Clinical Study Protocol Amendment 2	
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A Phase I, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD4041 Following Single Ascending Dose Administration to Healthy Volunteers

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): IND 144437

VERSION HISTORY

Version 1, 19 July 2019
Initial creation
Version 2, 29 April 2020
Protocol Amendment 1
Version 3, 15 June 2021
Protocol Amendment 2

This Clinical Study Protocol Amendment 2 has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol Amendment 2 is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

SPONSOR SIGNATURES

A Phase I, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD4041 Following Single Ascending Dose Administration to Healthy Volunteers

This Clinical Study Protocol Amendment 2 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this Clinical Study Protocol Amendment 2.

SIGNATURE OF PRINCIPAL INVESTIGATOR

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Activities - Cohorts 1 to 3

	Screening Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Follow–up Visit[a] (14 days post-dose)
Informed consent	X					
Inclusion/exclusion criteria	X	X	X			
Demographic data	X					
Medical history	X					
Urinary drug screen	X	X				
Alcohol screen	X	X				
Testing for HIV, hepatitis B and C	X					
Pregnancy testing[b]	X	X				
FSH testing in women	X					
Randomization			X			
Admission to CRU		X				
Discharge from CRU					X	
Height, body weight, and BMI[c]	X	X			X	X
Study drug administration			X			
Adverse event recording	X	X	X	X	X	X
Blood pressure, temperature, respiratory rate, and pulse rate	X	X	X[d]	X	X	X
12-lead paper safety ECG	X	X	X[e]	X[e]	X[e]	
12-lead digital ECG			X[e]	X[e]	X[e]	
Telemetry[f]		X	X			
Clinical laboratory evaluations[g]	X	X		X		X
Physical examination	X	X			X	X
Blood sampling for PK[h]			X	X	X	

[a] Tests will be performed at follow-up and also in cases of discontinuation.

[b] Serum pregnancy test will be performed at screening and check-in.

[c] Height will be measured at screening only.

[d] Blood pressure, temperature, respiratory rate, and pulse rate will be measured at pre-dose, then at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose.

[e] Paper and digital ECGs will be collected at the same time points as PK sampling. Recording of ECGs will precede PK sampling and check of vital signs at each time point.

[f] Telemetry for 4 to 6 hours on Day -1 to establish a baseline. Pre-dose to 24 hours post-dose.

[g] Clinical laboratory assessments must be repeated if first collected more than 2 weeks before dosing.

[h] Blood samples will be collected at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours.

BMI body mass index; CRU Clinical Research Unit; ECG electrocardiogram; FSH follicle stimulating hormone; HIV human immunodeficiency virus; PK pharmacokinetic(s)

Table 2 Schedule of Activities - Cohorts 4 to 6

	Screening Day -28 to Day -2	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Follow–up Visit[a] (14±2 days post-dose)
Informed consent	X							
Inclusion/exclusion criteria	X		X	X				
Demographic data	X							
Medical history	X							
Urinary drug screen	X		X					
Alcohol screen	X		X					
Testing for HIV, hepatitis B and C	X							
Pregnancy testing[b]	X		X					
FSH testing in women	X							
Randomization				X				
Admission to CRU		X						
Discharge from CRU							X	
Height, body weight, and BMI[c]	X		X				X	X
Study drug administration				X				
Adverse event recording	X	X	X	X	X	X	X	X
Blood pressure, temperature, respiratory rate, and pulse rate	X		X	X[d]	X	X	X	X
12-lead paper safety ECG	X		X	X[e]	X[e]	X[e]	X[e]	
12-lead digital ECG				X[e]	X[e]	X[e]	X[e]	
Telemetry[f]			X	X				
Clinical laboratory evaluations[g]	X		X		X			X
Physical examination	X		X				X	X
Blood sampling for PK[h]				X	X	X	X	
Blood sampling for testosterone, LH, FSH, and inhibin B (male subjects only)[i]			X	X	X	X	X	

[a] Tests will be performed at follow-up and also in cases of discontinuation.

[b] Serum pregnancy test will be performed at screening and check-in.

[c] Height will be measured at screening only.

[d] Blood pressure, temperature, respiratory rate, and pulse rate will be measured at pre-dose, then at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose.

[e] Paper and digital ECGs will be collected at the same time points as PK sampling. Recording of ECGs will precede PK sampling and check of vital signs at each time point.

[f] For all subjects in Cohort 4 and first 5 subjects in Cohort 5: Telemetry for 4 to 6 hours on Day -1 to establish a baseline. Pre-dose to 24 hours post-dose. For the remaining subjects in Cohort 5 and all subjects in Cohort 6: Telemetry for 24 hours on Day -1, and pre-dose to 48 hours post-dose.

[g] Clinical laboratory assessments must be repeated if first collected more than 2 weeks before dosing.

[h] Blood samples will be collected at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours.

[i] Male subjects only: samples for testosterone, LH, FSH, and inhibin B will be collected at 0 hour (0800 or 1000) and at 4, 6, 8, 12, 22, and 24 hours on Day -1 and at 0 hour (0800 or 1000) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours on Day 1 to Day 3. The '0' hour time point should be approximately the same time that dosing is scheduled for on Day 1. On Day 1, samples for testosterone, LH, FSH, and inhibin B will be collected at the same time as PK samples.

BMI body mass index; CRU Clinical Research Unit; ECG electrocardiogram; FSH follicle stimulating hormone; HIV human immunodeficiency virus; LH luteinizing hormone; PK pharmacokinetic(s)

1.2 Synopsis

Protocol title:

A Phase I, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of AZD4041 following single ascending dose administration to healthy volunteers

Rationale:

It is predicted that approximately 0.6 billion current smokers worldwide will die from smoking-related illnesses, such as chronic obstructive pulmonary disease, cardiovascular disease, and lung cancer (Ezzati and Lopez 2003, Doll et al 2004, Coe et al 2005, Mathers and Loncar 2006). If current trends in tobacco use persist, by 2020, smoking will become the largest single health problem worldwide, causing approximately 8.4 million deaths annually (Murray and Lopez 1997). Smokers who quit before the onset of tobacco-related illness can largely avoid the increased mortality risk (Doll et al 1994, Peto et al 2000). Nevertheless, approximately 80% of smokers currently attempting to quit will relapse within the first month of abstinence (Benowitz 2009). The development of more efficacious smoking cessation aids is perhaps the most cost-effective intervention possible within a health-care system (Knight et al 2009). Although clinically efficacious, current smoking cessation agents have limited utility. In smokers attempting to quit, approximately 23% treated with Chantix® (varenicline) and approximately 16% treated with Zyban (bupropion) remain abstinent after 1 year, compared with approximately 9% of those treated with placebo (Knight et al 2009). Pharmacotherapy is therefore an effective strategy to aid smoking cessation efforts, but there is considerable risk of relapse even when treated with the most efficacious medications currently available. Further, medications that are effective aids to smoking cessation are

associated with a range of adverse effects. For example, varenicline, the most effective medication in this category, is associated with a host of neuropsychiatric side effects, including changes in behavior, psychosis, anxiety, etc, and the use of varenicline may impair a person's ability to drive or use machines (eMC 2018). Bupropion, on the other hand, is associated with insomnia, dry mouth, and nausea (Cahill et al 2011). These adverse effects may lead to premature discontinuation of these medications, leading to relapse (Catz et al 2011). This highlights the pressing need to develop safer and more effective smoking cessation therapeutics.

The neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively) are hypothalamic neuropeptides that act through 2 closely related G protein-coupled receptors (GPCRs), the orexin 1 (OX1) and orexin 2 (OX2) receptors. Orexin A has high affinity for both receptors whereas orexin B has higher affinity for OX2 over OX1 receptors. Orexin transmission has been implicated in a diverse range of physiological functions, including feeding and energy homeostasis (Sakurai et al 1998), the sleep/wake cycle (Willie et al 2003; Gotter et al 2016), neuroendocrine homeostasis, cardiovascular functions (Samson et al 2007), and motivated behaviors (Kodadek and Cai 2010). Nicotine, which is the principal reinforcing component in tobacco smoke responsible for addiction (Stolerman and Jarvis 1995), activates orexin (hypocretin) neurons in the brain. This increase in orexinergic transmission is thought to play a crucial role in regulating the motivational properties of the drug that results in tobacco dependence (Kenny 2011). Further, OX1 receptors regulate the reinstatement of extinguished drug-seeking responses in abstinent rats (Boutrel et al 2005, Harris et al 2005, Kenny 2011) and mice, considered animal models with heuristic value for understanding relapse in abstinent human drug addicts. As such, OX1 receptor antagonists are considered one of the most promising novel therapeutic strategies to facilitate smoking cessation. Importantly, OX1 receptors play a similar role in regulating the addiction-related actions of opioids, psychomotor stimulants and alcohol, raising the possibility that OX1 receptor antagonists may have utility for the treatment of addiction across different classes of abused drugs.

AstraZeneca, in partnership with Eolas Therapeutics, Inc, has developed an OX1 receptor antagonist, AZD4041, which demonstrates favorable drug-like physiochemical properties. The high level of selectivity of AZD4041 between the OX1 and OX2 receptors substantially reduces the potential for hypnotic effects of this OX1 antagonist since it is thought that the OX2 receptor is primarily responsible for the effects of orexin on sleep/wake transitions and maintenance of sleep states (Boutrel et al 2005). Consistent with this possibility, AZD4041 does not induce sleep-like electroencephalogram (EEG) waveforms in rodents across a broad range of doses. AZD4041 does not measurably inhibit the activity of cytochrome P450 enzymes or cardiac potassium ion channels (hERG) nor does it have significant actions at any non-OX1 receptor targets so far screened. AZD4041 is highly brain penetrant in non-human

primates, and has relatively slow rates of clearance and high levels of oral bioavailability in dogs. AZD4041 demonstrates in vivo efficacy in rodents and non-human primates at relatively low exposures.

