Clinical trial results:
An Open-label Non-comparative, Multi-centre Study To Assess The Efficacy And Safety Of Bicalutamide When Used In Combination With Anastrozole For The Treatment Of Gonadotropin-independent Precocious Puberty In Boys With Testotoxicosis

Summary

EudraCT number	2004-000384-10
Trial protocol	GB FR
Global end of trial date	06 December 2017

Results information

Result version number	v1 (current)
This version publication date	08 June 2018
First version publication date	08 June 2018

Trial information

Trial identification

Sponsor protocol code	Doc ID-002099254

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	BATT: D6873C00047

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Clinical Trial Transparency, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	AstraZeneca, AstraZeneca Clinical Study Information Center, 0011 08772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000283-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2008
Global end of trial reached?	Yes
Global end of trial date	06 December 2017
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 assess the efficacy of bicalutamide when used in combination with anastrozole in terms of a reduction in growth rate after 12 months treatment of precocious puberty in boys with testotoxicosis.

Protection of trial subjects:

A data and safety monitoring board is not necessary for this study but an advisory panel, consisting of the international co-ordinating investigator and the following AstraZeneca personnel: the study physician, clinical kineticist and the product medical director, will determine the requirement of the 2 week anastrozole only period following enrolment of the first 4 subjects into the study. In addition, the starting dose of anastrozole and bicalutamide will be evaluated by the advisory panel after the first 4 subjects have been enrolled. Consequently, the starting dose of either product or both products may be adjusted for subsequent subjects entering the study. This process will be repeated for additional groups of 4 subjects until an appropriate dose regimen is established.
Any changes to the starting doses for either drug or elimination of the anastrozole only dosing period recommended by the advisory panel will be communicated in writing to all investigators and should be copied to the IRB/ IECs. The change may then be implemented immediately; no protocol amendments will be issued for such changes.
The timing and manner of any review and analysis of data collected after the first 12 months of therapy while subjects are being followed to final adult height will be agreed after discussion between the International Co-ordinating Investigator and AstraZeneca, and the FDA as appropriate, after the analysis at 12 months.

Background therapy:

Bicalutamide in combination with anastrozole

Evidence for comparator:

Non-comparative study

Actual start date of recruitment	22 November 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	14
EEA total number of subjects	1

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)	14
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 22 November 2004 and the last patient completed the 12 months visit on 7 May 2008. Patients were allocated treatment at 9 centres in 3 countries: India, the UK and the USA. Care for two patients, transferred from one US to a new approved US centre, therefore, patients were treated at 10 centres in total.

Pre-assignment

Screening details:

Of the 24 patients enrolled, 10 failed eligibility criteria and were classed as screening failures while the remaining 14 patients were allocated treatment.

Period 1

Period 1 title	Post-assignment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All treated

Arm description: -

Arm type	Non-comparative
Investigational medicinal product name	Bicalutamide in combination with anastrozole
Investigational medicinal product code	
Other name	CASODEX and ARMIDEX
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

The dosing of anastrozole and bicalutamide was tailored for each subject.

Number of subjects in period 1	All treated
Started	14
Completed	13
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Post-assignment

Reporting group description:

All-treated (AT) population will consist of any subjects who receive at least one dose of study medication and have at least one on-treatment measurement.

Reporting group values	Post-assignment	Total	
Number of subjects	14	14	
Age Categorical Units: Subjects			
2 - 11 years	14	14	
Age Continuous Units: years			
arithmetic mean	3.9		
full range (min-max)	2 to 9	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	14	14	

Subject analysis sets

Subject analysis set title	All-treated
Subject analysis set type	Full analysis

Subject analysis set description:

All-treated (AT) population will consist of any subjects who receive at least one dose of study medication and have at least one on-treatment measurement.

