Drug Product	CASODEX	**SYNOPSIS**	
Drug Substance	Bicalutamide		
Study Code	D6873C00047		
Edition Number	1		
Date	9 June 2008		

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

Study centres

Patients were enrolled at 14 centres in 6 countries but were allocated to treatment in only 9 centres in 3 countries as follows: India (2 centres), United Kingdom (1 centre) and United States (6 centres). Two patients who were allocated treatment transferred from one US centre to a new US centre during the study and so patients were treated at 10 centres in total.

Publications

None at the time of this report.

Study dates		**Phase of development**
First patient enrolled	22 November 2004	Therapeutic exploratory (II)
Last patient completed	7 May 2008	

Objectives

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.

The secondary objectives of the study were:

- to investigate the efficacy of bicalutamide when used in combination with anastrozole in terms of:
  - a reduction in growth rate after 6 months treatment
  - a reduction in bone age maturation rate after 6 and 12 months treatment
  - normalization of growth rate

  - increase in predicted adult height (PAH) after 12 months treatment
  - reduction of signs and symptoms of virilization

- to assess the safety and tolerability of bicalutamide when used in combination with anastrozole in terms of:
  - gynaecomastia and breast pain adverse events (AEs)
  - all other AEs, withdrawals and laboratory data.

- to assess pharmacokinetic and pharmacodynamic parameters in achieving an optimal dose of study treatment.

Study design

This was a multi-centre, open-label, non-comparative, observational phase II study to investigate the efficacy and safety of bicalutamide in combination with anastrozole for the treatment of testotoxicosis (familial male-limited precocious puberty). Patients were to be given study drugs (bicalutamide and anastrozole) daily for 12 months through individual titration to optimal doses of each drug independently and to be followed up at 3 monthly intervals at 3, 6, 9 and 12 months. After 12 months, all study patients (on or off treatment) were to be followed up annually until they attained their final adult height.

Target patient population and sample size

A total of 12 evaluable male patients, aged 2 years and above with a diagnosis of testotoxicosis, were required for this study. As clarified by protocol amendment 1, an evaluable patient (a completer) was defined as being one who had received a minimum of 300 days of study therapy over the 12 months treatment period (approximating to 80% treatment compliance) and had 12 months (± 2 months) of safety and efficacy data. In order to collect 12 months of efficacy and safety data on 12 patients it was anticipated that approximately 20 patients with testotoxicosis would need to be screened.

Investigational products: dosage, mode of administration and batch numbers

Anastrozole (ZD1033, ARIMIDEX™) orodispersible tablets and bicalutamide (ZD7054, CASODEX™) orodispersible tablets, were given orally once-daily (Table S1).

Table S1 Details of investigational products

Investigational Product	Dosage form and strength	Batches
ZD1033 Anastrozole	Tablet 0.5mg	22 batches. Individual batch numbers are included in the CSR.
ZD1033 Anastrozole	Tablet 1mg	4 batches. Individual batch numbers are included in the CSR.
ZD7054 Bicalutamide	Tablet 12.5mg	6 batches. Individual batch numbers are included in the CSR.
ZD7054 Bicalutamide	Tablet 25mg	20 batches. Individual batch numbers are included in the CSR.

Study medication was to be independently titrated in the following ascending doses:

- dispersible bicalutamide 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg
- dispersible anastrozole 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg

The dosing of anastrozole and bicalutamide was independently tailored for each patient. Anastrozole and bicalutamide dose revisions were driven by serum oestradiol and plasma bicalutamide concentrations, respectively. Doses of each drug were iteratively adjusted until a dose was reached that gave steady-state trough serum oestradiol concentrations of <10 pmol/L (2.7 pg/mL) and R-bicalutamide (the active isomer of bicalutamide) trough plasma concentrations within the range 5-15 μg/mL. Anastrozole dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

Duration of treatment

Patients were given study drugs (bicalutamide and anastrozole) daily for 12 months. After Month 12 all patients (on or off treatment) entered an extension phase with annual follow up. Patients who completed 12 months treatment were permitted to continue study drugs in the extension phase for as long as their treating physician considered it beneficial.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Change in growth rate after 12 months of treatment relative to the growth rate during the ≥6 months pre-study period.
- Secondary variables:
  - Change in growth rate after 6 months of treatment relative to the growth rate during the ≥6 months pre-study period.
  - Change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the ≥6 months pre-study period for patients with retrospective bone age data.
  - Change in bone age to chronological age ratio after 6 and 12 months of treatment relative to the ratio at baseline. This variable was added by protocol amendment 1 (11 March 2005).
  - Number and percentage of patients who achieve and/or maintain growth rates between the 5th and the 95th percentile for chronological age at 3, 6, 9 and 12 months of treatment.
  - Change in predicted adult height (PAH) after 12 months of treatment compared to baseline PAH.

- Evaluation of testicular volume and Tanner staging at 6 and 12 months of treatment, and number of acne lesions and aggressive behaviour as defined by parental observation using the Children's Aggression Scale - Parent Version (CAS-P) questionnaire at 3, 6 and 12 months of treatment.
- Descriptive statistics of the plasma concentrations of R-bicalutamide, anastrozole, and serum concentrations of oestradiol.

Safety

- AEs, withdrawals and laboratory data.
- Incidence of breast pain and gynaecomastia at the beginning and following 12 months of treatment.

Genetic

- Optional genetic samples were collected to evaluate, by molecular analysis, the presence of activating mutations of the Luteinizing Hormone (LH) receptor in the confirmation of testotoxicosis by an independent agent. No other genetic analyses were to be performed or linked to study results.

Statistical methods

The primary outcome variable was the change in growth rate after 12 months relative to the growth rate during the ≥6 month pre-study period. Two variables were analysed, one based on raw height data (cm/year) and another calculated after appropriate adjustment for the chronological age of the patient (expressed as a standard deviation [SD] score); these variables were analysed using a one sample t-test and a 95% 2-sided confidence interval was calculated for the mean change in growth rate. All other efficacy and safety endpoints are summarised using frequency and percentages or descriptive statistics as appropriate. Three analysis sets defined in the Clinical Study Protocol (CSP) have been used: a safety analysis set, consisting of patients who received at least one dose of study drug, an all treated (AT) analysis set, consisting of patients who were treated **and** had on-treatment data, and a protocol-valid (PV) analysis set for all patients who adhered to the protocol. The PV set comprised patients who provided data at the end of 12 months (±2 months) and had had ≥300 days of study drugs.

An inclusion criterion of the study was that the patients had to be naïve to anti-androgen therapy (ketoconazole and spironolactone were allowed, as was prior use of anastrozole or other aromatase inhibitors). Therefore, the AT set equates to the "treatment naïve" population specified in the FDA Pediatric Written Request. Data are also presented for two subsets of the AT set: those who had previously received treatment for testotoxicosis (hereafter referred to as the PT set) and those who had not (hereafter referred to as the NPT set). Previous treatment for testotoxicosis included ketoconazole, anastrozole and spironolactone.

Patient population

A total of 14 patients received study drugs and were included in the safety analysis set. One patient did not provide any on-treatment data and so 13 patients were included in the AT set all of whom were included in the PV set. Of these 13 patients, 7 were included in the NPT set and 6 were included in the PT set. The results based on the PV set were identical to the results obtained from the AT set, and are therefore not presented in detail in this report.

Results

This report considers the data relating to the first 12 months of treatment collected up to 7 May 2008, after all patients had completed the 12 month assessment or had withdrawn from the study. A separate analysis of the extension data will be conducted when all patients reach their adult height.

The final dose of anastrozole and bicalutamide is summarised in Table S2. Patient E0003004 was lost to follow-up from the study prior to reaching the stablised phase of the dose titration schedule; at that time he was on 25 mg bicalutamide and 1 mg anastrozole.

Table S2 Summary of final stabilised dose of anastrozole (mg) and final stabilised dose of bicalutamide (mg): Safety set

Anastrozole final dose (mg)	Number (%) of patients N=14 Bicalutamide final dose (mg)			
	12.5	25	50	100
0.5	0 (0.0)	0 (0.0)	7 (50.0)	3 (21.4)
1	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)

Efficacy results

For the 13 patients in the AT set, the mean change in growth rate was -1.62 cm/year, 95% CI (-4.72 to 1.48) p=0.278 (Table S3). Consequently, there is no statistical evidence that the growth rate has reduced following treatment. Similarly, when expressed as a SD score in relation to a reference population (obtained from the growth charts in the WHO Global Database on Child Growth and Malnutrition), the mean change in growth rate was -0.07 SD, 95% CI (-1.15 to 1.00) p=0.882 (Table S3). Identical results were seen in the PV set.

There was no statistical evidence that the growth rate had reduced following treatment in the PT set (Table S3). For the NPT set the mean change of –2.84 cm/year just failed to reach statistical significance at the 5% level (p=0.053) although the change in growth rate expressed as a SD score did not show as strong a trend (p=0.139). Growth rate at 12 months was reduced compared to baseline in 5/7 patients in the NPT set and 4/6 patients in the PT set. There was a general trend that the higher the baseline growth rate the bigger the change from baseline observed.

Table S3 Analysis of change in growth rates (cm/year and SD units) at 12 months (primary variable)

Variable	Analysis set	Number of patients	Mean	95% CI	p-value
Change in growth rate at 12 months (cm/year)	All treated (treatment-naïve)	13	-1.62	-4.72, 1.48	0.278
	Previously treated for testotoxicosis	6	-0.20	-7.39, 7.00	0.947
	No previous treatment for testotoxicosis	7	-2.84	-5.73, 0.06	0.053
	Protocol Valid	13	-1.62	-4.72, 1.48	0.278
Change in growth rate at 12 months (SD units)	All treated (treatment-naïve)	13	-0.07	-1.15, 1.00	0.882
	Previously treated for testotoxicosis	6	0.70	-1.58, 2.98	0.468
	No previous treatment for testotoxicosis	7	-0.74	-1.79, 0.32	0.139
	Protocol Valid	13	-0.07	-1.15, 1.00	0.882

"Treatment-naïve" – no prior anti androgen therapy; SD standard deviation;
The analyses of the AT set and the NPT and PT subsets have used a last observation carried forward approach in the event of a missing 12 month assessment.

Changes from baseline in growth rate, bone maturation rate and predicted adult height (PAH), at 6 months and 12 months, are summarised for the AT set in Table S4. Similar results were seen for the NPT and PT subsets.

Table S4 Summary of growth rate, bone maturation and predicted adult height at baseline, at 6 months and at 12 months: All treated

	n	Baseline	LOCF Month 6	Change from baseline	LOCF Month 12	Change from baseline
Mean (SD) growth rate (cm/year)	13	10.81 (4.22)	10.11 (2.63)	-0.70 (5.77)	9.19 (1.92)	-1.62 (5.13)
Mean (SD) growth rate (SD units)	13	0.41 (1.36)	0.27 (0.45)	-0.14 (1.67)	0.34 (0.62)	-0.07 (1.78)
Mean (SD) bone maturation rate[a]	6	3.10 (0.68)	1.07 (0.81)	-2.03 (0.38)	0.81 (0.48)	-2.29 (0.51)
Mean (SD) ratio of BA/CA	13	2.06 (0.51)	1.97 (0.46)	-0.09 (0.14)	1.82 (0.35)	-0.24 (0.18)
Number (%) of patients with normal[b] height	13	3 (23.1)	3 (23.1)	0	3 (23.1)	0
Mean (SD) PAH (cm) (B&P Method)[c]	9	163.19 (8.57)	NA	NA	168.65 (7.62)	6.21 (3.93)
Mean (SD) PAH (cm) (RWT Method)	12	184.68 (10.56)	NA	NA	186.06 (9.35)	1.38 (2.39)

[a] Calculated for patients in the AT set for whom a 6 month pre-study radiograph was available
[b] Patient's height is between 5th and 95th percentile compared to reference population
[c] If BA <6 years or if BA <7 years with BA ≥ (CA –1) then PAH can not be calculated using B&P method.

LOCF Last Observation Carried Forward; BA bone age; CA chronological age; PAH predicted adult height; B&P Bayley and Pinneau; RWT Roche-Wainer-Thissen; NA not applicable.

The mean rate of bone maturation (change in bone age/change in chronological age) could only be determined for the 6 boys in the AT set for whom a ≥6 month pre-study radiograph was available. The Bayley and Pinneau method for calculating PAH was only applicable for the 9 patients who had a bone age ≥7 years at baseline. An exploratory analysis using the Roche-Wainer-Thissen stature prediction model for PAH estimation was carried out by Lifespan Health Research Centre for 12 of the 13 patients in the AT set. One patient did not have data calculated by the Roche-Wainer-Thissen method because his parents did not provide consent for their height to be used.

Changes from baseline in testicular volume, Tanner staging and CAS-P scores, at 6 months and 12 months, are summarised in Table S5. Similar results were seen for the NPT and PT subsets.