Objectives and endpoints:

Objectives	Endpoint/variable:
Primary objective:	
To assess the safety and tolerability of AZD4041 following oral administration of single ascending doses	• Adverse events • Vital signs • Hematology, biochemistry, and urinalysis • ECG (12-lead and telemetry) • Testosterone, LH, FSH, and inhibin B (male subjects only)
Secondary objectives:	
To characterize the pharmacokinetics of AZD4041 following oral administration of single ascending doses of AZD4041	• C_{max} • T_{max} • AUC_{0-t} • AUC_{0-inf} • $t_{1/2\lambda z}$ • CL/F • V_{ss}/F
Exploratory objectives	
Characterize the pharmacodynamic relationship between drug exposure and QT interval	An exposure–response (E-R) analysis may be conducted with data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QT interval corrected for heart rate using Fridericia's formula (QTcF) parameter, as part of the cardiac safety evaluation and with the intention to obtain a Thorough QT (TQT) study substitute. The result of the E-R analysis may not be included in the main study report.

AUC_{0-t} Area under the curve from time 0 to time t; AUC_{0-inf} Extrapolation of the area under the curve from time 0 to infinity; CL/F Apparent total clearance of the drug from plasma after oral administration; C_{max} Maximum (peak) plasma drug concentration; ECG Electrocardiogram; E-R Exposure-response; FSH Follicle stimulating hormone; LH Luteinizing hormone; QTcF QT interval corrected for heart rate using Fridericia's formula; $t_{1/2\lambda z}$ Terminal half-life; T_{max} Time to reach maximum (peak) plasma concentration following drug administration; V_{ss}/F Apparent volume of distribution at steady state after non-intravenous administration

Overall design:

This is a Phase I, first-in-human (FIH), single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study in healthy vasectomized male and female subjects of non-childbearing potential, aged 18 to 55 years.

Study period:

Estimated date of first subject enrolled: Q3/2019

Estimated date of last subject completed: Q4/2021

Number of subjects:

The study plans to enroll 48 healthy subjects across 6 cohorts. Eight subjects will participate in each cohort. Within each cohort, 6 subjects will be randomized to receive AZD4041 and 2 subjects will be randomized to receive placebo. Subjects that drop out before dosing will be replaced. Dosing for each ascending dose cohort will proceed with 2 subjects in a sentinel cohort, such that 1 subject will be randomized to receive placebo and 1 subject will be randomized to receive AZD4041 in a blinded fashion.

Treatments and treatment duration:

The study comprises a screening period of up to 28 days (4 weeks), a 4-day in-patient period for Cohorts 1 to 3 and a 6-day in-patient period for Cohorts 4 to 6 during which a single oral dose of AZD4041 or placebo will be administered, and an out-patient follow-up period. The overall study duration (screening, treatment, and follow-up periods) will therefore be approximately 6 weeks.

Up to 6 dose levels of AZD4041 were planned to be investigated to explore the full dose range of AZD4041, with the highest dose that could be explored determined by the exposure cap based on the no-observed-adverse-effect level (NOAEL) exposure from the 28-day repeat dose toxicity study in dogs. Three cohorts have been dosed [redacted] Given that the exposure limits are predicted to be reached at [redacted], only vasectomised male and female subjects of non-childbearing potential will be enrolled in the remaining cohorts (Cohort 4 onwards). The highest dose that could be explored in these remaining cohorts will be determined by the exposure cap based on the NOAEL exposure in female dogs, from the 28-day repeat dose toxicity study.

The safety data from the sentinel subjects up to 24 hours post-dose will be reviewed by the Principal Investigator (PI), Clinical Research Organization (CRO) Medical Monitor, and AstraZeneca Study Physician before the remaining subjects in the cohort are dosed. The remaining 6 subjects for each cohort will be dosed at least 24 hours after the sentinel cohort.

Safety review committee

A Safety Review Committee (SRC) will review data from each cohort before progression to the next cohort occurs.

Statistical methods

Safety, tolerability, and pharmacokinetic (PK) data will be summarized descriptively as appropriate. Descriptive summary statistics for continuous variables will include number, arithmetic mean, standard deviation, minimum, median, and maximum, while for continuous PK variables, descriptive summary statistics will also include geometric mean and arithmetic coefficient of variation. Descriptive summary statistics for categorical data will include frequency and proportion. Tests of significance of group difference (drug dose versus placebo) on change from baseline in safety variables will also be performed. Model-based approaches will be used, if appropriate.

1.3 Schema

The general study design is summarized in Figure 1 (Cohorts 1 to 3) and Figure 2 (Cohorts 4 to 6).

Figure 1 Study design (Cohorts 1 to 3)

Cohort timing

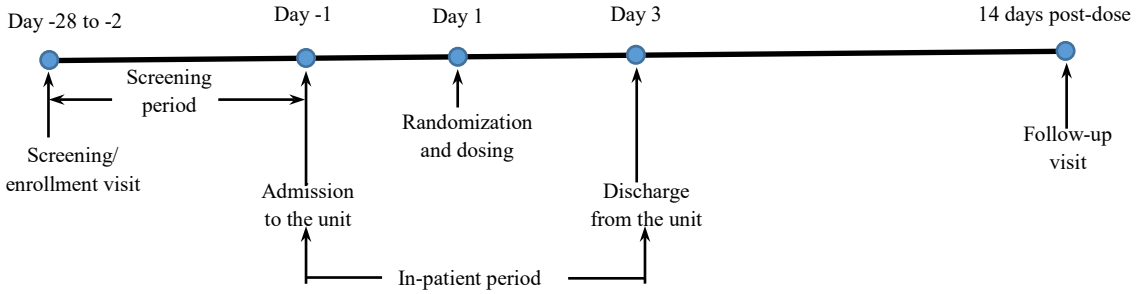
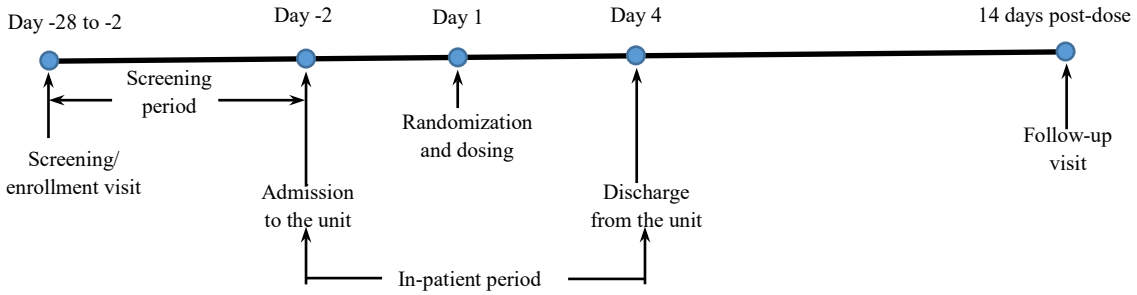


Figure 2 Study design (Cohorts 4 to 6)

Cohort timing



2 INTRODUCTION

Smoking is an epidemic of global proportions. It is the leading cause of morbidity and mortality in virtually every country in the world (Lim et al 2010). Smoking increases the risk of death by three-fold in smokers, compared with non-smokers (Jha et al 2013). It is predicted that approximately 0.6 billion current smokers worldwide will die from smoking-related illnesses, such as chronic obstructive pulmonary disease, cardiovascular disease and lung cancer (Ezzati and Lopez 2003, Doll et al 2004, Coe et al 2005, Mathers and Loncar 2006). If current trends in tobacco use persist, by 2020, smoking will become the largest single health problem worldwide, causing approximately 8.4 million deaths annually (Murray and Lopez 1997). Smokers who quit before the onset of tobacco-related illness can largely avoid the increased mortality risk (Doll et al 1994, Peto et al 2000). Nevertheless, approximately 80% of smokers currently attempting to quit will relapse within the first month of abstinence (Benowitz 2009).

The smoking epidemic comes with a great cost to society. It is estimated that the total economic cost of smoking resulting from health-care expenditures and loss of productivity totalled 1.8% of the world's annual gross domestic product, equivalent to US$1436 billion (Goodchild et al 2018).

The development of more efficacious smoking cessation aids is perhaps the most cost-effective intervention possible within a health-care system (Knight et al 2009). Although clinically efficacious, current smoking cessation agents have limited utility. In smokers attempting to quit, approximately 23% treated with Chantix (varenicline) and approximately 16% treated with Zyban (bupropion) remain abstinent after 1 year, compared with approximately 9% of those treated with placebo (Knight et al 2009). Pharmacotherapy is therefore an effective strategy to aid smoking cessation efforts, but there is considerable risk of relapse even when treated with the most efficacious medications currently available. Further, medications that are effective aids to smoking cessation are associated with a range of adverse effects. For example, varenicline, the most effective medication in this category, is associated with a host of neuropsychiatric side effects, including changes in behavior, psychosis, anxiety, etc, and the use of varenicline may impair a person's ability to drive or use machines (eMC 2018). Bupropion, on the other hand, is associated with insomnia, dry mouth, and nausea (Cahill et al 2011). These adverse effects may lead to premature discontinuation of these medications, leading to relapse (Catz et al 2011). This highlights the significant unmet need to develop safer and more effective smoking cessation therapeutics.

The neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively) are hypothalamic neuropeptides that act through 2 closely related G protein coupled receptors (GPCRs), the OX1 and OX2 receptors. Orexin A has high affinity for both

receptors whereas orexin B has higher affinity for OX2 over OX1 receptors. Orexin transmission has been implicated in a diverse range of physiological functions, including feeding and energy homeostasis (Sakurai et al 1998), the sleep/wake cycle (Willie et al 2003; Gotter et al 2016), neuroendocrine homeostasis, cardiovascular functions (Samson et al 2007), and motivated behaviors (Kodadek and Cai 2010). The OX1 receptor signals almost exclusively through Gq coupling. Nicotine, which is the principal reinforcing component in tobacco smoke responsible for addiction (Stolerman and Jarvis 1995), activates orexin (hypocretin) neurons in the brain. This increase in orexinergic transmission is thought to play a crucial role in regulating the motivational properties of the drug that results in tobacco dependence (Kenny 2011). Further, OX1 receptors regulate the reinstatement of extinguished drug-seeking responses in abstinent rats (Boutrel et al 2005, Harris et al 2005, Kenny 2011) and mice, considered animal models with heuristic value for understanding relapse in abstinent human drug addicts. As such, OX1 receptor antagonists are considered one of the most promising novel therapeutic strategies to facilitate smoking cessation. Importantly, OX1 receptors play a similar role in regulating the addiction-related actions of opioids, psychomotor stimulants and alcohol, raising the possibility that OX1 receptor antagonists may have utility for the treatment of addiction across different classes of abused drugs.

2.1 Study rationale

AstraZeneca, in partnership with Eolas Therapeutics, Inc, has developed an OX1 receptor antagonist, AZD4041, which demonstrates favorable drug-like physiochemical properties. [redacted] The high level of selectivity between the OX1 and OX2 receptors substantially reduces the potential for hypnotic effects of this OX1 antagonist since it is thought that the OX2 receptor is primarily responsible for the effects of orexin on arousal (Boutrel et al 2005). Consistent with this possibility, AZD4041 does not induce sleep-like EEG waveforms in rodents across a broad range of doses. [redacted]
Further details of these studies are provided in the Investigator's Brochure.

AZD4041 may therefore provide an attractive treatment option as a treatment for smoking cessation.

This study is being conducted to assess the safety, tolerability and PK of single doses of AZD4041 in a small number of healthy subjects, prior to advancing AZD4041 into larger clinical trials of longer duration.

2.2 Benefit/risk assessment

2.2.1 Benefit

AZD4041 has shown significant efficacy in the nicotine self-administration studies in rats and monkeys. These models are well established with drugs effective in smoking cessation; eg, varenicline, showing efficacy in these experiments (O'Connor et al 2010). AZD4041 was effective in a dose-dependent manner in blocking the withdrawal-induced nicotine-seeking response in the rat withdrawal model. Extrapolation of IC_{50} or in vivo 90% inhibitory concentration (IC_{90}) in the rat withdrawal model data with AZD4041 indicates that the target-free central nervous system exposure between [redacted], respectively, would be required for human efficacy.

It therefore appears that AZD4041 could represent a novel strategy in the treatment of addictive disorders such as smoking cessation, where it has the potential to address a significant unmet need.

The healthy volunteers who participate in this study are not expected to benefit from AZD4041.

2.2.2 Potential risks and mitigation strategies

There is no prior clinical information for AZD4041, as this is the FIH study. While a dual orexin receptor antagonist (suvorexant) is approved for the treatment of insomnia, no selective OX1 receptor antagonists have been approved for any indication so far. Limited safety data are available for the single and multiple dosing studies with 2 selective OX1 receptor antagonists (ACT-539313 [Kaufmann et al 2019] and JNJ-61393215 [Salvadore et al 2019]). Both appeared to be well-tolerated in these initial studies with the most common reported adverse events (AEs) being somnolence and headache. Thus, there is limited class information on the safety of this mechanism in humans. Therefore, the starting dose will be selected such that the predicted exposures at this dose are several fold lower than the lowest predicted efficacious dose (see Section 4.3).

In nonclinical studies, AZD4041 has been evaluated in repeat dose toxicity studies of 1 month duration in rats and dogs, in in vitro and in vivo genotoxicity studies, and in an in vitro phototoxicity study. Safety pharmacology studies assessing effects on the respiratory, cardiovascular, central and peripheral nervous systems, and in vitro effects on hERG, have also been conducted.

AZD4041 was negative in the Good Laboratory Practice (GLP) study in vitro Ames and chromosome aberration studies, and the GLP in vivo micronucleus study. AZD4041 was also negative in an in vitro 3T3 phototoxicity assay.

No significant effects of AZD4041 were noted on the central nervous system, locomotor function or motor coordination in rats. In the sleep/wake and EEG study in rats, AZD4041 significantly increased wakefulness at the expense of non-rapid eye movement (NREM) sleep when compared with control. [redacted] In this study, any effects on sleep/wakefulness will be assessed via AE reporting. Only healthy volunteers will be enrolled in this FIH study and any subject with a disease of the respiratory system will be excluded. Further, vital signs, including respiratory rate (RR), will be assessed at regular intervals after dosing (See Schedule of Activities [SoA], Table 1 and Table 2).

In the hERG assay, the [redacted]. In a panel of in vitro electrophysiological assays of recombinant human voltage-gated cardiac ion channels (hKv4.3/hKChIP2.2 – ITO; hKv7.1/hKCNE1 – IKS; hNav1.5 – INa; hKV1.5; hCav3.2; hHCN4) - AZD4041 had no activity. Therefore, a risk of QT prolongation is not expected with AZD4041. In the dog cardiovascular study, sustained durations of premature ventricular contractions, beginning approximately 7 hours after dosing and continuing up to 24 hours after dosing, [redacted]. The onset of the changes was soon after the approximate T_{max} [redacted] in the dog study. Hemodynamic parameters were largely unaltered and were maintained in the physiological range of heart rate and blood pressure. In a dog 14-day investigative study, lower heart rate, with associated higher PR and QT intervals were recorded at [redacted]; there were no changes in the rate-corrected QT interval and no arrhythmias were noted. There were no changes in ECG rhythm or waveform morphology attributable to AZD4041. Furthermore, there were no effects on ECG parameters or morphology in a 28-day dog study in which dogs received up to [redacted].

[redacted]

[redacted]

Table 3 [redacted]

[redacted]

CV Cardiovascular; PO Oral

While it is unclear what physiological mechanisms could be responsible for the observed arrhythmias, further risk mitigation measures are being added to the protocol in the form of extending the pre-dose telemetry for 24 hours on Day -1 to identify and exclude subjects at higher risk of arrhythmia events, extending the continuous cardiac telemetry for the first 48 hours after dosing, in addition to the regular monitoring for heart rate (HR) and blood pressure (BP). Subjects older than 55 years will be excluded in order to reduce the risk of observing benign background arrhythmic events, which are typically seen in older individuals. Stopping criteria based on corrected electrocardiogram (ECG) Q-T interval (QTc), HR and BP have been included in this FIH study.

In the 28-day GLP toxicity studies, the key findings were lower thymus weights and thymic atrophy in female dogs, and effects on the male reproductive tract in dogs. Other findings were increased liver weight, attributed to hepatocellular hypertrophy in rats and dogs; and increased thyroid weight, attributed to follicular cell hypertrophy and recorded in rats only. Due to the minimal severity and adaptive nature of the changes, the hepatic and thyroid changes were considered not adverse. Lower thymus weights were noted for female dogs and correlated with increased severity of thymic atrophy, characterized by decreased thickness of the cortex relative to the medulla, at the high dose. Taken together, the effect on thymus weight combined with the microscopic finding of atrophy was considered to be adverse.

There were no effects on organ weight or microscopic pathology noted for the thymus at the end of the recovery period, indicating recovery.

In the dog, effects in the form of tubular degeneration/atrophy of the testes, reduced luminal sperm in the epididymides and immaturity and/or single cell necrosis of the prostate glands, with associated effects on organ weight, were noted. There was some evidence of recovery at the end of the 4-week recovery period, in that findings were of a lesser severity compared to the main test and/or of a similar incidence/severity to the concurrent controls. There is some evidence that OX1 receptors are expressed in dog seminiferous tubules (Ligouri et al 2018) and that orexin A is involved in the regulation of spermatogenesis (Barreiro et al 2005, Hakovirta et al 1999, Yan et al 1999, Yan et al 2000), which may demonstrate a potential link between the pharmacological action of AZD4041 and the findings in the dog. The low dose in male dogs was identified as the NOAEL. It should be noted that similar findings were not seen after 14 days in the dog dose range finding study, albeit with smaller numbers. No effects on the male reproductive tract were seen in the rat 28-day GLP toxicity study.

For the purpose of a single dose study, testicular toxicity is not considered to be relevant for vasectomised male or female subjects of non-childbearing potential. Therefore, given that the exposure limits are predicted to be reached at doses [redacted] only vasectomised male and female subjects of non-childbearing potential will be enrolled in the remaining cohorts. The highest dose that could be explored in these remaining cohorts will be determined by the exposure cap based on the NOAEL exposure in female dogs, from the 28-day repeat dose toxicity study [redacted].

In addition to the above risk mitigation strategies, a number of other measures are being taken in this study to minimize any potential risk to participants, given that this is an FIH administration of this compound. The key measures among these include the following:

- This study will employ sentinel dosing, whereby only 2 subjects (1 active + 1 placebo) will be dosed in a blinded manner at the start of a cohort and their safety will be monitored for 24 hours before dosing the rest of the cohort;
- Further, this study will enroll only healthy non-smokers who will be carefully selected based on exhaustive inclusion and exclusion criteria to avoid placing such subjects at any significant risk;
- In addition, subjects will be confined to an in-patient unit that specializes in and is equipped for the conduct of FIH studies, starting from the day prior to dosing and for 72 hours after dosing.

2.2.3 Benefit/risk conclusion

The hepatic and thyroid effects were considered minimal, and adaptive and thymic atrophy fully recovered at the end of the recovery period. Effects on respiration seen in the Safety Pharmacology study will be monitored closely with extensive vital sign assessments and continuous cardiac telemetry, and ECGs will be used to comprehensively monitor any potential arrhythmic effect. The addition of risk mitigation measures in the form of extended telemetry and exclusion of subjects with abnormal pre-dose telemetry indicating a high risk of arrhythmia events, extension of post-dose telemetry and reduction in the upper age limit for eligible subjects, is considered adequate to address a potential risk of NSVT in the study population. In fertile (non-vasectomised) males, the dose-limiting toxicity was considered to be the testicular findings in the dog. Therefore, dosing in this study was restricted to a dose that was predicted to provide an exposure that was 10-fold below the NOAEL exposures in the Dog 28-day study [redacted] However, for cohorts where exposures are predicted to exceed the 10-fold margin below the Dog 28-day study NOAEL and therefore only vasectomised males or females of non-childbearing potential are being enrolled (Cohort 4 onwards), dosing will be limited by the thymic findings in female dogs, in the Dog 28-day study. Therefore, the revised exposure limits for these cohorts are proposed not to exceed a free [redacted], which correspond to the intermediate dose NOAEL exposures in the female dog at [redacted].

