STATISTICAL ANALYSIS PLAN

For:

AstraZeneca AB

PROTOCOL No. D7460C00003

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED SEQUENCE STUDY TO ASSESS THE EFFECT ON RESPIRATORY DRIVE OF MULTIPLE DOSES OF AZD4041 WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF MORPHINE IN HEALTHY RECREATIONAL OPIOID USERS

Altasciences Project No. AZN-P1-265

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STATISTICAL ANALYSIS PLAN AND SHELLS APPROVAL

We have carefully read this statistical analysis plan and corresponding shells and agree it contains the necessary information required to handle the statistical analysis of study data.

PPD

PPD _____ Date

Altasciences PPD

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On behalf of the Sponsor:

PPD

PPD _____ PPD Date

PPD & Sponsor Representative

VERSION CONTROL

Version	Date	Author	Description of Changes
1.0	*2023/02/23*	PPD	Not applicable
2.0	2023/09/07	PPD	Changes to presentation of TFL shells
3.0	2023/09/19	PPD	Updated the references

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ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating
CV%	Coefficient of Variation
dECG	Digital Electrocardiogram
DSMB	Data Safety Monitoring Board
DMP	Data Management Plan
DTS	Deviation Tracking System
ECG	Electrocardiogram
EClysis©	User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Center
EOS	End of Study
ET	Early Termination
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
LLOQ	Lower Limit of Quantification
ln	Natural Logarithm
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
NCA	Non-Compartmental Analysis
pECG	Paper Print-out Electrocardiogram
PK	Pharmacokinetic(s)
PR (PQ)	The interval measured from the onset of the P complex to the onset of the Q complex
PT	Preferred Term
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula

RR	The time elapsed between 2 consecutive R waves as measured by electrocardiogram
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from the Clinical Study Protocol D7460C00003. The analyses described in the SAP are based upon the Clinical Study Protocol 1.0, dated 2022/08/09.

2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 2-1.

Table 2-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
To assess the effect on respiratory drive of morphine administered after multiple doses of AZD4041 compared to morphine administered alone in healthy recreational opioid users	• $EtCO_2$ (mmHg): Incidence of increased $EtCO_2$ of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) • SpO_2 (%): Incidence of reduction in SpO_2 to <92% (sustained for at least 30 seconds)
Secondary	
To assess the safety and tolerability of multiple doses of AZD4041 when co-administered with a single dose of morphine in healthy recreational opioid users	• SpO_2 (%) ▪ Mean time to reduction in SpO_2 to <92% (sustained for at least 30 seconds) ▪ Mean duration of reduction in SpO_2 to <92% (sustained for at least 30 seconds) ▪ Maximum postdose reduction of SpO_2 adjusted for baseline ▪ Mean postdose SpO_2 • $EtCO_2$ (mmHg) ▪ Mean time to each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Mean duration of each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Maximum postdose increase in $EtCO_2$ adjusted for baseline ▪ Mean postdose $EtCO_2$

	• Respiratory rate (breaths/min) ▪ Incidence of reduced respiratory rate to <6 breaths/min (sustained for at least 30 seconds) ▪ Mean time to each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Mean duration of each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Maximum postdose decrease in respiratory rate adjusted for baseline ▪ Mean postdose respiratory rate • Incidence, frequency, severity, and relationship of AEs • Vital signs (blood pressure, heart rate, and oral temperature) • ECGs (12-lead safety ECGs, 12-lead digital ECGs, and ECG telemetry) • Clinical laboratory test results (clinical chemistry, hematology, coagulation, urinalysis) • Neurological examination findings • Columbia Suicide Severity Rating Scale (C-SSRS) findings • Physical examination findings • Type of medical intervention used, summarized for each event of significantly increased EtCO2, reduced SpO2, or reduced respiratory rate
To assess the pharmacokinetics (PK) of AZD4041 and morphine in healthy recreational opioid users	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites
To assess the impact of multiple dose administrations of AZD4041 on the PK of morphine and its metabolites	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites
To assess the impact of morphine on steady-state PK of AZD4041	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites
To assess the renal clearance of AZD4041	Urine concentrations as well as PK parameters for AZD4041

Abbreviations: AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetics

3 STUDY DESIGN

3.1 General Description

The target population is adults who use opioids recreationally. The design of the study is a 2-arm fixed-sequence, double-blind study performed at a single site. The IP being investigated is AZD4041 alone and in combination with morphine.

3.2 Treatments

The active and placebo treatment groups are presented as two sequences: Sequence 1 and Sequence 2. In Sequence 1, subjects are administered CCI of morphine on Day 1, then CCI of AZD4041 on Days 2 through 14, then both CCI of morphine and CCI of AZD4041 on Day 15. Sequence 2 is similar to Sequence 1, but with AZD4041 replaced with a placebo. Sequence 2 subjects receive CCI of morphine on Day 1, then placebo on Days 2 through 14, then both CCI of morphine and placebo on Day 15.

3.3 Study Procedures

For complete details on the study assessments to be performed for each study period, refer to APPENDIX A.