Reporting group values	All-treated		
Number of subjects	14		
Age Categorical Units: Subjects			
2 - 11 years	14		
Age Continuous Units: years			
arithmetic mean	3.9		
full range (min-max)	2 to 9		
Gender Categorical Units: Subjects			
Female	0		
Male	14		

End points

End points reporting groups	
Reporting group title	All treated
Reporting group description: -	
Subject analysis set title	All-treated
Subject analysis set type	Full analysis
Subject analysis set description:	
All-treated (AT) population will consist of any subjects who receive at least one dose of study medication and have at least one on-treatment measurement.	

Primary: Change in growth rate (cm/year) after 12 months treatment	
End point title	Change in growth rate (cm/year) after 12 months treatment
End point description:	
Change in growth rate after 12 months relative to the growth rate during the ≥6 month pre-study period, based on raw height data (cm/year).	
End point type	Primary
End point timeframe:	
Assessed after 12 months treatment	

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: cm/year				
arithmetic mean (standard deviation)				
12 months	-1.62 (± 5.13)	-1.62 (± 5.13)		

Statistical analyses

Statistical analysis title	Analysis of change in growth rate (cm/year)
Statistical analysis description:	
A 95% 2-sided confidence interval was calculated for the mean change in growth rate.	
Comparison groups	All treated v All-treated
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.278
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	-1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.72
upper limit	1.48

Primary: Change in growth rate (SD units) after 12 months treatment	
End point title	Change in growth rate (SD units) after 12 months treatment
End point description:	
Change in growth rate after 12 months relative to the growth rate during the ≥6 month pre-study period, calculated after adjustment for the chronological age of the patient (expressed as a standard deviation [SD] score).	
End point type	Primary
End point timeframe:	
Assessed after 12 months treatment	

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: SD units				
arithmetic mean (standard deviation)				
12 months	-0.07 (± 1.78)	-0.07 (± 1.78)		

Statistical analyses

Statistical analysis title	Analysis of change in growth rate (SD units)
Statistical analysis description:	
The primary efficacy parameter, change in growth rate (cm and SD units) after 12 months relative to the baseline growth rate was analysed using a one sample t-test.	
Comparison groups	All treated v All-treated
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.882
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	1

Secondary: Change in growth rate (cm/year) after 6 months treatment	
End point title	Change in growth rate (cm/year) after 6 months treatment
End point description:	
Change in growth rate after 6 months of treatment relative to the growth rate during the ≥6 months	

pre-study period.

End point type	Secondary

End point timeframe:

Assessed after 6 months treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: cm/year				
arithmetic mean (standard deviation)				
All treated	-0.07 (± 5.77)	-0.07 (± 5.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in growth rate (SD units) after 6 months treatment

End point title	Change in growth rate (SD units) after 6 months treatment

End point description:

Change in growth rate after 6 months of treatment relative to the growth rate during the ≥6 months pre-study period.

End point type	Secondary

End point timeframe:

Assessed after 6 months treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: SD units				
arithmetic mean (standard deviation)				
All treated	-0.14 (± 1.67)	-0.14 (± 1.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone age maturation rate (cm/year)

End point title	Change in bone age maturation rate (cm/year)

End point description:

Radiographs were used to assess the bone age at ≥6 months pre-study, baseline, 6 and 12 months. The rate of change in bone age at baseline was calculated from a radiograph taken at least 6 months prior to

study enrolment. The change in bone maturation after 6 months of treatment was calculated relative to the rate of change in bone age during the ≥ 6 months pre-study period.

End point type	Secondary

End point timeframe:

Assessed after 6 and 12 months treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	6		
Units: cm/year				
arithmetic mean (standard deviation)				
6 months	-2.03 (± 0.38)	-2.03 (± 0.38)		
12 months	-2.29 (± 0.51)	-2.29 (± 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone age to chronological age ratio

End point title	Change in bone age to chronological age ratio

End point description:

Change in bone age to chronological age ratio after 6 and 12 months treatment relative to the baseline ratio for all patients.

End point type	Secondary

End point timeframe:

Assessed after 6 and 12 months of treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: Ratio				
arithmetic mean (standard deviation)				
6 months	-0.09 (± 0.14)	-0.09 (± 0.14)		
12 months	-0.24 (± 0.18)	-0.24 (± 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of patients with height between 5th and 95th percentile

End point title	Number (%) of patients with height between 5th and 95th

	percentile

End point description:

The number of patients whose height lies between the 5th and 95th percentiles (using the percentile tables on the WHO database) for chronological age at the 12 month assessment.

End point type	Secondary

End point timeframe:

Assessed after 3, 6, 9 and 12 months of treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: Count				
3 months	3	3		
6 months	3	3		
9 months	3	3		
12 months	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in predicted adult height (PAH)

End point title	Change in predicted adult height (PAH)

End point description:

Radiographs are used to assess the bone age, the change in predicted adult height (PAH) is calculated from the bone age using the Bayley and Pinneau Method. The change in PAH is be calculated by subtracting the PAH at baseline from the PAH at 12 months.

End point type	Secondary

End point timeframe:

Assessed after 12 months treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: cm				
arithmetic mean (standard deviation)				
12 months	6.21 (± 3.93)	6.21 (± 3.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average testicular volume

End point title	Change in average testicular volume

End point description:

Testicular volume of both testes was measured using either ultrasound or an orchidometer. Testicular volume was measured at baseline and at 6 and 12 months. The change in testicular volume from baseline was calculated for the left and right testicle as well as the average across both testes by subtracting the baseline volume from the volumes at 6 and 12 months within each patient.

End point type	Secondary

End point timeframe:

Assessed after 6 and 12 months of treatment

End point values	All treated	All-treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: mL				
arithmetic mean (standard deviation)				
6 months	1.46 (± 2.29)	1.46 (± 2.29)		
12 months	2.69 (± 2.51)	2.69 (± 2.51)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Safety data was collected and summarised for patients receiving bicalutamide in combination with anastrozole for 12 months.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	All treated
Reporting group description: All-treated (AT) population consists of any subjects who receive at least one dose of study medication and have at least one on-treatment measurement.	

Serious adverse events	All treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All treated		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
ASTHENIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
FATIGUE			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Immune system disorders			

SEASONAL ALLERGY			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Reproductive system and breast disorders			
GYNAECOMASTIA			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	7		
BREAST TENDERNESS			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	1		
BREAST PAIN			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
STRIDOR			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			
CRYING			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

SUNBURN			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
SKIN LACERATION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
EOSINOPHILIA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
LYMPHADENOPATHY			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
MICROCYTOSIS			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	5		
ABDOMINAL PAIN			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
NAUSEA			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
DIARRHOEA			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all) CAFE AU LAIT SPOTS subjects affected / exposed occurrences (all) SKIN HYPERPIGMENTATION subjects affected / exposed occurrences (all)	 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Endocrine disorders PRECOCIOUS PUBERTY subjects affected / exposed occurrences (all)	 6 / 14 (42.86%) 6		
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL CHEST PAIN subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Infections and infestations CROUP INFECTIOUS subjects affected / exposed occurrences (all) GASTROENTERITIS subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) TONSILLITIS subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION	 2 / 14 (14.29%) 2 2 / 14 (14.29%) 2 2 / 14 (14.29%) 2 2 / 14 (14.29%) 2		

subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
EAR INFECTION				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
FURUNCLE				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
LABYRINTHITIS				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
LOWER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
OTITIS EXTERNA				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
PYODERMA				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
RESPIRATORY TRACT INFECTION VIRAL				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
RHINITIS				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
SINUSITIS				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
STAPHYLOCOCCAL ABSCESS				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
VARICELLA				

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
VIRAL INFECTION			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2005	Amendment Number 1
26 July 2005	Amendment Number 2
07 May 2009	Amendment Number 3
04 October 2016	Amendment Number 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported