



QUALIANCE

# Using RWD to inform the next study - A case-study

**Jean-Marc Ferran<sup>1</sup>, Navid Nedjatian<sup>2</sup>**

PHUSE EU Connect, Strasbourg – RE05 - 11. November 2024

<sup>1</sup>Qualiance ApS, Copenhagen, Denmark; <sup>2</sup>Novo Nordisk Health Care AG, Zurich, Switzerland

# DISCLOSURES

**Jean-Marc Ferran** is an external consultant at **Qualiance ApS** providing statistical support to Novo Nordisk Health Care AG.

**Navid Nedjatian** is employed at **Novo Nordisk Health Care AG** as a Global Medical Director in Medical Affairs department in Zurich, Switzerland.

**The views expressed in this presentation are the personal views of the presenter and do not necessarily represent the view of his past or current employer(s), clients and/or collaboration partners.**



<sup>1</sup>Children's National Hospital, Washington, DC, USA; <sup>2</sup>Schneider Children's Medical Center of Israel, Petah Tikva, Israel; <sup>3</sup>Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; <sup>4</sup>Qualiance ApS, Copenhagen, Denmark; <sup>5</sup>US Medical Affairs, Rare Endocrine Disorders, Novo Nordisk Inc, Plainsboro, NJ, USA; <sup>6</sup>Global Medical Affairs, Rare Endocrine Disorders, Novo Nordisk Health Care AG, Zurich, Switzerland; <sup>7</sup>Epidemiology, Novo Nordisk A/S, Søborg, Denmark; <sup>8</sup>Endocrinology Division/Genetic Endocrinology Unit, University of São Paulo School of Medicine, São Paulo, Brazil

## MATERIALS & METHODS

- ## RESULTS



# Agenda

RE05

## Background

- NordiNet® IOS and ANSWER Program overview
- Growth Hormone Treatment in Paediatric Indications and Idiopathic Short Stature
- Key endpoints and measures to consider

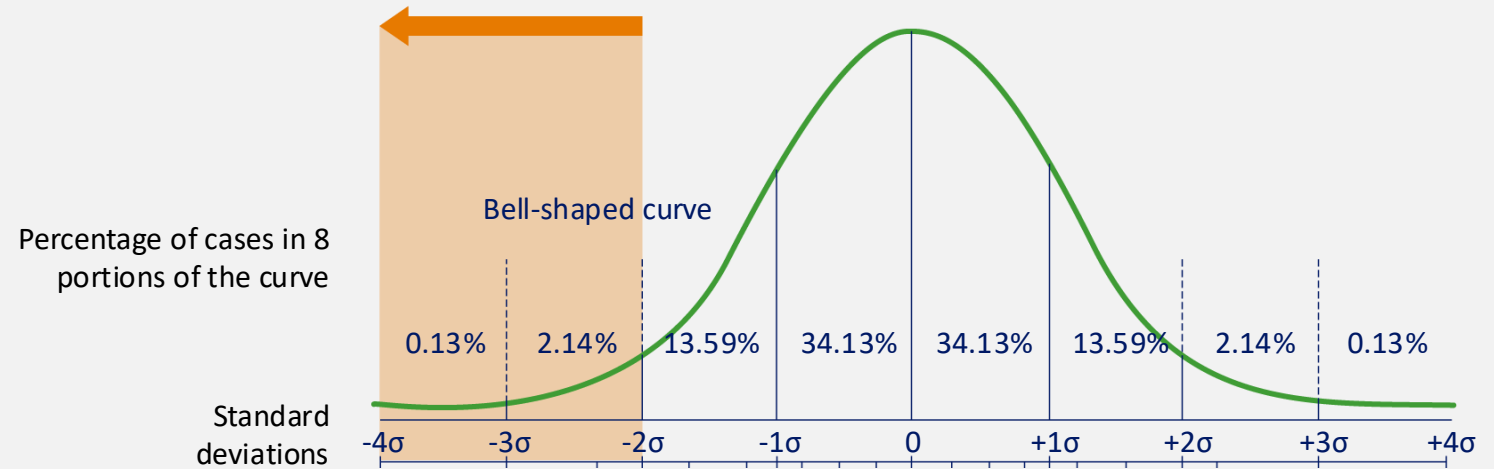
## Informing the next study...

- Defining our population
- Evaluating potential predictors
- Building a multivariate model
- Defining a new endpoint

## Conclusion

# Definition of Idiopathic Short Stature (ISS)

1. **Height  $<-2$  SDS** for population group
2. **No other abnormality** identified (normal birthweight and do not have growth hormone deficiency).
3. **Growth-Hormone Treatment approved in US but not yet in Europe** for ISS indication.
4. Growth-Hormone Treatment is approved in other indications such as **GHD, Small for Gestational Age, Noonan Syndrome, Turner Syndrome or Prader-Willy Syndrome**, which are further characterized.



# NordiNet<sup>®</sup> IOS and ANSWER Program overview

Non-interventional, multicentre studies evaluating long-term effectiveness and safety of Norditropin<sup>®</sup> (somatropin)\* as prescribed by treating physicians in a real-life clinical setting<sup>1</sup>

## NordiNet<sup>®</sup> IOS (NCT00960128)

- In 23 European countries (469 clinics)
- Paediatric and adult patients
- 485 ISS paediatric patients<sup>2</sup>

## ANSWER Program (NCT01009905)

- In the USA (207 clinics)
- Paediatric and adult patients
- 3,331 ISS paediatric patients<sup>2</sup>

ISS Pooled effectiveness analysis set (n=1,499)

\*Novo Nordisk A/S, Denmark

Effectiveness analysis set included patients who were GH-naïve at baseline, had valid height measurement and GH dosing information at baseline.