Based on this information regarding the risks of AZD4041 and the precautions included in this first clinical study, the risks are considered acceptable in relation to the significant unmet need in subjects attempting to quit smoking.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AZD4041 may be found in the Investigator's Brochure.

2.3 AZD4041 - D7460C00001 single ascending dose study - results as of 18 March 2021

The FIH SAD study in healthy volunteers with AZD4041 is currently ongoing and 4 cohorts have completed dosing and 15-day follow-up (Study AZD4041 - D7460C00001). The doses tested in Cohorts 1, 2, 3, and 4 were [redacted], respectively. The 5th cohort is partially completed (5 of 8 subjects) at an oral dose level of [redacted].

[redacted]

[redacted]

For cohorts 1, 2 and 3 the predicted exposure was planned not exceed a limit that is approximately 10-fold below the NOAEL exposures in males in the Dog 28-day study (Table 4). Subsequent cohorts in females of non-childbearing potential and vasectomised males have revised exposure limits that is proposed not to exceed the intermediate dose NOAEL exposures in the female dog at [redacted]. Utilizing geometric mean data, observed exposures at [redacted] provide a [redacted] margin to free C_{max} and an [redacted] margin to free $AUC_{0\text{-}inf}$ when compared to the female dog NOAEL derived from the 28 Day GLP toxicology study (Table 5). For the partial Cohort 5 data at [redacted] geometric mean data indicates a [redacted] margin to free C_{max} and an [redacted] margin to free $AUC_{0\text{-}inf}$ when the same comparison is made to the female dog NOAEL exposures.

Table 4 Observed exposures and margins to male dog NOAEL

Clinical dose (mg)	Human free C_{max} (ng/mL)	Human free C_{max}/Dose	C_{max} margin to male dog NOAEL	Human free $AUC_{0\text{-}inf}$ (ng·h/mL)	Human free $AUC_{0\text{-}inf}$/Dose	$AUC_{0\text{-}inf}$ margin to male dog NOAEL
[redacted]						
[redacted]						
[redacted]						

$AUC_{0\text{-}inf}$ Extrapolation of the area under the curve from time 0 to infinity; C_{max} Maximum (peak) plasma drug concentration; NOAEL No-observed-adverse-effect level

n/a = not applicable since male dog NOAEL was not utilized as exposure limit beyond Cohort 3

Note: Exposures are provided as geometric means (n=6).

Pharmacokinetic data within cohorts indicated that there was some variability in systemic exposure between individuals. As an example in Cohort 3, the coefficient of variation for C_{max} geometric mean was 24.7% and the coefficient of variation for $AUC_{0\text{-}inf}$ geometric mean was 43.7%. For 3 subjects within Cohort 3, extrapolation of $AUC_{0\text{-}inf}$ following noncompartmental analysis was >20%, indicating some uncertainty in the calculation of this parameter. However, with an extended sampling period and extrapolation of $AUC_{0\text{-}inf}$ following noncompartmental analysis of <20% in all subjects, variability in systemic exposure was still evident in Cohort 4, as exemplified by a coefficient of variation for C_{max} geometric mean of 21.2% and a coefficient of variation for $AUC_{0\text{-}inf}$ geometric mean of 52.4%.

Linear regression modelling with a linear scale has been employed to understand the relationship between C_{max} and $AUC_{0\text{-}inf}$. Utilizing predicted exposures from the linear regression model, doses of [redacted] and higher are expected to have a [redacted] margin to the

female dog NOAEL, for C_{max} and $AUC_{0\text{-}inf}$ (Table 5). This modelling and the projected systemic exposures will be revised as additional PK data becomes available. The SRC will evaluate the safety, tolerability, and PK of AZD4041 and determine the next dose. The dose level for a given cohort will be referenced from the applicable safety summary meeting minutes.

Table 5 Predicted exposures and margins to NOAEL

Clinical dose (mg)	Human free C_{max} (ng/mL)	Human free $AUC_{0\text{-}inf}$ (ng·h/mL)	C_{max} margin to female dog NOAEL	$AUC_{0\text{-}inf}$ margin to female dog NOAEL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] = observed data and margins based on observed PK parameters

$AUC_{0\text{-}inf}$ Extrapolation of the area under the curve from time 0 to infinity; C_{max} Maximum (peak) plasma drug concentration; NOAEL No-observed-adverse-effect level

3 OBJECTIVES AND ENDPOINTS

Table 6 Objectives and endpoints

Objectives	Endpoint/variable:
Primary objective:	
To assess the safety and tolerability of AZD4041 following oral administration of single ascending doses	• Adverse events • Vital signs • Hematology, biochemistry, and urinalysis • ECG (12-lead and telemetry) • Testosterone, LH, FSH, and inhibin B (male subjects only)
To characterize the pharmacokinetics of AZD4041 following oral administration of single ascending doses of AZD4041	• C_{max} • T_{max} • $AUC_{0\text{-}t}$ • $AUC_{0\text{-}inf}$ • $t_{1/2\lambda z}$ • CL/F • V_{ss}/F

Table 6 Objectives and endpoints

Objectives	Endpoint/variable:
Secondary objectives:	
Characterize the pharmacodynamic relationship between drug exposure and QT interval	An exposure–response (E-R) analysis may be conducted with data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QT interval corrected for heart rate using Fridericia's formula (QTcF) parameter, as part of the cardiac safety evaluation and with the intention to obtain a Thorough QT (TQT) study substitute. The result of the E-R analysis may not be included in the main study report.

AUC_{0-t} Area under the curve from time 0 to time t; AUC_{0-inf} Extrapolation of the area under the curve from time 0 to infinity; CL/F Apparent total clearance of the drug from plasma after oral administration; C_{max} Maximum (peak) plasma drug concentration; ECG Electrocardiogram; FSH Follicle stimulating hormone; E-R Exposure-response; LH Luteinizing hormone; QTcF QT interval corrected for heart rate using Fridericia's formula; $t_{1/2\lambda z}$ Terminal half-life; T_{max} Time to reach maximum (peak) plasma concentration following drug administration; V_{ss}/F Apparent volume of distribution at steady state after non-intravenous administration

4 STUDY DESIGN

4.1 Overall design

4.1.1 Overview

This is a Phase I, FIH, single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study in healthy vasectomized male and female subjects of non-childbearing potential, aged 18 to 55 years.

For an overview of the study design see Figure 1 and Figure 2, Section 1.3. For details on treatments given during the study, see Section 6.1, Treatments administered.

For details on what is included in the efficacy and safety endpoints, see Section 3, Objectives and endpoints.

4.2 Scientific rationale for study design

A single ascending dose design will be employed to assure that higher doses are administered to healthy subjects only after lower doses have demonstrated an acceptable safety profile as assessed by physical examination, clinical laboratory testing, and AE recording.

4.3 Justification for dose

The doses selected for this FIH study were based on appropriate methods to predict PK in humans using PK/pharmacodynamic (PD) modelling of data from an in vivo model to identify potentially efficacious target concentration and predicted exposure margins.

AZD4041 was predicted to exhibit low clearance and moderate volume of distribution in humans. The human clearance of AZD4041 was determined via scaling of intrinsic clearance data from in vitro human hepatocyte incubations and the application of the well-stirred model with appropriate hepatic scaling factors. The volume of distribution of AZD4041 was predicted utilizing in vitro and physicochemical properties and a physiologically-based PK model (PBPK) (Arundel 1997). Free efficacious exposure (C_{eff}) in humans was estimated by extrapolation of data from the withdrawal-induced nicotine-seeking model in rodents. Utilizing rat PK and withdrawal model PD data, the maximal efficacious exposure, as described by the IC_{90}, was determined using appropriate PK/PD modelling as [redacted] free. Human dose projections were then performed using the previously established PBPK model and clearance prediction, to estimate the once daily dose required to achieve this target-free C_{eff} at trough plasma concentration at steady state. Using this approach, the predicted human efficacious [redacted].

The starting dose for the first cohort was [redacted] with up to 5 planned dose escalations. At the starting dose of [redacted], there was a predicted 471-fold exposure margin to free C_{max} and a 338-fold exposure margin to free $AUC_{0\text{-}inf}$ when compared to the corresponding toxicokinetic parameters for dog NOAEL dose level in male dogs (Table 7). Dose levels for each subsequent cohort were selected based on the emerging safety and PK data; however, the predicted exposure was planned not exceed a limit that is approximately 10-fold below the NOAEL exposures in the Dog 28-day study [redacted]. Further details regarding data required for dose escalations were provided in the SRC Charter which was prepared prior to dosing. For a single [redacted] human dose, the corresponding predicted free C_{max} and free $AUC_{0\text{-}inf}$ exposure margins were expected to be 13- and 10-fold, respectively.

Table 7 Bases of predicted human exposure to AZD4041

Clinical dose (mg)	Predicted human free C_{max} (ng/mL)	Predicted C_{max} margin to male dog NOAEL	Predicted human free AUC_{0-inf} (ng·h/mL)	AUC_{0-inf} margin to male dog NOAEL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AUC_{0-inf} Extrapolation of the area under the curve from time 0 to infinity; C_{max} Maximum (peak) plasma drug concentration; NOAEL No-observed-adverse-effect level

Based on the PK exposures observed in Cohorts 1, 2, and 3 (Table 4) the exposure limits, based on the male dog NOAEL, were expected to be reached in the 4th cohort.

Therefore, the protocol was amended to only enroll female subjects of non-childbearing potential and vasectomised male subjects in the study in all subsequent cohorts.

The initial exposure limits set in the study were based on testicular toxicity seen in the 28-day dog GLP toxicity study. For the purpose of a single dose study, testicular toxicity is not considered to be relevant for vasectomised male or female subjects of non-childbearing potential. It is therefore considered appropriate to enroll vasectomised males or female subjects of non-childbearing potential only in cohorts where exposures are predicted to exceed the 10-fold margin below the Dog 28-day study NOAEL exposures, ie, Cohort 4 onwards.

In the 28-day GLP toxicity study, adverse effects in the form of increased incidence and severity of thymic atrophy characterised by decreased thickness of the cortex relative to the medulla, were noted at the high dose in female dogs. A similar increase in incidence and severity was not noted in the male dog. As a result, the NOAEL was set at the intermediate dose. Therefore, for cohorts where exposures are predicted to exceed the 10-fold margin below the Dog 28-day study NOAEL (Cohort 4 onwards), revised exposure limits are proposed not to exceed a free C_{max} of [redacted] which correspond to the intermediate dose NOAEL exposures in the female dog at [redacted]. Revised exposure margins for female and vasectomized male subjects are provided in Table 5.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing study treatment.

A subject is considered to have completed the study when the subject has completed his/her last scheduled visit or last scheduled procedure, shown in the SoA (Table 1 and Table 2).

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of CSP deviations to recruitment and enrollment criteria, also known as CSP waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures (refer to Section 5.4).

In this CSP, "enrolled" subjects are defined as those who sign informed consent. "Randomized" subjects are defined as those who undergo randomization and are assigned a randomization number.

For procedures for withdrawal of incorrectly enrolled subjects, see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1 Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this CSP.

2 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

3 Subjects must be ≥18 and ≤55 years of age at the time of signing the ICF.

4 Individuals who are healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring.

5 Individuals who weigh ≥50 kg and who have a body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive.

6 Either male or female.

7 Female subjects must have a negative pregnancy test result at screening and check-in and, on admission to the unit, must not be lactating.

8 Female subjects must be of non-childbearing potential, as confirmed at screening by fulfilling one of the following criteria:

(a) Post-menopausal women must have had ≥12 months of spontaneous amenorrhea with a follicle stimulating hormone (FSH) concentration consistently ≥40 mIU/mL and must have a negative pregnancy test result at screening and check-in.

(b) Surgically sterile women, defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), bilateral salpingectomy, or bilateral tubal ligation. Women who are surgically sterile must provide documentation of the procedure by an operative report or relevant medical records, or by ultrasound, and must have a negative pregnancy test result at screening and check-in.

9 Male subjects must be vasectomized.

5.2 Exclusion criteria

1 History of any clinically important disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

2 History of any significant psychiatric disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association 2013) which, in the opinion of the Investigator, could be detrimental to subject safety or could compromise study data interpretation.

3 Male subjects with a history of oligospermia or azoospermia or any other disorder of the reproductive system.

4 Subjects who are undergoing treatment or evaluation for infertility.

5 History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.

6 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of administration of IP.

7 Any clinically important abnormalities noted at the screening assessments in clinical chemistry, hematology, or urinalysis results as judged by the Investigator.

8 Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibodies.

9 Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

(a) Systolic BP <90 mmHg or ≥140 mmHg.

(b) Diastolic BP <50 mmHg or ≥90 mmHg.

(c) HR <45 or >85 beats per minute.

10 Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG and any clinically important abnormalities in the 12-lead ECG which, in the Investigator's opinion, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology.

11 ECG interval measured from the onset of the QRS complex to the end of the T wave (QT) interval corrected for HR using Fridericia's formula (QTcF) >450 ms or family history of long QT syndrome.

12 ECG interval measured from the onset of the P wave to the onset of the QRS complex (PR[PQ]) interval shortening <120 ms (PR >110 ms but <120 ms is acceptable if there is no evidence of ventricular pre-excitation).

13 PR(PQ) interval prolongation (>240 ms), persistent or intermittent second (Wenckebach block while asleep is not exclusive) or third degree atrioventricular (AV) block, or AV dissociation.

14 Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with ECG interval measured from the onset of the QRS complex to the J point (QRS) >110 ms. Subjects with QRS >110 ms but <115 ms are acceptable if there is no evidence of, eg, ventricular hypertrophy or pre-excitation.

15 In the pre-dose 24 hour telemetry, presence of ≥10 ventricular premature contractions (VPCs) during 1 hour, or ≥100 VPCs during 24 hours of Holter/telemetry or any occurrence of paired VPCs (ventricular couplets) or other repetitive ventricular rhythms including non-sustained or sustained (>30 second duration) "slow" (<100 bpm) or "fast" (≥100 bpm) ventricular tachycardias.

16 Vaccination with COVID-19 vaccine less than 14 days prior to the proposed date of randomization. If more than 1 dose of the vaccine is required as part of the vaccination regimen, a subject can only be randomized to receive study treatment 14 days after receiving the final dose of the COVID-19 vaccine.

17 Known or suspected history of drug abuse as judged by the Investigator.

18 Current smokers or those who have smoked or used nicotine products within the previous 3 months.

19 History of alcohol abuse or excessive intake of alcohol defined as an average weekly intake of >21 units or an average daily intake of >3 units for men or an average weekly intake of >14 units or an average daily intake of >2 units for women. One unit is equivalent to a half pint (250 mL) of beer, 1 measure (25 mL) of spirits, or 1 glass (125 mL) of wine. If a subject is currently diagnosed with abuse of or dependence on alcohol, the subject will not be allowed to enroll in the study, unless the alcohol abuse/dependence is in full (complete, not partial), sustained (>1 year) remission.

20 Positive screen for drugs of abuse at screening or admission to the unit or positive screen for alcohol at screening to the unit prior to administration of IP.

21 History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to AZD4041.

22 Plasma donation within 1 month of screening or any blood donation/blood loss >500 mL during the 3 months prior to screening.

23 Excessive intake of caffeine-containing drinks or food (eg, coffee, tea, chocolate) as judged by the Investigator.

24 Use of drugs with enzyme inducing properties, such as St John's wort, within 3 weeks prior to administration of IP.

25 Use of any prescribed or nonprescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to administration of IP or longer if the medication has a long half-life.

26 Use of any prescribed or nonprescribed oral and topical inhibitors/inducers of CYP3A4 (including shampoo).

27 Use of hormone replacement therapy.

28 Subjects who have previously received AZD4041.

29 Has received another new chemical entity (defined as a compound that has not been approved for marketing) within 3 months of administration of IP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit, whichever is the longest. Note: subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

30 Involvement of any AstraZeneca or study site employee or their close relatives.

31 Judgement by the Investigator that the subject should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

32 Subjects who are vegans or have medical dietary restrictions.

33 Subjects who cannot communicate reliably with the Investigator.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

No outside food or drink is permitted at the unit. All meals and snacks will be provided. Subjects will receive standard meals and snacks at regimented times during each residential period.

Subjects should not consume grapefruit juice or other grapefruit products for up to 7 days before dosing and throughout the study.

5.3.2 Caffeine, alcohol, and tobacco

Alcohol use is prohibited for 48 hours prior to the screening visit, for 48 hours prior to admission to the unit, during the residential period, and for 48 hours prior to the follow-up visit (14 days post-dose). Subjects should consume only moderate levels of alcohol for the duration of the study, defined as less than 3 units (1 unit=25 mL spirits, 125 mL wine or 250 mL beer or lager) in any 24-hour period for men and less than 2 units in any 24-hour period for women.

5.3.3 Activity

Strenuous activity is prohibited from 48 hours prior to admission to the Clinical Research Unit (CRU) until discharge from the CRU.

5.4 Screen failures

Screen failures are defined as subjects who signed the ICF to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

These subjects should have the reason for study withdrawal recorded in the electronic Case Report Form (eCRF).

6 STUDY TREATMENTS

Study treatment is defined as any IP (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the CSP.

Study treatment is to be administered in the morning under fasted conditions. Subjects will fast overnight (nothing to eat or drink except water) for at least 10 hours before receiving study treatment. Subjects will remain fasted for 4 hours after dosing with study treatment.

6.1 Treatments administered

6.1.1 Investigational products

Table 8 Study treatments

Study treatment name:	AZD4041
Dosage formulation:	[redacted]
Strength/Concentrations:	[redacted]
Placebo:	[redacted]
Route of administration:	Oral
Dosing instructions:	Oral syringe
Packaging and labelling:	Formulation to be prepared extemporaneously from drug substance at the clinical site. Stock solutions to be prepared on a weekly basis and stored under refrigerated conditions (2°C to 8°C). Dosing solutions to be prepared on a daily basis for use within 24 hours and may be stored under ambient conditions.
Provider:	AMRI, Albany, New York

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled and monitored (manual or automated) area, in accordance with the labelled storage conditions, with access limited to the Investigator and authorized site staff.

Details of study treatment preparation and administration are given in the Handling Instructions.

A formal system for drug accountability will be implemented. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3 Measures to minimize bias: randomization and blinding

PPD will generate the randomization schedule. Eligible sentinel subjects within each cohort will be randomly assigned in a ratio of 1:1 to Active:Placebo after all entry criteria have been satisfied before dosing on Day 1. Following review of sentinel safety data up to 24 hours post-dose, the remaining subjects within each cohort will be randomly assigned in a ratio of 5:1 to Active:Placebo.

6.3.1 Blinding Procedures

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dosage forms of similar appearance. Access to the randomization code will be strictly controlled according to the standard operating procedures of PPD.

6.3.2 Breaking the Blind

Blind breaking envelopes will be prepared. A subject or subjects may be unblinded in the event of a dose-limiting toxicity, SAE, or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will terminate. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

6.4 Treatment compliance

Any change from the dosing schedule, dose interruptions, dose reductions, or dose discontinuations should be recorded in the eCRF.

The Investigator is responsible for management of the IP from receipt by the study site until the destruction or return of all unused IP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use

- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

Table 9 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed):
Antacids Analgesics other than paracetamol/acetaminophen Herbal remedies Megadose (20 to 600 times recommended daily dose) vitamins Megadose minerals	In the 2 weeks prior to administration of IP, or longer if the medication has a long half-life, use of any of these medications constitutes a basis for exclusion from the study.
Grapefruit juice	Subjects should not consume grapefruit juice for up to 7 days before dosing and throughout the study.

IP Investigational product

Table 10 Prohibited medications

Prohibited medication/class of drug:
Any other investigational drugs than provided in this study
Any medication with enzyme inducing properties such as St John's wort
Hormone replacement therapy
Oral and topical inhibitors/inducers of CYP3A4
Vaccination with COVID-19 vaccine less than 14 days prior to the proposed date of randomization

Medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate section of the eCRF.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

As individual subjects are given only one dose of IP, there are no criteria for discontinuing study treatment. This section describes the criteria for study termination and the discontinuation of planned dose escalations within the study.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

The study may be stopped if, in the judgement of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to IP
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF.

In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' wellbeing.

After each cohort, an SRC will review and assess all the available safety and PK data from all of the cohorts to date in order to make a decision on the dose for the next cohort of subjects.

Data from a minimum of 6 subjects dosed per cohort must be reviewed before each dose escalation.

If any of the following scenarios occur within a cohort with a reasonable possibility of a causal relationship with AZD4041, escalation to the next, higher dosage level may not occur:

General

- One or more subjects, who receive AZD4041, report a SAE or experience AEs judged to be non-tolerable by the PI or the SRC, and are deemed related to AZD4041.

Cardiovascular criteria

- Two or more subjects, who receive AZD4041, have QTc prolongation defined as QTcF >500 ms, or a prolongation from baseline of >60 ms, confirmed (persistent for at least 5 minutes) and determined post-dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG.
- Two or more subjects, who receive AZD4041, have tachycardia defined as resting supine HR >125 beats per minute persisting for at least 10 minutes.
- Two or more subjects, who receive AZD4041, have symptomatic bradycardia defined as resting supine HR <40 beats per minute or asymptomatic bradycardia defined as resting supine HR <30 beats per minute while awake and persisting for at least 10 minutes.
- Two or more subjects, who receive AZD4041, develop hypertension defined as an increase in resting supine systolic BP >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
- Two or more subjects, who receive AZD4041, develop hypotension defined as an asymptomatic fall in systolic BP of >20 mmHg to <70 mmHg persisting for at least

10 minutes, or a symptomatic fall in resting supine BP >20 mmHg (excluding vasovagal reaction).

- Two or more subjects, who receive AZD4041, have tachycardia defined as resting supine heart rate >125 beats per minute persisting for at least 10 minutes.
- Two or more subjects, who receive AZD4041, have a non-sustained ≥5 beat if "slow" (<100 bpm), or "fast"(≥100 bpm) ventricular tachycardia.
- One or more subjects, who receive AZD4041, have a sustained ventricular tachycardia (ie, >30 second duration, or leading to hemodynamic consequences requiring immediate arrhythmia termination).

Laboratory findings

- One or more subjects, who receive AZD4041, fulfill Hy's Law defined as "An increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) and total bilirubin (TBL) ≥2x ULN, where no other reason can be found to explain the combination of increases; eg, elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis, or another drug." The elevations do not have to be at the same time or within a specified time frame.
- Two or more subjects, who receive AZD4041, have >3x ULN of either ALT or AST, or >2x ULN for TBL or ALP.

Criteria for halting dose escalation

PK data indicate that the predefined maximum exposure level/maximum plasma concentration (free C_{max} of [redacted] has been achieved, or is predicted to be achieved or exceeded should the dose be increased as planned. The exposure limits should be applied on mean values within a cohort. If this halting dose escalation criterion is met, the SRC will stop any further dose escalation. The SRC will determine whether a lower or the same dose should be tested or whether the study should be terminated.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if the subject fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject or next of kin by, eg, repeat telephone calls,

certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.

- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study, the subject should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A subject may withdraw from the study (eg, withdraw consent), at any time (IP and assessments) at the subject's own request. There will be no penalty or loss of benefit to the subject.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). Circumstances of withdrawal will be documented in writing by the Investigator.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, the subject may request destruction of any samples taken, and the Investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up with subjects as medically indicated.

See SoA (Table 1 and Table 2), for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1 and Table 2).

The Investigator ensures the accuracy and completeness of eCRFs, including eligibility and timeliness of the data recorded and of the provision of answers to data queries according to the Data Management Plan. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments (not applicable)

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Clinical safety laboratory assessments

The clinical chemistry, hematology, and urinalysis will be performed at a local laboratory at or near to the study site.

See Table 11 for the list of clinical safety laboratory tests to be performed and to the SoA (Table 1 and Table 2) for the timing and frequency. All CSP-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA (Table 1 and Table 2).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed, dated, and retained at center as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected and analyzed if clinically indicated at the discretion of the Investigator. The date of collection will be recorded on the appropriate CRF.

Table 11 Laboratory safety variables

Hematology (whole blood)	Clinical Chemistry (serum or plasma)
White blood cell (WBC) count	Alanine aminotransferase (ALT)
Red blood cell (RBC) count	Aspartate aminotransferase (AST)
Hemoglobin (Hb)	Alkaline phosphatase (ALP)
Hematocrit (HCT)	Gamma glutamyl transpeptidase (GGT)
Mean corpuscular volume (MCV)	Total bilirubin
Mean corpuscular hemoglobin (MCH)	Unconjugated bilirubin
Mean corpuscular hemoglobin concentration (MCHC)	C-reactive protein (CRP)
Neutrophils absolute count	Blood Urea Nitrogen
Monocytes absolute count	Creatinine
Eosinophils absolute count	Glucose (fasting)
Basophils absolute count	Albumin
Platelets	Phosphate
Reticulocytes absolute count	Potassium Calcium
Urinalysis	Sodium
Glucose	Bicarbonate
Protein	Thyroid stimulating hormone (TSH)[a]
Hemoglobin	Thyroxine (T_4)[b]
Microscopy (if positive for blood or protein)	Follicle stimulating hormone (FSH)[c]
Viral serology	**Pregnancy test (females only)**
Human immunodeficiency virus (HIV I and II) Hepatitis B surface antigen (HBsAg) Hepatitis C Virus antibody	Human beta chorionic gonadotrophin

[a] Screening only
[b] Reflex only (if TSH is abnormal)
[c] Screening for post-menopausal women

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN refer to Appendix C 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions

Urine will be tested for alcohol and cotinine (screening only) and the following drugs of abuse: amphetamines (includes methamphetamines and ecstasy/3,4-methylenedioxymetamphetamine), barbiturates, benzodiazepines, cannabinoids (includes tetrahydrocanabinol), cocaine metabolites, methadone, tricyclic antidepressants, opiates (includes heroin, codeine, and oxycodone), and phencyclidine.

8.2.2 Testosterone, Luteinizing Hormone, Follicle Stimulating Hormone, and inhibin B assessments

In order to monitor for effects on testicular function in male subjects, samples for assessment of testosterone, luteinizing hormone (LH), FSH, and inhibin B levels will be collected at 0 hour (0800 or 1000) and at 4, 6, 8, 12, 22, and 24 hours on Day -1 and at 0 hour (0800 or 1000) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours on Day 1, as listed in the SoA (Table 2). The results of these assessments will be taken into account at dose escalation meetings, prior to selecting the dose for the next cohort.

8.2.3 Physical examinations

A complete physical examination will be performed and include an assessment of the following systems: cardiovascular, chest/lungs/respiratory, gastrointestinal, thyroid/neck, lymphatics, dermatological/skin, musculoskeletal/extremities, neurological, and head/ears/eyes/nose/throat (including mouth).

Physical examination will be performed at timelines as specified in the SoA. Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs; see Section 8.3.7 for details.

8.2.4 Vital signs

Body temperature, pulse rate (PR), respiratory rate, and BP will be assessed.

Vital signs will be measured in a semi-supine position after 5 minutes rest. Supine and standing BP and PR will be measured using a semiautomatic recording device. Supine BP and PR should be taken after at least 5 minutes supine rest. Standing BP and PR should be taken approximately 3 minutes after the respective supine measurements. Three consecutive BP readings will be recorded at intervals of at least 1 minute. The average of the 3 BP readings will be recorded on the CRF.

Respiratory rate will be measured in breaths per minute by observation at the times indicated in the SoA (Table 1 and Table 2).

8.2.5 Electrocardiograms

For the timing of ECG assessments, see the SoA (Table 1 and Table 2) and Table 12.

Twelve-lead paper ECG (pECG) allows the PI to review the ECG tracings at bedside and determine any potential risks. Digital 12-lead ECGs are collected and electronically submitted to the AstraZeneca ECG Center for expert review and reporting of ECG intervals. Telemetry is used for continuous monitoring of ECG activity as a safety measure.

8.2.5.1 Resting 12-lead ECG

Twelve-lead pECGs will be obtained after the subject has been resting in the supine position for at least 10 minutes. All pECGs will be evaluated for HR, and for PR, RR, QRS, QT, and QTcF intervals, and the Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether or not 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 eCRF, and the paper printouts will be stored at the site.

The PI or delegate will evaluate the printout of the pECG in real time, and with particular attention to the effects of clinical importance on the PR, QRS, and QTcF intervals.

8.2.5.2 Electronic capture and analysis of 12-lead digital ECGs

The AstraZeneca ECG Center will perform the digital ECG (dECG) analysis and interpretation in this study, using the EClysis© system, version 4.0, or higher.