3.4 Randomization and Unblinding Procedures

Subjects will be randomized into treatments as Sequence 1 or Sequence 2, as described in section 3.2. Sequence 1 will include 28 subjects total and Sequence 2 will include 16 subjects total. The total 44 subjects will be assigned into 6 Blocks, with Block 1 including 4 subjects (Sequence 1 to Sequence 2, 1:1), Blocks 2 through 5 including 8 subjects each (Sequence 1 to Sequence 2, 5:3), and Block 6 includes 8 subjects (Sequence 1 to Sequence 2, 3:1). Replacements may be made if subjects drop out of the study before completion.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an Investigator for further treatment to the subject or to complete a SAE report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

Unblinding of the data will occur after database lock except in cases of emergency.

3.5 Determination of Sample Size

No formal sample size calculation was performed for this Phase 1 study.

4 ANALYSIS POPULATIONS

The following populations are defined for this study:

- **Randomized Population**: The randomized population will include all subjects who are randomized to the Treatment phase.
- **Safety population**: The safety population will include all subjects who received at least 1 dose of morphine, placebo, or AZD4041.
- **Completer Population**: The completer population will include all subjects in the safety population who completed the entire Treatment phase and the follow-up period (up to at least Day 22). This population will be used for inferential analysis of maximum postdose

increase in $EtCO_2$ ($E_{max\ (postdose - predose)}$), maximum postdose reduction in SpO_2 ($E_{max\ (predose - postdose)}$), and maximum postdose decrease in respiratory rate ($E_{max\ (predose - postdose)}$).

- **Pharmacokinetic Population:** All subjects in the safety population who received at least 1 dose of morphine or AZD4041 and have at least 1 PK concentration after dosing will be included in the PK population.

5 DATA HANDLING AND PRESENTATION

5.1 Safety Analysis Presentation

Adverse events and medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology as defined in the study Data Management Plan (DMP).

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHODrug) as defined in the study DMP.

In general, all safety summary tables will be presented for the safety population. Summaries for AEs will be presented by treatment and treatment sequence. Summaries for other safety endpoints will be presented by treatment if the endpoints are measured at the end of each period or by treatment sequence if the endpoints are not measured at the end of each period (End of Study only).

In general, the data listings will include all subjects in the safety population up to the point of study completion or discontinuation; exceptions will be listings pertaining to a subset of subjects only (eg, subjects with protocol deviations) or a subset of records/events (eg, abnormal laboratory values). Limited data for those not included in the safety population, eg, who failed screening, may be presented, as appropriate.

Categorical variables will be summarized using sample size (N), number of available data (n), and the percentage of available data (%) for each class. Continuous variables will be summarized using descriptive statistics, including N, n, arithmetic mean (mean), standard deviation (SD), minimum (min), median, and maximum (max).

The following general considerations may be applied:

- Study Day will be derived from the reference date (eg, the day of the first dose of study drug) and date of event as:

  Study Day = (date of event – reference date) +1, if event is on or after the reference date;

  Study Day = date of event – reference date, if event is before the reference date.

- Duration will be calculated using the general formula: (end date - start date) +1.

- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (eg, a character string is reported for a parameter of the numerical type), a coded value may be appropriately determined and used in the statistical analyses. In general, a value below the lower limit of normal range such as '<10' or '≤5' will be treated as half of the lower limit, '5' or '2.5', respectively, and a value above the upper limit of normal range such as '>100' will be replaced with a number deemed scientifically reasonable, eg, 101. However, the actual values as reported in the database will be presented in data listings.

- Unscheduled assessments will not be included in descriptive summary, except for baseline consideration. When assessments are repeated for a given timepoint or performed at unscheduled times, only the result which is the closest to the assessment time will be included in summary tables.

In general, summary statistics for raw variables (ie, variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data
- Means, medians, and quartiles (if presented) will be displayed to 1 additional decimal place
- Standard deviations will be displayed to 2 additional decimal places
- Percentages will be displayed to 1 decimal place; Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'
- P-values will be displayed to 3 decimal places; p-values that are less than .001 will be displayed as '<.001'

Derived variables (ie variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be displayed with the same precision as the raw data, as appropriate, then will follow similar rules in presentation of summary statistics.

All outputs will be generated using SAS software version 9.4 or higher.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and/or prior to breaking the blind. Any analyses performed subsequent to database lock and/or breaking the blind will be considered post hoc and exploratory, and will be identified in the Clinical Study Report (CSR).

5.2 Methods for Handling Missing Data

No imputation of missing data will be performed on data that is not PK.

6 STUDY SUBJECTS

Unless otherwise specified, all available data will be listed and summary table for disposition will be presented for the safety population.

6.1 Disposition

Subject disposition will be summarized by treatment sequence and overall, including:

- Number of subjects screened
- Number of subjects randomized
- Number of subjects who received any treatment compound (morphine, AZD4041 or placebo)
- Number of subjects who received IP (i.e. AZD4041 or placebo)
- Number (%) of subjects who completed the study

- Number (%) of subjects discontinued from the study overall and by primary reason for discontinuation
- Number (%) of subjects included in each of the analysis populations

The percentages will be calculated using the number of subjects who received at least one dose of a treatment.

Listings of subject's disposition and subjects included in each of the analysis populations will be provided.

6.2 Protocol Deviations

Deviations will be collected in the clinic deviation tracking system (DTS) and presented in a general protocol deviation listing.

7 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, all available data will be listed and summary tables for demographics and other baseline characteristics will be presented for the safety population.

Medical history will be recorded during screening.

Demographic and baseline characteristics including age, height, weight (at screening), and body mass index (BMI) will be listed and summarized by treatment sequence and overall. Descriptive statistics will be presented for age, height, weight, and BMI, while frequency counts and percentages will be presented for sex, ethnicity, and race.

The following will be presented in listings:

- Medical history
- Prior and concomitant medications
- Childbearing potential and contraceptive method
- Alcohol habits
- Smoking habits
- Recreational drug use history (Amphetamines, barbiturates, cannabinoids, cocaine, opiates, benzodiazepines, ethanol, and phencyclidine)

8 PHARMACOKINETIC ANALYSIS

The pharmacokinetic (PK) parameters from the concentration data for AZD4041, morphine, morphine-6-glucuronide and morphine-3-glucuronide will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.3 or higher (Certara) by the Clinical PK Scientist from AstraZeneca.

8.1 Handling of Measurements Below the Lower Limit of Quantification in the PK analysis

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration is set to a value of zero. After this time point, NQ plasma concentrations are set to missing for all

concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile is deemed to have terminated and therefore any further quantifiable concentrations are set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile is excluded from the PK analysis.

Cmax, tmax, and tlast are taken directly from the concentration-time profiles.

8.2 Handling of Measurements Below the Lower Limit of Quantification in the TFLs

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (e.g. Cmax, Cmax,ss) to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

8.3 Actual Time

PK analysis is, where data allow, carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS). Nominal sampling times may be used for any agreed interim PK parameter calculations.

8.4 Non-Compartmental Analysis

The PK parameters for AZD4041 are presented in Table 8-1.

Table 8-1 Pharmacokinetic Parameters of AZD4041

Parameter	Definition	Calculation
The following plasma PK parameters will be calculated for Days 2 to 15		
C_{trough}	Predose concentration observed immediately prior to the next successive dose	
The following plasma PK parameters will be calculated for Days 8 and 15		
$C_{max,ss}$	Maximum observed plasma concentration at steady-state	
$t_{max,ss}$	Time to reach peak or maximum observed concentration following drug administration at steady-state	
AUCτ	Area under the concentration time curve over the dosing interval at steady state, calculated from 0 to 24 hours (dosing interval)	Using the linear up/log down trapezoidal rule
$t_{1/2}\lambda z$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve (Day 15 only)	Using the linear up/log down trapezoidal rule ln(2)/ λz
C_{av}	Average concentration during a dosing interval at steady-state	AUCτ/τ
CL_{ss}/F	Apparent total body clearance at steady state	Dose/AUCτ
Vz_{ss}/F	Apparent volume of distribution at steady state, based on the terminal phase	(CLss/F)/λz
The following urine PK parameters will be calculated for AZD4041 (Day 15 only)		
Aeτ	Cumulative amount of unchanged drug excreted into urine over a dosing interval τ	Sum of amount excreted in the urine over the dosing interval τ
Aet1-t2	Amount of unchanged drug excreted into urine over a specified collection interval	Urine Volume for the specified collection interval (0-6, 6-12, 12-24, etc…)
Feτ/F	Apparent percentage of dose excreted unchanged in urine over a dosing interval	(Aeτ/Dose)*100 or (CL_R/CL)*100

Parameter	Definition	Calculation
Fe0-x/F	Apparent percentage of dose excreted unchanged in urine over a specified period of time.	(Ae0-x/Dose)*100 with x= 6, 12, and 24.
CL_R	Renal clearance	Aeτ/AUCτ
t½	Elimination half-life (on Day 15 only)	ln(2)/λz

The PK parameters for morphine, morphine-6-glucuronide and morphine-3-glucuronide on Days 1 and 15 are presented in Table 8-12.

Table 8-2 Pharmacokinetic Parameters of Morphine, morphine-6-glucuronide and morphine-3-glucuronide in Plasma (Days 1 and 15)

Parameter	Definition	Calculation
Cmax	Maximum observed concentration (Parent and Metabolites)	
tmax	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used (Parent and Metabolites)	
AUC_{0-t}	Area under the plasma concentration-time curve from time of last dosing to the time of last quantifiable concentration (tlast) (Parent and Metabolites)	Using the linear up/log down trapezoidal rule
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated to infinity (Parent and Metabolites)	$AUC_{0-t} + C_{last}/\lambda z$ where Clast is the last quantifiable concentration at tlast
$t_{1/2}\lambda z$	Terminal elimination half-life (Parent and Metabolites)	Using the linear up/log down trapezoidal rule ln(2)/ λz
tlast	Time of last measurable observed concentration (Parent and Metabolites)	
CL	Total body clearance(Parent drug only)	Dose/ $AUC_{0-\infty}$
Vz	Volume of distribution based on the terminal phase (Parent drug only)	CL/λz

Additional PK parameters may be calculated if deemed appropriate

The diagnostic PK parameters for AZD4041, morphine, morphine-6-glucuronide and morphine-3-glucuronide on Days 1, 8, and 15, as appropriate, are presented in Table 8-13. These parameters will not be summarized but will be listed.

