AstraZeneca

Revised Clinical Study Protocol

Drug Substance	AZD4901
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A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

Date

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
3			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

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PROTOCOL SYNOPSIS

A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

International Co-ordinating Investigator

Study centre(s) and number of subjects planned

This is a multi-centre study. Fifty-six patients (14 patients per cohort) with polycystic ovary syndrome (PCOS) will be enrolled to have approximately 12 evaluable patients in each of the 4 cohorts.

Study period	Phase of development
Estimated date of first subject enrolled	IIa
Estimated date of last subject completed	

Objectives

The primary objective of this study is to determine change from baseline of luteinizing hormone (LH) area under the concentration curve from time zero to 8 hours postdose [$AUC_{(0-8)}$] at Day 7 in comparison to placebo.

The secondary objectives of the study are:

- To determine the change from baseline of free and total testosterone on Days 7 and 28
- To assess the safety and tolerability of multiple dosing of AZD4901 in patients with PCOS
- To measure AZD4901 and AZ12592232 plasma exposure in patients with PCOS

- To evaluate the pharmacokinetic/pharmacodynamic relationship of AZD4901 and LH and testosterone

The exploratory objectives of this study are:

- To monitor changes from baseline of LH (Day 28 only); follicle-stimulating hormone (FSH), estradiol (E2), progesterone, prolactin, thyroid-stimulating hormone, T4 (total and free), and insulin-like growth factor-1 (as surrogate for growth hormone to avoid diurnal variation) on Days 7 and 28; and glycosolated haemoglobin on Day 28

- To explore the impact of AZD4901 on health-related quality of life as measured by change from baseline at Day 28

- To explore the impact of AZD4901 on PCOS-specific patient-reported outcomes symptoms as measured by change from baseline at Days 7, 14, 21, and 28

Results of the above exploratory analyses, if available, will be reported in the Clinical Study Report.

- To collect and store deoxyribonucleic acid for future exploratory research into genes that may influence response, ie, distribution, safety, tolerability, and efficacy of AZD4901 treatment

The results of the pharmacogenetic analysis, if performed, will be reported separately from the Clinical Study Report.

Study design

This is a randomised, double-blind, double-dummy, placebo-controlled, parallel-design study of a multiple dosing of placebo or AZD4901. Patients will be randomly assigned to 1 of the following 4 treatments: 20 mg AZD4901 once daily, 20 mg AZD4901 twice daily, 40 mg AZD4901 twice daily, or placebo. Investigational product will be administered orally beginning on Day 1 and continuing through the morning of Day 28. In order to maintain study blinding, patients will be administered two AZD4901 and/or matching placebo tablets twice daily as follows:

- 20 mg AZD4901 once daily: one 20-mg AZD4901 tablet and 1 placebo tablet for the morning dose and 2 placebo tablets for the evening dose

- 20 mg AZD4901 twice daily: one 20-mg AZD4901 tablet and 1 placebo tablet for both the morning and evening doses

- 40 mg AZD4901 twice daily: two 20-mg AZD4901 tablets for both the morning and evening doses

- Placebo: two matching placebo tablets for both the morning and evening doses

Study screening will begin up to 60 days prior to the baseline visit to allow a washout period for patients taking oral contraceptives. Patients who discontinue oral contraceptives and patients who do not require washout from oral contraceptives, but who have screening assessments more than 3 weeks prior to the baseline visit, will return to the clinic on Days -21 to -2 for repeat laboratory assessments. Patients not taking oral contraceptives who have screening assessments within 3 weeks of the baseline visit do not need to repeat laboratory tests.

Eligible patients will report to the clinic on Day -1 for baseline assessments and will receive supplies of investigational product to begin at-home dosing on Day 1 as an outpatient. A diary card will be provided to record the date and time of each dose. Patients will be given symptoms diary paper questionnaires for home assessments. On Days 7, 14, 21, and 28, patients will return to the clinic to take their morning dose of investigational product and to complete scheduled assessments. If it is not practical for patients to return to the clinic prior to the morning dose on Days 14 and 21, patients may take the morning dose at home and report to the clinic later in the day for study assessments. A follow-up visit will occur at approximately Day 42.

On Days -1, 7, and 28, multiple samples for the analyses of LH (every 10 minutes), FSH (hourly), and testosterone (hourly) profiles will be collected prior to dosing until 8 hours following the morning dose. On Day -1, sampling will begin just prior to the anticipated time of dosing on subsequent study days and continue for 8 hours. Patients will be asked to complete the health-related quality of life, short form 36 at baseline (Day -1) and on Day 28. A symptoms site questionnaire will be completed at each study visit from Day -1 through Day 28. A symptoms diary questionnaire will be completed at the patients' homes each evening from Day -1 through Day 28. Serial pharmacokinetic samples will be collected prior to dosing until 8 hours postdose on Days 7 and 28. Safety evaluations will be conducted at screening and at each study visit.

Target subject population

Women with PCOS between the ages of 18 and 45 years, inclusive, are eligible for study participation.

Investigational product, dosage, and mode of administration

AZD4901 20-mg tablets and matching placebo will be administered orally. On Days 7 and 28, patients will take their morning doses of investigational product in the clinic with 240 mL of water. On Days 14 and 21, patients may report to the clinic for their morning dose, if practical. Otherwise, all doses will be taken as an outpatient with a sufficient amount of water.

Duration of treatment

Following a screening period of 60 days maximum, the study duration from baseline through the follow-up visit will be approximately 6 weeks for each patient. Apart from required in-clinic dosing on the mornings of Days 7 and 28 and optional in-clinic dosing the mornings

of Days 14 and 21, investigational product will be taken on an outpatient basis twice daily from Day 1 through the morning dose on Day 28. A follow-up visit will occur at approximately Day 42.

Outcome variable(s):

- Pharmacokinetics: Where possible, the following pharmacokinetic parameters will be determined for AZD4901 and AZ12592232 for Day 7 and Day 28:

  - C_{max}: Maximum observed plasma concentration.
  - t_{max}: Time of C_{max}.
  - $AUC_{(0-8)}$: Area under the plasma concentration-time curve from time zero to 8 hours
  - C_{min}: Predose concentration
  - C_{max} metabolite to parent ratio: The ratio of AZ12592232 C_{max} to AZD4901 C_{max}
  - $AUC_{(0-8)}$ metabolite to parent ratio: The ratio of AZ12592232 $AUC_{(0-8)}$ to AZD4901 $AUC_{(0-8)}$

  The following will be calculated for 4-β-hydroxy cholesterol and 6-β-hydroxy testosterone:

  - Ratio of post treatment (Day 28) to pretreatment (Day -1) concentration

- Pharmacodynamics:

  - Primary: $AUC_{(0-8)}$ for LH on Day 7
  - Secondary: Change-from-baseline (Day-1) for free and total testosterone concentrations on Days 7 and 28; and $AUC_{(0-8)}$ for LH on Day 28

    Where possible, the following secondary pharmacodynamic parameters will be determined for LH, testosterone, and FSH samples collected on Days -1, 7, and 28: free and total testosterone $AUC_{(0-8)}$, FSH $AUC_{(0-8)}$, an evaluation of LH pulse interval and amplitude, free and total testosterone C_{max}, free and total testosterone C_{min}, FSH C_{max}, FSH C_{min}, and $AUC_{(0-8)}$ for LH.

  - Exploratory: Change-from-baseline (Day-1) for LH (Day 28 only), FSH, and the components of the monitoring sample (estradiol [E2], progesterone, prolactin, thyroid-stimulating hormone, T4 [total and free], and insulin-like growth factor- 1) on Day 7 and Day 28

- Safety: Assessments will include adverse events, vital sign measurements, electrocardiograms, physical examination results, Columbia-Suicide Severity Rating Scale assessments, and laboratory tests (chemistry, haematology, and urinalysis).

- Patient reported outcomes: Assessments will include the short form 36, a symptoms site questionnaire, and a symptoms diary questionnaire.

Statistical methods

The AZD4901 and AZ12592232 concentrations and pharmacokinetic parameters will be listed and summarised.

Observed pharmacodynamic concentrations, derived change from baseline results, and parameter values for individual patients will be listed and summarised with appropriate descriptive statistics across all treatments for LH, free testosterone, total testosterone, and FSH.

The primary analysis comparison of $AUC_{(0-8)}$ for LH at Day 7 and secondary comparison of $AUC_{(0-8)}$ for LH at Day 28, $AUC_{(0-8)}$, C_{max}, and C_{min} for total testosterone, free testosterone, and FSH will be conducted using an analysis of variance model on the ln-transformed ratio to baseline values. The results from this analysis of variance will be back-transformed to the linear scale to provide point estimates for each treatment as well as point estimates and 90% confidence intervals for the ratios versus placebo. The analyses of secondary pharmacodynamic parameters will be conducted using the same analysis of variance model described above. Descriptive statistics will be provided for absolute change, percent change from baseline, and ln-ratio to baseline values for LH and free and total testosterone. An evaluation of LH pulse interval and amplitude will be performed by AstraZeneca.

The pharmacokinetic/pharmacodynamic relationship of AZD4901 and LH and testosterone will be explored graphically if appropriate.

Responses from the patient-reported outcomes symptoms questionnaires and the health-related quality of life assessments will be listed and summarised, as appropriate.

Tabulations and listings of data for vital signs, physical examinations, electrocardiograms, Columbia-Suicide Severity Rating Scale assessments, and clinical laboratory tests will be presented. For clinical laboratory tests, listings of values for each patient will be presented with abnormal or out-of-range values flagged. Adverse events will be summarised by preferred term and system organ class for each treatment.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-8)}$	Area under the concentration-time curve from time zero (predose) to 8 hours postdose
BLQ	Below the limit of quantitation
BMI	Body mass index
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed concentration
C_{min}	Predose concentration
CPA	Clinical Pharmacology Alliance
CRF	Case report form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
HbA_{1c}	Glycosolated haemoglobin

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HPG	Hypothalamic pituitary gonadal
HRQoL	Health-related quality of life
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IGF-1	Insulin-like growth factor-1
IP	Investigational Product
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NK-3	Neurokinin-3
NKB	Neurokinin B
OAE	Other significant adverse event (see definition in Section 11.1.2)
OH	Hydroxy
PCOS	Polycystic ovary syndrome
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient reported outcomes
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SF-36	Short form 36
SOP	Standard operating procedure
t_{max}	Time to the maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of the normal range

1. INTRODUCTION

1.1 Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women, affecting approximately 5% to 10% of women overall (March et al 2010). Polycystic ovary syndrome is a heterogeneous disorder of unclear aetiology of which the principal clinical features are virilisation, disturbances of menstruation, infertility, metabolic derangement, and polycystic ovaries. Patients exhibit excessive amounts or effects of androgenic hormones, resulting in acne, hirsutism, and insulin resistance, often associated with obesity, Type 2 diabetes, and high cholesterol levels. The exact aetiology of the insulin resistance and metabolic derangement is uncertain. The symptoms and severity of the syndrome vary greatly among affected women. Long-term risks in such patients include coronary artery disease and cerebrovascular disease, as well as the risk of unopposed oestrogen and chronic anovulation: endometrial hyperplasia, dysfunctional uterine bleeding, and possibly endometrial cancer.

Patients with PCOS are known to have an altered hypothalamic-pituitary-gonadal (HPG) axis. Increased luteinizing hormone (LH) pulse amplitude and pulse frequency is a key characteristic of PCOS. While gonadotropin-releasing hormone (GnRH) pulsatile release cannot be assessed directly in humans, it is believed that peripheral LH pulses are directly related to hypothalamic GnRH. Normal GnRH pulses are approximately once every 90 to 100 minutes during the follicular stage with a gradual increase in GnRH pulsatility at mid cycle causing an LH surge and thus ovulation. Women with PCOS have GnRH pulses approximately once every 60 minutes, rarely obtain an LH surge, and thus are often anovulatory (Hall et al 1998, Knobil et al 2006).

Neurokinin B (NKB), by activation of neurokinin-3 (NK-3) receptors along with the coordinately secreted neuropeptides, kisspetin and dynophin, serves to regulate the pulsatile secretion of GnRH (Maeda et al 2010). AZD4901 binds with high affinity to human NK-3 receptors.

In both clinical pharmacology studies in healthy volunteers and in a study of schizophrenia (mainly in males), a reduction in testosterone, and to some degree LH, has been observed,

There are no treatments indicated specifically for PCOS. Current treatments for PCOS address the effects of the disease, eg, spironolactone and GnRH modulators as anti-androgen therapy, metformin for the metabolic derangement, oral contraceptive pills for normalization of menstruation, or the selective oestrogen receptor modulator, chlomiphene, to induce ovulation. All of these treatments address symptomatology but not pathophysiology and have significant side effects, eg, prevention of pregnancy or inducement of multiple/multi-fetal pregnancies, lactic acidosis, and ovarian hyperstimulation syndrome. None modify the underlying GnRH pulse generator to modify the disease.

Based on the clinical endocrine changes observed and an understanding of the mechanism of action, AZD4901 is now being evaluated for the treatment of PCOS. A treatment that could modulate the GnRH axis could potentially control the symptoms of PCOS and restore regular menses and ovulation.