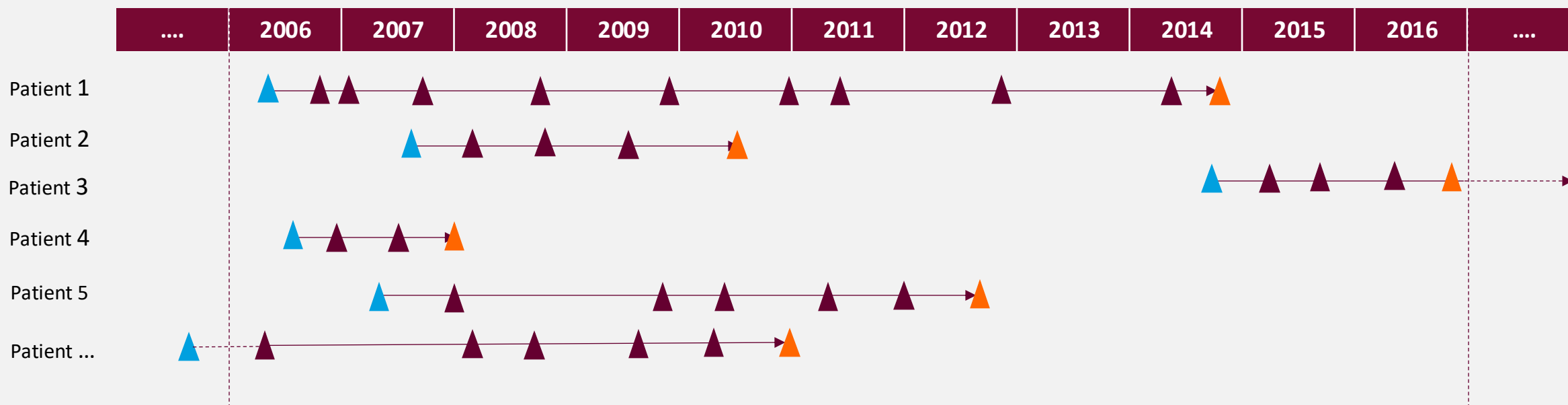
ISS, idiopathic short stature; IOS, International Outcome Study

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

2. Säwendahl et al. JCEM jc.2019-00775

# NordiNet<sup>®</sup> IOS and ANSWER Program Design

Average Duration: 2.41 years for ISS Effectiveness Set

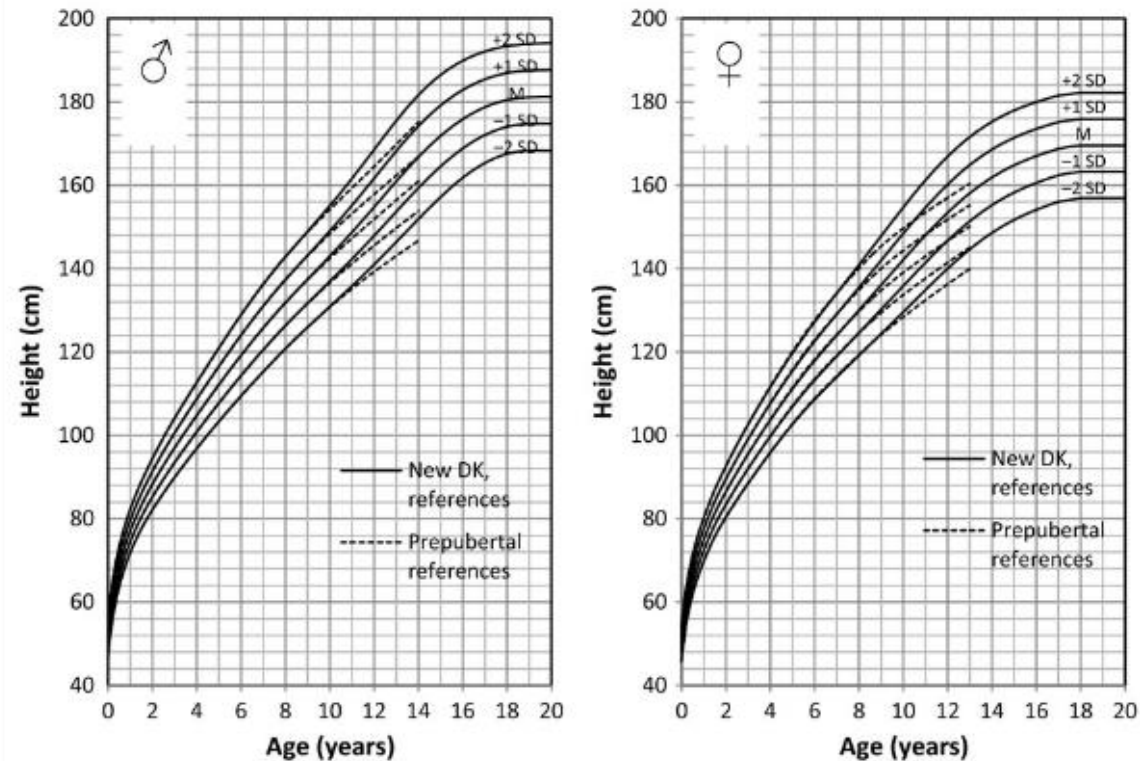


*Data collected through routine clinical appointments*

- ▲ Baseline: GH treatment start, Height, Demographics, Baseline Measures, Medical History, Concomitant Medication, etc.
- ▲ Follow-up: GH treatment update, Height, Follow-up measures, Adverse Events, Concomitant Medication, etc.
- ▲ Last visit: GH treatment update, Follow-up measures, Adverse Events, Concomitant Medication, Discontinuation Reason *if not lost to follow-up*, etc.

# Key Endpoints (1)

## Height SDS and Height Velocity



The 2014 Danish references from birth to 20 years for height, weight and body mass index, Tingaard 2014

## Pubertal Growth Spurt

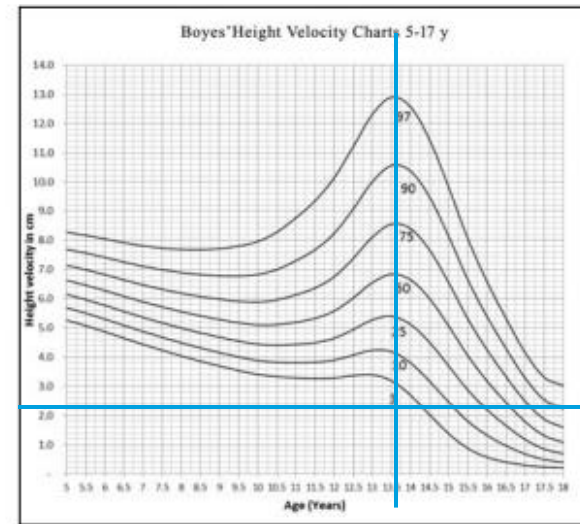


FIG. 1. Height velocity charts for boys aged 5-17 years.

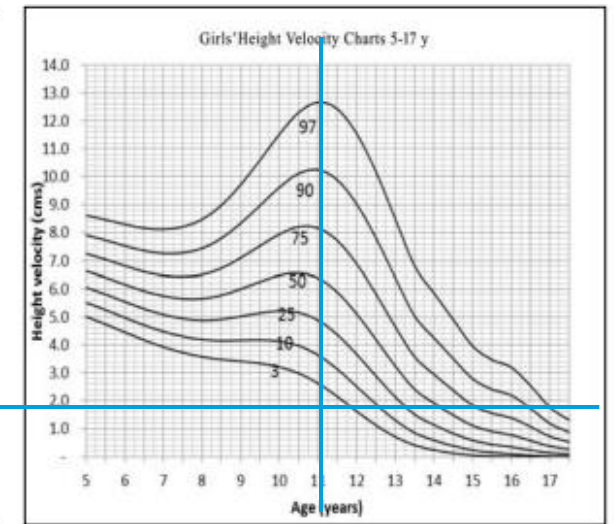


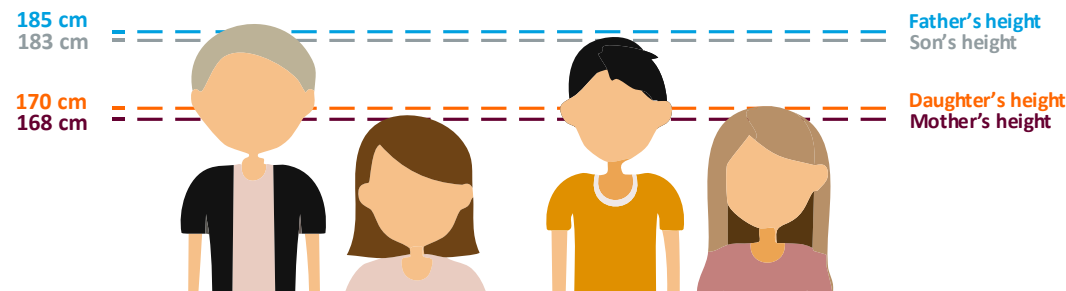
FIG. 2 Height velocity charts for girls aged 5-17 years.

Near  
Adult  
Height

Height Velocity Percentiles in Indian Children Aged 5-17 Years, Khadilkar, 2018

# Key Endpoints (2)

## Target Height and Near/Final Adult Height



$$\text{Target Height} = \frac{\text{Father's Height} + \text{Mother's Height} \pm 13 \text{ cm} (+: \text{Boys}, -: \text{Girls})}{2}$$



**Target Height** represents one's genetic potential...

**Target Height SDS** can then be derived...

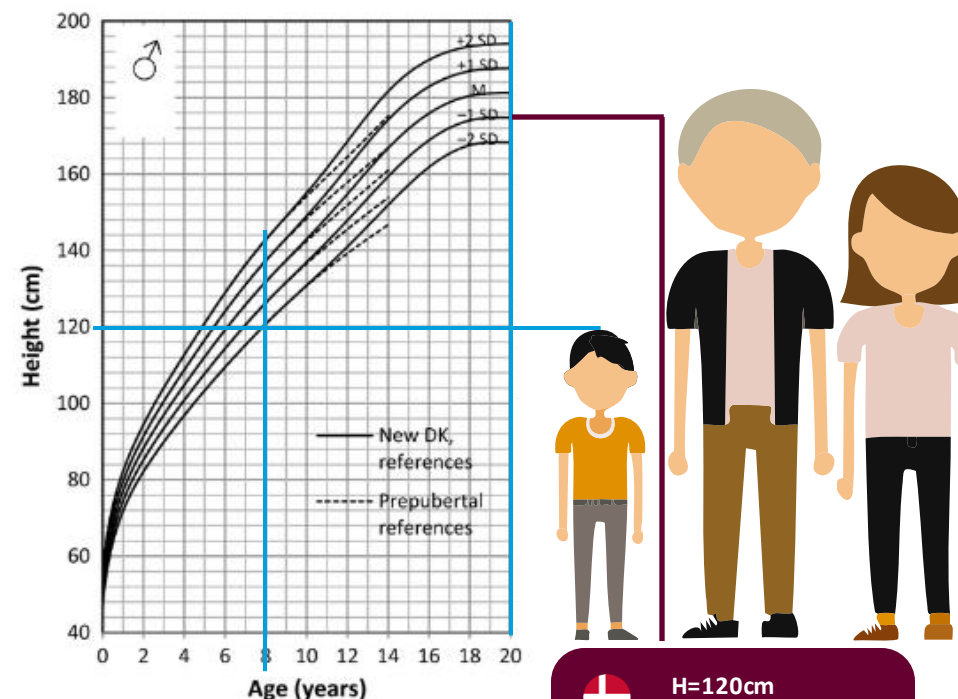
**Target Height SDS – current Height SDS** represents then the distance to one's genetic potential



**Near/Final Adult Height** remaining the ultimate endpoint...

**Near/Final Adult Height SDS...**

**Near/Final Adult Height SDS – Target Height SDS** to include genetic potential...



H=120cm  
HSDS=-2 SDS  
TH=175cm  
THSDS=-1 SDS  
dist.THSDS=-1 SDS

# ISS patients and Growth Hormone Therapy

## *The context of our Analysis*

- ✓ There is a large variability on how patients categorised as ISS react to Growth Hormone Therapy...
- ✓ Genetic factors may explain this variability...
- ✓ Novo Nordisk was designing back then a study (CT.GOV: NCT05894876) to identify these genetic factors...

