4)	31448.932 (± 33.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Rate Constant (Kel) of AP30663

End point title	Elimination Rate Constant (Kel) of AP30663[9]

End point description:

Kel represents the fraction of drug eliminated per unit of time. Elimination rate constant was calculated using linear regression on the terminal portion of the log-linear concentration versus time curve. Blood samples were collected at indicated timepoints. Pharmacokinetics was conducted using standard noncompartmental method. The PK Set included all subjects in the safety set who had at least one evaluable post-baseline drug concentration value. Here, "number of subjects analysed" signifies those subjects were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (pre-infusion) and at 5, 15, 25, 30, 45 minutes, 1 hour, 1.5 hours, 4 hours, 8 hours and 24 hours post-infusion

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pk data was evaluated only for AP30663.

End point values	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: per hour				
geometric mean (geometric coefficient of variation)	0.13092 (± 31.4)	0.11817 (± 18.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of infusion (Day 1) up to follow-up (Day 35)	
Adverse event reporting additional description:	
Safety set included all randomized subjects who were administered double-blind study treatment and had analyzed according to the treatment received.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Part 1 and 2: Pooled Placebo
Reporting group description:	
Subjects received a single IV infusion of AP30663 matched placebo for 30 minutes on Day 1 in both Part 1 and 2.	
Reporting group title	Part 1: AP30663 3mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 3mg/kg for 30 minutes on Day 1 in Part 1.	
Reporting group title	Part 2: AP30663 5mg/kg
Reporting group description:	
Subjects received a single IV infusion of AP30663 5mg/kg for 30 minutes on Day 1 in Part 2.	

Serious adverse events	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 26 (15.38%)	0 / 15 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 26 (15.38%)	0 / 15 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part 1 and 2: Pooled Placebo	Part 1: AP30663 3mg/kg	Part 2: AP30663 5mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 26 (50.00%)	4 / 15 (26.67%)	11 / 22 (50.00%)
Investigations			
Blood bilirubin increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Phlebitis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 26 (7.69%)	0 / 15 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 26 (26.92%)	1 / 15 (6.67%)	7 / 22 (31.82%)
occurrences (all)	7	1	7
Atrial flutter			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	3 / 22 (13.64%)
occurrences (all)	1	0	3
Atrioventricular block first degree			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 26 (3.85%)	2 / 15 (13.33%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Bundle branch block left			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Bundle branch block right			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Left ventricular failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Supraventricular tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness postural			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			

Diabetes mellitus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Hypokalaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2020	Amendment 1: • Update to study design to include adaptive design as Part 2 of the study and corresponding updates to sample size and addition of the new AP30663 doses relevant for Part 2. • Addition of criteria for interim analyses. • Updates to the study objectives to reflect that the assessments were pertaining to 1 or more dose levels of AP30663. • Addition of details for the DMC activities during the Part 2 of the study. • Update to the statistical analysis method for the primary endpoint. • Additional clarification of study procedures, including updates to: 1. time points for collection of plasma samples 2. prior and concomitant medications 3. role of investigators in process of treatment discontinuation 4. study drug administration 5. ECG reading and extraction windows 6. instructions for assessing local infusion site reactions.
01 June 2020	Amendment 2: • Update to the study design for Part I of the study: Changed the number of subjects for the first interim analysis to be "up to" 36 randomised subjects, rather than 36 randomised subjects. Added explanation that interim analysis could be planned on a reduced cohort if preliminary blinded safety and efficacy data were sufficient for the DMC to provide a recommendation for Part 2. • Clarification that "up to" 108 subjects were to be enrolled in Parts 1 and 2. • Update to the exclusion criteria to exclude subjects with any malignant cancer within 3 years of signing ICF and to exclude subjects who used any antiarrhythmic drug class I and/or III within 6 months before randomisation. • Update to the schedule of assessments and associated footnotes for clarification regarding testing TSH levels at screening visit, haematology and clinical chemistry testing at Day 1 visit, 12-lead 24-hour Holter (Day 2 stop continued assessment after the last PK sampling at 24 hours). • Update to the patient discontinuation/withdrawal section for clarification which subjects were to be replaced and to remove reference to low potassium and magnesium levels at screening. • Removal of retest of magnesium before randomisation. • Addition of a washout period of 6 months before randomisation for antiarrhythmic class I and III drugs. • Further administrative updates, minor clarifications and typographical and formatting changes that did not affect content.
23 March 2022	Amendment 3: • Updates to the exclusion criteria 4, 13 18, 20, 21, 22, 26. • Update to the introduction and study rationale with results of the completed phase 1 studies. • Addition of a 2 hour-window for efficacy endpoint proportion of subjects in SR at 24 hours. • Change from 24 hour-Holter ECG and 24 hour-telemetry to 8 hours post-infusion for both. • Updates and clarifications regarding study procedures, assessment parameters and collection windows in schedule of assessment and associated footnotes as well as in procedure sections. • Adjustment of the quality management and risk evaluation section. • Addition of preinfusion ECG QTcF above 450 ms as withdrawal criterion. • Updates to list of prohibited medications and associated washout periods. • Addition of 1 coagulation parameter (INR or APTT) at screening. • For AE collection, addition of reference to the Investigator's Brochure (IB) section on guidance for the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported