Statistical Analysis Plan for Interventional Studies

Sponsor Name: Acesion Pharma ApS

Protocol Number: AP30663 - 2001
Protocol Title: A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group Study of AP30663 Given Intravenously for Cardioversion in Patients with Atrial Fibrillation

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Revision History

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

AE	Adverse event
AERP	Atrial effective refractory period
AF	Atrial fibrillation
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AV	Atrioventricular
BBB	Bundle branch block
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
C_{max}	Observed peak concentration
CYP	Cytochrome P450
DC	Direct current
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
IC_{50}	Half maximal inhibitory concentration

ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
INR	International normalised ratio
IRAF	Immediate relapse of atrial fibrillation
IWRS	Interactive web randomization system
Kel	Elimination rate constant
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCA	Non-compartmental analysis
NOAEL	No observed adverse effect level
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PK	Pharmacokinetic
QTc	Corrected QT interval
SAE	Serious adverse reaction
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SR	Sinus rhythm
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time at which C_{max} occurs
TSH	Thyroid stimulating hormone
TTE	Transthoracic echo
WHO	World health organisation

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. Pharmacokinetic analysis will also be carried out by Syneos Health.

2.2. Timings of Analyses

The study will be conducted in two parts (Parts 1 and 2): Part 1 of the study is a fixed randomisation placebo-controlled parallel design, and Part 2 will be an adaptive design conducted in one or more further doses of AP30663 vs Placebo.

In Part 1 of the study, up to 36 patients will be randomised in a 1:1 ratio to receive AP30663 at 3 mg/kg or matching placebo. An interim analysis (IA) will be conducted once the randomised patients in Part 1 have completed Day 2 assessments or terminated the study(see section 8.1 of the protocol).

An interim analysis (Part 1) including efficacy, PK/PD, safety and tolerability data will be conducted after all randomised patients have completed Day 2 assessments of the study, in order to determine the starting dose(s) for Part 2 of the study. For further information see section 11. An independent data monitoring committee (DMC) will be convened to review the accumulating unblinded efficacy (including ECG and Holter ECG), PK/PD, safety and tolerability data for the study at the time of the interim analysis.

During Part 2, IAs will occur when 18, 36 and 54 patients have been randomised to open-doses including placebo, and have completed Day 2 assessments or terminated the study.

For Part 2, the DMC will give their recommendations regarding continuation or early termination of the study. Decision rules will be based on the AF conversion rate; however the DMC will also have the option to stop a dose arm (or the study) due to unacceptable safety and tolerability (including but not limited to increase in QTcF interval and number and severity of local injection site reactions).

An unblinded team (unblinded statistician and unblinded programming team) will be responsible for generating and delivering unblinded TFLs to the DMC members. Tables that will be delivered for the interim analysis are detailed in Section 16.

3. Study Objectives

3.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of one or more dose levels of AP30663 on the basis of the ability to convert atrial fibrillation (AF) after intravenous administration.

3.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To study the stability of rhythm control (immediate relapse of AF [IRAF], *i.e.* within 5 min after conversion from AF).
- To study the importance of AF duration with respect to the efficacy and safety of one or more dose levels of AP30663.
- To evaluate the safety and tolerability of one or more dose levels of AP30663.
- To study the relationship between systemic exposure and response, with special regard to the conversion from AF and the effect on QRS and QTcF.

3.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

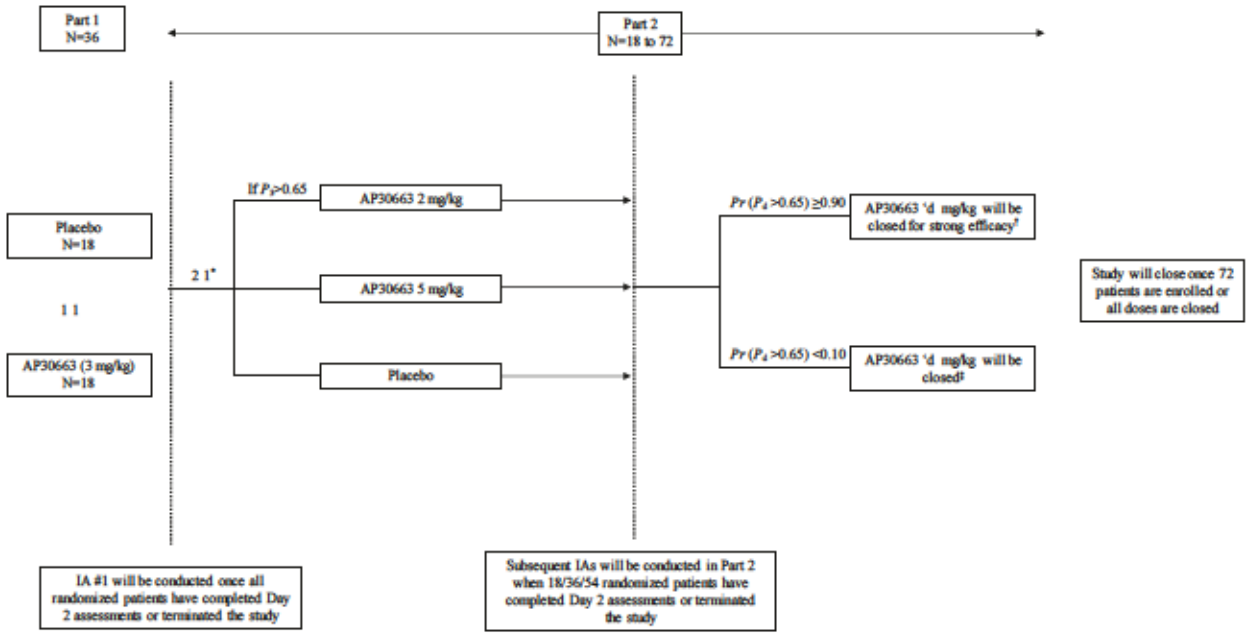
- To study demographic and echocardiographic variables, concomitant diseases, and concurrent medication with respect to the efficacy and safety of one or more dose levels of AP30663.
- To evaluate the PK of AP30663, including influence of dose, concomitant medication, concurrent diseases, and demographic variables.
- To explore the proportions of patients on AP30663 converting from AF and of patients randomised to placebo and converting at DC cardioversion.

3.4. Brief Description

This is a double-blind, randomised, placebo-controlled, parallel-group Phase 2a study of one or more dose levels of AP30663 for cardioversion in adult patients with AF.

The study will be conducted in two parts (Part 1 and 2): Part 1 of the study is a fixed randomisation placebo-controlled parallel design and Part 2 will be an adaptive design conducted in one or more further doses of AP30663 vs Placebo. The study is designed to identify the dose of AP30663 to be evaluated further in later-Phase research. Though the study investigates multiple doses of AP30663 versus placebo, the participating patients will be randomised to receive one dose of AP30663 (i.e. patients will not receive multiple dose levels).

Figure 1 Study Schema



Abbreviations: N=number of patients enrolled, P_3=conversion ratio at 3 mg/kg, P_d=conversion ratio at d mg/kg, *P*r=probability.
*All active AP30663 arms will be randomised equally for each interim analysis; randomisation will occur cumulatively in 2:1 ratio to receive either AP30663 or placebo across all open AP30663 arms.
†If one level below this dose (d-1) has never been opened, then dose d-1 will be opened
‡If dose 'd' is the highest dose opened so far, and dose 'd' is <6 mg/kg, then dose 'd+1' will be opened.

3.5. Patient Selection

3.5.1. Inclusion Criteria

See section 8.3.2 of the protocol

3.5.2. Exclusion Criteria

See section 8.3.3 of the protocol

3.6. Determination of Sample Size

The study is a proof of concept, designed to allow for a considered testing of a range of doses of AP30663, compared with placebo. Based on the study design, the sample size for randomisation will range from up to 36 to up to 108. The total sample size is dependent on the AP30663 dose arms opened

on the decision of the DMC. A total of 4 IAs and a final analysis are included in the design, and so it is foreseen that the total number of randomised patients will be either up to 36, 54, 72, 90 or 108 patients to have a sufficient number of patients evaluable for AF conversion at each IA.

The adaptive design utilises the probability that the response rate at a Dose d is greater than a success rate of 65% ($P_d > 0.65$, where d is the dose arm of AP30663), based on a Bayesian modelling procedure.

3.7. Treatment Assignment & Blinding

For Part 1 of the study, eligible patients will be randomised 1:1 (approximately 36 patients randomised to AP30663 or placebo). An additional 18 to 72 patients will be randomised cumulatively in a 2:1 ratio to 1 or more doses of AP30663 (dependent on dose arms open at time of randomisation) or placebo in Part 2 using an interactive web randomisation system (IWRS).

Two separate lists will be utilised for the study, one for Part 1 and a separate one for Part 2. Both lists will be provided by a separate unblinded biostatistical team and provided to the IWRS.

Acesion Pharma, investigators, and patients will remain blinded to the study treatment allocation until the end of the study. The randomisation list will be kept secure from the study team, investigators, and patients throughout the conduct of the study and until unblinding is authorised by Acesion Pharma and the blinded lead study statistician.The DMC will be unblinded according to the DMC charter, and a separate unblinded statistical team will be assigned to provide the analyses to the DMC and Interim Analysis. Further details of blinded and unblinded personnel will be included in the DMC charter.

3.8. Administration of Study Medication

Study drugs will either be AP30663 or placebo.

Prior to the interim analysis (Part 1 of the study), patients randomised to the AP30663 arm will receive AP30663 at a dose of 3 mg/kg.

The starting AP30663 dose(s) for Part 2 of the study will be determined during DMC review of the interim analysis at the end of Part 1. In Part 2, patients randomised to AP30663 may receive one of the following AP30663 doses: 2, 4, 5, or 6 mg/kg dependent on the results seen for the decision criteria, and the subsequent dose recommended by the DMC.

Patients randomised to the placebo arm will receive matching placebo infusion.

3.9. Study Procedures and Flowchart

The schedule of the planned study assessments during Part 1 and Part 2 is in section 8.1.2 from the protocol.The planned study assessments during Part 2 are the same as those that are planned for Part 1.

4. Endpoints

4.1. Primary Efficacy Endpoint

The proportion of patients that have converted from AF within 90 min from the start of infusion and subsequently have no AF recurrence within 1 min of conversion from AF.

4.2. Secondary Efficacy Endpoints

- The time to conversion from AF from start of infusion.
- The proportion of patients with relapse of AF within 5 min (IRAF) following pharmacological or direct-current (DC) cardioversion.
- The proportion of patients in SR at 3 h ± 1 h after start of infusion.
- The proportion of patients in SR at 24 h ± 2 h after start of infusion.
- The proportion of patients in SR at 30 days ± 5 days after start of infusion.

4.3. Exploratory Endpoints

- Correlation of drug exposure (plasma Cmax and area under the concentration time curve [AUC]) and the time of conversion.
- Correlation of atrial size and conversion rate.
- Correlation of atrial size to relapse or failure.
- Correlation of gender and age and conversion rate.
- Correlation of duration of current AF, conversion rate and - sinus rhythm at some timepoint .

4.4. Pharmacokinetic Endpoints

The PK endpoints are as follows:

- Systemic exposure derived from the population PK model.
- Population PK model parameter estimates derived from plasma concentrations of AP30663.

Concentration-derived PK parameters of plasma AP30663 will be determined using 2 approaches:

• A static analysis based on plasma concentration will be performed using a non-compartmental analysis (NCA);

• PK parameters will also be derived using a non-linear mixed-effect modeling approach.

4.5. Safety Endpoints

- Adverse events (AEs), electrocardiogram (ECG) variables including significant arrhythmia, physical examination, vital signs, and laboratory evaluations.
- Changes in QTcF interval data over time.

5. Analysis Sets

For purposes of analysis, the following populations are defined for both Parts 1 and 2.

5.1. Enrolled Set

The Enrolled Set will include all patients who sign the ICF. Unless specified otherwise, this set will be used for patient listings and for summaries of patient disposition. This set will include screen failures.

5.2. Randomised Set

The Randomised Set will include all patients who signed the ICF and were subsequently randomised into the study (Screen failure are excluded), regardless of study treatment administration.

