|  |  |
| --- | --- |
| Growth hormone treatment for short stature in the USA, Germany and France: 15 years of surveillance in the Genetics and Neuroendocrinology of Short-Stature International Study (GeNeSIS) | |
| Author(s): | **R Pfäffle1, C Land2, E Schönau3, PM Holterhus4, JL Ross5, C Piras De Oliveira6, CJ Child7, I Benabbad8, N Jia9, H Jung10, WF Blum11** |
| Author affiliation(s): | 1Dept of Paediatric Endocrinology, Children’s Hospital Leipzig, Germany, 2Practice for Children’s Endocrinology and Diabetology, Gauting, Germany, 3Department of Paediatrics, University Hospital of Cologne, Germany, 4Division of Paediatric Endocrinology and Diabetes, Christian-Albrechts-University Kiel & University Hospital Schleswig-Holstein, Kiel, Germany, 5Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, USA, 6Lilly USA LLC, Corporate Center, Indianapolis, IN, USA, 7Eli Lilly, Windlesham, UK, 8Medical Diabetes, Lilly France, Neuilly-sur-Seine, France, 9Eli Lilly, Indianapolis, IN, USA, 10Lilly Deutschland, Medical Department Diabetes, Bad Homburg, Germany, 11Children’s Hospital, University of Giessen, Giessen, Germany |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

**Supplementary Table 1.** Numbers and proportions of patients with GHD treated with GH, by diagnostic group and by country

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Diagnosisa | USA N=5184 | | Germany N=1736 | | France N=940 | |
|  | N | % | N | % | N | % |
| Organic GHD | 1065 | 20.5 | 336 | 19.4 | 217 | 23.1 |
| Congenital | 665 | 12.8 | 199 | 11.5 | 144 | 15.3 |
| Known genetic defect | 16 | 0.3 | 19 | 1.1 | 9 | 1.0 |
| Abnormal pituitary development | 522 | 10.1 | 138 | 7.9 | 116 | 12.3 |
| Pituitary aplasia | 28 | 0.5 | 11 | 0.6 | 2 | 0.2 |
| Pituitary hypoplasia | 139 | 2.7 | 43 | 2.5 | 67 | 7.1 |
| Pituitary stalk abnormalities | 28 | 0.5 | 12 | 0.7 | 13 | 1.4 |
| Ectopic posterior pituitary | 113 | 2.2 | 46 | 2.6 | 26 | 2.8 |
| Septo-optic dysplasia | 135 | 2.6 | 19 | 1.1 | 4 | 0.4 |
| Other pituitary abnormalities | 22 | 0.4 | 6 | 0.3 | 4 | 0.4 |
| Clinical syndromes | 57 | 1.1 | 20 | 1.2 | 6 | 0.6 |
| Mid-line palatal defect | 14 | 0.3 | 6 | 0.3 | 2 | 0.2 |
| Prader–Willi syndrome | 40 | 0.8 | 9 | 0.5 | 1 | 0.1 |
| Other | 3 | 0.1 | 5 | 0.3 | 3 | 0.3 |
| Other CNS malformations | 53 | 1.0 | 22 | 1.3 | 12 | 1.3 |
| Arachnoid cyst | 5 | 0.1 | 4 | 0.2 | 3 | 0.3 |
| Chiari malformation | 7 | 0.1 | 1 | 0.1 | 1 | 0.1 |
| Congenital hydrocephalus | 6 | 0.1 | 10 | 0.6 | 2 | 0.2 |
| Other | 29 | 0.6 | 7 | 0.4 | 6 | 0.6 |
| Acquired | 400 | 7.7 | 137 | 7.9 | 73 | 7.8 |
| Intracranial tumour | 273 | 5.3 | 112 | 6.5 | 53 | 5.6 |
| Craniopharyngioma | 73 | 1.4 | 45 | 2.6 | 16 | 1.7 |
| Medulloblastoma | 76 | 1.5 | 22 | 1.3 | 21 | 2.2 |
| Germinoma | 20 | 0.4 | 11 | 0.6 | 7 | 0.7 |
| Astrocytoma | 20 | 0.4 | 8 | 0.5 | 2 | 0.2 |
| Glioma | 11 | 0.2 | 5 | 0.3 | 1 | 0.1 |
| Adenoma | 21 | 0.4 | 6 | 0.3 | 1 | 0.1 |
| Ependymoma | 9 | 0.2 | 3 | 0.2 | 2 | 0.2 |
| Primitive neuroectodermal tumour | 13 | 0.3 | 1 | 0.1 | 0 | 0 |
| Other | 30 | 0.6 | 10 | 0.6 | 3 | 0.3 |
| Cranial irradiation | 23 | 0.4 | 1 | 0.1 | 5 | 0.5 |
| CNS trauma/infection | 16 | 0.3 | 10 | 0.6 | 1 | 0.1 |
| Histiocytosis | 17 | 0.3 | 5 | 0.3 | 2 | 0.2 |
| Other | 71 | 1.4 | 9 | 0.5 | 12 | 1.3 |
| Idiopathic GHDb | 4088 | 78.9 | 1394 | 80.3 | 717 | 76.3 |
| Classic | 3198 | 61.7 | 1131 | 65.1 | 658 | 70.0 |
| Neurosecretory dysfunction | 533 | 10.3 | 224 | 12.9 | 28 | 3.0 |

aEach patient was assigned a primary diagnosis, based on a predefined diagnostic scheme (see Supplementary text file). Information is described as reported by study investigators and was not always provided for the more detailed diagnostic levels.

bIncludes patients with isolated idiopathic GHD and multiple idiopathic pituitary deficiencies

Abbreviations: CNS=central nervous system, GH=growth hormone, GHD=growth hormone deficiency.

**Supplementary Table 2.** Baseline clinical characteristics and NAH data for GH-treated patients who reached NAH, by diagnostic group and by country

| **Diagnostic group** |  | USA |  | Germany |  | France |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | n | Mean ± SD (95% CI) | n | Mean ± SD (95% CI) | n | Mean ± SD (95% CI) |
| **Organic GHD** |  | (N=193) |  | (N=139) |  | (N=64) |
| Female, number (%) | 193 | 73 (37.8) | 139 | 67 (48.2) | 64 | 27 (42.2) |
| Baseline age (y) | 193 | 9.5 ± 4.4 (8.9;10.1) | 139 | 9.7 ± 4.3 (9.0;10.4) | 64 | 11.2 ± 3.2 (10.4;12.0) |
| Baseline height SDS | 193 | -2.15 ± 1.41 (-2.35;-1.95) | 139 | -2.32 ± 1.40 (-2.56;-2.09) | 64 | -2.01 ± 1.15 (-2.30;-1.73) |
| Baseline Ht SDS – target Ht SDS | 159 | -2.29 ± 1.48 (-2.52;-2.06) | 119 | -2.48 ± 1.38 (-2.73;-2.23) | 58 | -1.84 ± 1.15 (-2.14;-1.54) |
| Treatment duration (y) | 191 | 7.9 ± 4.8 (7.2;8.6) | 138 | 8.3 ± 4.7 (7.6;9.1) | 62 | 6.0 ± 3.7 (5.1;7.0) |
| Last GH dose (mg/kg/wk) | 190 | 0.27 ± 0.16 (0.25;0.29) | 138 | 0.17 ± 0.08 (0.16;0.18) | 63 | 0.22 ± 0.07 (0.20;0.24) |
| NAH SDS | 193 | -0.84 ± 1.66 (-1.08;-0.60) | 139 | -0.57 ± 1.32 (-0.79;-0.35) | 64 | -0.74 ± 1.03 (-1.00;-0.48) |
| NAH SDS gain | 193 | 1.31 ± 1.65 (1.07;1.54) | 139 | 1.75 ± 1.51 (1.50;2.00) | 64 | 1.27 ± 1.26 (0.96;1.59) |
| NAH SDS – target Ht SDS | 159 | -0.91 ± 1.59 (-1.15;-0.66) | 119 | -0.66 ± 1.19 (-0.87;-0.44) | 58 | -0.45 ± 1.10 (-0.74;-0.16) |
| **Isolated idiopathic GHD** |  | (N=587) |  | (N=398) |  | (N=242) |
| Female, number (%) | 587 | 169 (28.8) | 398 | 158 (39.7) | 242 | 116 (47.9) |
| Baseline age (y) | 587 | 12.1 ± 3.2 (11.9;12.4) | 398 | 10.5 ± 3.2 (10.2;10.8) | 242 | 11.8 ± 2.4 (11.5;12.1) |
| Baseline Ht SDS | 587 | -2.17 ± 0.85 (-2.24;-2.10) | 398 | -2.34 ± 0.77 (-2.42;-2.27) | 242 | -2.26 ± 0.57 (-2.33;-2.19) |
