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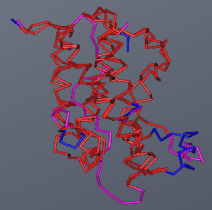
# Terapia con GH: Cosa è cambiato in 25 anni



"There are more things in heaven and earth, Horatio,
than are dreamt of in your philosophy…"
William Shakespeare, *Hamlet*

# Overview

- New indications
- New effects
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# EMA approved indications for human GH

1. Growth Hormone Deficiency
2. Turner syndrome
3. Prader-Willi syndrome
4. Chronic renal insufficiency
5. Children born SGA with subsequent growth failure at 4 years of age or later
6. Short stature homeobox-containing gene (SHOX) deficiency

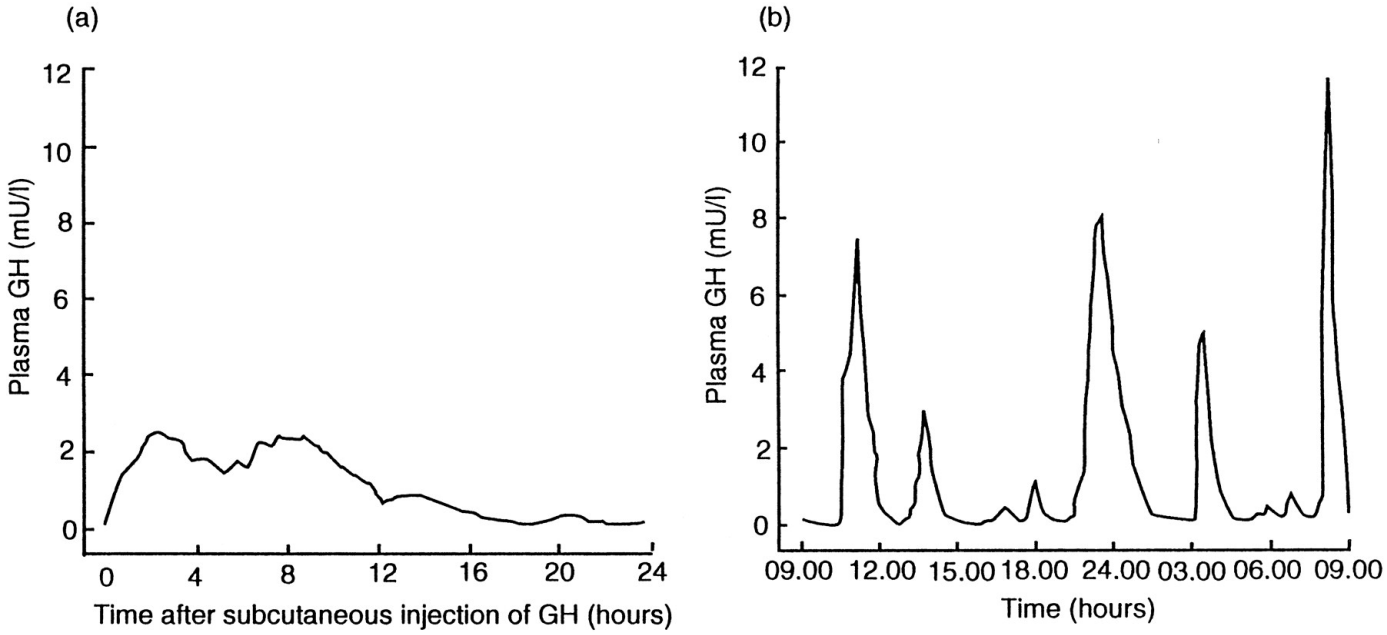
# FDA-approved indications for human GH

| Year of FDA approval[a] | Indication | Recommended doses[b] |
|---|---|---|
| 1985 | GH deficiency | 0.16–0. 3 mg/kg · wk (up to 0.7 mg/kg · wk approved in pubertal patients) |
| 1993 | Chronic renal insufficiency | Up to 0.35 mg/kg · wk until renal transplantation |
| 1996 | Turner syndrome | 0.33 mg/kg · wk; other approved doses are up to 0.375 or 0.469 mg/kg · wk |
| 1997 | Adult GH deficiency | FDA-approved starting dose, schedule for dose increase, and maximum doses vary[c] |
| 2000 | Prader-Wlli syndrome | 0.24 mg/kg · wk |
| 2001 | Small for gestational age (and failure to manifest catch-up growth by 2–4 yr) | 0.33 mg/kg · wk; other approved dose ranges are 0.231–0.469 mg/kg · wk based on initial height and response to treatment and up to 0.48 mg/kg · wk |
| 2003 | Idiopathic short stature | Approved doses are up to 0.3 mg/kg · wk, 0.37 mg/kg · wk, and, and 0.47 mg/kg · wk |
| 2003 | Short bowel syndrome in patients receiving specialized nutritional support (no pediatric studies when approved) | 0.1 mg/kg · d (0.7 mg/kg · wk), up to a maximum of 8 mg/d; administration for more than 4 wk was noted not to have been adequately studied |
| 2003 | HIV patients with wasting or cachexia (adults) | From 0.1 mg/kg · d (0.7 mg/kg/wk) if <35 kg to 6 mg/d if >55 kg |
| 2006 | SHOX (short stature homeobox-containing gene) deficiency | 0.35 mg/kg · wk |
| 2007 | Noonan syndrome | Up to 0.066 mg/kg · d (*i.e.* 0.469 mg/kg · wk) |

