Clinical trial results:
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

Summary

EudraCT number	2013-000788-98
Trial protocol	GB
Global end of trial date	25 July 2014

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	D5320C00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Pharmaceuticals LP
Sponsor organisation address	2 Kingdom Street, Paddington, London, United Kingdom, W6 6BD
Public contact	Martin L. Scott, MD/PhD, AstraZeneca Pharmaceuticals LP, 1 (781) 472-5130, martin.scott@astrazeneca.com
Scientific contact	Martin L. Scott, MD/PhD, AstraZeneca Pharmaceuticals LP, 1 (781) 472-5130, martin.scott@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The IDMC was charged with interpreting the results of an interim analysis

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	65
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 56 patients were to be enrolled (14 patients per treatment group) to ensure 12 evaluable patients in each of the 4 treatment groups.

Pre-assignment

Screening details:

Screening began up to 60 days prior to baseline visit allowing a washout period for patients taking OCP. Patients who had assessment more than 3 weeks prior to baseline returned to the site between Day -21 to -2 for repeat lab assessments. Patients not taking OCP who had had screening assessments within 3 weeks of baseline did not repeat lab tests

Period 1

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

Blinding implementation details:

Subjects were randomised 1:1:1:1 to one of three treatment levels or control

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Administered orally

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two placebo tablets twice per day

Arm title	20 mg AZD4901 once daily

Arm description:

20 mg AZD4901 once daily

Arm type	Experimental
Investigational medicinal product name	AZD4901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet + one placebo tablet once per day and two placebo tablets once per day

Arm title	20 mg AZD4901 twice daily

Arm description:

20 mg AZD4901 twice daily

Arm type	Experimental

Investigational medicinal product name	AZD4901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet + one placebo tablet twice per day

Arm title	40 mg AZD4901 twice daily

Arm description:

40 mg AZD4901 twice daily

Arm type	Experimental
Investigational medicinal product name	AZD4901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets twice per day

Number of subjects in period 1	Placebo	20 mg AZD4901 once daily	20 mg AZD4901 twice daily
Started	16	15	17
Completed	16	15	14
Not completed	0	0	3
Consent withdrawn by subject	-	-	1
Patient met exclusion criterion 16.	-	-	-
Adverse event, non-fatal	-	-	1
Dose administration non-compliance	-	-	-
Protocol deviation	-	-	1

Number of subjects in period 1	40 mg AZD4901 twice daily
Started	17
Completed	15
Not completed	2
Consent withdrawn by subject	-
Patient met exclusion criterion 16.	1
Adverse event, non-fatal	-
Dose administration non-compliance	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Administered orally	
Reporting group title	20 mg AZD4901 once daily
Reporting group description:	
20 mg AZD4901 once daily	
Reporting group title	20 mg AZD4901 twice daily
Reporting group description:	
20 mg AZD4901 twice daily	
Reporting group title	40 mg AZD4901 twice daily
Reporting group description:	
40 mg AZD4901 twice daily	

Reporting group values	Placebo	20 mg AZD4901 once daily	20 mg AZD4901 twice daily
Number of subjects	16	15	17
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	15	17
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous |			
Units: years			
arithmetic mean	27	29	27
standard deviation	± 3	± 6	± 6
Gender, Male/Female			
Units: Participants			
Female	16	15	17
Male	0	0	0

Reporting group values	40 mg AZD4901 twice daily	Total	
Number of subjects	17	65	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	17	65	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous |			
Units: years			
arithmetic mean	28		
standard deviation	± 6	-	
Gender, Male/Female			
Units: Participants			
Female	17	65	
Male	0	0	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Administered orally	
Reporting group title	20 mg AZD4901 once daily
Reporting group description: 20 mg AZD4901 once daily	
Reporting group title	20 mg AZD4901 twice daily
Reporting group description: 20 mg AZD4901 twice daily	
Reporting group title	40 mg AZD4901 twice daily
Reporting group description: 40 mg AZD4901 twice daily	

Primary: LH AUC(0-8) comparisons of active treatment vs Placebo

End point title	LH AUC(0-8) comparisons of active treatment vs Placebo[1]
End point description:	
End point type	Primary
End point timeframe: Day 7	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis, because it wasn't planned in the study.

End point values	Placebo	20 mg AZD4901 once daily	20 mg AZD4901 twice daily	40 mg AZD4901 twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	15
Units: AURatio (%)				
geometric mean (confidence interval 1%)				
Ratio (%) compared to placebo (Primary)	100 (100 to 100)	87.04 (58.52 to 129.47)	78.76 (53.41 to 116.16)	47.99 (32.73 to 70.36)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All SAEs recorded from the time of informed consent.
Nonserious AEs collected beginning at the baseline visit throughout the treatment period and including the follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	20 mg AZD4901 once daily
Reporting group description: -	
Reporting group title	20 mg AZD4901 twice daily
Reporting group description: -	
Reporting group title	40 mg AZD4901 twice daily
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	20 mg AZD4901 once daily	20 mg AZD4901 twice daily	40 mg AZD4901 twice daily
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	20 mg AZD4901 once daily	20 mg AZD4901 twice daily	40 mg AZD4901 twice daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	13 / 17 (76.47%)	5 / 17 (29.41%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Nodule			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Influenza Like Illness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pelvic Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Vaginal Discharge			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Rhinitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Procedural dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Muscle Strain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 15 (13.33%)	3 / 17 (17.65%)	4 / 17 (23.53%)
occurrences (all)	4	3	4
Migraine			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	2	0

Syncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 15 (0.00%)	2 / 17 (11.76%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 15 (13.33%)	1 / 17 (5.88%)	1 / 17 (5.88%)
occurrences (all)	2	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Appendicitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal Mycotic Infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal Infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)		
Vascular disorders			
Hot Flush			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Nodule			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Influenza Like Illness			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Pelvic Pain			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Vaginal Discharge			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Alanine Aminotransferase Increased			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Procedural dizziness			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Muscle Strain			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Migraine			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Eye disorders			

Conjunctivitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0		
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0		
Musculoskeletal and connective tissue			

disorders			
Muscle Spasms			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Appendicitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Vulvovaginal Mycotic Infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Gastrointestinal Infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2013	The supply of the investigational product to the patients for the duration of the study was clarified in the study design. The 0 hour sampling time was clarified in the study design and table of study design. A new footnote was added to the study design table to include information on discontinuation based on suicidal ideation/behavior as seen in the C-SSRS. Exclusion criterion 27, concomitant medication and table on restricted medications were modified. New exclusion criterion was added and discontinuation of investigational product updated based on C SSRS. Study stopping criteria was modified. Storage period of PGx samples was modified.
06 June 2013	This amendment was applicable for study sites only in UK. HIV testing was removed at all occurrences in the CSP.
18 October 2013	The rescreening window was amended to Day - 21 to Day -2 and the relevant sections were updated in the CSP. Study restriction (restriction #3) was amended.
20 March 2014	List of abbreviations, clinical studies section, benefit/risk and ethical assessment, and restricted medication table in the CSP were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported