AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Anastrozole
Study Code	D5390L00074
Edition Number	1
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A Randomized, Double-blind, Placebo-controlled Multicenter Trial to Assess the Safety and Efficacy of Anastrozole (ARIMIDEX™) in Increasing Predicted Adult Height of Adolescent Males with Growth Hormone Deficiency

Study dates: Study start date: November 2001
Last patient last visit: 22 June 2007

Phase of development: Therapeutic exploratory (II)

Study centre(s)

Patients were recruited from 7 study centres in the USA: The Nemours Children's Clinics in Jacksonville, Orlando and Pensacola; the Universities of Puerto Rico, California and South Carolina; and Mount Sinai Medical Centre, New York.

Publications

Mauras et al 2008
Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, Rapaport R, Schwartz ID, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. J Clin Endocrinol Metab 2008;93:823-31.

Objectives

The primary objective of this study was to determine whether long term oestrogen blockade by anastrozole treatment in pubertal, growth hormone (GH) deficient males treated concurrently with GH can increase predicted adult height.

The results for the primary objective were presented in a recent peer-reviewed publication (Mauras et al 2008). Efficacy objectives and endpoints were not covered in detail in the abbreviated Clinical Study Report (CSR) for this study, which was primarily concerned with safety data.

A secondary study objective relating to safety was defined in the CSP:

- to determine the effect of anastrozole treatment on bone mineralization in pubertal GHD males treated concurrently with GH.

Although this was defined as a secondary study objective, bone mineral density (BMD) was not a principal aim of the study and was performed primarily as a safety measure. Patients were not excluded from the study if they did not have BMD data at baseline.

Study design

This was a randomised, double-blind, multicentre study to compare the efficacy, safety and tolerability of anastrozole 1 mg in combination with GH, compared to placebo and GH, in the treatment of adolescent boys with growth hormone deficiency (GHD).

Target patient population

Patients were adolescent boys with GHD. Adolescent boys were defined as boys with genital Tanner stage ≥II. GHD was defined as peak GH responses to pharmacological stimuli ≤10 ng/ml, and evidenced in either

- short stature (more than 2 SDs below average, ie, standardized height is less than minus 2.0), or,

- profound growth deceleration (growth velocity ≤25% of corresponding chronological age population).

Investigational product and comparator(s): dosage, mode of administration and batch numbers´

Patients were randomised 1:1 to receive either anastrozole 1 mg or placebo. All patients received randomised study drug in combination with GH Nutropin®.

The details of the investigational products and other study treatments are given in Table S1.

Table S1 Details of investigational product and other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer(s)	Formulation number
Anastrozole	1 mg oral tablet, daily	AstraZeneca IPS	F11292
Anastrozole placebo	1 mg oral tablet, daily	AstraZeneca IPS	F11314
GH Nutropin®	~0.3mg/kg.w (≤0.4mg/kg.w)[a] subcutaneously at bedtime, daily	Genentech, Serono, Eli Lilly, Pfizer, Novo Nordisk	-

[a] GH dose was adjusted by the investigator for size/weight, and dose adjustment were made at least every 6 months.

Batch numbers were provided in the abbreviated CSR.

Duration of treatment

Patients continued on study treatment for 36 months or until completion of linear growth, whichever came first. Completion of linear growth was defined as achievement of a bone of ≥16 years and a growth velocity of <2 cm/year.

Criteria for evaluation - efficacy (main variables)

Efficacy objectives and endpoints were not covered in detail in the abbreviated CSR for this study, which was principally concerned with safety data.

Criteria for evaluation - safety (main variables)

- BMD Z-score
- Adverse events (AEs).
- Plasma concentration of insulin-like growth factor I (IGF I).
- Sex hormones:

  - oestradiol, testosterone.

- Lipid profile variables:
  - total cholesterol, HDL-C, triglycerides, LDL-C and the ratio of LDL-C to HDL-C.
- Glucose and osteocalcin.
- Other standard safety laboratory parameters
  - haemoglobin, haematocrit, white blood cells (WBC), platelets, aspartate aminotransferase, alanine aminotransferase, bilirubin (conjugated and total), albumin, random glucose and alkaline phosphatase.
- Body mass index (BMI).
- % body fat.
- Tanner pubertal stage.

Statistical methods

No formal statistical analyses were planned or performed for AEs, Tanner pubertal stage or the standard safety laboratory parameters; these endpoints were summarised.

For all other safety endpoints comparisons between the 2 treatment arms were made using an analysis of covariance (ANCOVA) test. The ANCOVA adjusted for pre-randomisation covariates; safety analyses were adjusted for baseline values and treatment received.

Subject population

Fifty-two patients were recruited for participation, 25 patients were randomised to receive anastrozole 1 mg and 27 to receive placebo.

Of the 52 randomised patients, 50 completed ≥12 months, ≥41 completed ≥24 months and 28 completed 36 months. Of those patients withdrawing before completion of 36 months of trial treatment:

- nine withdrew because they either: attained the predefined criteria for completion of linear growth; or they had psychosocial issues at home or school; or they were tired of taking medication.
- five patients were discontinued by the investigators because of poor drug compliance or were lost to follow-up. This included one patient, in the anastrozole treatment arm, who was discontinued by the investigator due to an AE (psychogenic emesis) that compromised drug compliance.

Summary of efficacy results

The purpose of the abbreviated CSR for this study was to report and evaluate the safety data from Study D5390L00074; therefore the efficacy results were not addressed in detail, however, a brief summary of the efficacy data is provided below.

The full details of the investigator's assessment and interpretation of the efficacy data were reported in a peer-reviewed publication (Mauras et al 2008). In the 2008 publication, the authors observed that linear growth was comparable between groups; however, there was a significantly slower increase in bone age advancement from baseline in the anastrozole group, compared to placebo after 24 months (+1.8 [±0.1] yr vs +2.7 [±0.1] yr, respectively; $p<0.0001$) and 36 months (+ 2.5 [±0.2] yr vs +4.1 [±0.1] yr, respectively; $p<0.0001$). This led to a net increase in predicted adult height of +4.5 (±1.2) cm at 24 months and +6.7 (±1.4) cm at 36 months in the anastrozole treatment group, compared with a 1 cm gain at both time points in the placebo group.

Summary of safety results

The ANCOVA analysis of whole body BMD Z-scores indicated that there was no statistically significant difference between the 2 treatment arms, in terms of absolute values or change from baseline, at 24 months ($p=0.2330$ [n=26]) or at 36 months ($p=0.3802$ [n=11]).

At both the population and individual patient level, lumbar spine BMD Z-scores improved overall in both treatment arms; the rate of increase in the placebo treatment arm was significantly higher at 24 months ($p=0.0088$ [n=27]) but not 36 months, compared to the anastrozole treatment arm ($p=0.2525$ [n=17]).

The incidence of events in each AE category was well balanced between the 2 treatment arms. The majority of patients reported at least one AE during the study (94.3% [50/53 patients]). AEs that were considered by the investigator to be causally related to study treatment were reported in 11/53 patients (20.3%).

There were more patients with serious adverse events (SAEs) in the anastrozole treatment arm compared to the placebo arm (4 patients [15.4%] vs 0 patients, respectively), although none of the SAEs were considered by the investigator to be causally related to anastrozole treatment. Only one patient, in the anastrozole treatment arm, withdrew from the study due to an AE. There were no patient deaths reported during the study.

Overall, there were no clinically significant differences between the 2 treatment arms in terms of clinical laboratory results, other than changes in oestradiol that are expected based on the mechanism of action of anastrozole.