### **Post-hoc Analysis objective**

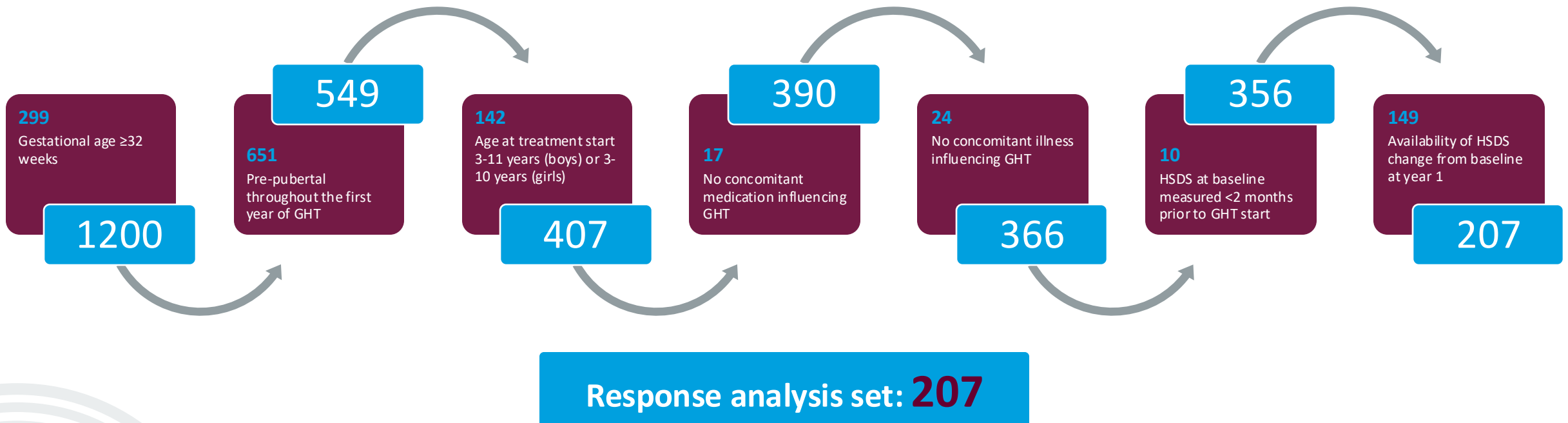
To identify clinical characteristics predictive of good and poor response during year 1 of GHT in ISS patients who received GH replacement therapy as part of the NordiNet<sup>®</sup> IOS and ANSWER Program

# Population

## Definition of Response Analysis Set

Number of patients with ISS from the effectiveness analysis set: **1499**

Patients excluded for not meeting the following inclusion criteria



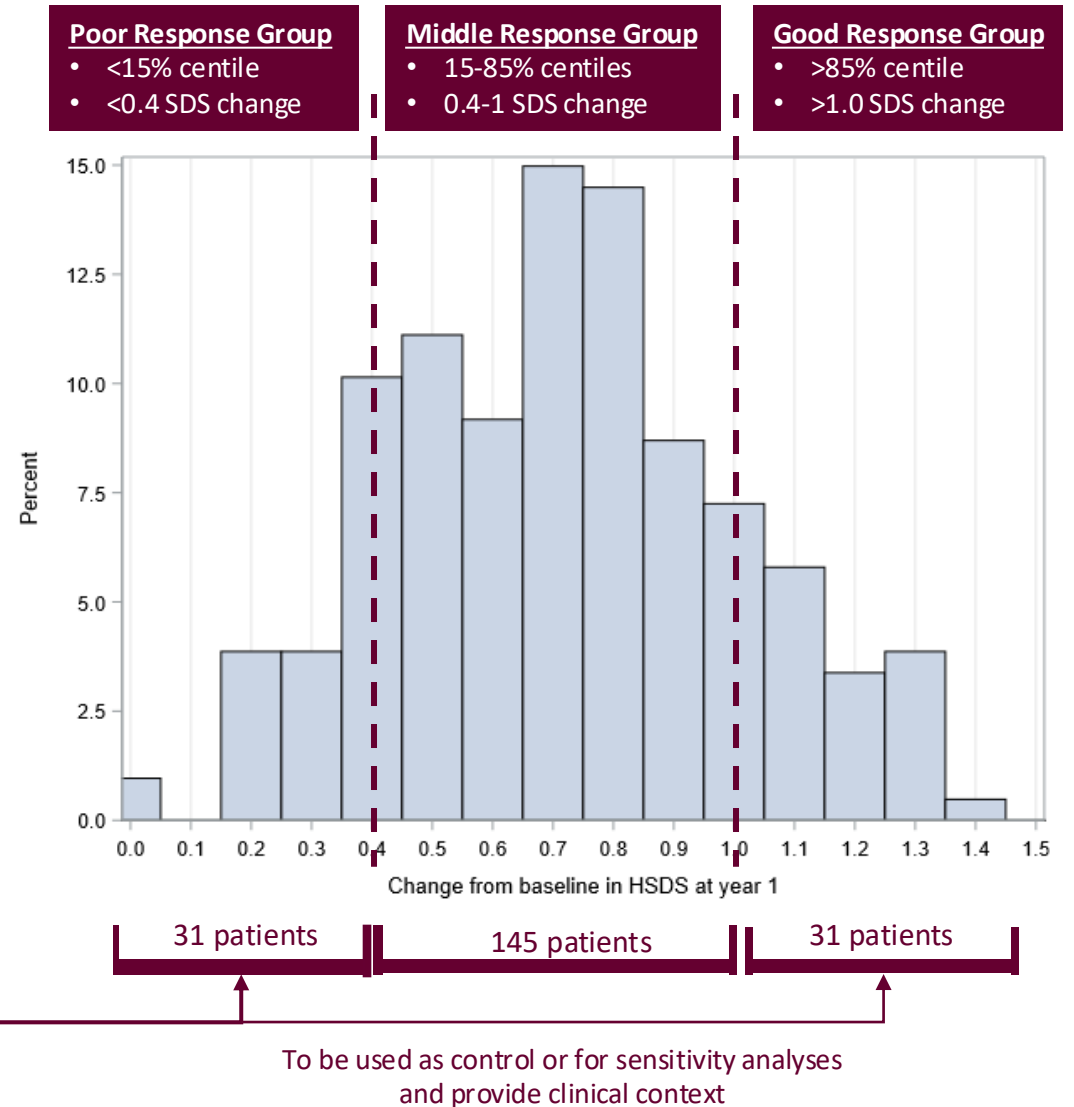
# Analysis

## Define Response Groups and Method



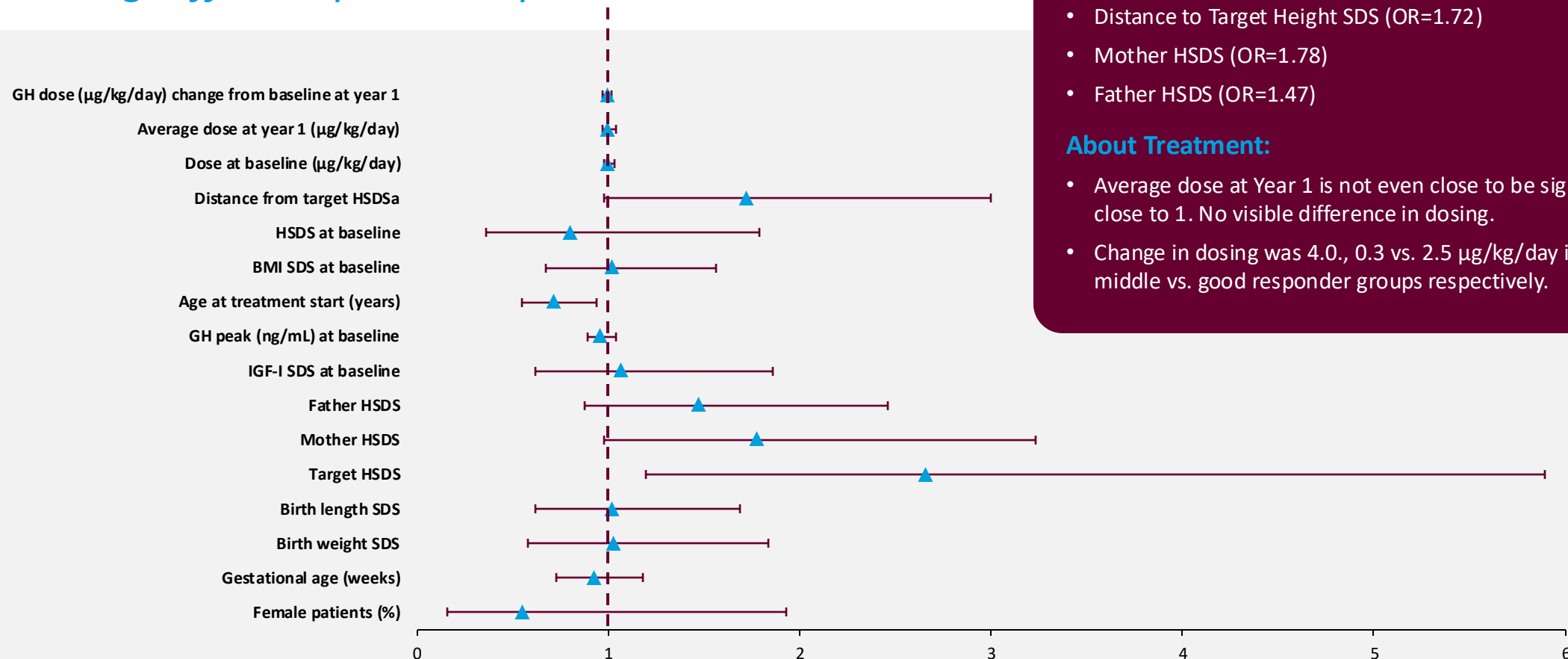
Used in **logistic regression** to model the probability of being in the poor vs. good response groups

1. Test **individual candidates** in univariate analyses
2. Build **multivariate model**



# Univariate Analysis

## Testing different potential predictors...



### Strongest candidates:

- Age at Treatment Start (OR=0.72)
- Target HSDS (OR=2.66)
- Distance to Target Height SDS (OR=1.72)
- Mother HSDS (OR=1.78)
- Father HSDS (OR=1.47)



### About Treatment:

- Average dose at Year 1 is not even close to be significant with an OR close to 1. No visible difference in dosing.
- Change in dosing was 4.0, 0.3 vs. 2.5  $\mu\text{g/kg/day}$  in mean across poor, middle vs. good responder groups respectively.

# Multivariate Analysis

*Iteratively refining a model from a pool of candidates...*

## Multivariate logistic regression of good versus poor response to GHT, Response analysis set

| Effect                                 | Odds ratio (95% CI) of good vs. poor response; p-value |
|----------------------------------------|--------------------------------------------------------|
| Female vs. male                        | 0.251 (0.050;1.248); p=0.0912                          |
| Age at treatment start                 | 0.689 (0.507;0.935); p=0.0169                          |
| Distance from target HSDS <sup>a</sup> | 2.050; (1.090;3.854); p=0.0259                         |
| Average dose at year 1                 | 0.769 (0.499;1.184); p=0.2333                          |

<sup>a</sup>Measured as target HSDS–HSDS at baseline.

The odds ratio estimate indicates the probability of being in the good vs. poor responders group. CI, confidence interval; GHT, growth hormone treatment; HSDS, height standard deviation score.



- Although not significant, it suggests that Female could respond worse than Male with ISS to treatment...
- The earlier treatment is started the higher the probability to make it to the “good responders” group...
- The further away from one’s genetic potential, the higher the probability to make it to the “good responders” group...
- Although “Average Dose at year 1” is not significant, it came with a OR < 1 suggesting that “higher the dose”, “the lower the response”...

### Hypothesis

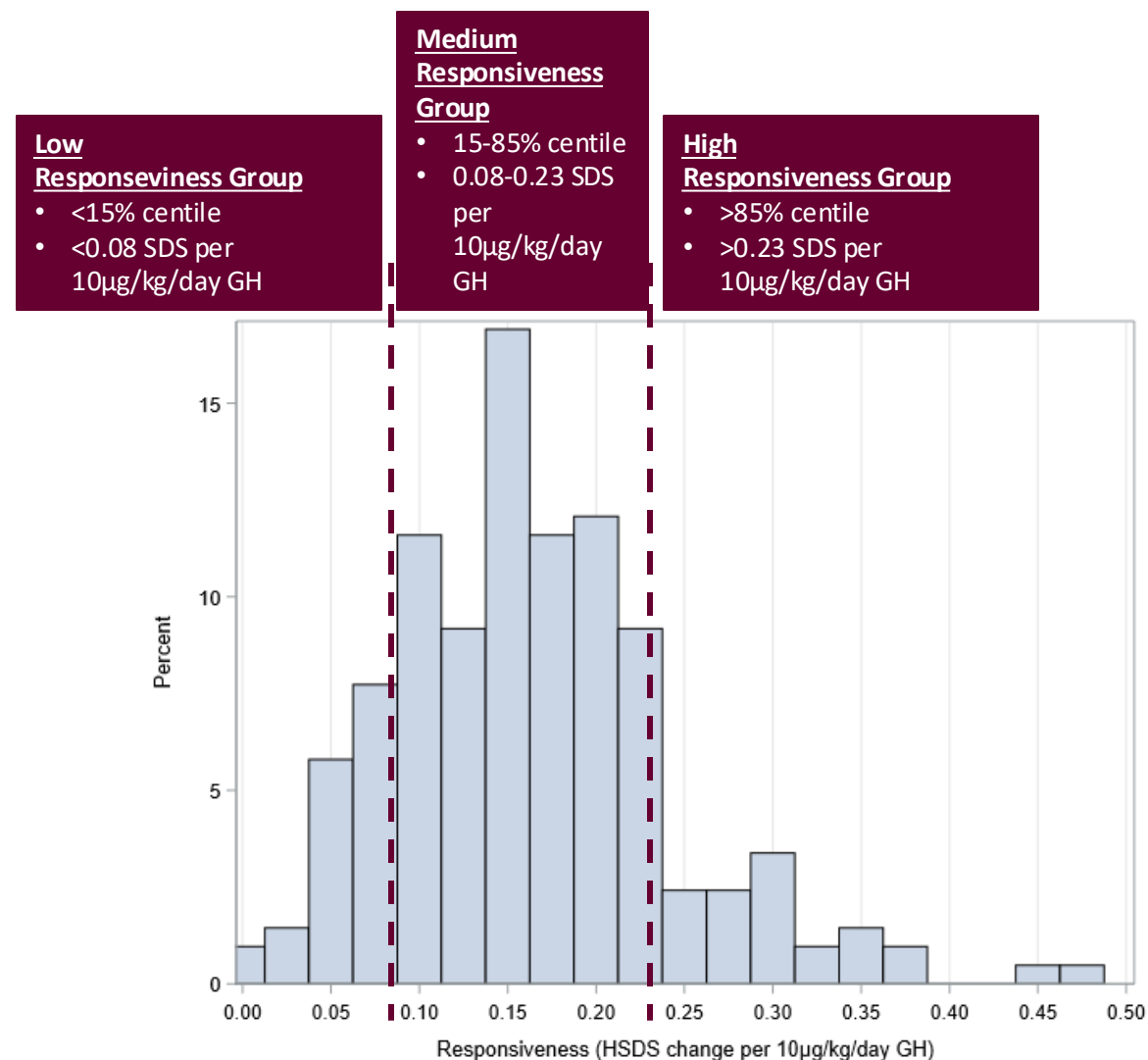
The increasing doses prescribed in year 1 in the low-response group as result of poor results, could explain this effect...

# Introducing a new Endpoint (1)

*From Response to Responsiveness...*

$$\text{Responsiveness} = \frac{\text{Annualised } \Delta\text{HSDS}}{\text{Average dose in year 1}}$$

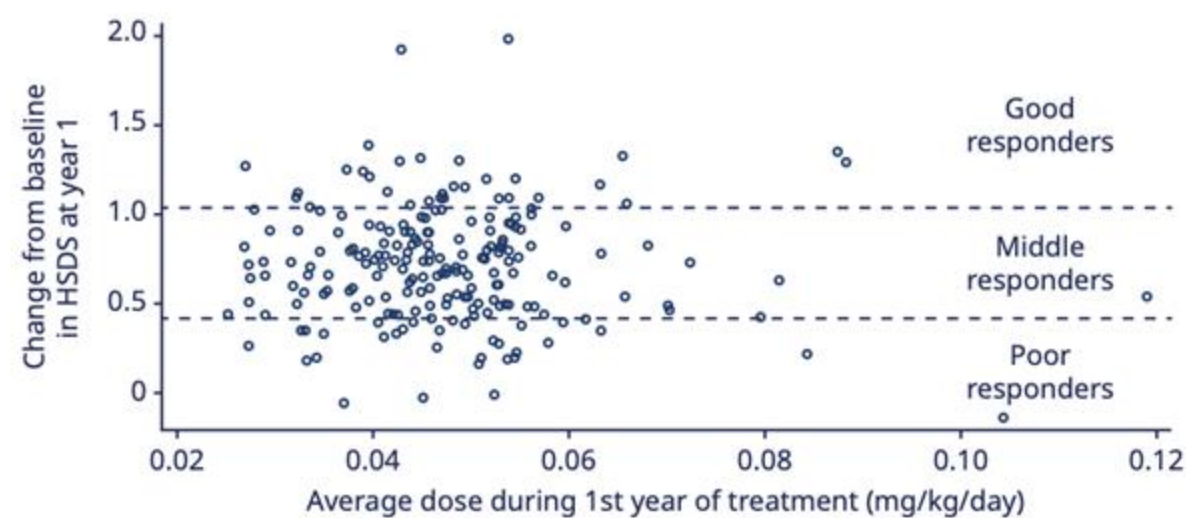
Average dose was computed as **the weighted average of relative doses for the duration of each treatment period during year 1**. This was done to mitigate instances of more than one prescription at year 1 of treatment.



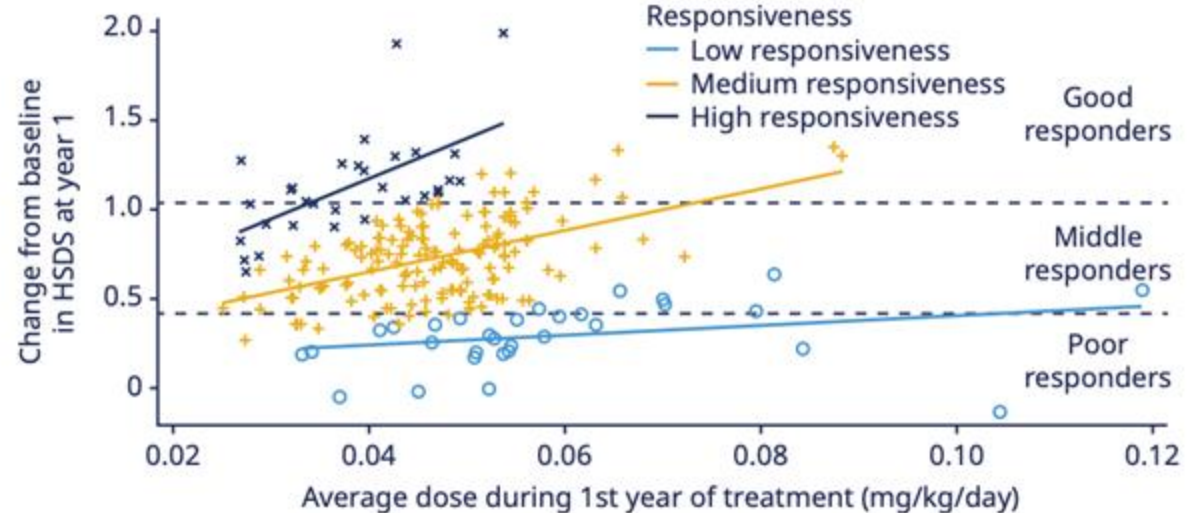
# Introducing a new Endpoint (2)

*From Response to Responsiveness...*

**Key figure.** Change from baseline in HSDS at year 1 of GHT plotted against average dose of GHT in year 1 without grouping (left) and with responsiveness groups (right)



GHT, growth hormone treatment; HSDS, height standard deviation score.



The positive correlation was significant for the high ( $p=0.0003$ ) and medium responsiveness ( $p<0.0001$ ) groups.

# Multivariate Analysis on New Endpoint

## Using Responsiveness

### Multivariate logistic regression of high versus low responsiveness to GH dose, Response analysis set

| Effect                                 | Odds ratio (95% CI) of high vs. low responsiveness; p-value |
|----------------------------------------|-------------------------------------------------------------|
| Female vs. male                        | 0.239 (0.060;0.950); p=0.0421                               |
| Age at treatment start                 | 0.871 (0.648;1.171); p=0.3607                               |
| Distance from target HSDS <sup>a</sup> | 1.847 (1.015;3.361); p=0.0446                               |

<sup>a</sup>Measured as target HSDS–HSDS at baseline.

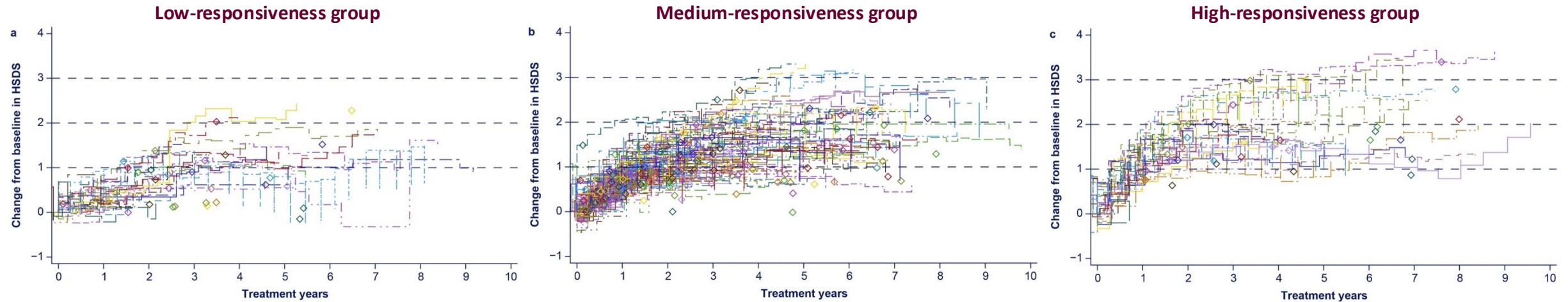
The odds ratio estimate indicates the probability of being in the high vs. low responsiveness group.  
CI, confidence interval; GH, growth hormone; HSDS, height standard deviation score.

- Gender is significant with an OR indicating that Females may response worse to treatment than Males with ISS...
- Age at treatment start is not significant anymore although going in same direction
  - Dosing is usually adjusted by age...
- Distance to Target HSDS is still significant and with an OR still close to 2.



# Look at longer-term effect

*Are the results from Year 1 correlated with longer-term ones?*



- The number of children who achieved a height within the normal range by the last recorded height measurement was 29 (94%) in the high-responsiveness group, 115 (79%) in the middle-responsiveness group, and 17 (55%) in the low-responsiveness group.
- In the same order, the last recorded height measurement was obtained after a median of 4.7, 3.2, and 2.8 years on treatment.



- Patients in high-responsiveness group seem to split into 2 subgroups after 1 year of GHT with one group progressing beyond +2SDS while another stagnating between +1 and +2 SDS.
- The subgroup with a higher progression was associated with earlier treatment start and therefore longer distance to puberty.



◇: Diamonds represent the timepoint at which females reached 10 years of age and males reached 11 years of age.