| Baseline Ht SDS – target Ht SDS | 513 | -1.79 ± 1.06 (-1.88;-1.69) | 381 | -2.00 ± 0.92 (-2.10;-1.91) | 233 | -1.52 ± 0.78 (-1.62;-1.42) |
| Treatment duration (y) | 584 | 4.9 ± 3.3 (4.6;5.1) | 390 | 6.2 ± 3.2 (5.9;6.5) | 237 | 4.6 ± 2.1 (4.3;4.8) |
| Last GH dose (mg/kg/wk) | 585 | 0.37 ± 0.13 (0.36;0.38) | 396 | 0.22 ± 0.08 (0.21;0.23) | 241 | 0.28 ± 0.08 (0.27;0.29) |
| NAH SDS | 587 | -0.83 ± 1.04 (-0.92;-0.75) | 398 | -0.89 ± 0.77 (-0.97;-0.81) | 242 | -0.96 ± 0.72 (-1.05;-0.87) |
| NAH SDS gain | 587 | 1.34 ± 1.03 (1.25;1.42) | 398 | 1.45 ± 0.83 (1.37;1.54) | 242 | 1.30 ± 0.67 (1.21;1.38) |
| NAH SDS – target Ht SDS | 513 | -0.42 ± 1.03 (-0.51;-0.33) | 381 | -0.55 ± 0.79 (-0.63;-0.47) | 233 | -0.21 ± 0.69 (-0.30;-0.12) |
| **Small for gestational age** |  | (N=39) |  | (N=44) |  | (N=93) |
| Female, number (%) | 39 | 12 (30.8) | 44 | 29 (65.9) | 93 | 56 (60.2) |
| Baseline age (y) | 39 | 11.0 ± 3.3 (9.9;12.0) | 44 | 9.9 ± 3.4 (8.9;10.9) | 93 | 11.3 ± 2.7 (10.7;11.8) |
| Baseline height SDS | 39 | -2.55 ± 1.35 (-2.99;-2.12) | 44 | -2.66 ± 0.86 (-2.92;-2.40) | 93 | -2.44 ± 0.61 (-2.56;-2.31) |
| Baseline Ht SDS – target Ht SDS | 30 | -1.88 ± 1.50 (-2.44;-1.32) | 39 | -2.35 ± 1.31 (-2.78;-1.93) | 84 | -1.53 ± 0.78 (-1.69;-1.36) |
| Treatment duration (y) | 39 | 6.0 ± 3.6 (4.9;7.2) | 43 | 5.9 ± 2.8 (5.0;6.8) | 92 | 4.6 ± 2.2 (4.1;5.1) |
| Last GH dose (mg/kg/wk) | 39 | 0.40 ± 0.12 (0.36;0.44) | 44 | 0.24 ± 0.08 (0.22;0.27) | 91 | 0.29 ± 0.08 (0.27;0.31) |
| NAH SDS | 39 | -1.56 ± 0.89 (-1.85;-1.27) | 44 | -1.47 ± 0.74 (-1.70;-1.24) | 93 | -1.46 ± 0.85 (-1.63;-1.28) |
| NAH SDS gain | 39 | 0.99 ± 1.33 (0.56;1.42) | 44 | 1.19 ± 0.85 (0.93;1.45) | 93 | 0.98 ± 0.83 (0.81;1.15) |
| NAH SDS – target Ht SDS | 30 | -0.93 ± 1.10 (-1.34;-0.52) | 39 | -1.15 ± 0.96 (-1.46;-0.83) | 84 | -0.47 ± 0.70 (-0.62;-0.32) |
| **Turner syndrome** |  | (N=191) |  | (N=141) |  | (N=53) |
| Baseline age (y) | 191 | 10.1 ± 3.6 (9.6;10.6) | 141 | 9.4 ± 3.1 (8.9;10.0) | 53 | 9.9 ± 3.2 (9.0;10.8) |
| Baseline Ht SDS | 191 | -2.78 ± 0.95 (-2.91;-2.64) | 141 | -2.47 ± 0.84 (-2.61;-2.33) | 53 | -2.70 ± 0.91 (-2.95;-2.45) |
| Baseline Ht SDS – target Ht SDS | 170 | -2.79 ± 1.14 (-2.97;-2.62) | 134 | -2.72 ± 1.00 (-2.89;-2.55) | 52 | -2.34 ± 0.89 (-2.58;-2.09) |