Continuous 12-lead dECG recordings will be performed using the site's Mortara Telemetry Surveyor equipment. At CSP-indicated time points in Table 12, 12-lead continuous dECG files will be extracted over at least 5 minutes from the Mortara Telemetry Surveyor continuous files and transmitted to the AstraZeneca central dECG repository, according to AstraZeneca ECG Center's standard procedures, settings, recording, and transmission of dECGs.

Table 12 SAD single dose time schedule for digital electrocardiogram assessments in D7460C00001 during the residential period

Study Days	ECG Number	Time-point	Start Time hour:min[a,b]	Dose	Stop Time	dECG cont.[c,d,e]	Other[f]
1			-01:30		-01:00		Apply the electrodes[d]
1			-00:40		-00:30		Rest in bed
1	1	Pre-dose	-00:30	Predose	-00:20	10 minutes	
1			-00:20		-00:05		Toilet use recommended
1			00:00	IP Admin			
1	2	30 min	00:25		00:30	5 minutes[e]	
1	3	1 h	00:55		01:00	5 minutes[e]	
1	4	1.5 h	01:25		01:30	5 minutes[e]	
1	5	2 h	01:55		02:00	5 minutes[e]	
1	6	3 h	02:55		03:00	5 minutes[e]	
1	7	4 h	03:55		04:00	5 minutes[e]	
1	8	6 h	05:55		06:00	5 minutes[e]	
1	9	8 h	07:55		08:00	5 minutes[e]	
1	10	12 h	11:55		12:00	5 minutes[e]	
2	11	24 h	23:55		24:00	5 minutes[e]	
2	12	36 h	35:55		36:00	5 minutes[e]	
3	13	48 h	47:55		48:00	5 minutes[e]	
4	14	72 h	71:55		72:00	5 minutes[e]	

[a] Time points for dECG may be adjusted according to emerging PK data.

[b] Times are approximate as dECG and safety ECGs need to be completed before blood sampling.

[c] The subject must be in the same supine body position (max. 30 degrees flexion in the hip) at each time point and at all visits. Subject's feet should not contact the footboard of the bed.

[d] Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.

[e] Subject must rest in bed for at least 10 minutes prior to each ECG time point.

[f] On the dosing days, safety ECG will be printed at the end of each dECG extraction window.

dECG Digital electrocardiogram; ECG Electrocardiogram; IP Investigational product; PK Pharmacokinetics; SAD Single ascending dose

The same recording device will be used for each subject at all time points, when possible. Date and time settings must be checked on the Mortara Telemetry Surveyor at the start of each study day and aligned with an official timekeeper.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement.

Electrode positions will be marked with an indelible pen at the start of each study day to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration of each relevant study day.

Subjects will rest in a supine position for at least 10 minutes (can be reduced to 5 minutes at collection time points within the first hour after dosing) before the start of each recording. The subject should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

The metadata for all dECG files will be checked by the responsible personnel at the study site to ensure that the files transferred to the AstraZeneca central dECG files repository can be approved by the AZ ECG Center to be made accessible to the ECG Scientific Advisors for analysis. As a standard, 10-second ECGs will be extracted by the EClysis© system twice per minute from the continuous recording and initially automatically analyzed by the software.

Lead V2 will be analyzed and reported as primary. Lead V5 will be analyzed, for all visits, as backup for the individual where analysis in lead V2 is not deemed possible for pre-dose, for significant parts of visits or for whole visits.

The ECG Scientific Advisor will perform all required manual corrections to the ECG annotations provided automatically by EClysis©.

To provide a decision basis for dose escalation, the ECG Scientific Advisor(s) will perform a preliminary analysis of the first 24 hours of dECG recordings in lead V2, with the main focus on QT changes, wave morphology changes, and dysrhythmia.

The AZ ECG Center Cardiologist will review the data, perform an evaluation and interpretation of the findings, and will provide a safety report for the SRC meeting.

The AZ ECG Center Cardiologist will review the totality of the data and perform all necessary adjustments before locking the EClysis© data into a read-only state, before the data will be exported.

The numerical values for ECG intervals and amplitudes will be exported and made accessible on the AstraZeneca dECG Central repository to accredited data management specialists for conversion into SAS® files.

The following dECG variables will be reported by the AstraZeneca ECG Center: RR, PR, QRS and QT intervals from the lead defined as the primary analyses lead. Derived parameters (QTcF, HR, and others, as applicable) are calculated by the study statistician or delegate.

8.2.5.3 Telemetry (real-time display)

To allow a real-time assessment of cardiac safety at the study site, subjects will be monitored by telemetry (for real-time assessment of cardiac rate and rhythm) for 24 hours on Day -1, and pre-dose to 48 hours post-dose. Subjects with NSVT and excessive VPCs will be excluded from pre-dose telemetry. Any clinically significant change noted on telemetry will be followed up with a 12-lead ECG. Further evaluation and treatment will be performed as deemed appropriate by the Investigator. Any finding of short, self-limiting, asymptomatic arrhythmia (eg, non-significant tachycardia, atrial fibrillation or flutter) that does not require any medical intervention, should be documented and further evaluated in the context of the individual subject's history and clinical status. Irrespective of the intervention, cardiac monitoring will be continued until the event resolves or the subject is deemed clinically stable by the Investigator.

8.3 Collection of adverse events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

An AE will be reported by the subject.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs, see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Serious AEs will be collected from the time of signature of ICF, throughout the treatment period, and including the follow-up period and last contact. Adverse events will be collected from the time of administration of IP. Non-SAEs occurring between the time of signature of the ICF and the administration of IP will be reported as medical history.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 8.4.1. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject's last visit and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 8.4.1 and Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Whether the AE caused the subject's withdrawal from study *(*yes or no*)*
- Outcome of the AE

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of the SAE

8.3.5 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship will also be assessed for other concomitant medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question can be found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: 'Have you had any health problems since you were last asked?' or revealed by observation, will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in CSP-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or qualify as AEs of interest.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

8.3.8 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3x ULN together with TBL ≥2x ULN may need to be reported as SAEs. Refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the Medical Monitor; the AstraZeneca study physician or physician designate; and MMS Holdings, Inc immediately, or no later than 24 hours after they become aware of the SAE (initial report) using the SAE Report Form provided by MMS Holdings. Telephone and email reports must be confirmed promptly either by facsimile or by overnight courier or mail.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel will inform the Medical Monitor; the AstraZeneca study physician or physician designate; and MMS Holdings, Inc of any follow-up information on a previously reported SAE immediately, or no later than 24 hours from when the Investigator becomes aware of it.

Contact information for the AstraZeneca study physician, the Medical Monitor, and MMS Holdings, Inc are included in the Study Manual.

For guidance on the definition of an SAE, see Appendix B.

8.4.2 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be reported to:

[redacted]

The reports should be made using the [redacted] Pregnancy Notification and Outcome Form.

8.4.2.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study.

Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to [redacted] using the Pregnancy Notification and Outcome Form.

If a subject becomes pregnant during the course of the study, all study drugs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs (Section 8.4.1, Reporting of serious adverse events). Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

8.4.2.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm for the duration of the treatment period and for 4 months after the last administration of IP.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) must be followed up, documented, and reported to [redacted] using the Pregnancy Notification and Outcome Form. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs (Section 8.4.1, Reporting of serious adverse events).

The outcome of any conception occurring from the date of administration of IP until 5 half-lives of AZD4041 or 12 weeks (whichever is longer) after the last administration of IP must be followed up, documented, and reported to [redacted]

8.4.3 Overdose

If a subject receives study medication in excess of that prescribed by the CSP, this will be considered an overdose. There are no data on overdosing with AZD4041, as this is the first clinical study of AZD4041. There is no known specific antidote. In case of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed as per the judgement of the Investigator.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

- In the event of an overdose, the Medical Monitor or physician designate should be contacted immediately to discuss the management plan for the subject. A description of the treatment administered for the overdose as well as the subject's clinical course will be recorded. In the event of an overdose, [redacted]
- For overdoses associated with an SAE, the standard reporting procedures and timelines apply; see Section 8.3.2 and Section 8.4.1.

8.4.4 Medication error

Medication errors with AstraZeneca IP are collected in all studies where medication error is possible. Refer to the Pre-Startup Safety Review (PSSR) or other appropriate project document for specific considerations for collection of medication errors.

For guidance, refer to the AstraZeneca Standard Operating Procedure (SOP) 'Reporting of Individual Safety Events in Clinical Studies'.

If a medication error occurs in the course of the study, the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day; ie, immediately but no later than 24 hours of when the Investigator becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is a SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

The Investigator is responsible for ensuring that expertise and facilities are available for the management of all suspected IP-related toxicities in accordance with local procedures and accepted standards of medical practice. There is no specific antidote to AZD4041. In case of suspected IP-related toxicity, an appropriate level of vital sign monitoring should be instituted; symptomatic and supportive treatment should be provided according to the judgement of the Investigator. Treatment of suspected IP-related toxicity may be guided by further investigations, and referral to a specialist center may be warranted.

Any case of suspected IP-related toxicity should be reported as an AE (Section 8.3) or SAE (Section 8.4.1).

8.4.6 Safety Review Committee

After each cohort, an SRC will evaluate the safety, tolerability and PK of AZD4041 and determine the next dose.

The data from at least 6 subjects in the previous cohort must be reviewed before a decision to escalate can be taken.

The SRC will consist of the following core members:

- Principal Investigator (Chair, voting member)
- AstraZeneca Lead Physician or delegate (must be a physician) (voting member)
- CRO Medical Monitor (voting member)
- CRO Project Manager (nonvoting member)
- Pharmacokineticist (nonvoting member)

The SRC may also request to have attendance of, or offline support and input from the following functions, as required:

- AstraZeneca and/or CRO Pharmacokinetic Scientists
- AstraZeneca Team Pharmacometrician
- CRO and AstraZeneca Statisticians
- AstraZeneca and/or CRO Medical Specialists (eg, neurologist, AZ ECG Center cardiologists, etc.)
- AstraZeneca and/or CRO Patient Safety Physician.