Table S5 Summary of testicular volume, Tanner staging, acne lesions and CAS-P score at baseline, at 6 months and at 12 months: All treated

	n	Baseline	LOCF Month 6	Change from baseline	LOCF Month 12	Change from baseline
Mean (SD) avg testicular volume (mL)	13	6.08 (2.78)	7.54 (2.93)	1.46 (2.29)	8.77 (2.12)	2.69 (2.51)
Mean (SD) Tanner stage (testes and scrotum)	12[a]	3.00 (0.74)	2.92 (0.79)	-0.08 (0.51)	3.25 (0.45)	0.25 (0.45)
Mean (SD) Tanner stage (Pubic hair)	13	2.62 (0.77)	2.31 (0.95)	-0.31 (0.63)	2.15 (0.99)	-0.46 (0.52)
Median number of acne lesions	13[b]	0	0	0	0	0
Mean (SD) CAS-P Total score	13	15.66 (12.02)	10.22 (8.86)	-5.44 (9.24)	7.71 (7.30)	-7.95 (5.91)

[a] Testes and scrotum Tanner stage was not recorded for Patient E0009001

[b] n=12 at LOCF month 6 because acne lesions for Patient E0013004 were not recorded at 3 or 6 months.

LOCF Last Observation Carried Forward; Avg average; SD standard deviation; CAS-P Children's Aggression Scale - Parent Version

Median acne lesion count was 0 at baseline and at all subsequent timepoints. There was a reduction in mean acne lesion count from 4.54 at baseline to 0.92 at 12 months but these data were skewed and hence are not presented in Table S5. Only 5 (38.5%) patients in the AT set had acne lesions at baseline and the acne lesion count was reduced after treatment for all of these 5 patients. Two patients who had no acne at baseline had one or more acne lesions at 12 months.

After 12 months, 12/13 (92.3%) patients had shown an improvement in CAS-P total score. The patient who did not show an improvement had a CAS-P total score of 0 at baseline and 0.67 after 12 months. Three of the patients who had a reduction in total CAS-P score at 12 months also had a score <10 at baseline indicating that these patients were not particularly aggressive to begin with.

Pharmacokinetic results

- Trough R-bicalutamide concentrations generally appeared to increase proportional to dose over the 12.5 to 100 mg dose range. In the majority of patients, steady-state trough R-bicalutamide concentrations appeared to be attained by Day 21.

- Trough anastrozole concentrations generally appeared to increase proportional to dose over the 0.5 to 1 mg dose range. Steady-state trough anastrozole concentrations appeared to be attained by Day 8.

- There was no apparent relationship between plasma bicalutamide and anastrozole trough concentrations and the age or weight of the patient. Thus, dose alterations dependent on the patients' age are not required.

Safety results

- The 14 patients allocated to study drugs had a median treatment duration of 349.0 days for bicalutamide and 362.0 days for anastrozole.

- Of the 14 patients exposed to study treatment 13 (92.9%) experienced at least one AE. The most frequently reported (≥3 patients) AEs were gynaecomastia (7 patients), precocious puberty* (6 patients), vomiting (5 patients), headache (3 patients) and pyrexia (3 patients). *Note that the investigator recorded these events as "central precocious puberty" and this codes to the MedDRA preferred term of "precocious puberty" (see also next bullet).

- Of the 90 AEs reported, the investigators considered 16 AEs in 6 (42.9%) patients to be possibly related to either anastrozole or bicalutamide. AEs considered possibly related to bicalutamide included gynaecomastia (6 patients), precocious puberty* (2 patients), breast tenderness (2 patients), breast pain (1 patient), asthenia (1 patient), increased alanine aminotransferase (ALT) (1 patient) and aspartate aminotransferase (AST) (1 patient) and musculoskeletal chest pain (1 patient). Only one AE (headache, 1 patient) was considered possibly related to anastrozole.

- Of the 14 patients exposed to study treatment 2 (14.3%) patients had a Common Terminology Criteria (CTC) grade 3 AE (gynaecomastia; furuncle). All other AEs reported were classified as CTC grades 1 or 2.

- None of the patients who received study drugs had gynaecomastia or breast pain at baseline but 3/14 (21.4%) patients reported breast pain and 7/14 (50.0%) reported gynaecomastia after 12 months and these AEs were ongoing in all cases.

- There were no deaths. One enrolled patient (E0019001) had a serious adverse event (SAE; renal tumour) prior to receiving study drugs. This patient was a screening failure (β-HCG out of range). Of the 14 patients who received study drugs, none experienced an SAE and none discontinued study drugs due to an AE.
- One patient had increased AST and ALT during the study and this was recorded as an AE (CTC grade 1), which the investigator considered related to bicalutamide. The enzyme elevations returned to normal without stopping treatment. There were no increases in total bilirubin observed for this patient at any time in the study.
- Six of the 14 patients who received study drugs had entered central precocious puberty (CPP) during the 12 months treatment period (none had entered CPP at baseline).
- No new safety signals or concerns were raised based upon the results of clinical laboratory tests collected as part of the study.

Date of the report

9 June 2008