In format provided by Ranke & Wit (doi:10.1038/nrendo.2018.22)

Supplementary Box S2. Non-GH deficient medical conditions accepted as indications for GH treatment

Chronic Renal Insufficiency (CRI) is associated with growth failure in many children with chronic kidney disease. Its pathophysiology is multifactorial but includes a secondary disturbance of the GH-IGF system[1]. GH only partly increases linear growth[2].

Turner Syndrome (TS) presents in females only and is caused by missing one X-chromosome or part of it. It is characterized by dysmorphic features, hypogonadism and severe short stature[3]. Shortness is predominantly caused by the loss of *SHOX* (located on the pseudo-autosomal region on the X- and Y chromosomes) and not associated with a disorder of the GH-IGF axis. GH treatment has become part of standard care in TS[3,4].

Prader-Willi Syndrome (PWS) is characterized by muscle hypotonia and failure to thrive in infancy followed by hyperphagia with massive overweight, short stature, and intellectual and behavioural deficits[5]. It is mostly caused by the loss of the paternal chromosomal region 15q11.2–q13 or a maternal UPD of the region[6]. The impairment of GH secretion is often combined with other hypothalamo-pituitary deficits. Treatment with rhGH is aiming foremost at improving body composition and metabolism. Height can be completely normalized and other positive effects of GH are maintained by treatment into adult life[7].

Small-for-gestational age (SGA) is defined by a low birth weight and/or length (<2 SDS in endocrine literature) but is also used for children born SGA who remain short in childhood. In these non-syndromic children the GH-IGF system is mostly unaffected, although subtle defects of the GH-IGF axis[8] and various genetic anomalies[9] have been discovered. In most countries rhGH is approved for short children born SGA, including children with Silver-Russell syndrome (SRS)[10] and also long-term efficacy has been shown[11,12].

Idiopathic Short Stature (ISS) is a descriptive term for children who are short for age, sex and the corresponding population, without evidence of a systemic disease, nutritional, psychological or chromosomal disorder, or overt hormonal abnormalities[13]. After the results became available of a placebo-controlled trial [14] and dose-response study[15] ISS was accepted as an indication by FDA in the USA[16], but the effect on adult height appears modest[17,18].

Short stature homeobox-containing gene (*SHOX*) is a gene located on the short arm of both sex chromosomes which escapes X inactivation. *SHOX* haploinsufficiency causes short stature with a wide range of clinical presentations, varying from severe mesomelic short stature by homozygous mutations (Langer syndrome) via a mesomelic skeletal dysplasia often associated with Madelung deformity (Léri-Weill dyschondrosteosis) to an almost normal clinical presentation (apparent ISS). Besides mutations and deletions of SHOX itself, deletions of the 5'and 3' enhancer regions and even some duplications of SHOX and its enhancers can cause the phenotype[19]. Short stature is probably due to lack of proper control of chondrocyte apoptosis via the FGF pathway[20]. Both short- and long term responses to rhGH are similar to those observed in Turner syndrome[21].

Noonan Syndrome (NS) is a disorder primarily defined by its phenotype (TS-like, short stature and cardiac anomalies, e.g. pulmonary stenosis)[22]. In 40% of the individuals a defect in PTPN11 results in

constitutional activation of a phosphatase (protein tyrosine phosphatase SHP-2), thus reducing the generation of IGF-I[23]. GH has been proven to be effective[24] and was approved by the FDA.

In children with **Short bowel syndrome** rhGH in conjunction with nutritional treatment has been proven to improve the condition (weight, growth, fluid loss), which led to an FDA approved indication[25,26]

Wasting and cachexia in HIV infected individuals was improved by rhGH due to its anabolic effect, and was approved by FDA and EMA[27,28].

Abbreviations in S2: UPD, uniparental disomy; rhGH, recombinant human growth hormone; EMA, European Medicines Agency; FDA, Federal Drug Administration; FGF, fibroblast growth factor; HIV, human immunodeficiency virus

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