The SRC voting members will make the decision for the next dose level or whether to stop the study after reviewing all the pertinent safety and PK data. Other internal or external experts may be invited to participate in the review or may be consulted.

If consensus among the voting SRC members cannot be reached then the PI, who has the ultimate responsibility for the safety of the subjects, will make the final decision on the next dose level or whether to stop the study. In any event, dose escalation can only occur if agreed by the PI.

The decisions of the SRC on the next dose level will be documented and provided to all the appropriate parties involved with the study, including the Pharmacist, to enable IP preparation for the next scheduled dosing day.

Initially the data will be reviewed blinded, but if the PI or the SRC consider it necessary due to a safety concern, data from individual subjects or the entire cohort may be unblinded to

enable decision-making. Before breaking the code, the potential decisions and actions should be determined. The code will be broken according to local SOPs. The SRC may stop dose escalation at any time if the SRC determines that dose escalation would pose undue risk to subjects. If dose escalation is not stopped, the SRC may recommend ascending to the planned next higher dosage level cohort, ascending to a dosage level lower than the planned next higher dosage level cohort, repeat dosing at the current dosage level, or continuing with a lower dose than the current dosage level.

Following review of data from a cohort of subjects, the timing of assessments and/or blood samples may be adjusted for subsequent cohorts.

Additional assessment or sampling times may be added if indicated by the data.

The following accumulated blinded safety data up to and including Day 15 post-dose follow-up data for a given cohort, as available, will be reviewed by the SRC:

- AE profile, including description, frequency, intensity, onset, duration, and Investigator assessment of the relationship to IP
- SAE listings and case narratives
- Vital sign parameters, including BP, orthostatic BP, and pulse rate
- 12-lead (paper) ECG assessments **and** interval data
- Safety report containing an analysis and review of dECG data, to be provided by the AstraZeneca ECG Center
- Clinical laboratory test results
- PK data
- Testosterone, LH, FSH, and inhibin B assessment results for male subjects

Full SRC details are described in the SRC Charter.

8.5 Pharmacokinetics

8.5.1 Determination of drug concentration

Samples for determination of drug concentration will be analyzed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR, but separately in a Bioanalytical Report.

8.5.2 Metabolite identification in plasma

Following determination of drug concentration and appropriate assessment of incurred sample reproducibility, residual or back-up plasma PK samples may be utilized for investigative metabolite identification studies. Utilizing appropriate analytical methods, this exploratory approach will aim to identify major circulating metabolites of AZD4041 in plasma. The results from the evaluation will not be reported in the CSR, but reported separately in a Metabolite Identification Report.

8.5.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Left-over PK samples may be used for analysis of safety, efficacy, or biomarker laboratory parameters if samples drawn for that purpose at the same time point were insufficient for the analyses needed.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 Pharmacodynamics

To characterize the PD relationship between drug exposure and QT interval, an exposure-response (E-R) analysis may be conducted with data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document for the QTcF parameter, as part of the cardiac safety evaluation and with the intention to obtain a Thorough QT study substitute. The result of the E-R analysis may not be included in the main study report.

9 STATISTICAL CONSIDERATIONS

Safety, tolerability, and PK data will be summarized descriptively as appropriate. Descriptive summary statistics for continuous variables will include number, arithmetic mean, standard deviation, minimum, median, and maximum, while for continuous PK variables, descriptive summary statistics will also include geometric mean and arithmetic coefficient of variation. Descriptive summary statistics for categorical data will include frequency and proportion. Tests of significance of group difference (drug dose versus placebo) on change from baseline in safety variables will also be performed. Model-based approaches will be used, if appropriate.

9.1 Statistical hypotheses

Based on the predicted human exposure following a [redacted] of AZD4041, a [redacted] exposure margin to free C_{max} and a [redacted] exposure margin to free $AUC_{0\text{-}inf}$ when compared to the corresponding toxicokinetic parameters for dog NOAEL dose level in male dogs is predicted. For a [redacted], the corresponding free C_{max} and free $AUC_{0\text{-}inf}$ exposure margins would be [redacted], respectively.

9.2 Sample size determination

Due to the exploratory nature of the study, sample size is not based on formal statistical considerations but is based primarily on a desire to obtain sufficient safety and tolerability information while exposing as few subjects as possible to the investigational treatment.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
PK analysis set	All subjects who received IP and for whom PK data are available
Safety analysis set	All subjects who received at least 1 dose of IP and for whom any post-dose data are available

9.4 Statistical analyses

A comprehensive statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 Pharmacokinetic analyses

Standard PK variables for a single ascending dose study will be derived.

- C_{max}
- T_{max}
- $AUC_{0\text{-}t}$
- $AUC_{0\text{-}inf}$
- $t_{1/2\lambda z}$
- CL/F (apparent total clearance of the drug from plasma after oral administration)
- V_{ss}/F (apparent volume of distribution at steady state after non-intravenous administration)

9.4.2 Safety analyses

All safety analyses will be performed on the Safety analysis set. Specific methods will be described in the SAP.

9.4.2.1 Safety and tolerability

Adverse events will be listed and summarized by Medical Dictionary for Regulatory Activities system organ class and preferred term, and by treatment regimen. The presentation period of AEs will be the time from first dose to follow-up.

Vital signs, body temperature, body weight and BMI, clinical laboratory measures, and dECG interval data will be summarized using descriptive statistics by treatment regimen and CSP time (eg, visit number, date, and time).

Individual data for vital signs, body weight and BMI, clinical laboratory measures, dECG intervals, overall pECG assessments (made by the Investigator), and physical examination results will be flagged and listed for any potentially clinically important (PCI) values for each subject according to predetermined PCI criteria.

Project-specific reference limits will be used in the statistical analysis. When project-specific reference limits are not available, the reference limits of the local laboratory will be used.

9.4.2.2 Pharmacokinetics

AZD4041 serum concentration data will be summarized using descriptive statistics by treatment regimen and scheduled sampling time. Individual and mean AZD4041 serum concentration versus time data will be plotted by treatment regimen.

PK parameters of AZD4041 will be summarized using descriptive statistics by treatment regimen. Dose proportionality and linearity of PK exposure parameters (AUC and C_{max}) will be evaluated using a regression (power) model relating log transformed C_{max} and AUC parameters to the log transformed dose.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Instutional Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject.

If a subject declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the subject and he/she will not be excluded from other aspects of the study.

Subjects who are re-prescreened are required to sign a new brief ICF. The brief ICF is used to obtain subject consent for sUA, eGFR, and UACR assessments. Subjects who are rescreened are required to sign a new full ICF. The full ICF is the master ICF for the study.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The subject will give a separate agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will indicate this in the ICF. If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Subject Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

Safety review committee (SRC)

An SRC will review data from each cohort before progression to the next cohort occurs.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Out-subject treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life- threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated). Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

2 moderate (discomfort sufficient to cause interference with normal activities). Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.

3 severe (incapacitating, with inability to perform normal activities). Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication
- Wrong drug administered to participant

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

B 9 Labelling and shipment of biohazard samples – International Airline Transportation Association 6.2 Guidance Document

The International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are, eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650
  Exempt – all other materials with minimal risk of containing pathogens
- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- Temperature in IATA 650 compliant packaging
  (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

C 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

C 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥3 × ULN **together with** TBL ≥2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

C 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

Central laboratories being used:

When a subject meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix C 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix C 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

C 4 Follow-up

C 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

C 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete the follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
  - Complete the 3 Liver CRF Modules as information becomes available

C 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously-submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Send an updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously-submitted PHL SAE report following the CSP process for SAE reporting, according to the outcome of the review amending, the reported term if an alternative explanation for the liver biochemistry elevations is determined.

References

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmocol Ther 2011; 89(6):806-815.

FDA Guidance for Industry Drug-induced liver injury: Premarketing clinical evaluation. 2009 July.

Appendix D Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	extrapolation of the area under the curve from time 0 to infinity
AV	atrioventricular
BBB	bundle branch block
BMI	body mass index
BP	blood pressure
CL/F	apparent total clearance of the drug from plasma after oral administration
C_{eff}	free efficacious exposure
C_{max}	maximum (peak) plasma drug concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRF	Case Report Form (electronic/paper)
CRO	clinical research organization
CRU	clinical research unit
CSP	clinical study protocol
CSR	clinical study report
CV	cardiovascular
dECG	digital electrocardiogram
E-R	exposure-response
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
eCRF	electronic Case Report Form
EEG	electroencephalogram
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPCR	G protein-coupled receptor
hERG	cardiac potassium ion channel

Abbreviation or special term	Explanation
HIV	human immunodeficiency virus
HL	Hy's Law
HR	heart rate
IBBB	incomplete bundle branch block
IC_{50}	half maximal inhibitory concentration
IC_{90}	in vivo 90% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational product
IRB	Institutional Review Board
IVCD	intraventricular conduction delay
LH	luteinizing hormone
NOAEL	no-observed-adverse-effect level
NREM	non-rapid eye movement
NSVT	non-sustained ventricular tachycardia
OX1	orexin 1 receptor
OX2	orexin 2 receptor
PBPK	physiologically-based pharmacokinetic model
PCI	potentially clinically important
PD	pharmacodynamic
pECG	paper electrocardiogram
PK	pharmacokinetic
PopPK	population pharmacokinetic
PR	pulse rate
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
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	corrected ECG Q-T interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	time elapsed between 2 consecutive R waves as measured by ECG
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SOP	Standard Operating Procedure

Abbreviation or special term	Explanation
SRC	Safety Review Committee
TBL	total bilirubin
$t_{1/2\lambda z}$	terminal half-life
T_{max}	time to reach maximum (peak) plasma concentration following drug administration
ULN	upper limit of normal
VPC	ventricular premature contraction
V_{ss}/F	apparent volume of distribution at steady state after non-intravenous administration