# The seven manufacturers marketing authorisations for somatropin for the following indications

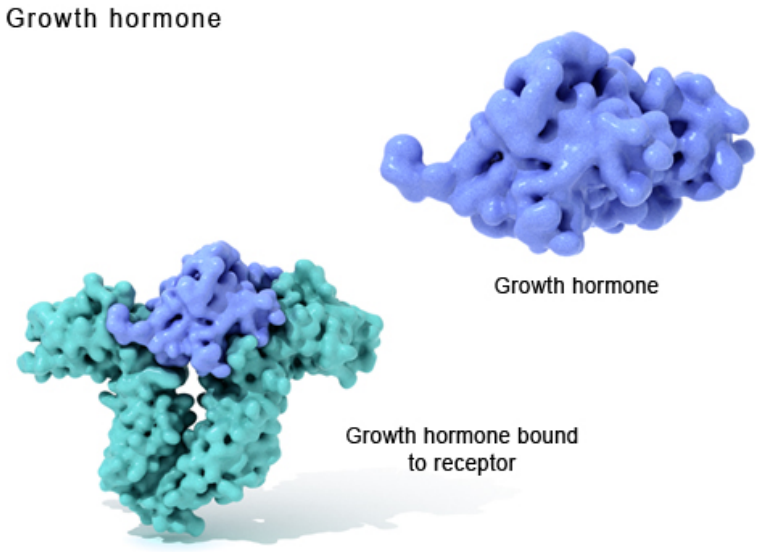
- Ferring (Zomacton): growth hormone deficiency and Turner syndrome.
- Ipsen (NutropinAq): growth hormone deficiency; Turner syndrome and CRI.
- Lilly (Humatrope): growth hormone deficiency; Turner syndrome; CRI; short children born small for gestational age and SHOX deficiency.
- Merck Serono (Saizen): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age.
- Novo Nordisk (Norditropin SimpleXx): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age.
- Pfizer (Genotropin): growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age.

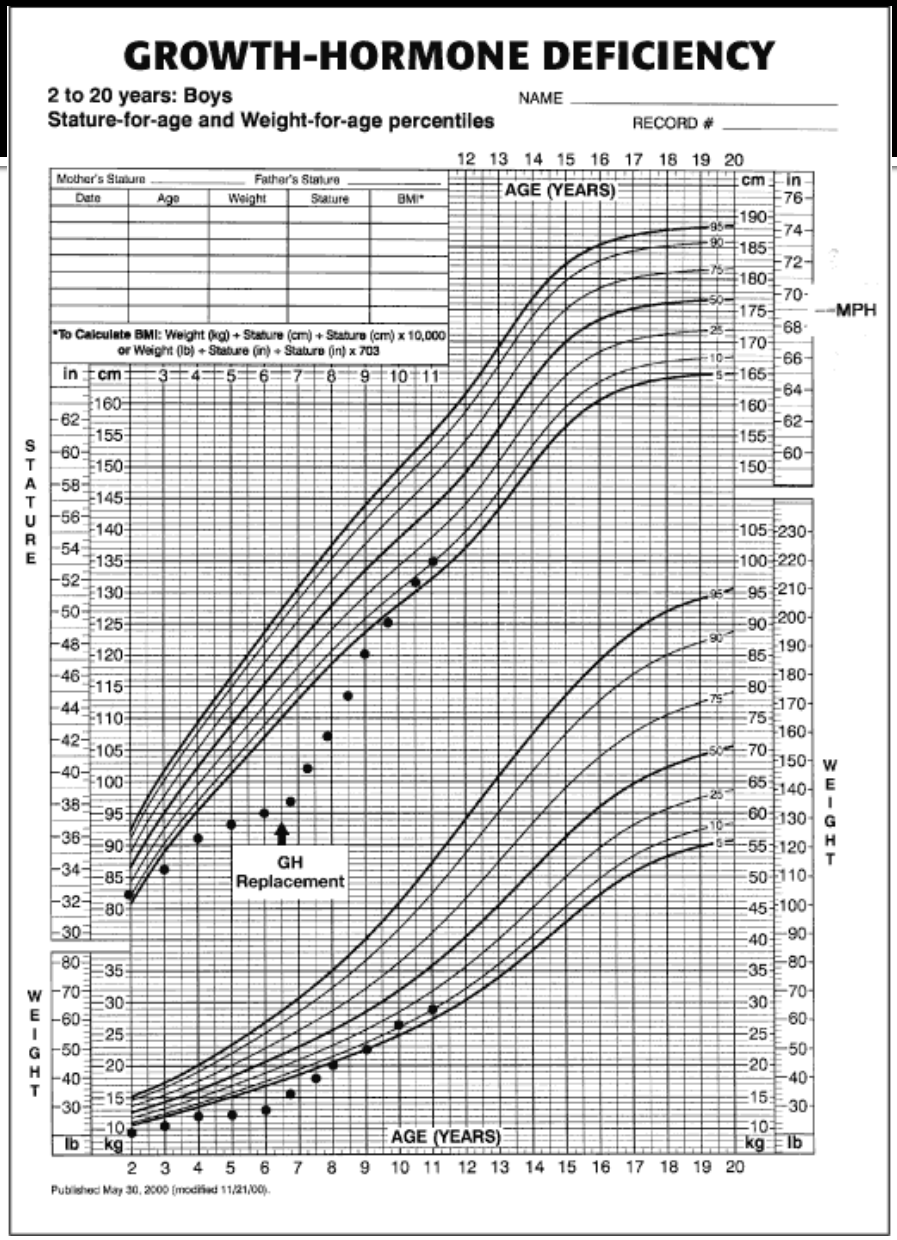
- *Sandoz (Omnitrope): growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age.*




**Drake, W. M. et al. Endocr Rev 2001;22:425-450**

# Response to long-term GH therapy



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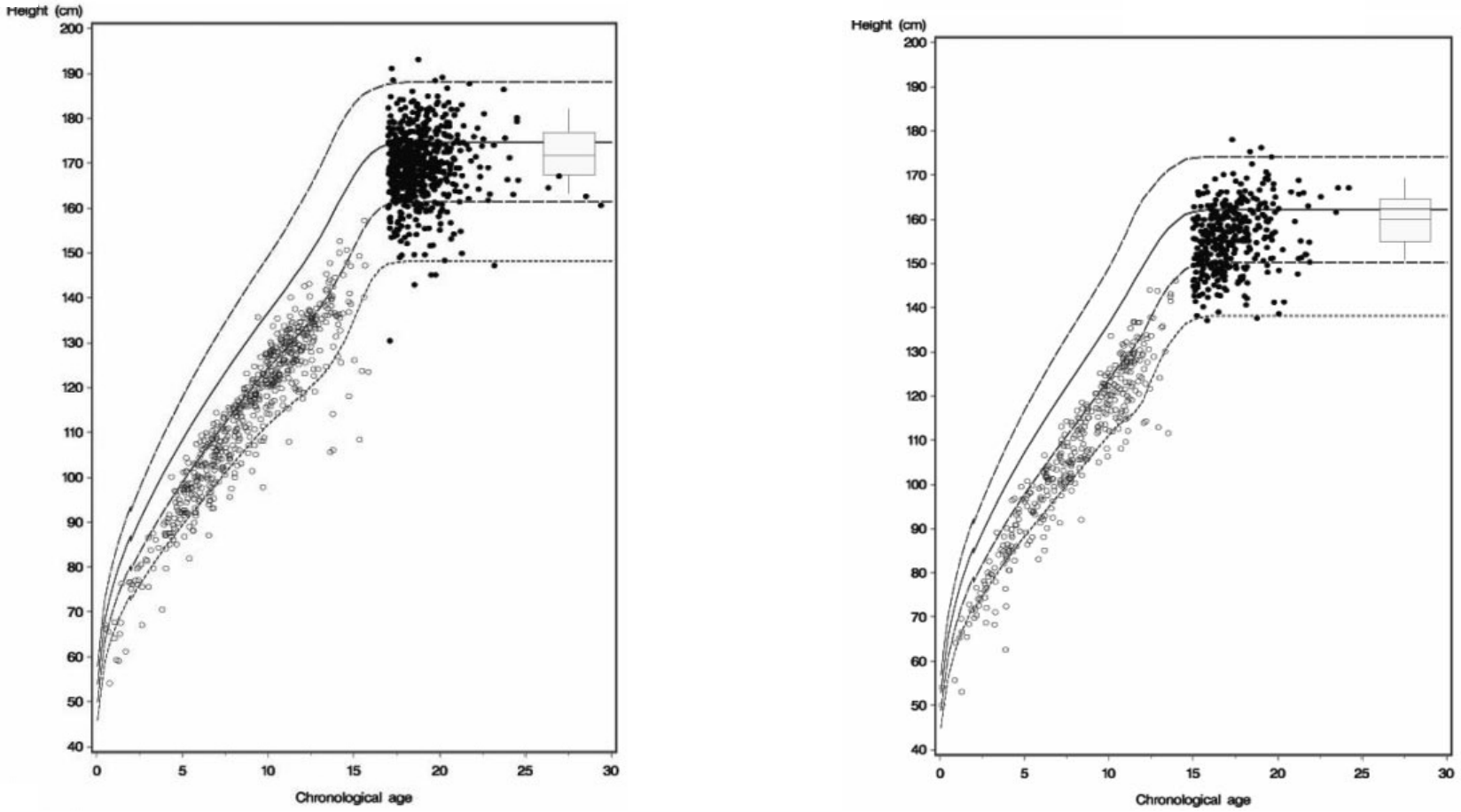
# Objectives of GH therapy

- Normalization of height during childhood.
- Attainment of normal adult height.

GH RESEARCH SOCIETY ON CHILD AND ADOLESCENT GH DEFICIENCY
***JCE & M 2000 Vol. 85 No. 11***

Starting height (E) and near-adult height (F) after GH treatment in male (A; n505) and female (B; n331) Caucasian children with idiopathic GHD. The curves represent means (*solid lines*), 2 SD (*broken lines*), and 4 SD (*dotted lines*). *Box plots* represent medians and 25th and 75th percentiles, with *whiskers* at the 10th and 90$^{th}$ percentiles.




Reiter EO et al. JCEM, 2006; 91:2047-2054

# Adult height in GHD patients treated with GH

**Adult height achieved at the end of therapy according to literature**

- Height: -0.7 to -1.3 SDS
- Height corrected for MPH: -0.4 to –0.6 SDS

**Predictive factors:**

- Height at initiation of GH therapy
- Age at initiation of GH therapy
- Treatment duration
- Height velocity during first year of treatment
- GH dose
- Baseline IGF-I levels
- Compliance
- Appropriate replacement therapy of associated pituitary deficiencies (such as thyroid hormone and glucocorticoids)

# Gains in final height for children treated with somatropin compared with untreated children

- Growth hormone deficiency 8–11 cm

- Turner syndrome approx. 7 cm
- CRI 3–9 cm
- Prader–Willi syndrome 10–11 cm + statistically significant changes in measures of body composition
- SGA approx. 6 cm favorable changes in measures of body composition
- ISS approx. 4 cm

# Cost per centimetre gained in final height

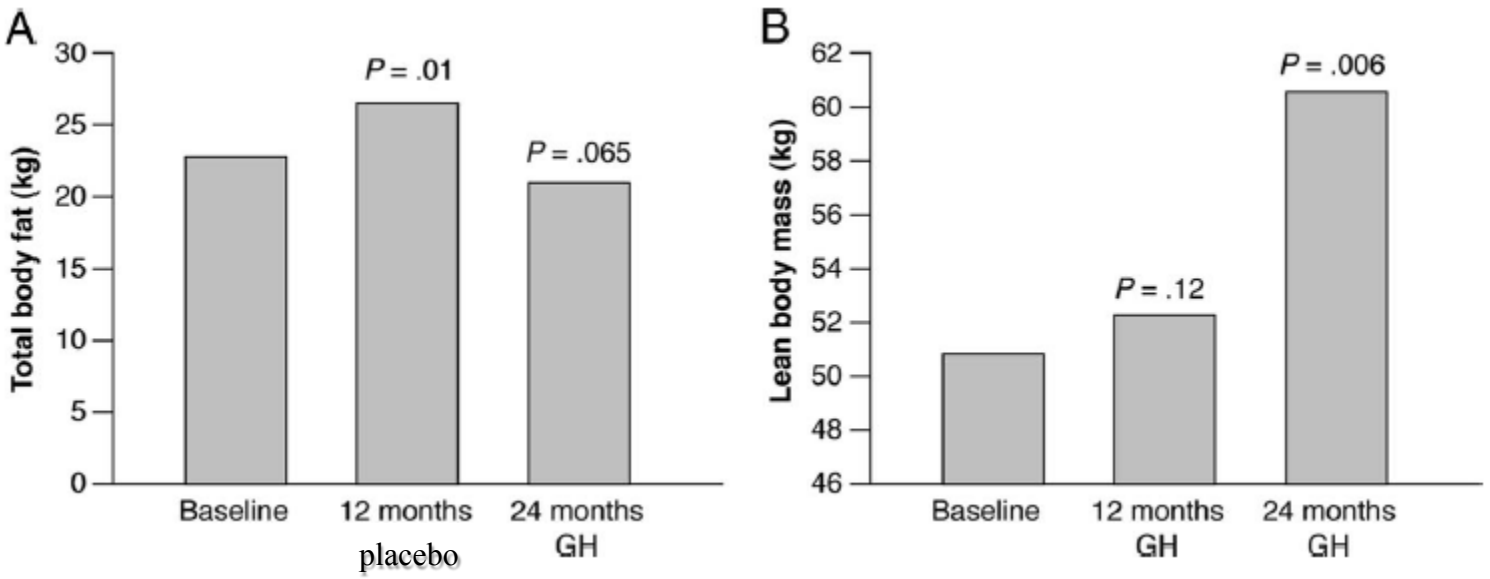
- £6000 per cm final height for growth hormone deficiency;
- from £15,800 to £17,300 per cm for Turner syndrome;
- from £7400 to £24,100 per cm for CRI;
- approximately £7030 per cm for Prader–Willi syndrome.

- *Approximately €25000 for SGA.*
- *Approximately €27000 for ISS.*

# Other beneficial effects of GH therapy

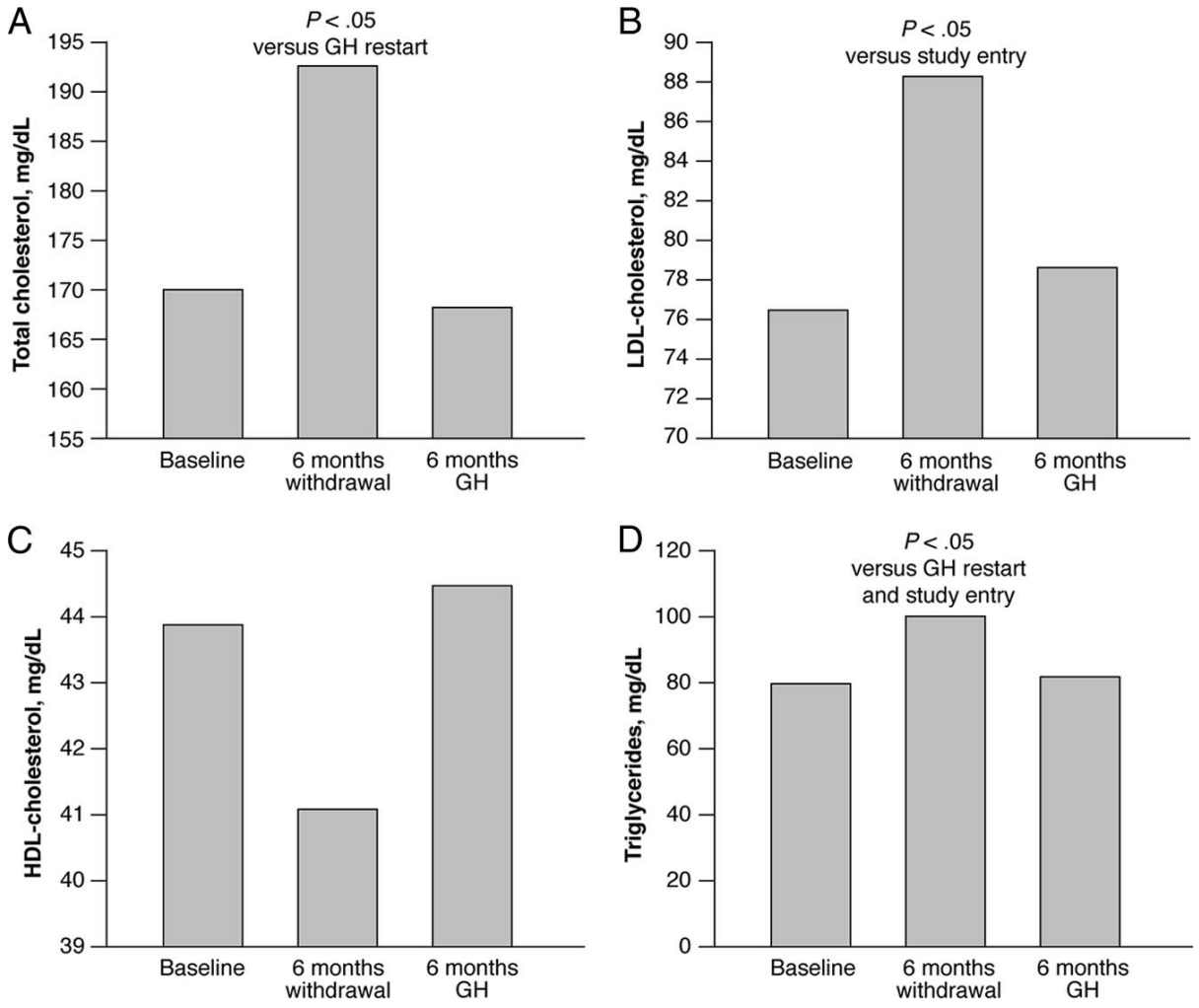
- Body composition
- Bone mineralization
- Lipid profile
- Quality of life??