5.3. Full Analysis Set

The Full Analysis Set will serve as the primary population for the analysis of efficacy and will consist of all randomised participants who were administered double-blind study treatment and have an evaluable AF conversion status within 90 min from the start of infusion.

Patients will be analysed according to the randomised treatment.

5.4. Per Protocol Set

The Per-Protocol Set includes all patients from the Full Analysis Set who have been treated according to the protocol and fulfil the following criteria:

1. All inclusion/exclusion criteria satisfied according to the latest AP30663-2001 Protocol Version 4.0
2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind
3. Adequate study drug compliance, which will be determined before breaking the blind

Patients will be analysed according to the randomised treatment.

5.5. Safety Set

All randomised patients who were administered double-blind study treatment. Patients will be analysed according to the treatment received. The Safety Set will be used for all analyses of safety endpoints.

5.6. Pharmacokinetic (PK) Set

The PK Set will include all patients in the Safety Set who have at least one evaluable post-infusion drug concentration value.

5.7. Protocol Deviations

Important protocol deviations will be collected in the eCTMS. Each instance of a protocol deviation will be reviewed by the Sponsor and determined to be either major or minor before DBL.
The major protocol deviations include, but are not limited to the following (to be finalized before DBL):

- Eligibility deviations (Inclusion/Exclusion criteria)
- Improper reconstitution and administration of study medication
- Noncompliance with study medication (stop of drug infusion prior to 30 min)
- Noncompliance with study procedures if the consequence of noncompliance would compromise either the patient's safety and/or the study integrity, primary endpoint, and/or is not in line with GCP/ICH guidelines
- Use of prohibited concomitant therapies

Patients with any major protocol deviations that likely affect the efficacy of treatment will not be included in the PP population.

Number (%) of patients with at least one major protocol deviation will be included in a summary table, using the Randomised Set.

All protocol deviations will be listed for all patients in the Randomised Set, including their assignment of minor, major or critical, and the date the deviation occurred.

6. General Aspects for Statistical Analysis

6.1. General Methods

- SAS Version 9.4 or higher will be used for programming and production
- The statistical analysis based on plasma concentration will be performed using a non-compartmental analysis (NCA), the PK analyses will be performed by Syneos Health using Phoenix WinNonlin® (release 8.0 or higher) and all other analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 (or higher).
- PK parameters will be derived using a non-linear mixed-effect modeling approach, PK analyses will be performed by Syneos Health using NONMEM® version 7.4.
- Unless otherwise specified, summaries will be presented for each treatment and overall.
- Unless otherwise specified, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.
- All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings.
- Handling of repeated measurements at the same visit

  If measurements were repeated at the same scheduled visit, the value actually flagged as scheduled will be the

  - ✓ Last non-missing repeated measurement, if visit is before start of infusion, and
  - ✓ First non-missing repeated measurement, if visit is after start of infusion.

  Generally, only scheduled measurements will be used for statistical summaries and analysis. Unscheduled measurements will not used for analysis, but only listed.

6.2. Key Definitions

6.2.1. Baseline Value

Unless otherwise specified, the baseline value for any variable will be the last value taken prior to the infusion of the double-blind study treatment on Day 1. This includes pre-dose Day 1 assessments.

6.2.2. Last assessment

Unless otherwise specified, last assessment is defined as Day 30 visit or early discontinuation visit.

6.3. Missing Data

Unless otherwise specified, no imputation will be performed for missing data.

6.3.1. Missing Dates for prior or concomitant medications

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining whether a medication is prior or concomitant only.

- For start dates:
  -if day is missing the first day of the month will be used.
  -If day and month is missing, 1st of January will be used.
  -If the start date is missing completely, the date of infusion will be used.
  -If the stop date is complete and the imputed start date is after the actual stop data, then the start date will be imputed as the stop date.

- For stop dates:
  -if the day is missing then the last day of the month will be used.
  -If the day and month is missing, then 31st December will be used.
  -If the stop date is completely missing, then the date of infusion will be used. If the start date is complete and the imputed stop date is earlier than the actual start date, the stop date will be imputed as the start date.

6.3.2. Missing Dates for adverse event

If the adverse event start date is partially or completely missing, then the following rules will be used to impute the start date for the purposes of determining treatment emergence status only :

- If the whole start date is missing then the date of infusion will be used.
- missing month : if the AE has occurred the same year as the date of infusion, replace the missing month of onset by the month of date of infusion.

  If the AE has occurred the subsequent year after the year of date of infusion, replace the missing month of onset by January.

  If the AE has occurred the previous year of the year of date of infusion, replace the missing month of onset by December.
- missing day : replace it by '01', and verify that the completed date is greater or equal to the date of infusion. If not, replace the incomplete date of onset by the date of infusion.

6.4. Visit Windows

Not applicable

6.5. Pooling of Centres

Not applicable

6.6. Subgroups

No subgroup for this study.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Patient Disposition and Withdrawals

The following frequencies (number and percent) will be displayed in the patient disposition table, by treatment group and overall:

Number of patients enrolled;

Number of patients screen failure;

Number of patients randomised;

Number (%) of patients in the FAS set (Full Analysis Set see definition in section 5);

Number (%) of patients in the PP set (Per-Protocol Set, see definition in section 5);

Number (%) of patients in the PK set (Pharmacokinetic Set, see definition in section 5);

Number (%) of patients in the Safety set (see definition in section 5);

Number (%) of patients who completed the study;

Number (%) of patients who discontinued the study early, and reasons for discontinuation.

The analyses of disposition will be based on the Enrolled Set.The denominators for the percent calculations will be the number of patients in the Randomised Set.

Table for Patient Dispostion will be presented by cohort at each Interim analysis.

Patient completion status, date of completion/discontinuation and reason for discontinuation will be listed.

7.2. Demographic and Other Baseline Characteristics

Gender and child-bearing potential (female patients only), ethnicity will be summarized by the number and percentage of patients in each treatment group. Age (years) will be summarized using descriptive summary statistics.
Demographics parameters will be also presented by cohort at each Interim Analysis.
Data from transthoracic echo (TTE) will be presented using summary statistics. Height and baseline weight will be also summarized.

Duration of current AF episode (in hours) (derivation see section 8.1) and time since initial AF diagnosis (in years) will be summarized in addition.