Table 8-3 Diagnostic PK Parameters for all Analytes in Plasma

Parameter	Definition	Calculation
λz	Terminal elimination rate constant	Estimated from linear regression of the terminal part of the log concentration versus time curve
λz lower	Lower (earlier) t used for λz determination	
λz upper	Upper (later) t used for λz determination	
λzN	Number of data points used for λz determination	
λz span ratio	Time period over which λz was determined as ratio of t½λz	(λz Upper –λz lower)/(t1/2λz)
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)	
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf	

8.4.1 Urine PK Parameters

Urine PK analysis is performed where there are quantifiable urine concentrations and available volume data from post-dose collection periods, using nominal time intervals. Urine concentrations below lower limit of quantification (LLOQ) are treated as numerical zero.

In cases of incomplete urine collection in any of the specified collection intervals (e.g. spilled sample), the calculation and reporting of urine PK parameters are at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS).

8.4.2 Plasma PK Parameters

For each analyte, plasma concentrations for each scheduled time-point are summarised by PK Day and Treatment sequence using appropriate descriptive statistics. Similar data (e.g. single dose or multiple dose for the same dosing regimen) from different Study Parts or PK Days/Visits may also be summarised together.

The following descriptive statistics are presented for plasma concentrations:

- n
- n below LLOQ
- geometric mean (gmean)
- geometric coefficient of variation (%) (gCV)
- arithmetic mean (mean)
- arithmetic standard deviation (Std Dev)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as $\exp(\mu)$, where μ is the mean of the data on the natural log scale.

The gCV is calculated as $100 \times \text{sqrt}[\exp(s^2)-1]$, where s is the Std Dev of the data on the natural log scale.

Where required for plots: The gSD is calculated as $\exp(\sigma)$, where σ is the standard deviation of the data on the natural log scale. The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as $\exp[\mu \pm s]$.

Protocol scheduled times are used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

8.4.3 Urine Concentration Data

Urine concentration and volume/weight data are listed only and not summarised. Any individual data excluded from the PK analysis are flagged with an appropriate footnote in the listing by the PK Scientist.

8.5 Pharmacokinetic Statistical Methodology

8.5.1 PK Parameter Listings

All reportable PK parameters, including individual diagnostic and lambda z related parameters, are listed for each subject by PK Day and Treatment sequence, for each analyte separately.

8.5.2 PK Paramater Descriptive Statistics

All PK parameters are summarised for each analyte by PK Day and Treatment sequence using appropriate descriptive statistics. Similar parameter data (e.g. single dose or multiple dose for the same dosing regimen) from different PK Days may also be summarised together.

The descriptive statistics for PK parameters are presented as follows:

- Ctrough, Cmax, Cmax,ss, Cav, AUCτ, AUC0-t, AUC0-∞, t½λz, CL, CLss/F, Vz, Vzss/F, CLR, Ae and fe: present n, geometric mean, geometric standard deviation (Geo Std Dev), arithmetic mean of non log-transformed data (mean), arithmetic standard deviation (Std Dev), gCV(%), median, min and max.
- tmax, and tlast: present n, median, min and max.
- Diagnostic parameters (e.g. λz , λz lower, λz upper, λzN, λz span ratio, n obs, Rsq adj and AUCextr): present n, arithmetic mean, Std Dev, gmean, gCV%, median, min and max.

Three values are required as a minimum for PK parameters to be summarised. Two values are presented as a min and max with the other summary statistics as NC.

If one or more values for a given parameter is zero, then no geometric statistics are calculated for that parameter and the results for geometric statistics are set to NA (Not Applicable).

The point estimate and associated two-sided 90% confidence intervals for the ratio of PK parameters (for AZD4041: AUCτ, Cmax,ss, Ctrough,ss; for morphine and metabolites: Cmax, AUC0-t, AUC0-∞) for each comparison of interest will be calculated:

For treatment sequence 1:

- AZD4041 in the absence of Morphine - Day 8 and AZD4041 in the presence of Morphine – Day 15
- Morphine in the absence of AZD4041 – Day 1 and Morphine in the presence of AZD4041 – Day 15
- Morphine metabolites in the absence of AZD4041 – Day 1 and Morphine metabolites in the presence of AZD4041 – Day 15

For treatment sequence 2:

- Morphine on Day 1 and 15.
- Morphine metabolites on Day 1 and 15.

8.5.3 Graphical Presentation of Pharmacokinetic Data Statistics

All mean (arithmetic mean and/or gmean) plots or combined plots showing all subjects by treatment and treatment sequence are based on the PK analysis set. Individua1 plots by subject are based on the Safety analysis set.

For consistency, the plasma concentration values used in the mean (arithmetic mean and/or gmean) data graphs are those given in the descriptive statistics summary table for each time point.

For gmean concentration-time plots, NQ values are handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted is zero for linear plots and missing for

semi-logarithmic plots. Any gmean±gSD error bar values that are negative are truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration are set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations are regarded as missing.

Data permitting, the following figures are presented as appropriate:

Figures for the mean (arithmetic mean and/or gmean) plasma concentration-time data (with ±Std Dev and/or ±gSD error bars) presented on both linear and semi-logarithmic scales using scheduled post-dose time as follows:

- AZD4041 in both the presence and absence of Morphine – Day 8 and 15
- Morphine in the absence and presence of AZD4041 – Day 1 and 15
- Morphine metabolites in the absence and presence of AZD4041 – Day 1 and 15

Individual subject plasma concentration-time data graphically presented on both linear and semi-logarithmic scales using actual time post-dose as:

- AZD4041 in the absence of Morphine - Day 8 and AZD4041 in the presence of Morphine – Day 15
- Morphine and its metabolites in the absence of AZD4041 – Day 1 and Morphine and its metabolites in the presence of AZD4041 – Day 15

Combined individual plasma concentration versus actual time after dose will be plotted on both the linear and semi-logarithmic scale, with the individual profiles for the same analyte in the different periods overlaid on the same plot as described below:

For treatment sequence 1:

- AZD4041 in the absence of Morphine - Day 8 and AZD4041 in the presence of Morphine – Day 15
- Morphine in the absence of AZD4041 – Day 1 and Morphine in the presence of AZD4041 – Day 15
- Morphine metabolites in the absence of AZD4041 – Day 1 and Morphine metabolites in the presence of AZD4041 – Day 15

For treatment sequence 2:

Morphine on Day 1 and 15.
Morphine metabolites on Day 1 and 15.

These plots will be based on the PK analysis set. Focus plots may be provided if there will be no clear distinction among profiles. Geometric mean (± gSD) plasma trough concentration (Ctrough) of AZD4041 versus study day will be plotted on linear scale. Additional plots may be produced if deemed appropriate to summarise and present PK data.

Figures presenting the point estimate and associated two-sided 90% confidence intervals for the ratio of PK parameters (for AZD4041: AUCτ, Cmax,ss, Ctrough,ss; for morphine and metabolites: Cmax, AUC0-t, AUC0-∞) for each comparison as mentioned above.

Figures for the arithmetic mean urine concentration-time data (with ±Std Dev error bars) presented on both linear and semi-logarithmic scales using scheduled post-dose time as follows:

- Arithmetic mean of accumulated fraction (%) of AZD4041

8.5.4 Plasma Concentration Data

PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

8.5.5 Pharmacokinetic Parameter Data

PK parameter listings are presented according to the following rules:

- Cmax, Ctrough: present to the same number of significant figures as received from the bioanalytical laboratory
- Tmax and tlast: present as received in the data, usually to 2 decimal places
- AUCinf, AUC(0-t), AUCτ, AUCextr, λz, t½λz, CL, CLss/F, Vzss/F, Vz, , all ratios of PK, Rsq adj, Ae, fe and CLR: present to 3 significant figures
- n obs: present as an integer (no decimals)

The descriptive statistics for PK parameter data are presented to 4 significant figures with the exception of the min and max which are presented to 3 significant figures apart from the following:

- λz: present to 5 significant figures with min and max to 3 significant figures
- tmax and tlast: present as received in the data, usually to 2 decimal places
- number of values (n): present as an integer

9 SAFETY ANALYSIS

9.1 Respiratory Depression Analysis

Summary statistics and inferential analysis for respiratory depression endpoints will be presented for all subjects who completed all $etCO_2$ assessments in addition to the Safety Population, when possible. Incidence of increased $EtCO_2$ of at least >50 mmHg will be summarized by treatment and time point using frequency tables. Mean time to each increased $EtCO_2$ episode of at least >50 mmHg, mean duration of each increased $EtCO_2$ episode of at least >50 mmHg, and mean postdose $EtCO_2$ will be summarized by treatment and time point using descriptive statistics. Maximum postdose increase in $EtCO_2$ $E_{max\ (postdose-predose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. $EtCO_2$ averages (predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis. For each event of significantly increased $ETCO_2$, type of medical intervention used will be listed.

Incidence of reduction in SpO_2 to <92% will be summarized by treatment and time point using frequency tables. Mean time to reduction in SpO_2 to <92%, mean duration of reduction in SpO_2 to <92%, and mean postdose SpO_2 will be summarized by treatment and time point using descriptive statistics. Maximum postdose reduction of SpO_2 $E_{max\ (predose-postdose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. SpO_2 averages (predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis. For each event of significantly reduced SpO_2, type of medical intervention used will be listed.

Incidence of reduced respiratory rate to <6 breaths/min will be summarized by treatment and time point using frequency tables. Mean time to each reduced respiratory rate episode of < 6 breaths/min, mean duration of each reduced respiratory rate episode of <6 breaths/min, and mean postdose respiratory rate will be summarized by treatment and time point using descriptive statistics. Maximum postdose decrease in respiratory rate $E_{max\ (predose-postdose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. Respiratory rate averages (predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis.

For $EtCO_2$, SpO_2, and respiratory rate the following figures will be generated:

1) Sequence 1: Mean (± SD) treatment by time point for Day 1 Morphine alone matched to Day 15 Morphine + AZD4041
2) Sequence 2: Mean (± SD) treatment by time point for Day 1 Morphine alone matched to Day 15 Morphine + Placebo
3) Mean (± SD) treatment by time point for Days 2-15 predose AZD4041 vs. Days 2-15 predose Placebo
4) Boxplot for E_{max} Day 1 Morphine alone matched to Day 15 Morphine + AZD4041
5) Boxplot for E_{max} Day 1 Morphine alone matched to Day 15 Morphine + Placebo
6) Boxplot for E_{max} Day 15 Morphine + AZD4041 vs. Day 15 Morphine + Placebo

For all inferential analysis on $EtCO_2$, SpO_2, and respiratory rate, mixed-effects models will be used for E_{max} and averaged measures. The models will include sequence, time (as a ordered factor variable), and the sequence-by-time interaction as fixed effects and baseline as a covariate, with 95% confidence intervals reported along with p-values. Homogeneity of treatment variances will be explored to determine if subject may be considered a random effect. The covariance structure for the mixed models will be heterogeneous compound symmetry. If the heterogeneous compound symmetry model does not converge, then a compound symmetry structure will be used and a footnote will be added to identify the results as using a different covariance structure than usual. The kenwood-roger adjustment for the degrees of freedom with be used when calculating p-values due to the small sample size.

The maximum postdose decrease in respiratory rate ($E_{max\ (predose - postdose)}$) is the primary criterion. In addition to the primary criterion, maximum postdose reduction in SpO_2 ($E_{max\ (predose - postdose)}$) and The maximum postdose increase in $EtCO_2$ ($E_{max\ (postdose - predose)}$) will have the following contrasts calculated in the mixed-effects models:

1) Morphine + AZD4041 (Day 15) vs Morphine alone (Day 1) [Sequence 1]
2) Morphine + Placebo (Day 15) vs Morphine alone (Day 1) [Sequence 2]
3) Morphine + AZD4041 (Day 15) vs Morphine + Placebo (Day 15) [Sequence 1 vs Sequence 2]

For $EtCO_2$, SpO_2, and respiratory rate averages (predose average from Days 2 to 15), and postdose average on Day 15, the following contrasts will be explored in the mixed-effects models:

1) (postdose): Morphine + AZD4041 (postdose average Day 15) vs (predose): AZD40401 (predose average Days 2-15)
2) (predose): Morphine + AZD4041 (predose average Days 2-15) vs (predose): Morphine + Placebo (predose average Days 2-15)

9.2 12-lead digital ECG Statistical Methodology

From the dECG data, the following parameters will be derived:

1) QTcF will be calculated as $QTcF = QT*RR^{-1/3}$, where the QT interval is in milliseconds and the RR interval is in seconds.
2) Heart rate will be calculated, based on the RR interval as HR = 60/RR interval, where the RR interval is in seconds.
3) Calculation of derived parameters will be performed after smoothing of QT and RR data.

The dECG data will be smoothed on an individual basis before performing the derivations above and prior to calculation of any changes from baseline or descriptive statistics. For each subject it will be done as follows: the mean value of all the measurements will be taken provided that at least 4 measurements are present and the time between the first and last is greater than 2.75 minutes or else, the smoothed value at the corresponding target time point will be set to missing.

Digital ECG results will be listed by treatment (Morphine and AZD4041 vs Morphine and placebo) for each subject and time point and will include all individual and smoothed values of PR, RR, QRS, QT interval, and the derived values of QTcF and HR. All smoothed and derived

parameters will have changes from baseline derived and presented within subject and treatment group.

Descriptive statistics will be presented by treatment arm andtime point for smoothed values and changes from baseline of smoothed values of PR, RR, QRS, QT; derived values and changes from baseline for QTcF and HR will also be included. The baseline for the dECG measurements will be the (smoothed) predose assessment on Day 1.

Outliers with respect to PR, QRS, HR, RR and QTcF will also be tabulated for the following categories, described below.

For QTcF these values will be reported per time point:

- Absolute value > 450 ms and ≤ 480 ms
- Absolute value > 480 ms and ≤ 500 ms
- Absolute value > 500 ms
- Increase from baseline > 30 ms and ≤ 60 ms
- Increase from baseline > 60 ms

The maximum postdose values for PR interval will be summarized by treatment according to the following categories:

- ≤220 ms
- >220 and ≤ 240 ms (all instances flagged in the listing*)
- >240 ms (all instances flagged in the listing **)

The maximum postdose values for QRS duration will be summarized by treatment according to the following categories:

- ≤115 ms
- >115 ≤ 119 ms (all instances flagged in the listing*)
- >119 ms (all instances flagged in the listing**)

The maximum/min postdose values for HR will be summarized by treatment according to the following categories:

- <40 bpm (all instances flagged in the listing**)
- 40 - <50 bpm (all instances flagged in the listing*)
- ≥50 bpm and ≤100 bpm
- >100 - ≤120 bpm (all instances flagged in the listing*)
- >120 bpm (all instances flagged in the listing**)