# Total body fat (A) and LBM (B) as assessed from dual-energy radiograph absorptiometry scan at baseline, and after 12 months of placebo followed by 12 months of GH treatment in young adults with GHD




Ross J et al. *Pediatrics 2010;125:e906–e918*

# Lipid levels in 10 adolescent patients with GHD at study entry, 6 months after withdrawal of GH, and 6 months after GH replacement was restarted.




Ross J et al. *Pediatrics 2010;125:e906–e918*

# QOL related issues

**Table 1.** Stature-related stereotypes

| |
|---|
| Children and adults with SS are treated poorly because of their stature |
| Children and adults with SS experience poor psychosocial adjustment |
| Children and adults with SS do less well at school/attain less education |
| Adults with SS hold lower-status occupations and are paid less |
| Short men are less physically attractive and desirable to women |

Adapted from Sandberg and Colsman [18].

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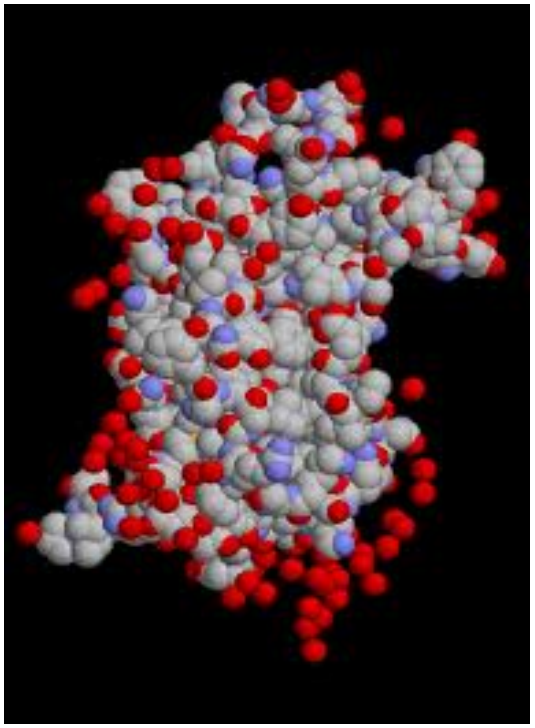
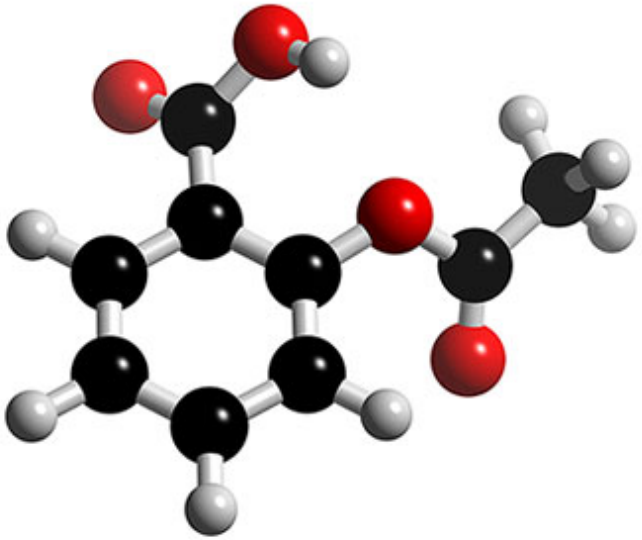
# Biopharmaceuticals are large molecules



Growth Hormone



Aspirin

# Definition of *Biosimilar (similar) biological medicinal product (biosimilar BMP)*

- A medicinal product developed by a new manufacturer and claimed to be similar to a known ('reference') BMP.

- A biosimilar BMP contains the same active substance as the reference BMP and is intended to be used for treating the same disease(s), at the same dose and using the same route of administration.

# Global market size of biopharmaceuticals with expiring patents

| Drug | Global market size (US$ bn, 2002) |
|---|---|
| Epoetins | 8.4 |
| Insulins | 4.4 |
| Interferon-α | 4.0 |
| Colony-stimulating factors | 2.7 |
| Interferon-β | 2.4 |
| Growth hormones | 1.7 |
| Follicle-stimulating hormones | 0.8 |

Reuters Business Insight healthcare report, 2003.

# EU Biosimilars Approvals, Status February 25, 2009.

| Biosimilar Product | Company | INN | Reference Product | Date of Approval |
|---|---|---|---|---|
| Omnitrope | Sandoz | Somatropin | Genotropin | April 12, 2006 |
| Valtropin | Biopartners | Somatropin | Humatrope | April 24, 2006 |
| Binocrit | Sandoz | Epoetin alfa | Erypo/Eprex | August 28, 2007 |
| Epoetin alfa Hexal | Hexal | Epoetin alfa | Erypo/Eprex | August 28, 2007 |
| Abseamed | Medice | Epoetin alfa | Erypo/Eprex | August 28, 2007 |
| Silapo | Stada | Epoetin zeta | Erypo/Eprex | December 18, 2007 |
| Retacrit | Hospira | Epoetin zeta | Erypo/Eprex | December 18, 2007 |
| Ratiograstim | Ratiopharm | Filgrastim | Neupogen | September 15, 2008 |
| Tevagrastim | Teva | Filgrastim | Neupogen | September 15, 2008 |
| Biograstim | CT Arzneimittel | Filgrastim | Neupogen | September 15, 2008 |
| Filgrastim ratiopharm | Ratiopharm | Filgrastim | Neupogen | September 15, 2008 |
| Zarzio | Sandoz | Filgrastim | Neupogen | February 6, 2009 |
| Filgrastim Hexal | Hexal | Filgrastim | Neupogen | February 6, 2009 |

# Budget cuts

- A recent estimation by the Congressional Budget Office estimates that enactment of biosimilars legislation would reduce total U.S. expenditures on biologicals by $25 billion over the 2009–2018 period, with competition beginning for most products not before the second half of this period. This would equal about 0.5% of national spending on all prescribed medicines.

# Warning

- The efficacy is demonstrated in therapeutic equivalence trial(s), the safety of a biosimilar BMP *may differ* from that of its reference BMP due to differences in the quality attributes of both products, which may or may have not been apparent during the quality comparability exercise.

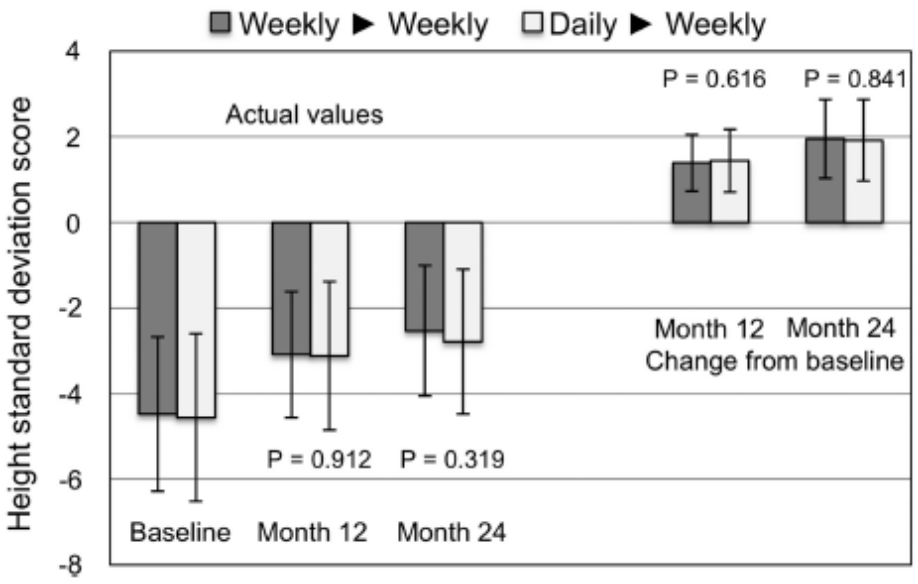
- Because such differences may have unforeseeable clinical consequences, *the clinical safety of a new biosimilar BMP must be extensively evaluated both before and after marketing authorization.*

