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Aromatase inhibitors in girls: Anastrozole combined to the LHRH analogue leuprorelin in Girls with early or precocious puberty and a compromised growth potential

Submission date
13/12/2014

Recruitment status
No longer recruiting

Registration date
13/01/2015

Overall study status
Completed

Last Edited
17/04/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
The pituitary gland is a pea-sized structure in the brain that makes, amongst other things, a chemical called the growth hormone. Growth hormone deficiency occurs when this gland does not produce enough growth hormone. This deficiency can develop at any age. In children, it results in slow growth compared to children of the same age with the affected child looking smaller and younger than their peers. Treatment with aromatase inhibitors have been shown to be successful in increasing predicted adult height (PAH) in boys, but, in girls, it has only shown to be successful for those that have McCune-Albright syndrome (a genetic disorder). Luteinising hormone is another hormone produced in the pituitary gland. It stimulates the production of the sex hormones, including oestrogen. Oestrogen promotes the maturation of the skeletal bones, which leads to a slow in growth. Blocking the production of luteinising hormone using a drug called leuprorelin slows down bone maturation and therefore potentially increases the amount of time available for growth. We want to investigate whether anastrozole (a aromatase inhibitor) combined with leuprorelin for up to 2 years (or until the age of 11 years) is a safe and effective treatment for improving PAH in girls with precocious (very early) or early puberty with a compromised (less than usual) growth potential, compared to leuprorelin alone.

Who can participate?
Girls with idiopathic precocious (breast development occurring before 7.5 years) or early puberty (breast development occurring between 7.5-9 years), that have not had hormone therapy before and a compromised growth potential .

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 receive a combination of leuprorelin and anastrozole for 2 years or until they reach the age of 11 years. Those in group 2 are given only leuprorelin for 2 years or until they reach the age of 11 years. After completing the initial phase of treatment , girls on the combined treatment are then randomised to receive anastrozole or no treatment at all and followed up every 6 months until

bone age reaches 14 years or they reach near adult height. Girls on leuprorelin only are followed up every 6 months with no relevant treatment until bone age reaches 14 years or near adult height is achieved. Follow-up includes clinical examination, hormonal and biochemical measurements, pelvic ultrasound and a bone age X-ray. DXA scans and X-rays of the lumbar spine are assessed yearly.

What are the possible benefits and risks of participating?
Parents are informed that anastrozole treatment is an off-label treatment and will be asked to sign a written informed consent. Anastrozole is safe for humans. While widely used off-label in boys, in girls it has been given mainly as a treatment for McCune-Albright syndrome. In a previous trial, 5 girls received the combined treatment. There were no side effects in any of the girls.

Where is the study run from?
1. Pediatric Endocrine Unit, Attikon University Hospital, Athens (Greece)
2. Department of Pediatric-Adolescent Endocrinology and Diabetes, Athens Medical Center, Athens (Greece)

When is the study starting and how long is it expected to run for?
January 2008 to December 2017

Who is funding the study?
Investigator initiated and funded (Greece)

Who is the main contact?
Dr Dimitrios T. Papadimitriou
info@pedoendo.gr

Contact information

Type(s)
Scientific

Contact name
Dr Dimitrios Papadimitriou

Contact details
58, av Kifisias
15125
Marousi
Greece
15125
+302103638536
info@pedoendo.gr

Additional identifiers

Protocol serial number
9804

Study information

Scientific Title
The aromatase inhibitor anastrozole combined to the LHRH analogue leuprorelin vs leuprorelin alone in ameliorating predicted adult height In girls with early or precosious puberty with a compromised growth potential

Acronym
GAIL (Girls treated with an Aromatase Inhibitor plus Leuprorelin)

Study objectives
Whether the combination of an aromatase inhibitor (anastrozole) with an LHRH analogue (leuprorelin) can significantly improve predicted adult height in girls with idiopathic precocious or early puberty and a compromised growth potential compared to inhibition of puberty alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Attikon University Hospital Ethics Committee, 2008, ref: 36/2008 13/3/08.

Study design
Prospective Phase IIa and IIb study, performed in two cooperating centers.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Compromised predicted adult height in girls with early or precocious puberty

Interventions
An initial phase IIa trial with 5 girls on the combined treatment for 1 year was performed. Girls with idiopathic precocious (<7.5yrs) or early (7.5-9yrs) puberty, all with a PAH lower than -2 or more than 1.5 SDS lower than their target height (TH) are randomized on leuprorelin 0.3 mg/kg /month plus anastrozole 1 mg/day p.o. (group-A) or on leuprorelin only (group-B) for 2 yrs or until the age of 11 yrs. After completion of this initial phase, girls on the combined treatment will be randomized to anastrozole monotherapy 1 mg/day p.o. or no treatment and followed every 6 months until bone age reaches reaches 14 years or near adult height is achieved (height velocity < 2 cm/year). The girls on leuprorelin only will be followed every 6 months without any relevant hormonal treatment until bone age reaches 14 years or near adult height is achieved.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
1. Anastrozole 2. Leuprorelin

Primary outcome(s)
1. Predicted adult height calculated according to the Bayley Pinneau tables with a bone age calculated according to the atlas of Greulich and Pyle, at 6-12-18-24 months.
2. Height velocity
3. Height for bone age
4. Bone age advancement
5. BMI

Participants are followed until bone age reaches 14 or near adult height is achieved.

Key secondary outcome(s))
1. Potential hyperandrogenism (clinical or biochemical)
2. Ovarian cyst formation (pelvic ultrasound)
3. Bone mineral density (evaluated yearly by DXA)
4. Radiological evaluation of the lumbar spine (yearly)
5. Reports of peculiar behavior

Completion date
31/12/2017

Eligibility

Key inclusion criteria
1. Idiopathic precocious (breast development < 7.5 yrs) or early puberty (breast development 7.5-9 yrs)
2. Previously naïve to any hormonal therapy
3. PAH lower than -2 SDS or -1.5 SDS lower than their target height (mid parental height -6.5 cm)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
Female

Total final enrolment
40

Key exclusion criteria
1. Organic precocious puberty
2. Syndromic, systemic or hereditary conditions that either impair growth or associate with PP
3. Bone diseases related to short stature (i.e. hypochondroplasia)

Date of first enrolment
01/01/2008

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
Greece

Study participating centre
Attikon University Hospital, 3rd Department of Pediatrics, Pediatric Endocrine Unit
Rimini 1
Haidari
Athens
Greece
12462

Study participating centre
Athens Medical Center, Department of Pediatric-Adolescent Endocrinology and Diabetes
58, av Kifisias
Marousi
Athens
Greece
15125

Sponsor information

Organisation
Attikon University Hospital

Organisation
Athens Medical Center

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2016		Yes	No
Results article		08/05/2020	08/02/2023	Yes	No
Other publications	results from the second phase of the GAIL study	02/04/2024	17/04/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes