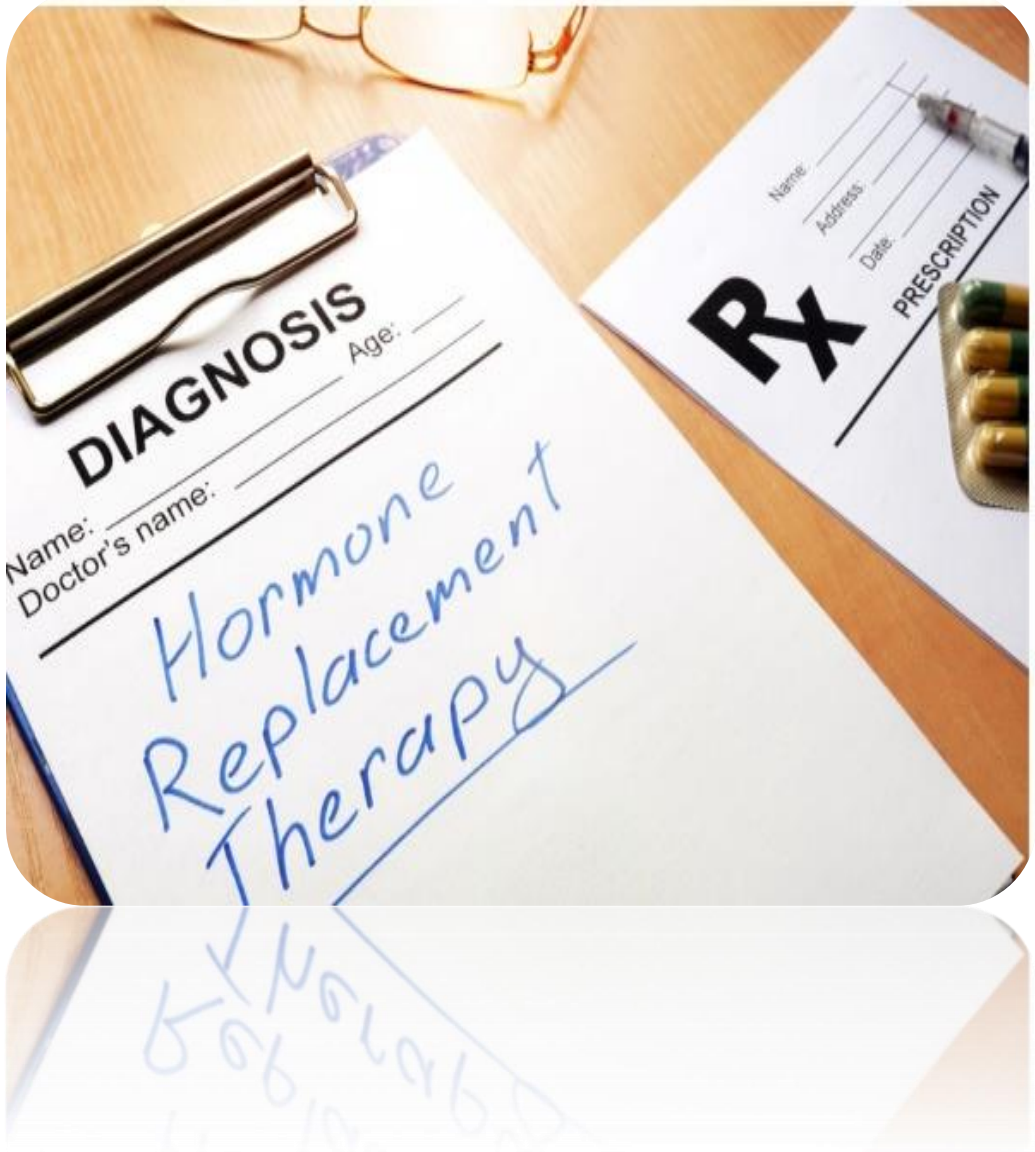

Safety of GH Replacement Therapy

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Outline

- Physiology of pituitary growth hormone.
- Growth hormone replacement therapy.
  - History.
  - Benefits.
  - Monitoring.
  - Indications.
  - Contraindications.
- Recognized side effects:
  - Low/intermediate/ high risk groups
  - IGF-1 sds (high dose GH with high IGF-1 sds)
  - Benign intracranial HTN, glucose homeostasis, malignancy risk, gynecomastia, orthopedic complications & long term mortality.
- NordiNet® IOS and ANSWER Program Results on long term GH complications ()
- Conclusions.

Growth hormone: Physiology

- GH is a 191 amino acid polypeptide hormone synthesized, stored and secreted by the somatotroph cells of anterior pituitary gland.
- GH synthesis and release is controlled by many hormonal agents including GHRH, Somatostatin, Ghrelin, IGF-1, thyroid hormones and glucocorticoids.
- Growth hormone is secreted in pulses (after infancy).
- GH secretion is increased in puberty then decreases subsequently.
- Growth hormone binding proteins binds GH and dampen the fluctuation of GH level associated with its pulsatile secretion.
- Growth promoting mediated actions are either directly via GH binding on its receptor of target cells or indirectly via IGF-1, includes most of its growth promoting action.

Ayyar VS. History of growth hormone therapy. Indian J Endocrinol Metab. 2011;15 Suppl 3(Suppl3):S162–S165. doi:10.4103/2230-8210.84852

GH Replacement Therapy :History

- Human growth hormone replacement therapy has been widely available for clinical purposes for more than 50 years.
- Human growth hormone has been used in GH deficient (GHD) children, adolescents & adults since 1958 “cadaveric pituitary extracts of human GH with Creutzfeldt-Jakob disease in hGH recipients .
- The year of 1985 witnessed a switch from cadaveric pituitaries to recombinant (rhGH) obtained from DNA-recombinant techniques.
- There has never been a case report of Creutzfeldt-Jakob with the use of rhGH.

Jørgensen *et al.* The Lancett 1989; 333: 1221-1225

GH Replacement Therapy

- Initially, growth hormone was injected intramuscularly.
- In mid 1980s, it was shown as effective when administered as a subcutaneous injection.
- Early in its use, growth hormone was administered twice weekly; this was increased to 3 times weekly.
- Currently 6-7 injections / week were shown to yield an even better growth response than administering injections 3 times per week.
- Daily administration is now the recommended use.

Ayyar VS. History of growth hormone therapy. Indian J Endocrinol Metab. 2011;15 Suppl 3(Suppl3):S162–S165. doi:10.4103/2230-8210.84852

Benefits of Growth Hormone Replacement

- Improves linear growth.
- Body composition changes producing a reduction in total and visceral fat and increase in lean body mass.
- Improvement in CV function and lipids.
- Improves Quality of life.
- Increases bone mineral density.
- Improves memory, alertness, and concentration.

Reed *et al. Front Endocrinol* 2013;4:64

Year of initial FDA approval	Indications for GH treatment
1985	Pediatric growth hormone deficiency
1993	Growth failure secondary to chronic renal failure up to the time of renal transplantation
1996	Adult growth hormone deficiency
1996	HIV wasting in adults
1996	Turner syndrome
2000	Prader-Willi syndrome
2001	Small for gestational age
2003	Idiopathic short stature
2003	Short bowel syndrome
2006	*SHOX* gene deficiency
2007	Noonan syndrome

Novonordisk doesn’t encourage use of its products outside their label indications

Monitoring of GH therapy

- Baseline clinical evaluations.
- Regular (3-6 monthly) measurement of IGF1 /IGFBP3 (keep it, within 2 sds).
- Bone age assessment (yearly).
- Thyroid function testing (in GH-deficient patients).
- Clinical assessment for scoliosis in every visit.
- Fundal examination if clinically indicated.
- Examining for prepubertal gynecomastia in prepubertal boys.
- Monitoring of HbA1c levels (yearly).

J Clin Endocrinol Metab. 2017 May 01; 102(5): 1661–1672. doi:10.1210/jc.2016-2046.

What are the contraindications of GH therapy?[1]

- **Acute Critical Illness** (following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure).

- **Active Malignancy:**

GHD may be an early sign of a pituitary /intracranial tumor. GH should not be used with any evidence of progression or recurrence of intracranial tumor.

- **Hypersensitivity**

- **Diabetic Retinopathy**

Active proliferative or severe non-proliferative diabetic retinopathy.

- **Closed Epiphysis:**

Should not be used for growth promotion in pediatric patients with closed epiphysis.

1. Norditropin KSA SmPC

Side effects of rhGH replacement therapy may include :

- Rash & pain at injection site.
- Transient fever.
- Mild arthralgia.
- Edema.
- Benign intracranial hypertension.
- Insulin resistance, Hyperglycemia/IGT.
- Slipped capital femoral epiphysis.
- Carpal tunnel syndrome
- Headache
- Gynecomastia?
- Since GH stimulates cell multiplication, development of neoplasms is a concern (new OR recurrence)?

Horm Res 1995;43(1-3):93-9. doi: 10.1159/000184245.

GH replacement & Benign intracranial HTN

- Has been reported in 1/1000 children receiving GH treatment.
- Benign intracranial hypertension “ pseudotumor cerebri” is the result of the physiological antidiuretic effect of human GH.
- Is more evident in (CRI) patients that cannot support a decrease in glomerular filtration rate.
- Pseudotumor cerebri can be clinically suspected in children complaining of headaches, nausea, vomiting and presenting papilledema at fundoscopic examination.
- Fundoscopic examination should be performed before initiation of GH treatment and repeated when clinically indicated.
- If the diagnosis of pseudotumor cerebri is confirmed, rhGH should be discontinued temporarily, and reinitiated later on, at lower doses.

Clin Pediatr Endocrinol. 2010 Apr; 19(2): 39–44.Published online 2010 May 22. doi: 10.1297/cpe.19.39

GH replacement & Glucose homeostasis

- GH physiologically antagonizes insulin effects in glucose and lipid metabolism by stimulating glycogenolysis and lipolysis.
- GH deficiency is expected to increase insulin sensitivity, which can be clinically observed in GHD neonates with severe and persistent hypoglycemia at birth.
- GH therapy is assumed to induce insulin resistance.
- T2DM is a classical feature in the context of excess GH in acromegaly.
- Diabetes mellitus is not contraindication to GH treatment in children.
- The incidence and age at diagnosis of type 1 diabetes mellitus during rhGH treatment is similar to the general population.
- Children with an increased risk of diabetes should be encouraged to modify their diet and exercise habits.

Clin Endocrinol (Oxf) 2017 Feb;86(2):192-198. doi: 10.1111/cen.13256. Epub 2016 Nov 21.

GH replacement & Gynecomastia

- Gynecomastia occurs in about 70% of boys during puberty, but prepubertal gynecomastia is rare.
- There is not much literature on gynecomastia with growth hormone therapy in prepubertal boys.
- Is one of the rarest complications of growth hormone treatment.
- Prepubertal gynecomastia is rare & self-limited adverse effect of children in use of rhGH.
- Usually, equivalent to Tanner-stage 2 in female breast development.
- The time from the initiation of therapy to the diagnosis of gynecomastia varying between 0.5 month to 8 years.
- In general, there is no need for alteration in rhGH dosage, or discontinuation of medication, since gynecomastia is usually self-limited and will resolve with time.

Clin Endocrinol (Oxf) 1993 Oct;39(4):417-25. doi: 10.1111/j.1365-2265.1993.tb02388.X

GH replacement & Orthopedic complications

- Slipped capital femoral epiphysis (SCFE) occurs more frequently in periods of rapid height gain.
- Incidence of 73.4 / 100,000 patients year , while in the general population prevalence is 10.8 cases / 100,000.
- Children with GHD are more prone to the development of SCFE, and rhGH replacement therapy may increase that risk by seven -fold.
- Children with CRI, GHD, and TS have an increased risk of developing slipped capital femoral epiphysis.
- Complaints of limping or hip or knee pain need to be evaluated with radiographic studies if there is limited hip movement.
- Although there is no evidence that treatment with GH causes scoliosis, children with pre-existing scoliosis should be observed for rapid progression after starting GH treatment.

J Pediatr Orthop B 2011 Jan;20(1):57-61. doi: 10.1097/BPB.0b013e32833ed967.

GH Replacement & Malignancy Risk

- As both GH & IGF-1 have mitogenic & anti-apoptotic properties, there has always been a concern that rhGH might induce tumorigenesis.
- There are three issues involved in the relationship between GH & neoplastic induction:
  - recurrence of a previously treated tumor.
  - induction of a second neoplasm.
  - appearance of a de novo malignancy.
- The old (1993) report of twelve cases of hematologic malignancy in a Japanese cohort on rhGH therapy raised concern on the safety of the medication.[1]
- The current position on rates of new leukemia in non-Japanese patients without any known risk factors, on rhGH replacement therapy are not greater than the expected ones for the general population.[2]

1-(J Pediatr Endocrinol. 1993;6(1):99-108)
2- (Current topics. J Pediatr. 1996;128(5 pt 2):S8-13).

GH Replacement & Malignancy Risk

- Certain groups who receive GH treatment carry increased risk of developing malignancies, including, those with Neurofibromatosis type 1, Fanconi anemia, Downs & Bloom syndromes.
- Hence, current data suggests that the use of rhGH does not increase the risk of development of malignancy.
- Serum levels of IGF-I have been epidemiologically associated with increased risk of malignancy , monitoring is imperative, so that IGF-1 serum levels do not exceed the normal range for sex and age.

Swerdlow A, et al. J Clin Endocrinol Metab 2017;102:1661–72

NordiNet® IOS and ANSWER Program®

Complementary, large-scale, non-interventional studies

Same electronic platform

NordiNet®/NovoNet®

Similar aims

1. To assess long-term effectiveness and safety of Norditropin® (somatropin) as prescribed to patients in routine clinical practice
2. To provide insight into the diseases of the specific endocrine patient populations managed with GH therapy

Höybye C, et al. Clin Epidemiol 2013;5:119–27

NordiNet® IOS interim analysis: long-term safety findings

- 13,834 children enrolled
- Within dose range reflecting usual clinical practice
- Treatment received between 1998 and 2013
- Approximately 4-year mean duration of therapy during this study

Sävendahl L, et al. Eur J Endocrinol 2016;174:681–91

NordiNet® IOS methodology: three risk groups

Risk stratification	Criteria
Low risk	Isolated GHD, ISS, SGA or isolated GHD with minor craniofacial malformation • Subdivided into GHD/ISS and SGA
Intermediate risk	MPHD, paediatric syndromes (Turner syndrome, Prader Willi syndrome), benign pituitary tumours and chronic paediatric diseases
High risk	Treated for cancers, craniopharyngioma and CRI

Note: Norditropin® is approved for ISS only in Korea
MPHD, multiple pituitary hormone deficiency; CRI, chronic renal insufficiency

Sävendahl L, et al. Eur J Endocrinol 2016;174:681–91

NordiNet® IOS and ANSWER Program®: safety endpoints

NordiNet® IOS

- Adverse events (AE) include
  - Any undesirable medical event that happens to a patient registered in a study
- Serious adverse events (SAEs) include
  - Death, or a life-threatening experience
  - Hospitalisation or prolongation of existing hospitalisation
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect

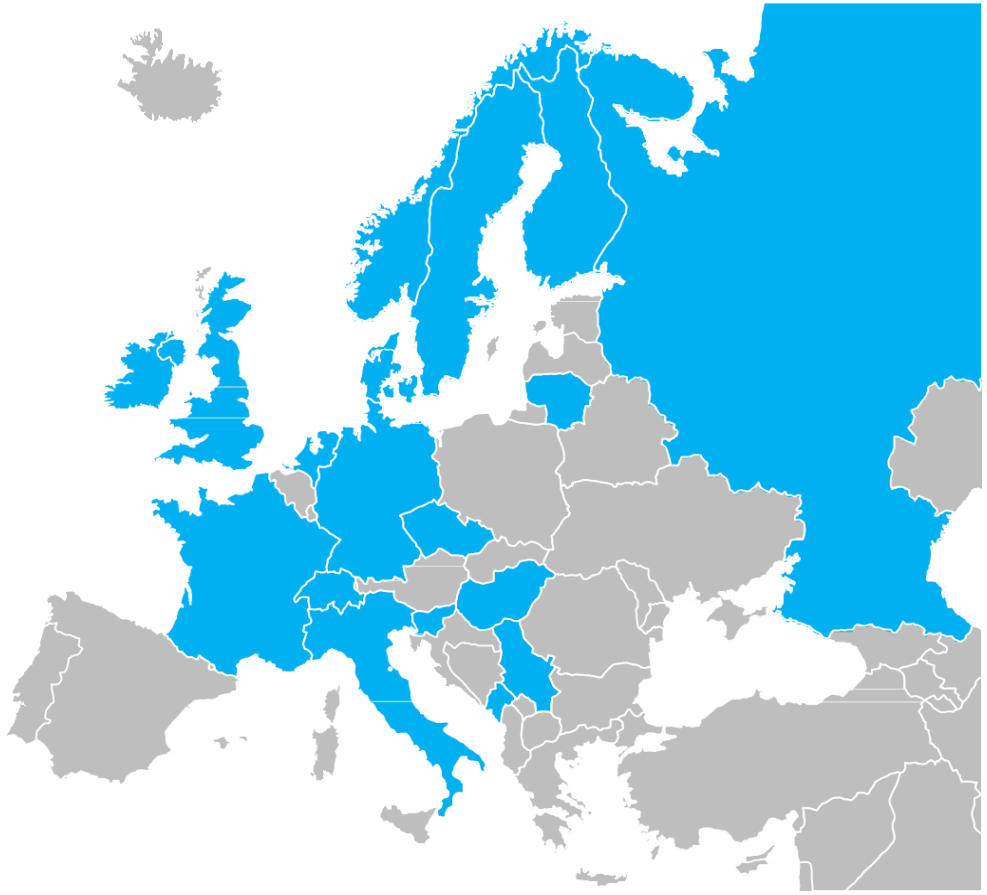
NordiNet® IOS and ANSWER Program®

- Adverse reactions (ARs)
  - An AE/SAE for which the causal relationship between the product and the AE was suspected
- Serious adverse reactions (SARs)
  - Any of the seriousness criteria applied to SAEs
- Non-serious adverse reactions (NSARs)
  - An AR that did not meet a seriousness criterion was considered to be an NSAR

Novo Nordisk. Available at: http://www.novonordisk-trials.com Accessed: 1 March 2018

Safety findings from NordiNet® IOS: overall results for full safety population

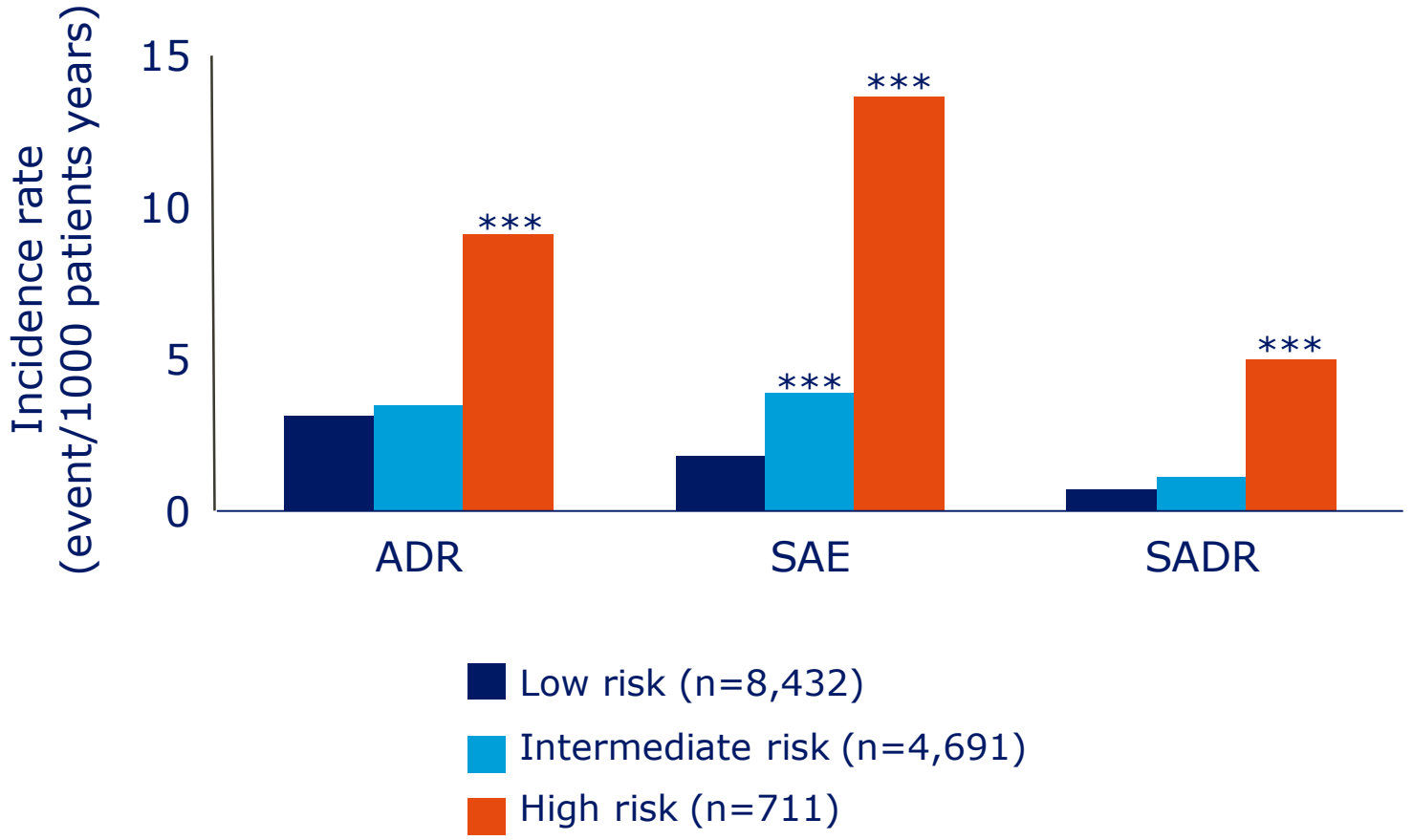
- ARs were reported in
  - 334 children (1.89%)
  - 82 adults (3.3%)
- SAEs reported in
  - 224 children (1.26%)
  - 119 adults (4.8%)



Novo Nordisk. Available at: http://www.novonordisk-trials.com Accessed: 1 March 2018

NordiNet® IOS: highest incidence of adverse events for children in high-risk group

- Total cohort N=13,834
  - 302 events reported in 261 patients
  - Average GH dose until first event lowest in high-risk group



***p<0.0001 vs. low-risk group

Sävendahl L, et al. Eur J Endocrinol 2016;174:681–91

ANSWER Program®: ARs in children with GHD

- n=12,891, mean GH dose: 46 µg/kg/day
- 226 ARs reported in 156 children with GHD
  - 128 had non-serious ARs, 97 (76%) reported a single event
  - 30 had SARs, 19 (63%) reported a single SAR; 10 (33%) reported 2 SARs
  - One case of hyperglycaemia and one case of type 2 diabetes
- 2 deaths, both considered unlikely to be related to GH treatment: one due to respiratory distress and one due to unknown cause

SARs reported at least twice	Number of events	Number of patients
Papilledema	2	2
Condition aggravated	3	3
Epiphysiolysis	4	4
Scoliosis	3	3
Benign intracranial hypertension	2	2
Intracranial pressure increased	7	6

Novo Nordisk. Available at: http://www.novonordisk-trials.com Accessed: 1 March 2018

ANSWER Program®: most patients showed increased IGF-I

- IGF-I SDS was higher after treatment vs at baseline and above 0 at all time points
- Between the year-1 and year-7 follow-up visits, 25.9–29.3% of patients had IGF-I SDS above 2

IGF-I, insulin-like growth factor

Novo Nordisk. Available at: http://www.novonordisk-trials.com Accessed: 1 March 2018

Summary of paediatric data from NordiNet® IOS and ANSWER Program®

- Data from NordiNet® IOS do not reveal any new safety signals and confirm a favourable overall safety profile[1]
  - No association between GH dose and the incidence of AEs[1]
  - Risk of progression to prediabetes or diabetes is low[2]
- In the ANSWER Program® low incidence of ARs was observed in children[3]

1. Sävendahl L, et al. Eur J Endocrinol 2016;174:681–91; 2. Kotnik P, et al. Horm Res Paediatr 2016;82(Suppl 1):P1–316
3. Novo Nordisk. Available at: http://www.novonordisk-trials.com Accessed: 1 March 2018

GH Safety Workshop 2016

Majority view of the effect of GH treatment for approved indications on cancer risk in children and adults (including those with a childhood-onset of GH deficiency)

Age at onset of GH treatment	New Primary Cancer	Recurrence of Previous Primary Cancer in Cancer Survivors	Second or Subsequent Neoplasms
Child	No evidence for GH treatment effect Level: robust	No evidence for GH treatment effect Level: robust	Risk present but diminishes with time from onset of GH treatment Level: suggestive
Adult	No evidence for GH treatment effect Level: suggestive	Insufficient data available	Insufficient data available

Robust: multiple supportive publications
Suggestive: ≤3 supportive publications
Insufficient: inadequate published evidence

GH Safety Workshop; Allen DB, et al. Eur J Endocrinol 2016;174:P1–9

Conclusions

- Surveillance of long-term GH safety is important given the theoretical associated risks
- A safety workshop examined the available data and concluded that the evidence was limited
- Numerous industry-sponsored registries monitor the long-term safety of GH therapy in adults and children
- Data from the recently completed NordiNet® IOS and ANSWER Program® studies provide reassurance that long-term GH therapy has a good safety profile in children and adults


Thanks