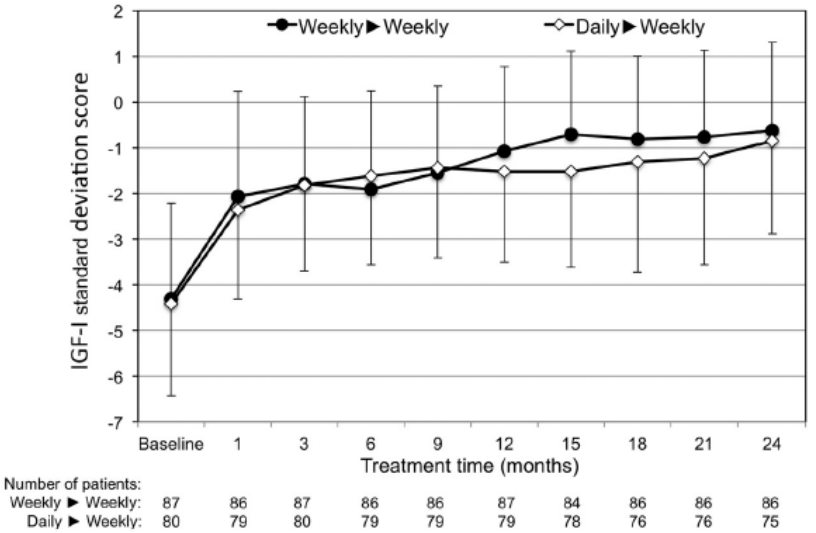
# Interchangeability and Substitution

- Detected or undetected differences between the biosimilar and the reference BMP may cause differences in safety or the efficacy profile.
- Considering that these differences may not be observed until more experience with these biosimilar BMPs is acquired, a systematic and uncontrolled substitution, does not appear reasonable at this time.
- In principle it is not recommended to switch patients from one BMP to another. There is no reason to depart from this recommendation for a biosimilar product.
- Since biosimilar and biological reference medicines are not identical, EMEA recommends that the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional *[EMEA, Questions and Answers on biosimilar medicines (similar biological medicinal products), EMEA/74562/2006, 2007*]. Automated substitution of biopharmaceuticals (including biosimilars) on the pharmacy level has been excluded by legal or administrative regulations in several European countries.

# 24-Month Use of Once-Weekly GH, LB03002, in Prepubertal Children with GH Deficiency

J Clin Endocrin Metab. First published ahead of print October 29, 2013 as doi:10.1210/jc.2013-2502



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# SAGHE

## Safety and Appropriateness of Growth Hormone treatments in Europe

SEVENTH FRAMEWORK PROGRAMME

# EUROPE


F.Y.R.O.M. - The Former Yugoslav Republic of Macedonia
Greenland (DENMARK)
Jan Mayen (NORWAY)
Greenland Sea
Denmark Strait
Reykjavik
ICELAND
Norwegian Sea
Arctic Circle
Barents Sea
Hammerfest
Tromsø
Murmansk
Kiruna
White Sea
Arkhangel'sk
Luleå
Oulu
NORWAY
FINLAND
Umeå
Lake Onega
Trondheim
SWEDEN
Gulf of Bothnia
Tórshavn
Faroe Islands (DENMARK)
Tampere
Lake Ladoga
SHETLAND ISLANDS
Gävle
Turku
Helsinki
St. Petersburg
Bergen
Oslo
Stockholm
ÅLAND ISLANDS
Gulf of Finland
RUSSIA
Rockall (U.K.)
ORKNEY ISLANDS
Tallinn
ESTONIA
HEBRIDES
Stavanger
Moscow
North Atlantic Ocean
Aberdeen
Göteborg
Gotland
Riga
LATVIA
Glasgow
Edinburgh
North Sea
Baltic Sea
Vitsyebsk
Smolensk
UNITED
DENMARK
Oland
LITHUANIA
Vilnius
Belfast
Malmö
Copenhagen
Kaliningrad
RUSSIA
Mahilyow
Minsk
Isle of Man (U.K.)
Bornholm
BELARUS
Dublin
Irish Sea
Gdańsk
Hrodna
Homyel'
IRELAND
Leeds
Manchester
Liverpool
Hamburg
Bremen
Berlin
Poznań
Warsaw
Brest
KINGDOM
Birmingham
Amsterdam
NETH.
POLAND
Kiev
Cardiff
Rotterdam
Łódź
Rivne
London
Celtic Sea
Essen
Cologne
Leipzig
Wrocław
UKRAINE
Brussels
Lille
Bonn
Frankfurt am Main
Prague
Kraków
L'viv
English Channel
Guernsey (U.K.)
Jersey (U.K.)
Luxembourg
LUX.
CZECH REPUBLIC
Brno
SLOVAKIA
Chernivtsi
Mykolayiv
Paris
Stuttgart
Bratislava
Chisinau
Strasbourg
Munich
Budapest
Cluj-Napoca
Iaşi
MOLDOVA
Odesa
Nantes
Vienna
AUSTRIA
HUNGARY
ROMANIA
LIECH.
Zürich
Vaduz
Geneva
FRANCE
Bay of Biscay
Ljubljana
Zagreb
Bucharest
Constanţa
Black Sea
Lyon
Turin
Milan
Venice
SLOVENIA
A Coruña
Bordeaux
CROATIA
Belgrade
Varna
Bilbao
Genoa
SAN MARINO
BOSNIA AND HERZEGOVINA
Toulouse
Sarajevo
SERBIA AND MONTENEGRO
BULGARIA
MONACO
Andorra la Vella
Marseille
Florence
Sofia
Porto
ANDORRA
Ligurian Sea
Adriatic Sea
Istanbul
Skopje
F.Y.R.O.M.
Zaragoza
Corsica
Rome
Bursa
Madrid
VATICAN CITY
Tirana
ALB.
Thessaloniki
PORTUGAL
Barcelona
Naples
TURKEY
Lisbon
Balearic Sea
Tyrrhenian Sea
Aegean Sea
İzmir
SPAIN
Valencia
Sardinia
GREECE
Athens
BALEARIC ISLANDS
Cagliari
Ionian Sea
Sevilla
Mediterranean Sea
Palermo
Rhodes
Gibraltar (U.K.)
Málaga
Sicily
Strait of Gibraltar
Ceuta (SPAIN)
Alborán Sea
Melilla (SPAIN)
Oran
Algiers
Tunis
Crete
Rabat
Casablanca
MOROCCO
ALGERIA
TUNISIA
Valletta
MALTA
Scale 1: 19,500,000
Lambert Conformal Conic Projection, standard parallels 40°N and 56°N
300 Kilometers
300 Miles
Boundary representation is not necessarily authoritative.
803060AI (R01083) 3-04