The maximum/min postdose values for RR will be summarized by treatment according to the following categories:

- <500 ms (all instances flagged in the listing**)
- 500 ms - < 600 ms (all instances flagged in the listing*)
- ≥ 600 ms ≤ 1200 ms
- > 1200 ms ≤ 1500 ms (all instances flagged in the listing*)
- >1500 ms (all instances flagged in the listing**)

All calculations of dECG parameters and reporting described in this section will be performed by AltaSciences who also will produce tables, box plots and graphs presenting the results. An Exposure Response (ER) analysis may be conducted that may include modelling of digital ECG variable data versus PK data of Morphine and/or morphine metabolites with and without AZD4041 co-administration and/or versus PK data of AZD4041 with and without morphine co-administration. This potential analysis will be described in a separate technical document and reported outside the final CSR for the study.

9.3 Clinical Laboratory Evaluations

Laboratory data will be presented using units as reported by the clinical laboratory.

The laboratory categories and parameters as defined in the protocol will include the tests listed in Table 9-1 List of Laboratory Tests.

The following listings will be presented:

- All laboratory values by category
- Out-of-range laboratory values
- Clinically significant laboratory values

For protocol-specified laboratory parameters, summary tables on observed and change from baseline values will be presented by treatment and visit for each category. Summary statistics will be presented for each laboratory test.

Table 9-1 List of Laboratory Tests

Laboratory Test Panel	Description
General biochemistry:	Alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bilirubin total, chloride, creatinine (including eGFR using the MDRD equation), glucose, potassium, sodium, BUN, magnesium, calcium
Endocrinology	FSH
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume, and platelet count
Coagulation tests:	Activated partial thromboplastin time, prothrombin time, INR
Serology:	HIV Ag/Ab Combo, Hepatitis B surface antigen and Hepatitis C virus,
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein

Abbreviations: BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; INR = international normalization ratio; MDRD = Modification of Diet in Renal Disease

9.4 Vital Signs

Vital signs will include systolic and diastolic blood pressures, pulse rate, and body temperature.

The following listings will be presented:

- All vital signs
- Clinically significant vital signs

Summary tables on observed and change from baseline values will be presented by treatment, visit, and/or timepoint.

9.5 12-lead Safety Electrocardiogram

Resting 12-lead safety Electrocardiogram results: Standard safety 12-lead ECGs will be performed as described in the CSP.

The 12-lead safety ECG results will be listed for each subject. All 12-lead safety ECGs will be evaluated for HR, and for PR, time elapsed between two successive R-waves of the QRS signal on the ECG (RR), QRS, QT, and QTcF intervals, and an investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not clinically significant, and the reason for the abnormality will be recorded. The date/time, physician interpretation (normal, abnormal clinically significant, abnormal not clinically significant), and all evaluated parameters and intervals will be recorded in the electronic CRF (eCRF), and the paper printouts will be stored at the site. An investigator (or designee) will evaluate the printout of the 12-lead ECG in real time, and with particular attention to the effects of clinical importance on the PR, QRS, and QTcF intervals. Timepoints for 12-lead safety ECG measurements are specified in the CSP. The results per time point and for extra unscheduled ECGs requested by PI (Normal/Abnormal and CS or NCS, if CS it will be specified) from the 12-lead safety ECG will be listed for each subject.

The following listings will be presented:

- All ECGs
- Clinically significant ECGs

Summary tables on observed and change from baseline values will be presented by treatment, visit, and/or timepoint.

9.6 Telemetry Results

Telemetry results will be reviewed by the investigator, listed by date and time, described and reported, if considered clinically significant.

9.7 Physical Examination Findings

The following listings will be presented:

- All physical examination
- Clinically significant physical examination

9.8 All Other Safety Analysis

Summary statistics for all other safety analysis will be done using the Safety Population.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and characterized as pre-treatment and treatment-emergent according to the intake of the study drugs. The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term and by treatment. The occurrence and incidence of TEAEs will also be

summarized by severity and by relationship to the study drugs. Adverse events leading to discontinuation and SAEs will be listed.

Values within and outside the reference range will also be summarized using frequency tablets. Physical examination abnormalities and C-SSRS findings will be listed.

Unless otherwise specified, all available data will be listed and summary tables for safety assessments will be presented for the safety population.

10 EFFICACY ANALYSIS

There is no efficacy assessment defined in the protocol.

11 INTERIM ANALYSES

Interim review on blinded safety and/or PK data may be performed near the end of the study. These reviews will also ensure subjects' assignments are not unblinded.

12 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document as common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics.

APPENDIX A STUDY SCHEDULE(S)

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Informed Consent[3]	X															
Eligibility Criteria Review (Inclusion/Exclusion)	X	X	X	X												
Demographics	X															
Height, Weight, and Body Mass Index	X														X[4]	
Medical History	X	X[5]														

[1] Individual end of study procedures may either be performed at the time of last confinement to the clinical site or at the last study visit.

[2] All predose activities will be performed within a 60-minute window prior to treatment administration

[3] The latest version of the consent form must be signed prior to a subject's inclusion (prior to any study-related procedures).

[4] Weight only

[5] Any changes since the last visit will be documented.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Medical & Recreational Drug Uses History	X	X[6]														
Study Restrictions Review		X													X	X
Admission to CRU		X														
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge from CRU[7]															X	
Randomization			X													
Vital Signs[8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead safety ECG[9]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead continuous digital ECG and ECG extractions[10]			X[11]	X	X	X	X	X	X	X	X	X	X	X	X	

6 Any changes since the last visit will be documented.

7 Discharge from the clinical site will occur approximately 72 hours after the last study drug administration.

8 Vital sign measurements are detailed in Section 6.1.5 of the protocol.

9 12-lead safety ECG measurements are detailed in Section 6.1.6.1 of the protocol.

10 12-lead continuous digital ECG and ECG extractions are detailed in Section 6.1.6.2 of the protocol.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
ECG telemetry[12]			X	X	X	X	X	X	X	X		X	X	X	X	
Continuous SpO_2, Respiratory Rate and $EtCO_2$ Monitoring[13]				X					X			X				
Spot SpO_2[14]	X	X		X	X	X	X	X	X	X	X	X	X			X
Spot Respiratory rate[15]	X	X		X	X	X	X	X	X	X	X	X	X			X
Spot $EtCO_2$[16]				X	X	X	X	X	X	X	X	X	X			

11 After the 24-hour Holter recording (starting on Day -1 and ending approximately 1 hour before the end of morphine infusion), the Holter card will be replaced with a new one.

12 ECG telemetry is detailed in Section 6.1.7 of the protocol.

13 Continuous SpO_2, respiratory rate and $EtCO_2$ monitoring from up to 1 hour predose (prior to start of morphine infusion on Day 1) up to at least 6 hours postdose (after end of morphine infusion on Day 1), or longer if judged medically necessary.

14 SpO_2 measurements are detailed in Section 6.1.8 of the protocol.

15 Respiratory rate measurements are detailed in Section 6.1.10 of the protocol.

16 $EtCO_2$ measurements are detailed in Section 6.1.9 of the protocol.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Physical Examination[17]	X	X						X			X				X	X
Neurological Examination[18]	X	X						X			X				X	X
General Biochemistry, Hematology, Coagulation, Urinalysis[19]	X	X						X			X				X	X
FSH (Females only)	X															
Serology[20]	X															
Alcohol and Drugs of Abuse Screen	X	X														
Serum Pregnancy Test (Females only)	X	X														X

[17] Symptom-directed physical examination will be performed on Day 7 and Day 14 and a complete physical examination will be performed at all other timepoints. Details of the physical examination are presented in Section 6.1.3 of the protocol.

[18] Neurological examination is detailed in Section 6.1.4 of the protocol.

19 General biochemistry, hematology, coagulation tests, and urinalysis will be performed as detailed in Section 6.1.11 and APPENDIX 6 of the protocol.

[20] Serology will be performed as detailed in Section 6.1.11 and APPENDIX 6 of the protocol.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
C-SSRS[21]	X	X			X						X				X	X
Naloxone Challenge/COWS		X														
Morphine Administration[22]				X								X				
AZD4041 or Placebo Administration[23]					X	X	X	X	X	X	X	X				
Blood Sampling for PK (morphine and its metabolites)[24]				X	X							X	X	X	X	
Blood Sampling for PK (AZD4041)[25]					X	X	X	X	X	X	X	X	X	X	X	
Urine Sampling for PK (AZD4041)[26]												X	X	X	X	

[21] The "Baseline/Screening" C-SSRS form will be completed at the Screening Visit, and the "Since Last Visit" C-SSRS form will be completed on Day 2, Day 14, at discharge or ET.

[22] On Day 1: Morphine will be intravenously administered. On Day 15: AZD4041 or Placebo will be orally administered immediately (within 1 minute) after morphine administration (end of intravenous infusion).

[23] On Days 2 to 14, AZD4041 or Placebo will be orally administered once daily. On Day 15, AZD4041 or Placebo will be orally administered immediately (within 1 minute) after morphine administration (end of intravenous infusion).

24 Blood samples for morphine and its metabolites will be collected as detailed in Section 6.2.1 of the protocol.

25 Blood samples for AZD4041 will be collected as detailed in Section 6.2.1 of the protocol.

26 Urine samples for AZD4041 will be collected as detailed in Section 6.2.2 of the protocol.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Adverse Event Monitoring[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[28]
Concomitant Medication Recording[29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event, COWS = Clinical Opioid Withdrawal Scale, C-SSRS= Columbia-Suicide Severity Rating Scale, ECG= electrocardiogram, $EtCO_2$ = end tidal carbon dioxide, FSH = Follicle-Stimulating Hormone, PK = pharmacokinetics, SpO_2 = oxygen saturation

Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion with the exception of the PK sampling time points for AZD4041 which are relative to AZD4041/placebo administration.

27 Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using non-leading questions.

28 Adverse events check must be done at the last scheduled study visit.

29 Medications taken within 30 days prior to Screening and throughout the duration of study participation will be recorded.