1.1.1 Preclinical studies

AZD4901 binds with high affinity to human NK-3 receptors, with a dissociation constant of an inhibitor of 2 nM versus [125I]His, MePhe7 NKB agonist. AZD4901 completely blocked agonist (senktide) induced calcium flux in Chinese hamster ovary (CHO) cells stably expressing human NK-3 receptors with a concentration of drug causing half-maximal inhibitory concentration (IC_{50}) of 2.57 nM. AZ12592232, a metabolite of AZD4901, completely blocked agonist (senktide) induced calcium flux in CHO cells stably expressing human NK-3 receptors with an IC_{50} value of 9.05 nM.

1.1.2 Clinical studies

The early clinical program conducted with AZD4901 for the indication of schizophrenia was comprised of 2 single ascending dose studies (1 in Japanese volunteers) and 2 multiple ascending dose studies (1 in Japanese volunteers) in healthy male volunteers, a relative bioavailability study in healthy male and female volunteers, and a Phase II study in patients with schizophrenia. One hundred and sixty subjects (6 females) received AZD4901 at doses ranging between 1 and 80 mg (single doses), 30 mg twice daily (multiple dose study), or for up to 28 days at 40 mg once daily. Both suspension and tablets (20-mg strength) have been utilised.

Pharmacokinetic (PK) properties have been well investigated in healthy male volunteers. AZD4901 was quickly absorbed following oral dosing. The elimination half-life for AZD4901 was approximately 7 hours. Both the area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}) appeared to be dose proportional for both AZD4901 and the active metabolite, AZ12592232. Renal elimination of AZD4901 or AZ12592232 was negligible.

Following multiple dose administration, PK steady state was achieved within 4 days, at which the exposure to AZ12592232 was approximately 66% of the parent; the accumulation of AZD4901 in the plasma was minimal following once-daily dosing and was greater following twice-daily dosing. AZD4901 PK appeared to be time independent. Limited exposure observed in females suggests no difference in PK properties between females and males. Based on limited observations, oral administration of AZD4901 suspension or tablets with food (a high-fat meal) increased the rate of absorption (suspension: 25% increase in C_{max}; tablet: 75% increase in C_{max}). To date, there has been no clear demonstration of C_{max}-related toxicity in humans receiving up to 80 mg of the suspension.

Cytochrome P450 (CYP) enzymes *CYP2C9*, *CYP3A4*, and *CYP3A5* in vitro appeared to be involved in the metabolism of AZD4901. AZD4901 exhibited weak to moderate inhibitory effect on *CYP3A4/5* with an apparent IC_{50} of 7.1 and 19.8 μM in midazolam and testosterone

assays, respectively. AZD4901 may also have the the potential to induce *CYP3A4/5* enzymes. Clinical drug/drug interaction studies have not yet been performed.

Across the single- and multiple-ascending dose studies, there were no discontinuations due to adverse events (AEs) and no other significant AEs. Data obtained from these studies in healthy volunteers did not identify any safety or tolerability concerns that preclude development of AZD4901 in patients with PCOS. As noted above, a reduction in testosterone, and to some degree LH, has been observed in subjects receiving AZD4901.

Additional information may be found in the Investigator's Brochure.

AstraZeneca will immediately notify the Investigator of important safety data that become available during the study.

1.2 Research hypothesis

The study will evaluate the hypothesis that modulation of the GnRH axis by AZD4901 will result in lowering of LH levels in patients with PCOS.

1.3 Rationale for conducting this study

In the previous neuroscience studies of AZD4901 decreased testosterone was observed. In healthy male volunteers the effect increased with dose and levels remained below baseline at the higher once-daily doses and upon twice-daily dosing. Luteinizing hormone- and testosterone-lowering effects have also been documented with other NK-3 receptor antagonists that were in development for schizophrenia and irritable bowel syndrome.

Patients with PCOS are known to have an altered HPG axis. Normal healthy women release GnRH pulses from the hypothalamus approximately once every 90 to 100 minutes during the follicular stage with a gradual increase in GnRH pulsatility mid cycle causing an LH surge and thus ovulation. Women with PCOS have GnRH pulses approximately once every 60 minutes, resulting in an excess of pituitary LH secretion leading to failure of ovulation and increased ovarian testosterone production (Clarke 1982, Hall et al 1998, Levine et al 1982, Waldstreicher et al 1988).

In vitro and in-vivo data indicate that NKB, the ligand for the NK-3 receptor, is 1 of 3 generators of GnRH pulsatility (Lehman et al 2010, Maeda et al 2010). Blockade of the effect of NKB through NK-3 receptor antagonism is hypothesised to decrease GnRH pulse activity, with the consequent observed effects on LH and downstream gonadal hormones.

Given the clinical signal of decreased testosterone observed with AZD4901 and the recently-documented role of NKB in stimulating GnRH pulsatility, it is hypothesised that the clinical effect of AZD4901 would be to reduce the 'over-activity' of the GnRH pulse generator in patients with PCOS, thereby normalizing the hormonal axis.

As an NK-3 receptor antagonist has not been tested in PCOS, the testosterone-lowering effect of AZD4901 and other NK-3 receptor antagonists in healthy male volunteers is considered the

best predictor of effect in human females. In concert with the fact that preclinical models of PCOS are poor representations of the human disease, a clinical trial with AZD4901 in patients with PCOS is required.

1.4 Benefit/risk and ethical assessment

In clinical trials to date, AZD4901 has been well tolerated and dose escalations have been driven by the effects on testosterone levels that are now a key marker for efficacy in this new development. Nonclinical data indicate a potential for hepatotoxicity, but this has not been observed in the clinical program to date and patient's liver function will be monitored during their participation in the current trial.

AZD4901 may have the potential to induce and also inhibit *CYP3A4/5* enzymes. Due to the potential CYP induction/inhibition risk, concomitant use of AZD4901 with narrow therapeutic index drugs that are metabolised by *CYP3A4/5* should be avoided. Investigators should be aware that the exposure of other drugs metabolised by *CYP3A4* could be altered. See Table 3 for a list of restricted medications.

As a disease of younger females, the patients in the trial are necessarily of childbearing potential, although PCOS often impairs fertility. Patients will be required to use reliable contraception throughout the trial. Hormonal contraception is disallowed as it could impact the primary efficacy measurements.

Polycystic ovary syndrome can result in disruption of menstruation, infertility, virilisation, and, in the longer term, serious metabolic consequences. Treatments are available, but are intended to suppress symptoms of PCOS with variable effectiveness. AZD4901 represents a possibility to effect the underlying biology of PCOS and this study is the first step to validate that hypothesis. As such, the benefit:risk is positive and administration of AZD4901 to women with PCOS is justified.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine change from baseline of LH area under the concentration curve from time zero to 8 hours postdose [$AUC_{(0-8)}$] at Day 7 in comparison to placebo.

2.2 Secondary objectives

The secondary objectives of the study are:

- To determine the change from baseline of free and total testosterone on Days 7 and 28

- To assess the safety and tolerability of multiple dosing of AZD4901 in patients with PCOS

- To measure AZD4901 and AZ12592232 plasma exposure in patients with PCOS

- To evaluate the PK/pharmacodynamic (PD) relationship of AZD4901 and LH and testosterone

2.3 Exploratory objectives

The exploratory objectives of this study are:

- To monitor changes from baseline of LH (Day 28 only); follicle-stimulating hormone (FSH), estradiol (E2), progesterone, prolactin, thyroid-stimulating hormone (TSH), T4 (total and free), and insulin-like growth factor-1 (IGF-1; as surrogate for growth hormone to avoid diurnal variation) on Days 7 and 28; and glycosolated haemoglobin (HbA_{1c}) on Day 28

- To explore the impact of AZD4901 on health-related quality of life (HRQoL) as measured by change from baseline at Day 28

- To explore the impact of AZD4901 on PCOS-specific patient-reported outcomes symptoms as measured by change from baseline at Days 7, 14, 21, and 28

Results of the above exploratory analyses, if available, will be reported in the Clinical Study Report (CSR).

- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence response, ie, distribution, safety, tolerability, and efficacy of AZD4901 treatment

The results of the pharmacogenetic analysis, if performed, will be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a randomised, double-blind, double-dummy, placebo-controlled, parallel-design study of a multiple dosing of placebo or AZD4901 to investigate effects of AZD4901 on the GnRH axis. Women with PCOS between the ages of 18 and 45 years, inclusive, are eligible for study participation. Patients will be randomly assigned to 1 of the following 4 treatments: 20 mg AZD4901 once daily, 20 mg AZD4901 twice daily, 40 mg AZD4901 twice daily, or placebo. There will be 56 patients enrolled (14 patients per cohort) to have approximately 12 evaluable patients in each of the 4 cohorts. The investigational product (IP) will be administered orally beginning on Day 1 and continuing through the morning of Day 28. To

maintain study blinding, AZD4901 and/or matching placebo will be administered such that 2 tablets are taken twice daily for all treatment groups (see Section 5.5.2).

Study screening will begin up to 60 days prior to the baseline visit to allow a washout period for patients taking oral contraceptives. Patients who discontinue oral contraceptives and patients who do not require washout from oral contraceptives, but who have screening assessments more than 3 weeks prior to the baseline visit, will return to the clinic on Days -21 to -2 for repeat laboratory assessments. Patients not taking oral contraceptives who have screening assessments within 3 weeks of the baseline visit do not need to repeat laboratory tests.

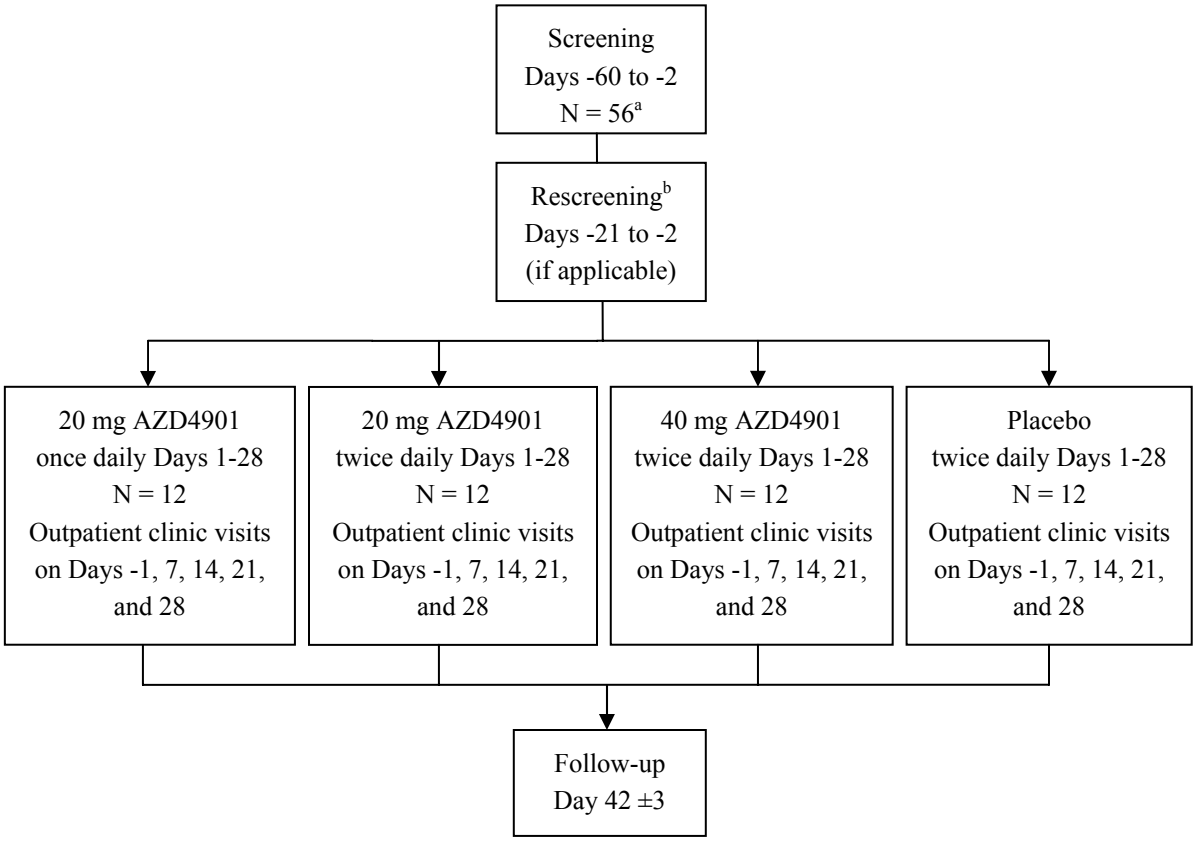
Following the screening period, the study duration from baseline through the follow-up visit will be approximately 6 weeks for each patient. Eligible patients will report to the clinic on Day -1 for baseline assessments and will receive supplies of IP to begin dosing on Day 1 as an outpatient. A diary card will be provided to record the date and time of each dose. Patients will be given symptoms diary paper questionnaires for home assessments. On Days 7, 14, 21, and 28, patients will return to the clinic to take their morning dose of IP and to complete scheduled assessments. If it is not practical for patients to return to the clinic prior to the morning dose on Days 14 and 21, patients may take the morning dose of IP at home and report to the clinic later in the day for study assessments. A follow-up visit will occur at approximately Day 42.

On Days -1, 7, and 28, multiple samples for the analyses of LH, FSH, and testosterone profiles will be collected prior to dosing until 8 hours following the morning dose. On Day -1, sampling will begin just prior to the anticipated time of dosing on subsequent study days and continue for 8 hours. Intensive sampling should begin by 9 AM on Day -1 and will be initiated at approximately the same time on each subsequent visit (±1 hour). Patients will be asked to complete the HRQoL short form 36 (SF-36; see Appendix E) at baseline (Day -1) and on Day 28. A site symptoms questionnaire will be completed at each study visit from Day -1 through Day 28 (see Appendix F). A symptoms diary questionnaire will be completed at the patients' homes each evening from Day -1 through Day 28. Serial PK samples will be collected prior to dosing until 8 hours following the morning dose on Days 7 and 28. On Days 14 and 21, patients will report to the clinic to undergo safety assessments.

Safety evaluations will include assessment of AEs, use of concomitant medications, clinical laboratory tests, measurement of vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments.

A study flow chart is presented in Figure 1, a schedule of all assessments is presented in Table 1, and the details of blood sample collection are presented in Table 2.

Figure 1 Study flow chart



Outpatient administration of IP begins the morning of Day 1 for all treatments. A window of ±1 day is allowed for the Day 7, 14, 21, and 28 visits.

[a] There will be 56 patients (14 per each treatment group) enrolled to have approximately 12 evaluable patients in each treatment group.

[b] Applies only to patients who require washout of oral contraceptives or have a screening visit more than 3 weeks prior to the baseline visit.

Table 1 Study plan

	Screening[a]		Baseline					Follow-up	Early discontinuation
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day relative to first dose	**-60 to -2**	**-21 to -2**	**-1**	**+7±1**	**+14±1**	**+21±1**	**+28±1**	**+42±3**	
Informed consent	X								
Review of inclusion/exclusion criteria	X	X							
Demography	X								
Medical/surgical history	X								
Ultrasound	X[b]								
Serology assessment[c]	X								
Test for alcohol and drugs of abuse[d]	X		X						
Pregnancy test	X[e]	X	X	X	X	X	X	X	X
Randomisation			X						
Dispense IP[f]			X						
Dispense dosing diary[g]			X						
Fast for 2 hours prior to and 1 hour following morning dose				X			X		
Administer morning dose in clinic				X	X[h]	X[h]	X[i]		
Assessment of compliance				X	X	X	X		
Return of unused IP[f]				X	X	X	X		
Record concomitant medications[j]	X	X	X	X	X	X	X	X	X
Record AEs[k]	X	X	X	X	X	X	X	X	X
Physical examination[l]	X		X				X	X	X

Table 1 Study plan

	Screening[a]		Baseline					Follow-up	Early discontinuation
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day relative to first dose	**-60 to -2**	**-21 to -2**	**-1**	**+7±1**	**+14±1**	**+21±1**	**+28±1**	**+42±3**	
Weight	X		X	X			X	X	X
Height and BMI	X								
Vital signs[m]	X		X	X			X	X	X
12-lead ECG	X		X	X[n]			X[n]	X	X
Haematology[o]	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X
Urinalysis	X	X					X	X	X
C-SSRS[p]			X	X	X	X	X	X	X
Pharmacokinetic samples[q]				X			X		X
HRQoL - SF-36			X				X		X
Symptoms site questionnaire			X	X	X	X	X		X
Symptoms diary questionnaire[r]			X	X	X	X	X		
High frequency LH samples[s]			X	X			X		
Well-defined FSH[t]			X	X			X		
Single sample LH	X	X						X	X
Single sample FSH	X							X	X
Single sample testosterone (total/free)	X	X						X	X
Well-defined testosterone (total/free)[t]			X	X			X		
4-β-OH cholesterol			X				X[u]		

Table 1 Study plan

	Screening[a]		Baseline					Follow-up	Early discontinuation
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day relative to first dose	**-60 to -2**	**-21 to -2**	**-1**	**+7±1**	**+14±1**	**+21±1**	**+28±1**	**+42±3**	
6-β-OH testosterone			X				X[u]		
TSH and T4 (total and free)[v]	X		X	X			X	X	X
HbA_{1c} [v]			X				X	X	X
IGF-1, progesterone, E2[v]			X	X			X	X	X
Prolactin[v]	X		X	X			X	X	X
Consent and blood sample for genetic analysis (optional)[w]				X					

BMI body mass index; HIV human immunodeficiency virus; OH hydroxy; SAE serious AE.

[a] Patients who must discontinue the use of oral contraceptives prior to the study will return to the clinic on Days -21 to -2 for repeat laboratory assessments. Patients who do not require a washout of oral contraceptives, but screening assessments were performed more than 3 weeks from the baseline visit, will also return to the clinic on Days -21 to -2 for repeat laboratory assessments.

[b] May be performed if there is no previously-documented ultrasound for diagnosis of PCOS.

[c] Screen for HIV, hepatitis B, and hepatitis C.

[d] Random drug and alcohol screening at subsequent visits may be performed at the discretion of the Investigator. See Section 6.3.5 for a list of analytes.

[e] Serum pregnancy tests will be performed at screening only; urine tests will be performed at all other time points.

[f] The first dose of IP is to be taken the morning of Day 1 as an outpatient. On Day -1, patients will be given sufficient IP for at-home dosing for the duration of the study. At each clinic visit, the patient should return all unused supplies of IP.

[g] The patient will be asked to record the dosing dates and times for all IP administration and bring the diary to each clinic visit for review. On Days 6 and 27, ie, the days prior to the serial PK and PD assessments, the sites should contact the patients by telephone to ensure the morning and evening doses were recorded and to remind patients to hold the morning dose on Days 7 and 28 until clinic arrival.

[h] On Days 14 and 21, it is suggested patients take their morning dose of IP in the clinic; however, if this is not practical, dosing may occur at home with the patient reporting to the clinic later in the day for scheduled procedures.

[i] On Day 28, only a morning dose is taken.

[j] All concomitant medications taken from 12 weeks prior to dosing are to be recorded.

[k] All SAEs will be recorded from the time informed consent is signed; nonserious AEs will be recorded beginning at the baseline (Day -1) visit.

[l] Full physical examinations will be performed at screening and follow-up/early discontinuation; brief examinations will be performed on Days -1 and 28. See Section 6.3.6 for details of the assessments.

[m] Blood pressure and pulse rate will be measured after patient has rested in a supine position for 10 minutes.

[n] Electrocardiograms will be recorded at 2 hours postdose on Days 7 and 28.

[o] Including hematocrit at screening and at the follow-up (or early termination) visit.

[p] A patient reporting suicidal ideation of Type 4 or 5 or suicidal behaviour as measured by the C-SSRS during the study will be discontinued and referred for appropriate assessment and treatment.

[q] On Days 7 and 28, PK samples will be collected prior to the morning dose, and at 20 minutes, 40 minutes, and 1, 1.5, 2, 3, 4, 6, and 8 hours postdose. A single sample will be collected in the event of early discontinuation.

[r] The symptoms diary questionnaire should be completed at home each evening before patients go to bed.

[s] Luteinizing hormone samples will be collected prior to the morning dose (on Days 7 and 28; on Day -1, the 0 h sample will be collected prior to the anticipated time of dosing on subsequent study days) and every 10 minutes following dosing through 8 hours postdose. Intensive sampling should begin by 9 AM and will be initiated at approximately the same time at each visit (±1 hour). The first sample will be collected within 30 minutes prior to dosing or at an approximately matched time at the baseline visit.

[t] Testosterone (total and free) and FSH will be collected prior to dosing (on Days 7 and 28; on Day -1, the 0 h sample will be collected prior to the anticipated time of dosing on subsequent study days) and hourly for 8 hours postdose; the first sample will be collected within 30 minutes prior to dosing or at an approximately matched time at the baseline visit.

[u] The 4-β-OH cholesterol and 6-β-OH testosterone samples will be collected prior to dosing on Day 28.

[v] Component of the monitoring sample (includes estradiol [E2], progesterone, prolactin, TSH, T4 [total and free], HbA_{1c}, and IGF-1) and will be collected ±1 hour of the same time each scheduled day beginning on Day -1 and for all subsequent visits. Thyroid tests (TSH and total/free T4) and prolactin only will be performed at screening to assess study eligibility. The HbA_{1c} will not be performed on Day 7.

[w] If informed consent is given for the optional genetic sampling, a single sample may be collected on Day 7 (Visit 3) or at any time after randomisation and stored for future analysis.

Table 2 Blood sample collection schedule

Study day	Scheduled time	Safety laboratory[a]	PK	LH	FSH	Testosterone (total/free)	4-β-OH cholesterol/ 6-β-OH testosterone	Monitoring sample[b]	Genetic
Screening		X		X[c]	X[c]	X[c]		X[d]	
Rescreening[e]		X		X[c]		X[c]			
Day -1	0 h	X		X	X	X	X	X	
	0-8 hours[f]			Every 10 min	Hourly	Hourly			
Day 7	0 h (predose)	X	X	X	X	X		X[g]	X[h]
	0-8 hours[i]		Serial[j]	Every 10 min	Hourly	Hourly			
Day 14		X							
Day 21		X							
Day 28	0 h (predose)	X	X	X	X	X	X	X	
	0-8 hours[i]		Serial[j]	Every 10 min	Hourly	Hourly			

Table 2 Blood sample collection schedule

Study day	Scheduled time	Safety laboratory[a]	PK	LH	FSH	Testosterone (total/free)	4-β-OH cholesterol/ 6-β-OH testosterone	Monitoring sample[b]	Genetic
Follow-up		X		X[c]	X[c]	X[c]		X	
Early termination		X	X[c]	X[c]	X[c]	X[c]		X	

[a] Haematology and clinical chemistry at all time points with serology and serum pregnancy assessments at screening only and hematocrit at screening and follow-up.
[b] Monitoring sample includes estradiol (E2), progesterone, prolactin, TSH, T4 (total and free), HbA_{1c}, and IGF-1.
[c] Single sample only.
[d] Only TSH, total/free T4, and prolactin assessed at screening to determine study eligibility.
[e] Applies only to patients who require washout of oral contraceptives or have a screening visit more than 2 weeks prior to the baseline visit.
[f] On Day -1, LH samples will be collected prior to the anticipated time of the morning dose on subsequent study days and every 10 minutes through 8 hours; FSH and testosterone (total and free) will be collected prior to the anticipated time of the morning dose on subsequent study days and every hour through 8 hours.
[g] HbA_{1c} will not be collected on Day 7.
[h] If informed consent is given for the optional genetic sampling, a single sample may be collected on Day 7 (Visit 3) or at any time after randomisation and stored for future analysis.
[i] On Days 7 and 28, LH samples will be collected prior to the morning dose and every 10 minutes through 8 hours postdose; FSH and testosterone (total and free) will be collected prior to the morning dose and every hour through 8 hours postdose.
[j] On Days 7 and 28, PK samples will be collected prior to the morning dose, and at 20 minutes, 40 minutes, and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose.

3.2 Rationale for study design, doses and control groups

The current study design includes an oral administration of AZD4901 tablets to fully explore the PD, safety, and PK of AZD4901 with an 8-hour intensive collection of blood samples at a predose baseline then on Days 7 and 28 following the daily dose. As GnRH levels cannot be measured in this study, it is anticipated that any modulation of GnRH release in patients receiving AZD4901 will result in a change from baseline in LH $AUC_{(0-8)}$ hours and this is the primary endpoint of the study.

Day 7 has been selected as the primary endpoint for LH measurement as AZD4901 will be at steady state and also to avoid any impact should a patient have downstream hormonal effects from the modulation of their HPG axis. Day 28 has been selected to assess the longer term efficacy on testosterone and the duration of the effects on LH secretion.

In vitro AZD4901 completely blocked agonist (senktide)-induced calcium flux in CHO cells stably expressing human NK-3 receptors with a concentration of drug causing an IC_{50} of 2.57 nM.

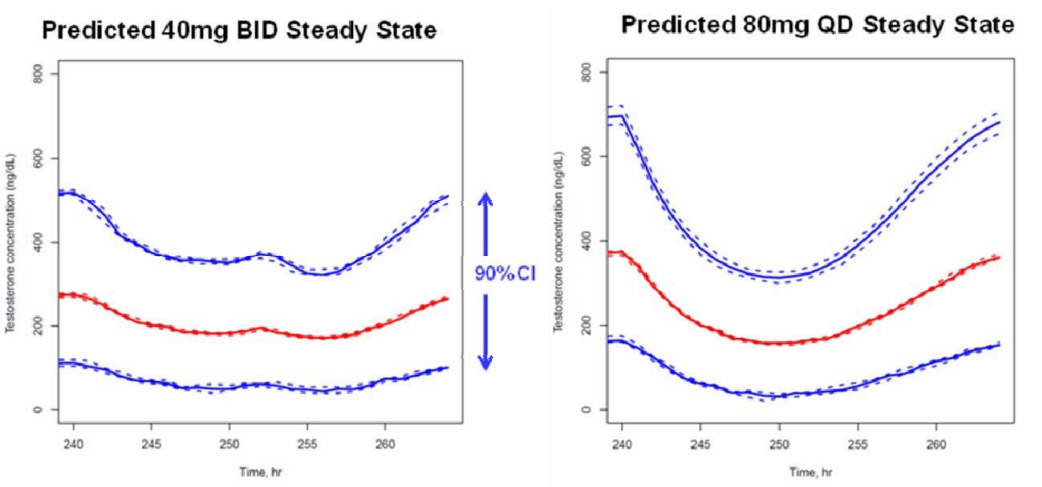
In vivo AZD4901 dose-dependently reversed senktide-induced suppression of locomotor activity in the gerbil by both the intraperitoneal and oral routes. In this study, the brain:plasma ratio for AZD4901 was approximately 0.2. However, there is evidence that the NK-3 receptors relevant to the current development are to be exposed to the systemic circulation (Norsted et al 2008).