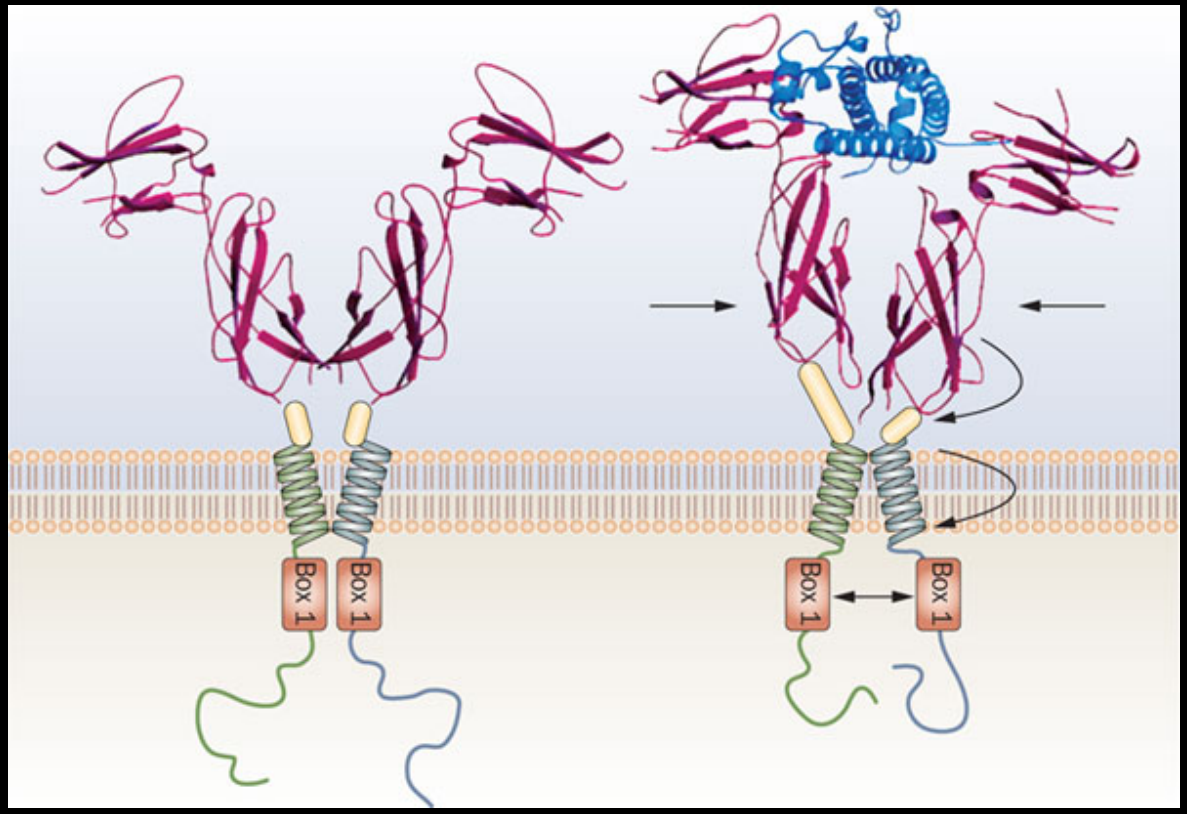
# All-causes mortality – exposure to growth hormone

| | Observed | Expected* | SMR | (95% CI) |
|---|---|---|---|---|
| Overall | 93 | 69.67 | 1.33 | (1.08 - 1.64) |
| Mean growth hormone dose (µg/kg/day) | | | | |
| 0 - 20 (n = 2277) | 32 | 29.77 | 1.07 | (0.74 - 1.52) |
| 20 - 30 (n = 3196) | 35 | 29.07 | 1.20 | (0.84 - 1.67) |
| 30 - 50 (n = 578) | 5 | 3.54 | 1.41 | (0.45 - 3.29) |
| >50 (n = 285) | 6 | 1.76 | 3.41 | (1.25 - 7.43) |
| Treatment duration (years) | | | | |
| 0 - 2 (n = 1467) | 29 | 15.87 | 1.83 | (1.22 - 2.62) |
| 2 - 4 (n = 2650) | 36 | 29.72 | 1.21 | (0.85 - 1.68) |
| >4 (n = 2285) | 26 | 21.12 | 1.23 | (0.80 - 1.80) |

| France | Neoplasms | Observed | Expected | SMR (95% CI) |
|---|---|---|---|---|
| | Malignant neoplasm of bone and articular cartilage | 3 | 0.60 | 5.00 (1.01-14.61) |
| | Cerebrovascular diseases | 4 | 0.76 | 5.29 (1.42-13.55) |

| Sweden, The Netherlands, Belgium | Cause of Death | Number of deaths |
|---|---|---|
| | Traffic accident | 5 |
| | Accident | 2 |
| | Suicide | 4 |
| | Homicide | 1 |
| | Poisoning | 4 |
| | Pneumonia | 1 |
| | Other Endocrine Dysfunction | 1 |
| | Primary cardiomyopathy | 1 |
| | Immune deficiency | 1 |
| | Coagulation defect | 1 |
| | *Cancer* | *0* |
| | *Cerebrovascular diseases* | *0* |

# Model for the activation of the growth hormone receptor by growth hormone




Brooks, A. J. & Waters, M. J.
The growth hormone receptor: mechanism of activation and clinical implications
*Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2010.123