Time since initial AF diagnosis (in years) = date of randomization – date of initial AF diagnosis (based on MHDECOD = 'Atrial Fibrillation')

In case of an incomplete date of initial AF diagnosis, the first day of the month will be used for a missing day, 1st January will be used for a missing day and month.

All demographic data will be presented in a data listing.

7.3. Medical History and Concomitant Diseases

Medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or an updated version.

Data will be summarized by SOC and PT and sorted alphabetically. Conditions that are reported more than once for a given SOC and PT will be counted only once per patient on the PT level for each SOC

A corresponding data listing will be presented.

7.4. Medication

Section 6.3.1 describes how missing dates will be imputed for the purpose of determining prior/concomitant medication status.

7.4.1. Prior Medication

Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHODRUG), WHODrug Global B3 Sep 2018.

Prior medications will include medications started and stopped prior to the infusion date of the study drug.

For the summary tables, the count and percentage of patients under each anatomical therapeutic chemical (ATC) class level 2 and PT will be summarized by treatment group.
If a patient has taken prior medications more than once, the patient will be counted only once under any given drug class.

7.4.2. Concomitant Medication

Concomitant medications will include medication started on or after the infusion date of study drug. Medication that started before the infusion of study drug and continued on or after the infusion date will be considered as concomitant medication.

For the summary tables, the count and percentage of patients under each anatomical therapeutic chemical (ATC) class level 2 and PT will be summarized by treatment group.
If a patient has taken concomitant medications more than once, the patient will be counted only once under any given drug class.

A listing of prior and concomitant medications will be provided for all patients in the safety set. A flag will be included in the listing to distinguish prior and concomitant medications.

8. Efficacy

8.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is defined as the proportion of patients who have converted from AF within 90 min from the start of infusion, and subsequently have no AF recurrence within 1 min of conversion from AF.

For the analysis of the primary endpoint (proportion of patients who have cardioversion within 90 min from the start of infusion) a Bayesian model will be utilised. The prior probability of success at a dose, d, is modelled with a $P_d \sim$ Beta (1,1) prior (uniform) for each dose. Across both Parts 1 and 2 of the study, the potential doses (arms) in the trial are d = 0 (placebo), 2, 3, 4, 5, and 6 (all mg/kg dose units).

Let X_d be the number of successes and N_d be the number of observations at dose d. The posterior distribution is calculated for each dose independently using a Beta posterior distribution,

$$P_d \sim \text{Beta}\ (1 + X_d,\ 1 + N_d - X_d).$$

The adaptive design utilises the probability that the response rate at a dose is greater than a 65% success rate. This is ($P_d > 0.65$), for each dose d.

This modelling will occur for each interim analysis, and at the final analysis as primary method. At the conclusion of the study, each AP30663 dose will be considered to be superior to placebo, if the posterior probability of AP30663 dose having a higher success rate than placebo is greater than 0.95.

Further to the above, the primary endpoint will also be analysed by means of a logistic regression model. The model will include treatment and duration of current AF episode.

Duration of current AF episode (in hours) = date/time of randomisation – date/time of AF symptom onset

If no time of AF symptom onset is available, '00:00' will be used for the calculation of the duration.

All statistical tests will be 2-sided and conducted at the 5% significance level. All presented confidence intervals will be 2-sided 95% confidence intervals.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Time to conversion from AF from start of infusion

The time to conversion from AF from start of infusion will be analysed using Kaplan-Meier methods. The number of patients that reached cardiac conversion within 90 mins of start of study drug infusion will be summarized using the median time to cardiac conversion along with the interquartile range (IQR) .

A Kaplan Meir plot stratified by treatment group will be presented. A logrank test will be used to compare treatment groups.

Time to conversion (in min) will be calculated using the formulae:

Time to conversion (in min) = (Time of conversion or censoring - time of start of infusion).

In case of AF persistence at 90 min after start of infusion, a direct-current (DC) electrical cardioversion is to be done within 180 min post-infusion start. Patients who have electrical cardioversion will be censored. The time of censoring will be 90 min.

8.2.2. Proportion of patients with relapse of AF within 5 min (IRAF)

The proportion of patients with relapse of AF within 5 min (IRAF) following pharmacological or DC cardioversion will be presented by treatment and analysed using a logistic regression model. The model will include treatment, and duration of current AF episode.

In addition the same analysis will be done for the proportion of patients with relapse of AF within 5 min (IRAF) following pharmacological cardioversion only.

8.2.3. Proportion of patients in SR

The proportion of patients in SR after start of infusion at different timepoints (3 h ± 1 h, 24 h ± 2 h and 30 days ± 5 days after start of infusion) will be presented by treatment group and analysed using a logistic regression model. The model wil include treatment and duration of current AF episode.

9. Analysis of Pharmacokinetics

All PK analyses will be conducted using the PK Set.

9.1. PK Sampling Schedule

Plasma samples will be taken at baseline (pre-infusion) and at the following time points after start of infusion: 5 min ± 1 min, 15 min ± 1 min, 25 min ± 1 min, 30 min - 1 min (the infusion will not be stopped before the 30-min plasma sample has been collected), 45 min ± 5 min, 1 h ± 5 min, 1 h 30 ± 5 min, 4 h ± 5 min, 8 h ± 5 min, and 24 h ± 2 hour (based on protocol version 4.0). In the case of conversion from atrial fibrillation during infusion, an additional sample will be taken immediately after conversion.

9.2. Derived and Imputed Data for PK Endpoint

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of start of the infusion of AP30663. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to infusion, which will always be reported as zero (0.000), regardless of the time difference.