In the clinical trials to date, suppression of testosterone was seen at all doses, with the effect persisting for 24 hours at the highest monotherapy dose of 80 mg once daily or with 15 mg twice daily or 30 mg twice daily. It appears that AZD4901 modulates the HPG axis but does not suppress it completely.

Based on population PK-PD modelling and simulation, the observed PK differences (higher C_{max}, similar AUC) in the fed compared to the fasted state, will not lead to significant differences in testosterone change. It was also concluded that following a 40 mg twice-daily treatment, trough AZD4901 concentration will be higher compared to 80 mg once daily. The time above IC_{50} for testosterone inhibiton after 40 mg twice daily of AZD4901 is 80.9% time of the dosing interval compared to only 55.7 % after 80 mg once daily. The mean predicted peak testosterone concentrations at steady state are lower and overall less variable during 24 hours for a 40 mg twice-daily dose compared to an 80 mg once-daily dose. These findings suggest twice-daily dosing provides a sustained testosterone suppression effect during the dose interval.

Modelling data are presented in Figure 2.

Figure 2 **Serum testosterone concentration over 24 hours at AZD4901 steady state**



Note: the curves are modelled from the existing clinical dataset. BID twice daily; QD once daily.

4-β-hydroxy cholesterol is being measured in the study to give an early indication of whether AZD4901 has the potential to induce *CYP3A4*. 6-β-hydroxy testosterone is being measured to support the conclusion that any reduction in testosterone levels have been caused by AZD4901 action at the NK3R rather than changes in *CYP3A4* metabolism.

Based on previous clinical observations in PK and PD responses, expected bioavailability, safety profiles, toxicity investigation in preclinical species, and on the assumption that receptor occupancy needs to be maintained for continuous suppression of testosterone, the doses of 20 mg once daily, 20 mg twice daily, and 40 mg twice daily have been selected to allow characterisation of the dose response curve.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the patient screening log, of patients who entered prestudy screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfil the following criteria:

1. Provision of signed and dated, informed consent prior to any study specific procedures

2. Female patients between the ages of 18 to 45 years (inclusive) with suitable veins for cannulation or repeated venipuncture

3. A diagnosis of polycystic ovary disease; patient must fulfil all of the following criteria:

   - Polycystic ovaries (previously documented ultrasound from records are acceptable)

   - Free testosterone at screening greater than 85% of the age-specific upper limit of normal (ULN) as specified in Appendix I

   - Total testosterone < 5 nmol/L at screening

4. Amenorrhea or oligomenorrrhea (defined as ≤ 6 menses per year)

5. Body mass index (BMI) between 18 and 40 kg/m^2 (inclusive)

6. Females must have a negative serum pregnancy test at screening and a negative urine pregnancy test before randomisation, must not be breast-feeding, must not have been pregnant within the 6 months prior to screening, and must not expect to conceive within the projected duration of the study

7. Patient is permanently or surgically sterilised or practices abstinence as a lifestyle choice, or who agrees to use/have their partner use effective methods of birth control for the duration of their study participation

   Permanent sterilisation includes bilateral salpingectomy but excludes bilateral tubal occlusion. Effective methods of birth control within the study treatment period are defined as partner use of male condom plus one of the following: spermicide, vasectomy, tubal occlusion, or an intrauterine device that does not contain steroid hormones.

For inclusion in the optional genetic component of the study:

8. Provision of signed, written, and dated informed consent for optional genetic research. If a patient declines to participate in the genetic component of the study, the patient will not be excluded from the other aspects of the study.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Is perimenopausal or has reached natural menopause, defined as FSH > 10 IU/L

2. Has menstruated within the month prior to the baseline visit

3. Clinically relevant disease and abnormalities (past or present), and in particular causes of abnormal vaginal bleeding, which, in the opinion of the Investigator, may either put the patient at risk to participate in this study or may influence the results of the study or the patient's ability to participate in the study

4. Significant illness, as judged by the Investigator, within 2 weeks of Day -1

5. Patient has clinical, laboratory, or ECG evidence of uncontrolled hypertension (defined as systolic blood pressure of ≥ 160 mmHg and/or diastolic blood pressure of ≥ 100 mmHg); uncontrolled diabetes; or significant pulmonary, renal, hepatic, endocrine, or other systemic disease in the opinion of the Investigator

6. Patients who have had a hysterectomy or bilateral oophorectomy or both; if the patient has had prior ovarian cystectomy(ies), unilateral oophorectomy, uterine surgery such as myomectomy(ies) or polypectomy(ies), etc., then these patients may be considered on a case-by-case basis by the AstraZeneca Medical team, with the aim to exclude anyone who no longer has ovarian function or a functional endometrium

7. Patient has a history of Gilbert's syndrome, infectious hepatitis, or other significant hepatic disease (eg, chronic hepatitis, cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, nonalcoholic steatohepatitis, or hereditary liver disease) in the opinion of the Investigator

8. Patient has a history of gastric or small intestinal surgery (including gastric bypass surgery or banding), or has a disease that causes malabsorption

9. Patient has a history of hypothyroidism or evidence of hypothyroidism from the screening thyroid tests, as judged by the Investigator

10. Clinically significant abnormal ECG and/or abnormalities in ECG at screening as judged by the Investigator

11. A marked prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval > 450 ms)

12. A history of additional risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, or family history of long QT syndrome)

13. The use of concomitant medications that prolong the QT/QTc interval

14. Positive human immunodeficiency virus (HIV), hepatitis B, or hepatitis C serology evaluations at the screening visit

15. Patient has a history of hypersensitivity to more than 2 chemical classes of drugs, including prescription and over-the-counter medications

16. Past (within 1 year of enrolment) or present alcohol or substance abuse or a positive test for alcohol or drugs of abuse at screening or is a "recreational user" of illicit drugs or prescription medications

17. Patient consumes 3 or more alcoholic drinks per day (Note: 1 drink = 12 oz [360 mL] can/bottle of beer, 4 oz [120 mL] of wine, or 1 oz [30 mL] of liquor)

18. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 3 months of the first 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: patients consented and screened, but not randomised in this study or a previous study are not excluded.)

19. Blood loss in excess of 200 mL within 30 days of Day -1, in excess of 500 mL within 56 days of Day -1, in excess of 1350 mL within 1 year of Day -1, or donation of blood products within 14 days of Day -1

20. Patient has a history of neoplastic disease within 5 years prior to signing informed consent, except for adequately treated basal cell, squamous cell skin cancer, or in situ cervical cancer

21. Involvement in the planning and/or conduct of the study (applies to any or AstraZeneca employee and their close relatives and/or staff at the study site, regardless of their role in accordance with their internal procedures)

22. Previous randomisation to treatment in the present study

23. Inability to understand or cooperate with the requirements of the study

24. Patient is legally or mentally incapacitated

25. Patient has abnormal screening laboratory values as per the guidelines listed below or other clinically significant, unexplained laboratory abnormality according to the Investigator:

    - Aspartate aminotransferase (AST) >1.5 times ULN
    - Alanine aminotransferase (ALT) > 1.5 times ULN
    - Total bilirubin >1.5 times ULN
    - Serum creatinine >2.0 times ULN
    - Hematocrit less than the lower limit of normal
    - Prolactin >2.0 times the ULN

26. Patients who are withdrawing from oral contraceptives if their LH levels are below 3 IU/L when retested within 21 to 2 days of the baseline visit

27. Patient has taken any potent or moderate CYP3A4 or CYP2C9 inhibitors, potent or moderate CYP3A4 or CYP2C9 inducers, hormonal contraceptives, antiandrogenic drugs, or other medications for the time frame specified in Table 3

28. Patient reporting suicidal ideation of Type 4 or 5 in the past 2 months or suicidal behaviour in the past 6 months as measured by the C-SSRS at baseline

In addition, the following are considered criteria for the exclusion from the optional genetic component of the study:

29. Previous bone marrow transplant

30. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

Procedures for withdrawal of incorrectly enrolled patients are discussed in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients will be required to:

1. Patients are to fast from 2 hours prior to the morning dose until 1 hour after dosing on Days 7 and 28.

2. Patients will be provided with a dosing diary to record the time they take their medication each day and symptom diary paper questionnaires to be completed every evening before bedtime.

3. Patients are to abstain from taking any medication (prescribed or over the counter products) except acetaminophen (up to 4 gram per day) or topical preparations, as specified in Section 5.6, until completion of the follow-up visit.

4. Patients are to abstain from blood or plasma donation until 3 months after completion of the follow-up visit.

5. Patients are not to consume more than 3 alcoholic drinks per day from screening until completion of the final study visit.

6. Patients who are not permanently or surgically sterile must use effective non-hormonal methods of birth control, such as strict abstinence or use/have their partner use effective non-hormonal methods of birth control for the duration of their

study participation. Acceptable barrier methods of contraception include condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

7. Any intake of grapefruit, Seville oranges, or products containing grapefruit or Seville oranges, within 7 days of the first administration of IP and through duration of IP administration is not permitted.

8. Patients should not increase level of strenuous exercise or increase caffeine intake during participation in the study.

5.2 Subject enrolment, randomisation, and initiation of investigational product

The Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed

2. Assign potential patient a unique enrolment number, beginning with 'EXXX1001', where 'XXX' represents the site number

3. Determine patient eligibility. See Section 4.1 and Section 4.2

4. Assign eligible patient a unique randomisation code (patient number), beginning with '1001'

If a patient withdraws from participation in the study, then her enrolment/randomisation code cannot be reused.

Procedures for randomisation

Fifty-six patients (14 patients per treatment group) with PCOS will be randomly assigned to 1 of 4 treatment groups to have approximately 12 evaluable patients in each treatment group. A randomization scheme will be produced by using the AstraZeneca Global Randomisation system.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation. If a patient withdraws from participation in the study, then her enrolment/randomisation code will not be reused. Any replacement patients will be assigned to the same treatment as the patient they are replacing, and adding 100 to the original randomisation code.

5.3 Procedures for handling subjects incorrectly enrolled, randomised, or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive IP. There can be no exceptions to this rule. Patients

who are incorrectly enrolled, but are not yet randomised or initiated on treatment, should be withdrawn from the study.

Where patients who do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the Investigator should inform the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician immediately. The AstraZeneca CPA Physician must ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

In order to maintain study blinding, patients will be administered 2 AZD4901 and/or matching placebo tablets twice daily in a double-dummy design as described in Section 5.5.2. Investigational product will be packaged for each patient as described in Section 5.5.1.

The following personnel will be unblinded as to the exact content of investigational treatments (ie, the randomization code):

- Personnel analyzing the PK samples

The randomization list will be kept in a secure location until the end of the study.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists at the study centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious AEs (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. The interim administrative data review will be blinded to the study team.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
AZD4901	Plain, round, biconvex, white film-coated tablets, 20-mg	AstraZeneca
Placebo	Matching placebo tablets	AstraZeneca

Each patient will receive 1 box(es) for the morning doses and 1 box(es) for the evening doses. Each box will contain 2 bottles where the patient will take 1 tablet from each bottle at each dosing occasion. Bottles will be clearly labelled as to whether they are for morning or evening doses.

5.5.2 Doses and treatment regimens

At Visit 2, eligible patients will be randomly assigned to 1 of 4 treatment groups as below.

The IP will be administered as two AZD4901 and/or placebo tablets twice daily from Day 1 through the morning dose on Day 28, as follows:

- 20 mg AZD4901 once daily: one 20-mg AZD4901 tablet and 1 placebo tablet for the morning dose and 2 placebo tablets for the evening dose
- 20 mg AZD4901 twice daily: one 20-mg AZD4901 tablet and 1 placebo tablet for both the morning and evening doses
- 40 mg AZD4901 twice daily: two 20-mg AZD4901 tablets for both the morning and evening doses
- Placebo: two matching placebo tablets for both the morning and evening doses

Patients will be required to fast from 2 hours prior to the morning dose until 1 hour postdose on Days 7 and 28.

On Days 7 and 28, the morning dose of IP will be administered in the clinic with 240 mL water. On Days 14 and 21, it is suggested patients take their morning dose of IP with sufficient water in the clinic; however, if this is not practical, dosing may occur at home with the patient reporting to the clinic later in the day for scheduled procedures. Otherwise, all doses are taken with sufficient water on an outpatient basis and recording of dates and times in the dosing diary. At each study visit, patients are to bring diaries and unused IP supplies for assessment of treatment compliance. At the last study visit, patients are to return any unused IP supplies.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into the local language.

5.5.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label on the bottle will specify the appropriate storage.

5.6 Concomitant and post-study treatment(s)

Study screening will begin up to 60 days prior to the baseline visit to allow a washout period for patients taking oral contraceptives. Patients who discontinue oral contraceptives must demonstrate acceptable LH and testosterone levels upon repeat assessments on Days -21 to -2 prior to the baseline visit (see Section 4.1 and Section 4.2 for inclusion and exclusion criteria, respectively).