# How did it translate in new study? (1)

**NCT05894876** - *to identify the genetic predictors of having a good or poor response to GHT in prepubertal children with ISS using whole genome sequencing*

Recruiting ⓘ

**A Study of the Genetic Basis of Response to Growth Hormone Treatment in Children With Idiopathic Short Stature**

ClinicalTrials.gov ID ⓘ **NCT05894876**

Sponsor ⓘ Novo Nordisk A/S

Information provided by ⓘ Novo Nordisk A/S (Responsible Party)

Last Update Posted ⓘ 2024-10-09

Download

Bookmark

+ Expand all content

— Collapse all content

Study Details

Researcher View

No Results Posted

Record History

On this page

Study Overview

Contacts and Locations

Participation Criteria

Study Plan

Collaborators and Investigators

Study Record Dates

More Information

**Study Overview**

Brief Summary

The study doctor will collect information from participants with Idiopathic Short Stature, who were treated with growth hormone for at least a year when they were children, before they reached puberty. The word "Idiopathic" refers to "unknown cause", and as such the study participants have/had short stature with no identifiable medical cause. The purpose of the study is to identify differences in the genetic characteristics of participants who responded well or poorly to growth hormone therapy. No medications or other treatments are provided to the participants by Novo Nordisk as part of this study. The study will last for up to 1 year. The participants will attend their usual doctor's appointments. If the participants are not usually visiting the clinic, they will need to do it only once as part of this study. If the participant agrees to take part in the study, they will be asked to read and sign the 'Agreement to take part form'.  
[Show less](#)

Official Title

A Study of the Genetic Determinants of Response to Growth Hormone Treatment in Children With Idiopathic Short Stature

Conditions ⓘ

Idiopathic Short Stature

Study Start (Actual) ⓘ

2024-04-29

Primary Completion (Estimated) ⓘ

2025-12-31

Study Completion (Estimated) ⓘ

2025-12-31

Enrollment (Estimated) ⓘ

700

Study Type ⓘ

Observational

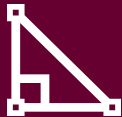
350 patients in each group...

# How did it translate in new study? (2)

NCT05894876

| How is the study designed?                                                                                                                                                                                                                                  |                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| <b>Design Details</b>                                                                                                                                                                                                                                       |                                                                                                                     |
| <b>Observational Model</b> : Cohort                                                                                                                                                                                                                         |                                                                                                                     |
| <b>Time Perspective:</b> Retrospective                                                                                                                                                                                                                      |                                                                                                                     |
| <b>Groups and Interventions</b>                                                                                                                                                                                                                             |                                                                                                                     |
| Groups/Cohorts                                                                                                                                                                                                                                              | Intervention/Treatment                                                                                              |
| Good responders                                                                                                                                                                                                                                             | Other: No treatment is given                                                                                        |
| Participants on previous treatment with growth hormone will have one study visit for taking a non-invasive biological sample. Participants with a change in height Standard Deviation Score (SDS) more than (>) 1.0, corresponding to >85th percentile.     | <ul style="list-style-type: none"><li>No treatment is provided to the participants as part of this study.</li></ul> |
| Poor responders                                                                                                                                                                                                                                             | Other: No treatment is given                                                                                        |
| Participants on previous treatment with growth hormone will have one study visit for taking a non-invasive biological sample. Poor responders are defined as participants with a change in height SDS less than (<) 0.4, corresponding to <15th percentile. | <ul style="list-style-type: none"><li>No treatment is provided to the participants as part of this study.</li></ul> |

| What is the study measuring?                                                                 |                         |                                       |
|----------------------------------------------------------------------------------------------|-------------------------|---------------------------------------|
| <b>Primary Outcome Measures</b>                                                              |                         |                                       |
| Outcome Measure                                                                              | Measure Description     | Time Frame                            |
| The frequency of genetic variants that significantly differ between the two responder groups | Measured as odds ratio. | One year after growth hormone therapy |
| <b>Secondary Outcome Measures</b>                                                            |                         |                                       |
| Outcome Measure                                                                              | Measure Description     | Time Frame                            |
| The enrichment of genetic variants per gene/pathway                                          | Measured as count.      | One year after growth hormone therapy |

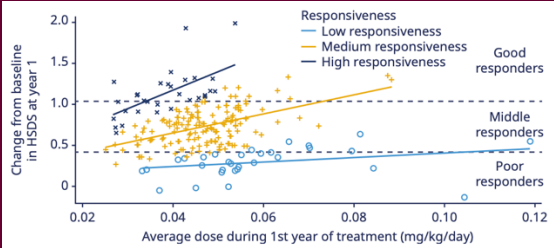




**Response** was preferred to be used in the **Protocol** primarily for recruitment by physician as directly computable with the defined thresholds of 0.4 and 1.0.



**Responsiveness** will be used as alternative endpoint and specified in **Statistical Analysis Plan**.



# Conclusion

## *What did we learn for next study?*

- Which levels to apply to define poor and good responder groups to recruit patients accordingly and specify in protocol.
- Using these levels, we could reproduce results from other studies identifying independent factors predicting response to treatment.
- The results from the first year of treatment are consistent with longer-term ones.
- We have introduced a new endpoint, responsiveness, which enable to account for the variability in dosing across patients and regions and provide a robust alternative to build a prediction model and inform the next analysis based on genotype data and to specify in SAP.
  - And the differing levels of responsiveness of patients with ISS to GH dose indicates that a variable sensitivity to GHT exists in this population. This variability could be due to the genetic heterogeneity of the ISS population.

## **Limitations**

- Data relating to clinical determinants and individual factors associated with patient health were not always available from all patients. This could have limited the analytical power of this study.
  - Genetic testing was not part of the two registry studies used in this analysis
- Data on final height of children in each response group were not available for the majority of patients; thus, data of last recorded measurement were included in the analyses instead.

# THANK YOU!

*Jean-Marc Ferran*

*Consultant & Owner*

 JMF@qualiance.dk

 +45 6016 0456

 [www.qualiance.dk](http://www.qualiance.dk)

 [Linkedin.com/in/jeanmarcferran](https://www.linkedin.com/in/jeanmarcferran)



QUALIANCE