For NCA approach, the following PK parameters including, but not limited to, will be determined for each patient based on plasma concentrations:

- $AUC_{0\text{-}0.5}$: Area under the concentration time curve from pre-dose concentration up to 30 min. $AUC_{0\text{-}0.5}$ includes the plasma drug concentration up to the end of infusion
- $AUC_{0\text{-}t}$: Area under the concentration time curve up to the last measurable concentration
- $AUC_{0\text{-}inf}$: Area under the concentration time curve from pre-dose through concentration to infinity (extrapolated), calculated as $AUC_{0\text{-}t} + C_t/K_{el}$, where C_t is the last observed non-zero concentration
- C_{max}: The observed peak drug concentration
- T_{max}: The time at which C_{max} occurs
- $t_{1/2}$: the terminal half-life value will be calculated using the equation ln2/ K_{el}, with K_{el} being the elimination rate constant
- K_{el}: Elimination rate constant. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. At least 3 concentration points will be used in estimating Kel. The time point where ln-linear K_{el} calculation begins (K_{el} Lower), and the actual sampling time of the last quantifiable concentration used to estimate the K_{el} (K_{el} Upper) will be reported with the correlation coefficient from the linear regression to calculate K_{el}.

From the developed population PK model (Pop-PK), PK parameters like volume of distribution and clearance will be estimated. Additional PK parameters including, but not limited to, area under the curve at steady-state (AUC_{SS}) will be derived from the individual Bayes estimates from the pop-PK model. A separate analysis plan will be created to detail this approach.

9.2.1. Handling of Dropouts, Particularities, Missing Data or Data Below the Lower Limit of Quantification

Missing concentration data for all patients who are administered scheduled study treatment will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For NCA approach, plasma concentrations below the limit of quantification (BLQ) will be set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations will be set to missing. For the computation of PK variables, the BLQ concentrations prior to the first measurable concentration will be set to zero and other BLQ concentrations will be set to missing.

Samples taken far outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to database lock.

9.3. Planned Statistical Models for PK Parameters and Concentrations

The plasma concentration at each time point will be summarized as n, number and percentage BLQ, arithmetic and geometric mean, SD and arithmetic coefficient of variation (CV (%)) (calculated as 100*SD/mean), median, minimum and maximum

Descriptive statistics (n, arithmetic mean, SD, arithmetic CV (%), geometric mean, geometric CV(%), minimum, median and maximum) by treatment group will be calculated for all derived PK endpoints.

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of plasma concentrations:

PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	In the same precision as PK results, *i.e.* with 3 decimal places
Mean (arithmetic and geometric), Median	one more decimal place than the PK results, *i.e.* with 4 decimal places
Standard deviation	Two more decimal places than the PK results, *i.e.* with 5 decimal places
CV and Geometric CV	1 decimal place

9.4. PK Interim Analyses

After all patients in Part 1 have completed Day 2, corresponding to 24 hours after the stop of the infusion, an unblinded interim analysis (IA) will be performed using NCA and pop-PK model. The list of Topline Results for the interim analyses are described below for each method of derivation:

NCA:

- Mean (± SD) AP30663 Plasma Concentrations - Linear and semi-Log Scales – PK Set
- Overlay of Individual and Mean AP30663 Plasma Concentrations by Treatment - Linear and semi-Log Scales - PK Set

These figures will be also provided during Part 2 where IAs will occur when 18, 36 and 54 patients have been randomised to open-doses including placebo, and have completed Day 2 assessments or terminated the study.

Pop-PK model:

Interim results including average PK parameters determination will be provided using descriptive statistics and graphical evaluation.A summary report including conclusion/recommendation for the dose of Part 2 will be generated.

9.5. Deviation from Analyses Planned in Protocol

No deviation from PK analyses described in the Protocol is planned.

10. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed on the basis of adverse event (AE) or adverse drug reactions (ADR) reports, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

10.1. Extent of Exposure

Extent of exposure will be summarized by treatment group for duration of infusion .

Duration of infusion will be derived as:

Duration of infusion (in min)= (Stop Time of Study Drug Infusion- Start Time of Study Drug Infusion) – duration of infusion interruption

Extent of exposure (expected total volume to infuse and infused volume) will be summarized by treatment group.

10.2. Treatment Compliance

Number (%) of patients completing the full infusion treatment, number (%) of patients with infusion interruption and reasons for stopping will also be summarized.

10.3. Adverse Events / Adverse Drug Reactions

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or an updated version. Summaries will be presented by system organ class (SOC) and preferred term. Treatment-emergent AEs (TEAEs) are defined as any AE occurring or worsening on or after the first dose of study medication. Partial AE dates will be imputed.

The frequency and incidence of TEAEs will be presented by SOC and preferred term for each treatment group (number and percentage of patients experiencing at least one TEAE per preferred term as well as the number of observed events per preferred term; percentages will be based on the number of patients in the safety set).
The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

Separate tables will be presented by severity and by relationship, and for SAEs, related TEAEs, and TEAEs leading to study discontinuation.
Relationships of 'very likely', 'probable' and 'possible' are to be considered as related to study drug for the summary tables. Relationships of 'unlikely' and 'unrelated' are to be considered not related to study drug.

In case of missing relationships, AEs will be considered as related.

All AEs will be presented in full in a comprehensive listing including patient number, treatment group, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop, and duration. TEAEs will be flagged in the listings.

Details of SAEs and AEs leading to withdrawal will be listed separately.

10.4. Laboratory Evaluations

The haematology and clinical chemistry laboratory analyses will be performed at local laboratories. Reference ranges will be supplied by local laboratories and used by the investigator to assess the laboratory data for clinical significance and pathological changes. The following laboratory safety tests will be performed at the times outlined in the Study Procedures and Flowchart in Section 3.9.

Haematology

Haemoglobin, haematocrit, red blood cells (erythrocytes), white blood cells (leukocytes, total and differential), basophils, eosinophils, lymphocytes, monocytes, neutrophils, and platelets.

Clinical Chemistry

ALT, AST, bilirubin (direct, indirect, total), creatinine, gamma-glutamyltransferase, glucose (random), eGFR, urea (BUN), sodium, potassium, calcium, and magnesium.

Other Laboratory Variables

INR/APTT and TSH. These variables will be summarized and listed within clinical chemistry.

For all laboratory parameters, the following summary tables will be presented by visit and treatment for each test:

- Actual and changes from baseline for continuous variables
- Shift from baseline
- Number and percent of patients with clinically significant changes

All laboratory results in SI units will be included in data listings. Tests will be listed in alphabetical order. Abnormal lab values will be flagged in the listing .