Concomitant use of AZD4901 with narrow therapeutic index drugs that are metabolised by *CYP3A4/5* should be avoided. The coadministration of potent and moderate inhibitors and inducers of *CYP3A4* and *CYP2C9* is prohibited for the time frames described in Table 3. Given the potential for AZD4901 to interact with *CYP3A4*, the suitability of coadministration of drugs metabolised by *CYP3A4* should be guided by the approved label for that drug and recommendation for coadministration with *CYP3A4* inhibitors and inducers.

The use of concomitant medications that prolong the QT/QTc interval is prohibited.

The use of oral, transdermal, or implantable hormonal contraception and oestrogen, progesterone or androgens; and antiandrogenic drugs, 5-α-reductase inhibitors, GnRH analogs, ovulation induction drugs, and anti-progestogens are restricted for time frames provided in Table 3. Antidiabetic medications, including metformin used to treat PCOS symptoms, should be stable for the time frame specified in Table 3.

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP3A4* inhibitors, including but not limited to: cyclosporine, systemic (oral/intravenous) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, nefazodone, HIV protease inhibitors, aprepitant, verapamil, and diltiazem	4 weeks prior to screening and throughout the study period

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP3A4* inducers, including but not limited to: rifampicin, rifabutin, carbamazepine, phenytoin, barbiturates, systemic glucocorticoids (replacements and inhaled are permitted), nevirapine, efavirenz, pioglitazone, primidone, and St. John's wort	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP2C9* inhibitors, including but not limited to: amiodarone, fluconazole, miconazole, and oxandralone	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP2C9* inducers, including but not limited to: carbamazepine and rifampin	4 weeks prior to screening and throughout the study period
Antidiabetic medications, including metformin administered for PCOS	Stable dose for 8 weeks prior to screening and throughout the study period
Oral contraception, transdermal or implantable hormonal contraception, oestrogen, progesterone, or androgens	8 weeks prior to dosing and throughout the study period
Antiandrogenic drugs (eg, spironolactone, any other antiandrogenic drugs), 5-α-reductase inhibitors, GnRH analogs (eg, Lupron®, any others), ovulation induction drugs (eg, clomiphene and any other antiestrogenic compounds, and gonadotropins, including all forms of FSH, LH, and human chorionic gonadotropin), and anti-progestogens	12 weeks prior to screening and throughout the study period

If any medication is necessary, it should be prescribed by the Investigator, and the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician should be informed. Information on any treatment in the 12 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the case report form (CRF).

5.7 Treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

Patients will be given a diary card at the Day -1 (baseline) visit for recording of the dates and times of all IP administration. The diary cards will be reviewed at each clinic visit for treatment compliance. On Days 6 and 27 (the days prior to serial PK sample collection), the site will contact patients by telephone to confirm recording of the dates and times of dosing

has been completed and to remind patients to hold the morning doses on Days 7 and 28 until clinic arrival.

Accountability

The IP provided for this study will be used only as directed in this CSP. The study personnel will account for all IP dispensed to and returned from the patient.

Study site personnel will account for all IP received at the site, unused IP, and for appropriate destruction or return (as applicable). Certificates of delivery, destruction, and return (as applicable) should be signed.

5.8 Discontinuation of investigational product

Patients will be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- The patient has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the Investigator, AstraZeneca or representative, or the patient
- Patient has a positive pregnancy test
- Severe noncompliance to study protocol
- A patient reporting suicidal ideation of Type 4 or 5 or suicidal behaviour as measured by the C-SSRS during the study will be discontinued and referred for appropriate assessment and treatment.

If a patient discontinues from the study prematurely, every effort should be made to conduct a discontinuation visit (see Section 6.2.2).

Patients will discontinue treatment with AZD4901 if any of the following are observed:

- Increase in ALT or AST to a level higher than 5 times ULN, or
- Increase in ALT or AST more than 3 times ULN and signs and symptoms of possible hepatic injury (fatigue, nausea, vomiting, or right upper quadrant tenderness) or drug allergy (fever, rash, or eosinophilia), or
- Increase in ALT or AST more than 3 times ULN and total bilirubin >2 times ULN

If an increase in ALT or AST more than 3 times ULN but less than 5 times ULN with normal total bilirubin level and no signs or symptoms of possible hepatic injury occurs, this will be confirmed with a repeat test immediately. If the repeat ALT and AST are trending up, the

patient must be discontinued from the study. However, if the repeat ALT and AST levels are trending down, the elevations may be monitored for up to 14 days from the initial finding with a frequency of 2 to 3 times per week. If the levels have not normalised by the fourteenth day after the initial finding, the patient must be discontinued from the study.

In case a patient shows an AST or ALT 3 or more times ULN and total bilirubin 2 or more times ULN, please refer to Appendix D 'Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law' for further instructions.

Procedures for discontinuation of a subject from investigational product

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (see Section 6.3.3 and Section 6.3.4); dosing diary cards, symptoms diary questionnaires, and all IP should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

5.8.1 Study stopping criteria

The study will be stopped if, in the judgment of the Sponsor, trial participants are placed at undue risk because of findings in 2 or more patients of clinically significant or serious AEs which meet individual stopping criteria, are causally related to study drug, and are not consistent with continuation of the study.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (see Section 6.3.3 and Section 6.3.4); dosing diary cards, symptoms diary questionnaires, and all IP should be returned by the patient.

Withdrawn patients will be replaced at the discretion of AstraZeneca and the Investigator(s) if needed to have approximately 12 evaluable patients in each treatment group.

All patients who withdraw must be asked specifically if they are continuing their consent for the optional exploratory genetic research.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below. The study plan and timing of these assessments are detailed in Table 1 and Table 2.

It is important that PD sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

Paper ECG

Vital signs (blood pressure and pulse rate)

Pharmacodynamic (LH, FSH, and testosterone) blood samples (Note: PD sampling must be performed at the precise protocol scheduled time.)

Pharmacokinetic blood sample (Note: PK sampling must be performed as close as possible to the protocol scheduled time.)

Clinical laboratory testing

Apart from the predose blood sampling, which should occur within 30 minutes prior to dosing, other predose assessments may be performed up to 60 minutes prior to administration of the IP or at an approximately matched time at the baseline visit (Day -1). Additional details on the collection of blood samples will be provided in the Laboratory Manual.

6.1 Recording of data

The Investigator will ensure that data are recorded on the CRFs as specified in this CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study sites.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

At screening (Visit 1), each potential patient will provide written informed consent prior to starting any study-specific procedures. Demographic data and other characteristics will be recorded and will include date of birth, gender, race, ethnicity, history of alcohol consumption, and drug use history.

Each patient will undergo screening during the 60 days prior to admission for Visit 2 (Day -1) to assess eligibility. This will consist of:

- Review of inclusion and exclusion criteria
- A standard medical and surgical history
- A complete physical examination

- An ultrasound to confirm diagnosis of PCOS may be performed, if no documentation of previous ultrasound is available.
- Measurement of height, weight, and BMI
- Collection of blood and urine samples for LH, FSH, prolactin, and screening testosterone (total and free); routine clinical chemistry, haematology (including hematocrit), and urinalysis; thyroid tests (TSH and total/free T4); screening for HIV, hepatitis B, and hepatitis C; serum pregnancy test; and screening for alcohol and drugs of abuse
- Measurement of vital signs (blood pressure and pulse rate)
- A 12-lead ECG
- Recording of prior and concomitant medications
- Assessment of SAEs (beginning from time of informed consent)

Patients who discontinue oral contraceptives and patients who do not require washout from oral contraceptives, but have screening assessments more than 3 weeks prior to the baseline visit, will return to the clinic on Days -21 to -2 for repeat assessments of haematology, clinical chemistry, urinalysis, LH, testosterone (total and free), and a urine pregnancy test. Any SAEs or new concomitant medications since the screening visit will be recorded.

6.2.2 Follow-up procedures

Patients will return for a poststudy follow-up visit approximately 2 weeks after the last dose of IP (Day 42 ±3 days). Follow-up evaluations will include:

- A complete physical examination, including weight
- Collection of blood and urine samples for routine clinical chemistry, haematology (including hematocrit), and urinalysis; urine pregnancy test; testosterone (total and free); LH; FSH; and monitoring sample (estradiol [E2], progesterone, prolactin, TSH, T4 [total and free], HbA_{1c}, and IGF-1)
- Measurement of vital signs (blood pressure and pulse rate)
- A 12-lead ECG
- C-SSRS assessment
- Recording of concomitant medications
- Assessment of AEs

In the event of early discontinuation, the following assessments will be performed in addition to the follow-up assessments noted above:

- HRQoL SF-36
- Symptoms site questionnaire
- Collection of a sample for PK analysis

6.3 Safety

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

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix B to this CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

All SAEs will be recorded from the time of informed consent.

Nonserious AEs will be collected beginning at the baseline visit throughout the treatment period and including the follow-up period.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient'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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or intensity or changes in intensity, rated according to the following scale:
  - Mild (awareness of sign or symptom, but easily tolerated)
  - Moderate (discomfort sufficient to cause interference with normal activities)
  - Severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome

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 hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between the 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 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 is found in Appendix B to this CSP.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/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.

Adverse Events based on examinations and tests

The results from CSP-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, or ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a patient shows an AST **or** ALT ≥3 times the ULN **or** total bilirubin ≥ 2 times the ULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.4 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, then Investigators or other site personnel should inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel should inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Investigators or other site personnel are to send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). The date and time of collection for all laboratory tests will be recorded in the CRF. Safety laboratory variables to be measured are presented in Table 4. Collection of the PD markers, LH, FSH, and testosterone, as well as the monitoring samples, are discussed in Section 6.6. Sample collection for 4-β-hydroxy (OH) cholesterol and 6-β-OH testosterone is discussed in Section 6.5.

Table 4 Safety laboratory variables

Haematology	Clinical Chemistry	Urinalysis
Haemoglobin	Albumin	Blood
Hematocrit[a]	Alkaline phosphatase	Glucose
Leucocyte count	ALT	Total protein
Leucocyte differential (absolute counts)	AST	
Platelet count	Total bilirubin	Alcohol screen[b]
HbA_{1c}	Total calcium	Drug screen[b]
	Creatine kinase	Pregnancy test[c]
	Creatinine	
	Gamma-glutamyl transferase	
	Potassium	
	Sodium	
	T4 (total and free)[d]	
	Testosterone (total)[d]	
	TSH[d]	
	Serology screen[e]	
	Pregnancy test[c]	
	Prolactin[d]	

[a] Performed only at screening, follow-up, and in the event of early termination.

[b] Urine will be tested at the screening visit and on Day -1 for alcohol and the following drugs of abuse: amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, 3,4-methylenedioxymethamphetamine (ecstasy), phencyclidine, tetrahydrocannabinol, and opiates. If a patient tests positive for drugs of abuse, a retest may be performed and she may be excluded from entering the study, as judged by the Investigator. Random urine drug and alcohol screens at subsequent visits may be performed at the discretion of the Investigator.

[c] Serum pregnancy tests will be performed at screening; urine pregnancy tests will be performed at each subsequent visit.

[d] Thyroid tests (TSH and total/free T4), total testosterone, and prolactin are collected at screening to determine study eligibility. See Section 6.6 for additional information on thyroid, testosterone, and prolactin levels measured as part of the PD assessments.

[e] Serology tests (HIV, hepatitis B, and hepatitis C) are performed at screening only.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Patients in whom suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator. Further details are provided in the Laboratory Manual.

The safety laboratory samples will be analysed using routine methods at the central clinical laboratory.

NB. In case a patient shows an AST **or** ALT ≥3 times the ULN **or** total bilirubin ≥ 2 times the ULN, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

For AEs based on clinical laboratory tests, see Section 6.3.3.

For clinical laboratory blood volumes, see Section 7.1.

6.3.6 Physical examination

A physical examination will be performed as indicated in the study plan (see Table 1). A full physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory, and neurological systems.

A brief physical examination, which will include assessments of the following: general appearance, skin, head and neck, lymph nodes, cardiovascular status, respiratory, and abdomen, will be performed at the times specified in the study plan (see Table 1).

Height (in centimetres) and weight (in kilograms) will be measured only at the times specified in the study plan (Table 1). Measurements should be taken without shoes and on a calibrated scale for all measurements. The BMI will be calculated from the screening height and weight measurements.

The outcome of the physical examination is to be recorded as normal/abnormal in the CRF, with any abnormalities specified. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

For AEs based on examinations and tests, see Section 6.3.3.

6.3.7 ECG

A 12-lead resting paper ECG will be performed on the days indicated in the study plan (Table 1). Patients must rest in a supine position for 10 minutes before each assessment. The overall evaluation (normal/abnormal) will be recorded in the CRF. If the ECG is abnormal,

the abnormality and its clinical significance will be specified in the CRF. The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File and the source medical records, along with a signed and dated copy (if the print-outs are not on archive-quality paper).

For AEs based on examinations and tests, see Section 6.3.3.

6.3.8 Vital signs

Supine blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device using the appropriate cuff size after the patients have rested for 10 minutes on a bed. For timings of assessments refer to the study plan (Table 1). Additional blood pressure and pulse rate assessments may be taken for safety at the discretion of the Investigator.

6.3.9 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used for assessing suicidality before and after treatment. The C-SSRS is a low burden, clinician-administered tool designed to track suicidal AEs throughout any treatment trial and is considered to be the "gold standard" for assessment (Posner et al 2007). The measure succinctly covers the full spectrum of suicidality addressing both behaviour and ideation. For timings of assessments refer to the Study Plan (see Table 1).

The Investigator and all applicable site personnel will be trained on use of the assessment prior its implementation. For information regarding how this scale is assessed, refer to Appendix H.

6.4 Patient reported outcomes

Patient-reported outcome (PRO) is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. These PROs, including HRQoL, have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered at the time indicated in the study plan (see Table 1): HRQoL SF-36 (version 2 - standard) and 2 symptom questionnaires. Copies of the instruments are included in Appendices E, F, and G.

6.4.1 Health-related quality of life short form-36

The SF-36 version 2 (standard) consists of 36 items combined into 8 scales that aggregate 2 to 10 items each, and 2 aggregated summary measures (a mental component summary and a physical summary component) (Ware et al 2007). The 8 scales are physical functioning (items 3a to 3j), role-physical (role limitations caused by physical health problems, items 4a to 4d), bodily pain (items 7 and 8), general health (items 1 and 11a to 11d), vitality (items 9a, 9e, 9g, and 9i), role-emotional (role limitations caused by emotional problems, items 5a to 5c), social functioning (items 6 and 10), and mental health (items 9b, 9c, 9d, 9f, and 9h) (Ware et al 2007). All but 1 of the 36 items (self-reported health transition) are used to score the 8 SF-36 scales. Each item is used in scoring only 1 scale.

6.4.2 Symptoms site questionnaire

The symptoms site questionnaire consists of the following 4 items:

- "During the past 7 days, how severe was the growth of visible hair on your face?"
- "During the past 7 days, how severe was the growth of visible hair on your body (all body except face)?"
- "During the past 7 days, what was the worst degree of acne you had?"
- "During the past 7 days, how severe was the worst hair loss you had?"

Each item uses a 0 to 10 numerical rating scale with the following anchors: 0 (absent) and 10 (worst imaginable), respectively.

6.4.3 Symptoms diary questionnaire

The symptoms diary questionnaire consists of the following 4 items:

- "During the past 24 hours, how severe was your worst stomach pain?"
- "During the past 24 hours, how severe was your worst stomach cramps?"
- "During the past 24 hours, how severe was your worst stomach bloating?"
- "During the past 24 hours, have you had any vaginal bleeding?"

Each item, except the final, uses a 0 to 10 numerical rating scale with the following anchors: 0 (absent) and 10 (worst imaginable), respectively. The final item uses a dichotomous "yes/no" response scale. If patients respond "yes", they are asked to indicate whether they believe the bleeding was menstrual (yes/no)."

6.4.4 Administration of patient reported outcomes

Standard procedures for minimising bias and enhancing PRO compliance will be followed throughout the study. Patient reported outcomes will be filled out at patients' homes and on site visits, according to Table 1. Site assessments should be made prior to any other site activities and encounters with physician. The patients will be instructed to complete the PROs independently. The site will have a designated quiet space for patients to use when completing the assessments. Dedicated investigational staff at the site will be responsible for ensuring that the PRO administration will be followed according to the specific instructions from the clinical study team. The site staff will be required to monitor that the patients have completed the appropriate PRO instruments at the site visits.

6.5 Pharmacokinetics

6.5.1 Collection of samples

Blood samples will be collected on Day 7 and Day 28 to measure plasma concentrations of AZD4901 and its metabolite, AZ12592232. Samples will be collected at the times specified in Table 1 and Table 2.

Blood samples will be collected on Day -1 and Day 28 to measure 4-β-OH cholesterol and 6-β-OH testosterone concentrations. Samples will be collected at the times specified in Table 1 and Table 2.

The dates and times of all sample collections will be recorded in the CRF. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood volumes, see Section 7.1.

6.5.2 Determination of drug concentration

Samples for the determination of concentrations of AZD4901 and its metabolite, AZ12592232, in plasma on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

All samples still within the known stability of AZD4901 and AZ12592232 at time of receipt by the bioanalytical laboratory will be analysed.

For each placebo patient, samples will only be analyzed on a 'for cause' basis, eg, if no quantifiable concentrations were observed in a patient's samples when the drug was expected to be present.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses, if performed, will be reported separately from the CSR.

6.5.3 Determination of 4-β-hydroxy cholesterol and 6-β-hydroxy testosterone concentrations

Analysis of 4-β-OH cholesterol will be performed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

Analysis of 6-β-OH testosterone will be performed using a high-performance liquid chromatography tandem mass spectrometry method.

6.6 Pharmacodynamics

6.6.1 Collection of pharmacodynamic markers

Pharmacodynamic markers in this study include LH, FSH, testosterone (total and free), and components of the monitoring sample (estradiol [E2], progesterone, prolactin, TSH, T4 [total and free], HbA1c, and IGF-1). Samples will be collected at the times specified in Table 1 and Table 2. The dates and times of all sample collection will be recorded in the CRF.

Intensive LH sampling (prior to the time of anticipated dosing [for Day -1 sampling] or the morning dose [for Day 7 and 28 sampling] and 1 sample every 10 minutes through 8 hours following the morning dose) at baseline (Day -1) and on Days 7 and 28 will be performed to capture changes of LH AUC, pulse interval, and amplitude over the 8-hour sample collection interval. Hourly measurement of FSH and free and total testosterone will also be performed during these periods of intensive monitoring (see Table 1 and Table 2).

Direct determination of total testosterone will be carried out using high-performance liquid chromatography-tandem mass spectrometry. Subsequent calculation of free testosterone levels will be done by a standard method involving immunoassay of sex hormone binding globulin levels in samples drawn at the same time as those for testosterone determination. will perform these assays.

The analyses for other PD markers will be performed by using standard clinical laboratory methods.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For pharmacodynamic blood volume, see Section 7.1.

6.7 Pharmacogenetics

All patients will have the option to provide separate optional genetic consent for their DNA samples to be stored and used for possible future exploratory research into other genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to AZD4901. Participation in the optional exploratory genetic research is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the patients on Day 7 (Visit 3) or any time after randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on Day 7, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

If applicable, a record of the date the patient consented to optional future exploratory genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

For pharmacogenetic blood volume, see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is presented in Table 5.

Table 5 Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	2.0	8	16.0
	Haematology/HbA_{1c}[a]	1.2	8[b]	9.6
	Serology	2.0	1	2.0
	Serum pregnancy	1.1	1	1.1
PD	LH/FSH	1.1	150[c]	165.0
	Testosterone (total)	2.0	30	60.0
	Testosterone (free)	2.0	30	60.0
	TSH/T4 (total and free)[a]	1.1	5	5.5
	Estradiol[a]	1.1	4	4.4
	Progesterone, prolactin[a,d]	1.1	5	5.5
	IGF-1[a]	1.1	4	4.4
PK	AZD4901/AZ12592232	1.2	20	24.0
	4-β-OH cholesterol	3.0	2	6.0
	6-β-OH testosterone	2.0	2	4.0
Pharmacogenetic		6.0	1	6.0
Discard volume[e]				147
Total				520.5

[a] Component of monitoring sample (estradiol, progesterone, prolactin, TSH, T4 (total and free), HbA_{1c}, and IGF-1).
[b] Includes HbA_{1c} (component of the monitoring sample) on Days -1, 28, and follow-up.
[c] Includes FSH at screening (single sample) and on Days -1, 7, and 28 (9 samples on each day), and at follow-up (single sample).
[d] A single sample of prolactin only will be collected at screening to confirm eligibility.

[e] If using an indwelling catheter, 1.0 mL of blood will be removed to flush the catheter prior to each serial PD sample collection time point.

The maximum volume to be drawn from each patient will not exceed 530 mL.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research can be retained at Research and Development site, on behalf of AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR.

7.2.1 Pharmacokinetic, pharmacodynamic, and biomarker samples

Pharmacokinetic samples from the analysis of AZD4901 and its metabolite, AZ12592232, will be disposed of or anonymized by pooling after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Pooled, anonymized samples may be used for analytical method development. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, 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.

Selected PK samples may be used for metabolite identification and/or quantitation. These samples will be retained by, or on behalf of, AstraZeneca for a maximum of 25 years following the finalization of the CSR. The results from any metabolite investigation, if performed, will be reported separately from the CSR.

Pharmacodynamic samples will be disposed of after finalization of the CSR.

7.2.2 4-β-hydroxy cholesterol and 6-β-hydroxy testosterone samples

The 4-β-OH cholesterol 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.

The 6-β-OH testosterone samples will be disposed of after finalization of the CSR.

7.2.3 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of the last patient's last visit, after which they will be destroyed. Deoxyribonucleic acid is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'International Airline Transportation Association 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped, and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate), and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of, or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator(s) at each study centre:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately, and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

A single DNA sample will be collected for the optional exploratory genetic research.

A patient can withdraw consent to the use of their DNA sample for exploratory genetic research. If this occurs, AstraZeneca or its representative will ensure that the patient's DNA sample is not used for exploratory genetic research. This action will be documented. If the patient's DNA sample has already undergone exploratory genetic research, AstraZeneca or its representative is not obliged to destroy the results of this research, but no further exploratory genetic research will be conducted.

As the exploratory genetic research is an optional part of the study, then the patient may continue in the study.

The Investigator ensures patient's withdrawal of informed consent to the use of donated samples for exploratory genetic research is notified immediately to AstraZeneca or its representative.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The informed consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the informed consent form that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the informed consent form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

Each Investigator is responsible for providing the Ethics Committees/Institutional Review Board with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed informed consent form is given to the patient
- Ensure that any incentives for patients who participate in the study, as well as any provisions for patients harmed as a consequence of study participation, are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Coordinating Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to each Investigator. For distribution to Ethics Committee, see Section 8.3.

If a CSP amendment requires a change to a centre's informed consent form, AstraZeneca and the centre's Ethics Committee are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to, or approved by, each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

will be managing the study on behalf of AstraZeneca.

9.1 Prestudy activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the Investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, the Investigator(s) or delegate will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilised, as appropriate.

The Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, regular monitoring visits will be conducted by on behalf of AstraZeneca, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Investigator at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of the CSP shall prevail with respect to the conduct of the study, and

the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Investigator(s) should be in place before any study-related procedures can take place, or patients are enrolled.

Archiving of study documents

The Investigator(s) will follow the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Quarter 2 and to end by Quarter 3

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD4901.

10. DATA MANAGEMENT

Data management will be performed by When the completed paper CRFs have been scanned and indexed, the data are entered into the study database and proofread.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca, and/or third party contracted

to work with AstraZeneca to analyse samples. The results from this genetic research, if performed, will be reported separately from the CSR.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change from baseline

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests (safety haematology, clinical chemistry, and urinalysis): Day -1
- Vital signs (including supine blood pressure and pulse): Day -1

If a patient is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluations exist, then the baseline value will be treated as missing and no change-from-baseline value will be calculated.

11.1.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation of IP due to AEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2 Calculation or derivation of patient reported outcome variables

Scoring of the HRQoL SF-36 will be conducted as per the SF-36 Health Survey Manual and Interpretation Guide (Ware et al 2007). The 8 domains plus 2 overall summary scores, (the physical component score and the mental health component score), will be derived at the end-of-treatment (Day 28) visit.

If less than 50% of the items in 1 scale are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in 1 scale are missing, that subscale will be treated as missing. The SF-36 (including the 8 subscores and the physical component

score and mental component score) will be summarised in terms of change from baseline. Change from baseline in the scores will be calculated at the end-of-treatment (Day 28) visit.

The symptoms site questionnaire will be calculated as change from baseline at each scheduled assessment post-baseline (Day -1). The symptoms diary questionnaire will be calculated as change from baseline as the mean of daily assessments for Day 1 to Day 7, Day 8 to Day 14, Day 15 to Day 21, and Day 22 to Day 28, respectively.

11.3 Calculation or derivation of pharmacokinetic variables

The PK analyses will be the responsibility of pharmacokineticist at . standard operating procedures (SOPs) and Work Instructions will be used as the default methodology, if not otherwise specified. The actual sampling times will be used in the PK calculations.

Pharmacokinetic parameters will be derived using standard noncompartmental methods with WinNonlin® Professional Version 5.2, or higher (Pharsight Corp., Mountain View, California, United States). All PK computations will be performed using WinNonlin® Professional Version 5.2 (or higher), or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, United States).

Patients who withdraw from the study following administration of the IP, but prior to study completion, will be included in the PK analysis provided they have evaluable concentrations over the planned collection period. Patients with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

Where possible, the following PK parameters will be determined for AZD4901 and AZ12592232 for Day 7 and Day 28:

- C_{max}: Maximum observed plasma concentration.
- t_{max}: time of C_{max}.
- $AUC_{(0-8)}$: Area under the plasma concentration-time curve from time zero to 8 hours calculated by linear up/log down trapezoidal summation.
- C_{min}: predose concentration
- C_{max} metabolite to parent ratio: The ratio of AZ12592232 C_{max} to AZD4901 C_{max}
- $AUC_{(0-8)}$ metabolite to parent ratio: The ratio of AZ12592232 $AUC_{(0-8)}$ to AZD4901 $AUC_{(0-8)}$

The following will be calculated for 4-β-OH cholesterol and 6-β-OH testosterone:

- Ratio of post treatment:pre treatment concentration

11.4 Calculation or derivation of pharmacodynamic variable(s)

The PD analyses will be performed at with select analyses performed by AstraZeneca or designee. SOPs and Work Instructions will be used for analyses performed by as the default methodology if not otherwise specified.

Change-from-baseline (Day-1) for LH, FSH, free and total testosterone concentrations, and the components of the monitoring sample (estradiol [E2], progesterone, prolactin, TSH, T4 [total and free], HbA_{1c}, and IGF-1), as appropriate, will be calculated as:

- Absolute change: X_t-X_0
- Percent change from baseline: $100 \times (X_t\text{-}X_0)/X_0$
- Ln-ratio: $\ln(X_t/X_0)$

where X_t is a patient's measured value at time t and X_0 is the time matched measurement at baseline for LH, FSH and free and total testosterone and a single value baseline for other analytes listed above.

Primary

- LH $AUC_{(0\text{-}8)}$ on Day 7: Area under the plasma concentration-time curve from time zero to 8 hours calculated by linear up/log down trapezoidal summation on observed concentrations

Secondary

- Change-from-baseline (Day-1) for free and total testosterone concentrations on Days 7 and 28
- $AUC_{(0\text{-}8)}$ for LH on Day 28 on observed concentrations

Where possible, the following PD parameters will be determined for observed concentrations of LH, testosterone, and FSH samples collected on Days -1, 7, and 28:

- $AUC_{(0\text{-}8)}$ for LH
- Free and total testosterone $AUC_{(0\text{-}8)}$, calculated by linear up/log down trapezoidal summation
- FSH $AUC_{(0\text{-}8)}$, calculated by linear up/log down trapezoidal summation
- An evaluation of LH pulse interval and amplitude (Johnson 2008) (to be performed by AstraZeneca)

- Free and total testosterone C_{max}: Maximum observed plasma concentration, obtained directly from the observed concentration versus time data
- Free and total testosterone C_{min}: Minimum observed plasma concentration, obtained directly from the observed concentration versus time data
- FSH C_{max}, obtained directly from the observed concentration versus time data.
- FSH C_{min}, obtained directly from the observed concentration versus time data.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for PD, safety, and PK, respectively.

The as-treated principle will be applied to all evaluations; ie, patients who received another treatment than the one assigned in the randomization list will be analysed as belonging to the actual treatment group and not that assigned by randomisation.

In general, descriptive statistics will follow the rounding convention in SOPs.

12.1.2 Safety analysis set

All patients who receive at least 1 dose of IP, including placebo, and for whom any postdose data are available will be included in the safety population.

12.1.3 Pharmacokinetic analysis set

The PK analysis set will be a subset of the safety analysis set and will include only patients who receive at least 1 dose of AZD4901 and have at least 1 postdose PK measurement without important CSP deviations or violations thought to significantly affect the PK (eg, patient vomited at or before 2 times median t_{max}, wrong dose administered, prohibited concomitant medication, etc).

For the evaluation of the 4-β-OH cholesterol and 6-β-OH testosterone results, this population will be further restricted to include only patients who did not receive any inhibitors/inducers within 12 weeks prior to dosing.

12.1.4 Pharmacodynamic analysis set

The PD analysis set will include all patients who receive at least 1 dose of AZD4901 or placebo and for whom evaluable PD data appropriate for the evaluation of interest are

available without important CSP deviations or violations thought to significantly affect either the PK or PD.

12.2 Methods of statistical analyses

12.2.1 General principles

The PD (except the evaluation of LH pulse interval and amplitude), PK, and safety summaries, individual figures, and data listings, as well as the statistical analysis of PK variables will be the responsibility of the study biostatistician at using SAS® Version 9.2 or higher and, where appropriate, additional validated software. An evaluation of LH pulse interval and amplitude will be performed by AstraZeneca or designee.

Quantitative continuous variables will be summarised using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Additionally, for PK parameters, (except for t_{max}), geometric means and geometric coefficient of variation (CV) will be reported. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a ln scale. The CV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a ln scale. Mean, SD, geometric mean, and CV will not be calculated for t_{max}.

Categorical variables (eg, gender) will be summarised in frequency tables (frequency and proportion of patients in the analysis set).

In general, descriptive statistics will follow the rounding convention in

Baseline characteristics will be summarised across all patients.

12.2.2 Subject characteristics

Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, and maximum) and categorical variables will be summarised in frequency tables (frequency and proportion) for each treatment and for all patients overall.

12.2.3 Safety

All safety data (scheduled and unscheduled) will be presented in the data listings.

Safety variables (eg, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics by scheduled time point, but will be included in data listings. All AEs and clinical laboratory outliers that occur following the first dose of IP will be included in the

tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

All available data from patients in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilised for missing values or for patients who withdraw prior to completing the study, neither will analyses be restricted to patients with complete data.

Adverse events beginning at the time of first IP administration will be summarised by preferred term and system organ class using MedDRA vocabulary by treatment and across all AZD4901 treatments. Furthermore, listings of SAEs and AEs that lead to withdrawal will be made and the number of patients who have any AEs, SAEs, AEs that lead to withdrawal, and AEs with severe intensity will be summarised.

Tabulations and listings of data for vital signs and clinical laboratory tests will be presented, as appropriate. Electrocardiogram results, physical examination findings, and C-SSRS assessments will be listed. All continuous safety data will be summarised across all treatments for the observed value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each patient will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

12.2.4 Patient reported outcomes

Observed and change-from-baseline data for HRQoL SF-36 and symptoms site and diary questionnaire assessments will be listed. Observed and change-from-baseline data for HRQoL SF-36 (including the 8 subscores and the physical component score and mental component score) and symptoms questionnaire assessments will be summarised using descriptive statistics.

12.2.5 Pharmacokinetics

The PK blood sample collection times, as well as derived sampling time deviations, and plasma concentrations will be listed for all patients. Plasma concentrations will be summarised by treatment using descriptive statistics (eg, n, arithmetic mean, SD, minimum, median, maximum, geometric mean, and CV).

Plasma concentrations that are below the lower limit of quantitation (LLOQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are below the limit of quantitation (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV will be set to Not Determined. The maximum value will

be reported from the individual data, and the minimum and median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable will be reported for SD and CV and BLQ will be reported for mean, geometric mean, minimum, median, and maximum.

- The number of BLQ values (n below LLOQ) will be reported for each time point.

Plasma parameters will be summarised by treatment using descriptive statistics (eg, n, arithmetic mean, SD, minimum, median, maximum, geometric mean, and CV). For t_{max}, only n, median, minimum, and maximum will be reported.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries.

Concentration and PK parameters [$AUC_{(0-8)}$, C_{min}, and C_{max}] for AZD4901 and AZ12592232 will be presented graphically for Day 7 and Day 28 for each treatment.

Results for 4-β-OH cholesterol and 6-β-OH testosterone will be summarised by treatment and collection time. For 4-β-OH cholesterol and 6-β-OH testosterone, descriptive statistics will include the ratio of post treatment to pre treatment concentration with 90% confidence intervals (CIs) calculated by ln-transformed data.

12.2.6 Pharmacodynamics

Observed PD concentrations (including those of the monitoring samples) and their corresponding change-from-baseline values will be listed for individual patients and summarised with appropriate descriptive statistics across all treatments and sample collection points. Descriptive statistics will be provided for absolute change, percent change from baseline, and ln-ratio to baseline values (as defined in Section 11.4). Descriptive statistics for the ln-ratio to baseline will be exponentiated for display in linear scale.

Pharmacodynamic parameter ($AUC_{(0-8)}$, C_{max}, C_{min}) values for individual patients will be listed for LH, free testosterone, total testosterone and FSH.

Descriptive statistics (n, mean, geometric mean, SD, and CV) will be calculated for the PD parameters ($AUC_{(0-8)}$ for LH and $AUC_{(0-8)}$, C_{max}, and C_{min} for free and total testosterone and FSH, including ratio to baseline in $AUC_{(0-8)}$, C_{max}, and C_{min}).

Comparisons of $AUC_{(0-8)}$ for LH, total testosterone, free testosterone, and FSH will be conducted using an analysis of variance (ANOVA) model on the ln-transformed ratio to baseline values (ln[$AUC_{(0-8)}$ /$AUC_{(0-8)}$ at baseline]) with fixed effect for treatment. Ln-transformed baseline $AUC_{(0-8)}$ value will be used as a covariate. The results from the ANOVA will be back-transformed to the linear scale to provide point estimates for each treatment as well as point estimates and 90% CI for the ratios versus placebo. The analyses of

other PD parameters (ie, C_{max} and C_{min} for total testosterone, free testosterone, and FSH) will be conducted using same ANOVA model described above.

The evaluation of LH pulse interval and amplitude (Johnson 2008) will be performed by AstraZeneca or designee.

12.2.7 Pharmacokinetic/pharmacodynamic correlation

The PK/PD relationship of AZD4901 and AZ12592232 to LH, AZD4901 and AZ12592232 to testosterone, and AZD4901 and AZ12592232 to FSH parameters will be explored graphically, if appropriate.

12.2.8 Interim analyses

An interim administrative review will be conducted when Day 28 laboratory results are available for approximately 40 patients. Data will be blinded to the study team and will be used to inform program decisions external to this study; study duration will not be changed based on the interim review. Interim data will be communicated as summary tables of testosterone and LH only and no patient-identified data will be revealed.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The proposed sample size is 12 evaluable patients per dose cohort with a total of 56 patients for the entire study (2 dropouts per group assumed). This study provides 76 % power versus placebo to detect a 30% change from baseline in LH at Day 7 and testosterone for the cohort at Day 28 (see Table 6).

Table 6 Sample size power

Assumed LH and testosterone change from baseline at Day 28	**Evaluable subjects required**		
	70% power	**80% power**	**90% power**
30% change	11	14	18
40% change	7	8	11

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4**

In the case of a medical emergency, the Investigator may contact the CPA Physician. If the CPA Physician is not available, the Investigator should contact the CPA Program Director.

Name	Role in the study	Address & telephone number
	AstraZeneca CPA Programme Director	AstraZeneca Research and Development
	AstraZeneca CPA Physician	Translational Medicine, Infection AstraZeneca Pharmaceuticals LP
	24-hour emergency cover at central Research and Development site	
	International Coordinating Investigator	

13.2 Overdose

For the purposes of this study, exceeding the dosage requirements specified in this CSP represents an overdose. In case of suspected overdose, the patient should be treated according

to standard medical practice based on the Investigator's judgment. Cases of overdose will be recorded as follows:

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other site personnel must inform the appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform the appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 6.3.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Only women are included in this study.

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Clinical Study Protocol Appendix B

Drug Substance	AZD4901
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient'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).

Hospitalisation

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

Important medical event or medical intervention

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, hospitalisation, disability, or incapacity but may jeopardize the patient or may require medical intervention 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.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous 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 anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered 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 patient 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?

- Dechallenge 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 aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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 (DGR) 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 (HIV) 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.

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Clinical Study Protocol Appendix D	
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Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (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 Medicinal Product (IMP).

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory 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 patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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 patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria were met.

No later than 3 weeks 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 IMP. The AstraZeneca Medical Science Director 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.

If 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, record the AE /SAE in the CRF accordingly and follow 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 IMP:

- Report an 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 3 weeks, 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- 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 met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix E

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Appendix E
Health-related Quality of Life Questionnaire - Short Form 36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

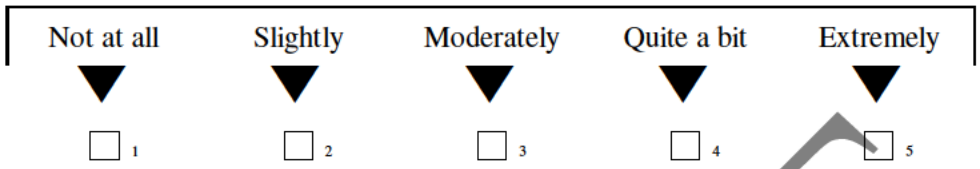
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

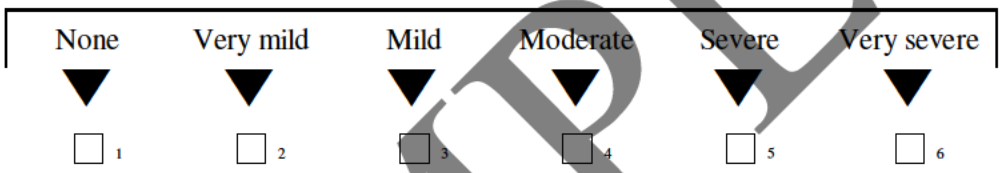
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

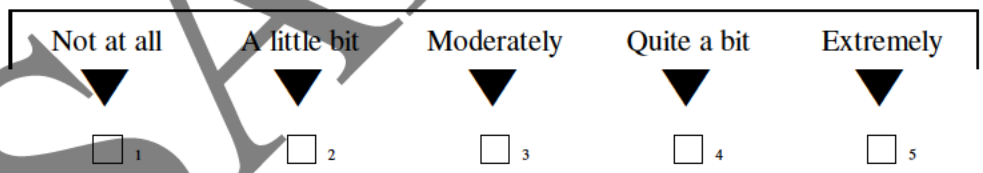
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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Clinical Study Protocol Appendix F

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Appendix F
Symptoms Site Questionnaire

Symptoms site questionnaire

Date (please write today's date): _____

Instructions

We kindly ask you to respond to this questionnaire when at a clinic visit.