10.5. Vital Signs

Vital signs will be recorded as indicated in the Study Procedures and Flowchart in Section 3.9. Blood Pressure, heart rate, and heart rhythm (from ECG) will be included and recorded in a standardized manner, *i.e.*, after the patient has rested in the (semi)supine position for 5 min and before blood sampling or laboratory tests. Vital signs measurements will be repeated in case of clinically significant abnormalities.

All vital signs (absolute values and change from baseline) will be summarized by visit, heart rhythm and timepoint for each treatment group.

All vital signs data will be listed chronologically by parameter and included in data listings.

10.6. ECG

A 12-lead digital ECG will be performed at the times outlined in the Study Procedures and Flowchart in Section 3.9 in a standardized manner (*i.e.* after the patient has rested in the [semi]supine position for at least 5 min).

The investigator will assess ECG abnormalities (*e.g.* ischemia, conduction abnormalities, and rhythm abnormalities) and define the ECG intervals as part of the screening of eligibility and according to the inclusion/exclusion criteria, and as part of an adverse event assessment.

12-lead digital ECG will be overread by the central ECG laboratory. The following measurements will be provided for all PK time points: RR, PR, QRS, QT, QTcF (Fridericia's correction of QT interval), heart rate, as well as T- and U-wave morphology classifications.

Bedside safety ECGs will be collected by the site, printed and reviewed by the investigator on site.

ECG intervals based on these safety ECGs will only be recorded if part of an adverse event.

A summary table for actual and change from baseline will be provided by treatment.

Results for 12-Lead ECGs will be summarized by the number and percentage within each category ("normal", "abnormal, not clinically significant", and "abnormal, clinically significant") .

Abnormal results for 12-Lead ECGs will be summarized as below:

- Absolute QTc interval prolongation:
  - QTc F interval > 450 ms
  - QTc F interval > 500 ms
- Change from baseline in QTc interval:
  - QTc F interval increases from baseline >30 ms
  - QTcF interval increases from baseline >60 ms

ECG data will be listed for all patients, and any clinically significant findings in ECG values will be flagged.

A cardiac Statistical Analysis Plan will be developed by Clario.

10.7. Physical Examination

At screening, weight and height will be recorded and a physical examination will be performed, followed by a brief physical examination at baseline (pre-infusion on Day 1) and Day 30. Any changes from the screening and baseline visit to Day 30 will be recorded. Full and brief physical examination will include the following assessments:

Assessment	Full physical examination	Brief physical examination
General appearance	x	x
Head, ears, eyes, nose, throat	x	-
Cardiovascular	x	x
Respiratory	x	x
Gastrointestinal	x	x
Dermatological	x	-
Neurological	x	-
Musculoskeletal	x	-
Lymphatic	x	-
Other (at the investigator's discretion)	x	x

Body systems will be classified as "Normal", "Abnormal Clinically Significant" and "Abnormal Not Clinically Significant". Shift tables comparing physical examination results from baseline to last assessment will be presented by treatment.

Physical examination data will also be listed.

11. Interim Analyses

An interim analysis for efficacy (including ECG and Holter ECG), PK/PD, safety and tolerability will be conducted after all randomised patients have been recruited into Part 1 of the study and either completed Day 2 or terminated the study.

Interim Analysis at End of Part 1:

During the first IA the following will occur, regardless of the response seen for the AP30663 3 mg/kg dose:

- Dose 3 (3 mg/kg AP30663) will be stopped.
- Dose 5 (5 mg/kg AP30663 versus placebo) will be opened.

Additionally, the following decision will be made dependent on the response rate seen for 3 mg/kg AP30663:

- If the proportion of patients achieving a response under AP30663 3 mg/kg is > 0.65 then Dose 2 (2 mg/kg AP30663) will additionally be opened for Part 2 (in parallel to Dose 5).

Interim Analyses during Part 2:

Interim analyses will occur when 18, 36 and 54 randomised patients have completed Day 2 assessments or terminated the study in Part 2. At these IAs the following rules will be utilised:

a) If an open Dose d has at least 10 randomised patients having completed Day 2 assessments and satisfies: $(P_d > 0.65) \geq 0.90$ then Dose d will be closed for sufficient efficacy response.
    - If the dose one level below this dose has never been opened, then dose d-1 is opened.

b) If an open Dose d has at least 10 randomised patients having completed Day 2 assessments and satisfies $(P_d > 0.65) < 0.10$ then Dose d will be closed.
    - If Dose d was the largest dose thus far open, and Dose d is < 6 mg/kg, then dose d + 1 will be opened.

The study will continue until all doses of AP30663 have been closed or the maximum of 72 patients during Part 2 (up to 108 patients total across Part 1 and Part 2) have been enrolled.

While the algorithm, and the DMC's decision for dose increase/decrease, is based on AF conversion rate only, the DMC will also convene to review safety and tolerability data at defined time points; review of this data may also lead to further decisions being made by the DMC.

12. Changes from Analysis Planned in Protocol

None

13. Reference List

None

14. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4. (SAS Institute Inc., Cary, NC, USA) . Computer-generated table, listing and figure output will adhere to the following specifications.

The static analysis based on plasma concentration will be performed using a non-compartmental analysis (NCA), the PK analyses will be performed by Syneos Health using Phoenix WinNonlin® (release 8.0 or higher) and all other analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 (or higher).

PK analyses will be performed using NONMEM® version 7.4.

14.1. General Considerations

- One SAS program can create several outputs
- One output file can contain several outputs.
- Output files will be delivered in Rich Text Format (RTF) that can be manipulated in MSWord
- Numbering of TFLs will follow ICH E3 guidance

14.2. Table, Listing, and Figure Format

14.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help

display math symbols (*e.g.*, µ). Certain subscripts and superscripts (*e.g.*, cm2, Cmax) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
- Acesion Pharma ApS

  Protocol: AP30663 - 2001
- Draft/Final Run <*date*>
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (*i.e.*, the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date/time of the generation of the output should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (*i.e.*, Table 14.1.1). ICH E3 numbering.A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
FAS Analysis Set

14.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (*e.g.*, counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

14.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (*e.g.*, Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more patient.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (*e.g.*, 7 (12.8), 13 (5.4)). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- The percentage of of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000).

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (*e.g.*, 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (*e.g.*, treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date/time the program was run, and the listing source (*i.e.*, 'Program : myprogram.sas Listing source: 16.x.y.z').

15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

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Table 14.1.1.1	Patient Disposition	Enrolled Set	
Table 14.1.1.2	Patient Disposition – Cohort only	Enrolled Set	Only for IA
Table 14.1.2.	Major Protocol Deviations	Randomised Set	
Table 14.1.3.1.1	Demographics	Safety Set	✓
Table 14.1.3.1.2	Demographics – Cohort only	Safety Set	Only for IA
Table 14.1.3.2	Baseline Characteristics	Safety Set	
Table 14.1.3.3	Medical /Surgical History	Safety Set	
Table 14.1.4.1	Prior Medications	Safety Set	
Table 14.1.4.2	Concomitant Medications	Safety Set	
Table 14.1.5.1	Exposure to Study Treatment	Safety Set	✓
Table 14.1.5.2	Compliance with Study Treatment	Safety Set	
Table 14.2.1.1.1	Conversion from AF within 90 Minutes from Start of Infusion : Summary of Response Rate, Bayesian Model	Full Analysis Set	✓
Table 14.2.1.1.2	Conversion from AF within 90 Minutes from Start of Infusion : Summary of Response Rate, Bayesian Model	Per Protocol Set	
Table 14.2.1.1.3	Conversion from AF within 90 Minutes from Start of Infusion : Summary of Response Rate, Logistic Regression	Full Analysis Set	✓
Table 14.2.1.1.4	Conversion from AF within 90 minutes from start of infusion : Summary of Response Rate, Logistic Regression	Per Protocol Set	
Table 14.2.2.1.1	Time to Conversion from AF – Descriptive Statistics, Kaplan-Meier Analysis	Full Analysis Set	✓
Table 14.2.2.1.2	Time to Conversion from AF – Descriptive Statistics, Kaplan-Meier Analysis	Per Protocol Set	
Table 14.2.2.2.1	Relapse of AF within 5 min following Pharmacological or DC Conversion – Summary of relapse rate - Logistic Regression	Full Analysis Set	
Table 14.2.2.2.2	Relapse of AF within 5 min following pharmacological or DC conversion – Summary of relapse rate	Per Protocol Set	

Table Number	Name	Analysis Set	Delivered for Interim analysis/DMC
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Table 14.2.2.2.4	Relapse of AF within 5 min following Pharmacological Conversion – Summary of relapse rate - Logistic Regression	Per Protocol Set	
Table 14.2.2.3.1	Proportion of Patients in SR after Start of Infusion at Different Timepoints - Logistic Regression	Full Analysis Set	✓
Table 14.2.2.3.2	Proportion of Patients in SR after Start of Infusion at Different Timepoints - Logistic Regression	Per Protocol Set	
Table 14.2.3.1	Descriptive Statistics of Plasma Concentration over Time by Treatment	PK Set	
Table 14.2.3.2	Summary of Pharmacokinetic Parameters – NCA Approach	PK Set	
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Set	✓
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set	
Table 14.3.1.3	Treatment-Emergent Adverse Events Related to Study Treatment	Safety Set	✓
Table 14.3.1.4	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set	✓
Table 14.3.1.5	Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Safety Set	
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Table 14.3.4.1.1.1	Summary statistics of Laboratory Data: Haematology	Safety Set	
Table 14.3.4.1.1.2	Change from Baseline in Laboratory Data: Haematology	Safety Set	
Table 14.3.4.1.1.3	Laboratory Data: Haematology Relationship to Reference Range – Shift from Baseline	Safety Set	

Table Number	Name	Analysis Set	Delivered for Interim analysis/DMC
Table 14.3.4.1.1.4	Laboratory Data: Haematology Clinical Significance	Safety Set	
Table 14.3.4.1.2.1	Summary statistics of Laboratory Data: Clinical Chemistry	Safety Set	
Table 14.3.4.1.2.2	Change from Baseline in Laboratory Data: Clinical Chemistry	Safety Set	
Table 14.3.4.1.2.3	Laboratory Data: Clinical Chemistry Relationship to Reference Range – Shift from Baseline	Safety Set	
Table 14.3.4.1.2.4	Laboratory Data: Clinical Chemistry Clinical Significance	Safety Set	
Table 14.3.4.2.1	Summary of Vital Signs	Safety Set	
Table 14.3.4.2.2	Change from Baseline in Vital Signs	Safety Set	✓
Table 14.3.4.3.1	Summary of 12-Lead ECG Parameters	Safety Set	
Table 14.3.4.3.2	Change from Baseline in 12-Lead ECG Parameters	Safety Set	✓
Table 14.3.4.3.3	12-Lead ECG Clinical Significance	Safety Set	✓
Table 14.3.4.3.4	12-Lead ECG QTc Intervals: Categorical Analysis	Safety Set	✓
Table 14.3.4.4	Brief Physical Examination - Shift from Baseline	Safety Set	

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Figure 14.2.2.1.3	Kaplan-Meier curve for Time to Conversion from AF – Full analysis set	
Figure 14.2.3.3	Mean (±SD) Plasma Concentration - Linear and Semi-Log Scales - PK Set	✓ For interim analysis this graph will be provided by the PK group
Figure 14.2.3.4	Overlay of Individual and Mean AP30663 Plasma Concentrations by Treatment - Linear and Semi-Log Scales - PK Set	✓ For interim analysis this graph will be provided by the PK group
Figure 14.2.3.5	Scatter plot of Plasma Concentration Immediately After Conversion versus Time to Conversion – PK set	
Figure 14.2.3.6	Mean (±SD) Cmax vs. AP30663 Dose Level - PK Set	
Figure 14.2.3.7	Mean (±SD) AUC0-t vs. AP30663 Dose Level - PK Set	
Figure 14.2.3.8	Mean (±SD) AUC0-0.5 vs. AP30663 Dose Level - PK Set	
Figure 14.2.3.9	Scatter Plot of Cmax vs. Time to Conversion - PK Set	
Figure 14.2.3.10	Scatter Plot of AUC0-t vs. time to conversion- PK Set	
Figure 14.2.3.11	Scatter Plot of AUC0-0.5 vs. Time to Conversion - PK Set	
Figure 14.2.3.12	Bar chart of conversion rate vs. Age – Full analysis set	
Figure 14.2.3.13	Bar chart of conversion rate vs. Gender – Full analysis set	
Figure 14.2.3.14	Bar chart of conversion rate vs. Left Atrial Dimension/Diameter (Anterior Posterior, End Systolic)– Full analysis set	
Figure 14.2.3.15	Bar chart of Conversion Rate vs. Duration of Current AF episode– Full Analysis Set	