Please respond to the following four questions by circling the appropriate number on the response scale for each question (only circle one number on each scale):

---

1. During the past 7 days, how severe was the growth of visible hair on your face?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

---

2. During the past 7 days, how severe was the growth of visible hair on your body (all body except face)?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

---

3. During the past 7 days, what was the worst degree of acne you had?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

---

4. During the past 7 days, how severe was the worst hair loss you had?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

Thank you for completing this questionnaire.

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Clinical Study Protocol Appendix G

Drug Substance	AZD4901
Study Code	D5320C00001
Edition Number	1
Date	

Appendix G
Symptoms Diary Questionnaire

Symptoms diary questionnaire

Date (please write today's date): _____

Instructions

We kindly ask you to respond to this questionnaire every evening before bedtime throughout the clinical study you are participating in.

Please respond to the following three questions by circling the appropriate number on the response scale for each question (only circle one number on each scale):

1. During the past 24 hours, how severe was your worst stomach pain?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

2. During the past 24 hours, how severe was your worst stomach cramps?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

3. During the past 24 hours, how severe was your worst stomach bloating?

Absent 0 1 2 3 4 5 6 7 8 9 10 **Worst Imaginable**

Please respond to the following question by ticking the appropriate box:

4. During the past 24 hours, have you had any vaginal bleeding?

- ❑ **Yes**
- ❑ **No**

If yes, do you believe the bleeding was menstrual (*if you responded "no" to question 4, please do not respond to the last question*)?

- ❑ **Yes,** I believe the bleeding was menstrual
- ❑ **No,** I do not believe the bleeding was menstrual

Thank you for completing this questionnaire.

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Clinical Study Protocol Appendix H	
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Appendix H
Columbia-Suicide Severity Rating Scales

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale (C-SSRS) are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioural suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; enquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead

Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up.

Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts

General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan.

Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it*".

Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them*".

Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: _____ *Type # (1-5)* _____ *Description of Ideation*

Frequency

How many times have you had these thoughts?

(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

___

Duration

When you have the thoughts, how long do they last?

(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

___

Controllability

Could/can you stop thinking about killing yourself or wanting to die if you want to?

(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

___

Deterrents

Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

___

Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

___

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent maybe inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behaviour?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale (C-SSRS) are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behaviour depends on the judgment of the individual administering the scale.

Definitions of behavioural suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; enquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it*".
Have you been thinking about how you might do this?
Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan
Active suicidal thoughts of killing one self and subject reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them*".
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply
____

Version 14/01/2009

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behaviour?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____

AstraZeneca

Clinical Study Protocol Appendix I

Drug Substance	AZD4901
Study Code	D5320C00001
Edition Number	1
Date	

Appendix I
85% of the Age-specific Upper Limit of Normal For Free Testosterone (Derived From ARUP Laboratories data)

85% of the Age-specific Upper Limit of Normal For Free Testosterone (Derived From ARUP Laboratories Data)

18 to 30 years: 6.3 pg/mL
31 to 35 years: 7.1 pg/ml
36 to 40 years: 7.8 pg/mL
41 to 51 years: 4.9 pg/mL

AstraZeneca

Clinical Study Protocol Amendment	
Amendment Number	4
Drug Substance	AZD4901
Study Code	D5320C00001
Date	20 March 2014
Protocol Dated	

A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment applies to all study sites.

The protocol for the study is to be amended as follows:

The Clinical Study Protocol is updated to include new information and guidance due to recently derived information concerning possible of effects of AZD4901 on the transporter proteins OATP1B1, OATP1B3, and Breast Cancer Resistance Protein (BCRP). These effects might result in clinical drug-drug interactions.

Section of protocol affected:

List of abbreviations and definition of terms, page 12 and page 13

Previous text:

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ALT	Alanine aminotransferase

Abbreviation or special term	Explanation
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-8)}$	Area under the concentration-time curve from time zero (predose) to 8 hours postdose
BLQ	Below the limit of quantitation
BMI	Body mass index
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed concentration
C_{min}	Predose concentration
CPA	Clinical Pharmacology Alliance
CRF	Case report form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
HbA_{1c}	Glycosolated haemoglobin
HPG	Hypothalamic pituitary gonadal
HRQoL	Health-related quality of life
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IGF-1	Insulin-like growth factor-1
IP	Investigational Product

Abbreviation or special term	Explanation
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NK-3	Neurokinin-3
NKB	Neurokinin B
OAE	Other significant adverse event (see definition in Section 11.1.2)
OH	Hydroxy
PCOS	Polycystic ovary syndrome
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient reported outcomes
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SF-36	Short form 36
SOP	Standard operating procedure
t_{max}	Time to the maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of the normal range

Revised text:

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-8)}$	Area under the concentration-time curve from time zero (predose) to 8 hours postdose
BCRP	**Breast Cancer Resistance Protein**
BLQ	Below the limit of quantitation

Abbreviation or special term	Explanation
BMI	Body mass index
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed concentration
C_{min}	Predose concentration
CK	**Creatine kinase**
CPA	Clinical Pharmacology Alliance
CRF	Case report form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
HbA_{1c}	Glycosolated haemoglobin
HPG	Hypothalamic pituitary gonadal
HRQoL	Health-related quality of life
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IGF-1	Insulin-like growth factor-1
IP	Investigational Product
LDL	**Low density lipoprotein**
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
NK-3	Neurokinin-3
NKB	Neurokinin B
OAE	Other significant adverse event (see definition in Section 11.1.2)
OH	Hydroxy
PCOS	Polycystic ovary syndrome
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient reported outcomes
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SF-36	Short form 36
SOP	Standard operating procedure
t_{max}	Time to the maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of the normal range

Reason for Amendment:

Addition of new abbreviations for the protocol in relation to Section 1.1.2, Section 1.4, and Section 5.6.

Section of protocol affected:

Section 1.1.2 Clinical studies, page 15

Previous text:

...

Cytochrome P450 (CYP) enzymes *CYP2C9*, *CYP3A4*, and *CYP3A5* in vitro appeared to be involved in the metabolism of AZD4901. AZD4901 exhibited weak to moderate inhibitory effect on *CYP3A4/5* with an apparent IC_{50} of 7.1 and 19.8 µM in midazolam and testosterone assays, respectively. AZD4901 may also have the the potential to induce *CYP3A4/5* enzymes. Clinical drug/drug interaction studies have not yet been performed.

...

Revised text:

...

Cytochrome P450 (CYP) enzymes *CYP2C9*, *CYP3A4*, and *CYP3A5* in vitro appeared to be involved in the metabolism of AZD4901. AZD4901 exhibited weak to moderate inhibitory effect on *CYP3A4/5* with an apparent IC_{50} of 7.1 and 19.8 µM in midazolam and testosterone assays, respectively. AZD4901 may also have the the potential to induce *CYP3A4/5* enzymes. Clinical drug/drug interaction studies have not yet been performed.

Drug metabolism and pharmacokinetic studies carried out on Caco-2 cell monolayers using [^{3}H]-rosuvastatin suggested that AZD4901 may function as an inhibitor of the human efflux transporter Breast Cancer Resistance Protein (BCRP; ABCG2) with an apparent IC_{50} of 2.2 µM. Data obtained in these studies suggest that AZD4901 may have the potential to increase exposure to some statins in vivo, with AUCs for atorvastatin, rosuvastatin, and fluvastatin potentially increasing approximately 2.5 to 3-fold. Because pitavastatin and pravastatin are not impacted by BCRP or *CYP3A4* inhibition, no interaction risk for these statins is predicted. Clinical AZD4901-statin drug interaction studies, however, have not been performed.

...

Reason for Amendment:

Addition of the results of recent in vitro studies of the interaction between AZD4901 and BCRP. These studies suggest a clinically significant drug-drug interaction increasing the serum levels of certain statins may occur, though such an outcome has not been documented directly in vivo.

Section of protocol affected:

Section 1.4 Benefit/risk and ethical assessment, page 17

Previous text:

...

AZD4901 may have the potential to induce and also inhibit *CYP3A4/5* enzymes. Due to the potential CYP induction/inhibition risk, concomitant use of AZD4901 with narrow therapeutic index drugs that are metabolised by *CYP3A4/5* should be avoided. Investigators should be aware that the exposure of other drugs metabolised by *CYP3A4* could be altered. See Table 1 for a list of restricted medications.

...

Revised text:

...

AZD4901 may have the potential to induce and also inhibit *CYP3A4/5* enzymes. **It may also have the potential to inhibit BCRP-mediated drug transport.** Due to the potential CYP induction/inhibition **and BCRP inhibition** risk**s**, concomitant use of AZD4901 with narrow therapeutic index drugs that are metabolised by *CYP3A4/5* **or transported by BCRP** should be avoided. Investigators should be aware that the exposure of other drugs metabolised by *CYP3A4* **or transported by BCRP** could be altered. See Table 1 for a list of restricted medications.

...

Reason for Amendment:

Additional guidance concerning potential drug-drug interactions involving AZD4901 and BCRP is provided.

Section of protocol affected:

Section 5.6 Concomitant and post-study treatment(s), page 35

Previous text:

...

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP3A4* inhibitors, including but not limited to: cyclosporine, systemic (oral/intravenous) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, nefazodone, human immunodeficiency virus protease inhibitors, aprepitant, verapamil, and diltiazem	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP3A4* inducers, including but not limited to: rifampicin, rifabutin, carbamazepine, phenytoin, barbiturates, systemic glucocorticoids (replacements and inhaled are permitted), nevirapine, efavirenz, pioglitazone, primidone, and St. John's wort	4 weeks prior to screening and throughout the study period

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP2C9* inhibitors, including but not limited to: amiodarone, fluconazole, miconazole, and oxandralone	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP2C9* inducers, including but not limited to: carbamazepine and rifampin	4 weeks prior to screening and throughout the study period
Antidiabetic medications, including metformin administered for PCOS	Stable dose for 8 weeks prior to screening and throughout the study period
Oral contraception, transdermal or implantable hormonal contraception, oestrogen, progesterone, or androgens	8 weeks prior to dosing and throughout the study period
Antiandrogenic drugs (eg, spironolactone, any other antiandrogenic drugs), 5-α-reductase inhibitors, GnRH analogs (eg, Lupron®, any others), ovulation induction drugs (eg, clomiphene and any other antiestrogenic compounds, and gonadotropins, including all forms of FSH, LH, and human chorionic gonadotropin), and anti-progestogens.	12 weeks prior to screening and throughout the study period

...

Revised text:

...

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP3A4* inhibitors, including but not limited to: cyclosporine, systemic (oral/intravenous) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, nefazodone, human immunodeficiency virus protease inhibitors, aprepitant, verapamil, and diltiazem	4 weeks prior to screening and throughout the study period

Table 3 Restricted medications

Therapy	Time frame
Potent and moderate *CYP3A4* inducers, including but not limited to: rifampicin, rifabutin, carbamazepine, phenytoin, barbiturates, systemic glucocorticoids (replacements and inhaled are permitted), nevirapine, efavirenz, pioglitazone, primidone, and St. John's wort	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP2C9* inhibitors, including but not limited to: amiodarone, fluconazole, miconazole, and oxandralone	4 weeks prior to screening and throughout the study period
Potent and moderate *CYP2C9* inducers, including but not limited to: carbamazepine and rifampin	4 weeks prior to screening and throughout the study period
Antidiabetic medications, including metformin administered for PCOS	Stable dose for 8 weeks prior to screening and throughout the study period
Oral contraception, transdermal or implantable hormonal contraception, oestrogen, progesterone, or androgens	8 weeks prior to dosing and throughout the study period
Antiandrogenic drugs (eg, spironolactone, any other antiandrogenic drugs), 5-α-reductase inhibitors, GnRH analogs (eg, Lupron®, any others), ovulation induction drugs (eg, clomiphene and any other antiestrogenic compounds, and gonadotropins, including all forms of FSH, LH, and human chorionic gonadotropin), and anti-progestogens	12 weeks prior to screening and throughout the study period

Table 3 Restricted medications

Therapy	Time frame
Concomitant use of statin drugs other than pitavastatin and pravastatin	**Up to a 3 fold increase in statin exposure may occur when some statins are coadministered with AZD4901. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information. Monitoring of low-density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be undertaken**

...

Reason for Amendment:

The table of restricted medications is modified to include new dosing, clinical, and laboratory monitoring guidelines appropriate for concomitant statin use in patients receiving AZD4901. These recommendations are based on recently available preclinical data describing the interaction of AZD4901 with the transport protein BCRP. Pitvastatin and pravastatin are currently exempted because their absorption is not modulated by BCRP drug transport.

Persons who initiated the Amendment:

AstraZeneca Global Drug Safety Physician

Clinical Study Protocol	Amendment 4 Appendix A
Drug Substance	AZD4901
Study Code	D5320C00001
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

Date
(Day Month Year)

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double-blind, Placebo-controlled Phase IIa Study to Assess the Pharmacodynamics, Safety, and Pharmacokinetics of AZD4901 When Given in Multiple Doses to Females with Polycystic Ovary Syndrome

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Centre No.:

Signature:

Date
(Day Month Year)