Figure Number	Figure Title	Delivered for Interim analysis/DMC
Figure 14.2.3.16	Bar Chart of Conversion Rate vs. Treatment Group – Full Analysis Set	

18. Index of Listings

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Listing 16.2.3.1	Inclusion/Exclusion Criteria not met	Randomised Set	
Listing 16.2.3.2	Patients Excluded from Analysis Set	Randomised Set	
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Listing 16.2.4.2	Baseline Characteristics	Safety Set	
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Listing 16.2.4.4	Prior and Concomitant Medications	Safety Set	
Listing 16.2.5.1	Study Drug Administration	Safety Set	
Listing 16.2.6.1	Efficacy : Conversion	Full Analysis Set	
Listing 16.2.7.1	Adverse Events	Safety Set	
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Listing 16.2.7.3	Adverse Events Leading to Treatment Discontinuation	Safety Set	
Listing 16.2.8.1.1	Haematology	Safety Set	
Listing 16.2.8.1.2	Clinical chemistry	Safety Set	
Listing 16.2.8.2.	Vital Signs	Safety Set	✓ Based on Randomised Set
Listing 16.2.8.3.	12-Lead ECG	Safety Set	✓ Based on Randomised Set
Listing 16.2.8.4	Physical Examination	Safety Set	
Listing 16.2.8.5	Plasma concentrations	PK Set	
Listing 16.2.8.6	Pharmacokinetics Parameters – NCA Approach	PK SET	

19. Appendices

APPENDIX I SAMPLE SAS CODE IN STATISTICAL ANALYSIS

1) Sample Code for Efficacy Analysis

The logistic regression will be used to analyze all efficacy endpoints relating to proportions

The following is an example of the SAS codes used to perform the analysis of this LOGISTIC model.

****

* SAS Codes: *LOGISTIC* model

* Variables in the model:

* resp = proportion of patients who have converted from AF within 90 mn from the start of infusion

* Duration of current AF episode = Dur

*trtp = treatment planned

**********;

```
proc logistic data=eff descending;
class trtp (param=ref ref='Placebo');
model resp (event="Yes")= trtp dur;

contrast 'Pairwise'  trt 1 -1 0 /estimate=exp;
contrast 'Pairwise'  trt 1 0 -1 /estimate=exp;

ods output Contrastestimate=est;
run;
```

A Kaplan-Meier analysis was used for time to conversion. An example of the SAS code to perform this analysis is below.

****

* SAS Code: Kaplan-Meier Analysis

* Variables in the model:

* timeconv = The time to conversion from AF from start of infusion

* Censor = censor variable (0=patients with conversion, 1=censored patients, no pharmacological conversion)

*trtp = treatment planned

**********;

```
proc lifetest data=dataset plot;
```

```
time timeconv*censor(1);
strata trtp/ test=(logrank) diff=control('Placebo');
ods output quartiles/quartile
run;
```

2) Sample Code for graph

```
**************************************************************************
* SAS Code: Graph Concentration response relationship:
 QTcF versus AP30663 plasma concentrations
* PCTRESN = Plasma concentration
* AVAL = QTcF
**************************************************************************;


proc sgplot data=PKPD;
reg x=PCSTRESN y=AVAL /CLM alpha=.05;
refline 0/axis=y;
label PCSTRESN="Plasma concentration (unit)";
run;
```

AP30663_2001_SAP_Text_4.0_20Feb2023

Final Audit Report 2023-02-20

Created:	2023-02-20
By:	PPD
Status:	Signed
Transaction ID:	PPD

"AP30663_2001_SAP_Text_4.0_20Feb2023" History

Document created by PPD
2023-02-20 - 2:01:32 PM GMT- IP address: PPD

Signer PPD entered name at signing as PPD
2023-02-20 - 2:04:32 PM GMT- IP address: PPD

PPD verified identity with Adobe Acrobat Sign authentication
2023-02-20 - 2:04:34 PM GMT

Document e-signed by PPD
Signing reason: I am the author
Signature Date: 2023-02-20 - 2:04:34 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-02-20 - 2:04:36 PM GMT

Signer PPD entered name at signing as PPD
2023-02-20 - 2:15:30 PM GMT- IP address: PPD

PPD verified identity with Adobe Acrobat Sign authentication
2023-02-20 - 2:15:32 PM GMT

Document e-signed by PPD
Signing reason: I am accepting the terms of service
Signature Date: 2023-02-20 - 2:15:32 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-02-20 - 2:15:33 PM GMT

Email viewed by PPD
2023-02-20 - 2:16:08 PM GMT- IP address: PPD

Signer PPD entered name at signing as PPD
2023-02-20 - 2:17:19 PM GMT- IP address: PPD

PPD verified identity with Adobe Acrobat Sign authentication
2023-02-20 - 2:17:21 PM GMT

Document e-signed by PPD
Signing reason: I am the reviewer
Signature Date: 2023-02-20 - 2:17:21 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-02-20 - 2:17:23 PM GMT

Email viewed by PPD
2023-02-20 - 2:46:01 PM GMT- IP address: PPD

PPD verified identity with Adobe Acrobat Sign authentication
2023-02-20 - 2:47:12 PM GMT

Document e-signed by PPD
Signing reason: I am the approver
Signature Date: 2023-02-20 - 2:47:12 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-02-20 - 2:47:14 PM GMT

Email viewed by PPD
2023-02-20 - 2:50:31 PM GMT- IP address: PPD

PPD verified identity with Adobe Acrobat Sign authentication
2023-02-20 - 2:51:28 PM GMT

Document e-signed by PPD
Signing reason: I am the approver
Signature Date: 2023-02-20 - 2:51:28 PM GMT - Time Source: server- IP address: PPD

Agreement completed.
2023-02-20 - 2:51:28 PM GMT