| Treatment duration (y) | 191 | 6.6 ± 3.7 (6.0;7.1) | 140 | 6.5 ± 2.9 (6.0;7.0) | 50 | 5.8 ± 3.0 (5.0;6.8) |
| Last GH dose (mg/kg/wk) | 189 | 0.37 ± 0.11 (0.36;0.39) | 140 | 0.28 ± 0.07 (0.27;0.29) | 49 | 0.34 ± 0.08 (0.31;0.36) |
| NAH SDS | 191 | -1.85 ± 0.87 (-1.98;-1.73) | 141 | -1.54 ± 0.93 (-1.69;-1.38) | 53 | -1.94 ± 0.91 (-2.19;-1.69) |
| NAH SDS gain | 191 | 0.92 ± 0.88 (0.80;1.05) | 141 | 0.94 ± 0.72 (0.82;1.06) | 53 | 0.76 ± 0.83 (0.53;0.99) |
| NAH SDS – target Ht SDS | 170 | -1.91 ± 1.02 (-2.06;-1.75) | 134 | -1.75 ± 0.89 (-1.90;-1.60) | 52 | -1.55 ± 0.98 (-1.83;-1.28) |
| **SHOX deficiency** |  | (n=13) |  | (N=36) |  | (N=58) |
| Female, number (%) | 13 | 8 (61.5) | 36 | 24 (66.7) | 58 | 42 (72.4) |
| Baseline age (y) | 13 | 10.7 ± 2.4 (9.3;12.1) | 36 | 11.3 ± 2.4 (10.5;12.1) | 58 | 10.6 ± 2.4 (9.9;11.2) |
| Baseline Ht SDS | 13 | -2.40 ± 0.58 (-2.75;-2.05) | 36 | -2.26 ± 0.99 (-2.59;-1.92) | 58 | -2.50 ± 0.65 (-2.67;-2.33) |
| Treatment duration (y) | 13 | 6.0 ± 3.6 (3.8;8.1) | 35 | 3.8 ± 2.0 (3.1;4.5) | 56 | 5.1 ± 2.6 (4.4;5.8) |
| Last GH dose (mg/kg/wk) | 12 | 0.37 ± 0.16 (0.27;0.48) | 36 | 0.28 ± 0.06 (0.26;0.30) | 54 | 0.34 ± 0.09 (0.32;0.37) |
| NAH SDS | 13 | -1.36 ± 0.87 (-1.89;-0.84) | 36 | -1.49 ± 0.92 (-1.80;-1.18) | 58 | -1.61 ± 1.04 (-1.89;-1.34) |
| NAH SDS gain | 13 | 1.04 ± 0.82 (0.55;1.53) | 36 | 0.76 ± 0.99 (0.43;1.10) | 58 | 0.89 ± 0.94 (0.64;1.13) |
| NAH SDS – target Ht SDS | 12 | -0.32 ± 1.06 (-0.99;0.36) | 34 | -0.65 ± 0.91 (-0.97;-0.33) | 58 | -0.49 ± 0.98 (-0.75;-0.23) |

Abbreviations: CI=confidence interval, GH=growth hormone, GHD=growth hormone deficiency, Ht=height, NAH=near-adult height, SD=standard deviation, SDS=standard deviation score, *SHOX*=short-stature homeobox containing gene, wk=week, y=year.

**Supplementary Table 3.** Serious adverse events for GH-treated patients, by main diagnostic group and by countrya

|  |  |  |  |
| --- | --- | --- | --- |
|  | USA | Germany | France |
| **GHD** |  |  |  |
| Patients evaluable for safety | 5187 | 1736 | 940 |
| Patients with ≥1 SAE | 94 (1.8%) | 56 (3.2%) | 52 (5.5%) |
| Most common SAEsa |  |  |  |
| Seizure | 7 (0.1%) | 1 (0.1%) | 1 (0.1%) |
| Pneumonia | 5 (0.1%) | 3 (0.2%) | - |
| Dehydration | 5 (0.1%) | 1 (0.1%) | - |
| Appendicitis | 4 (0.1%) | 1 (0.1%) | 1 (0.1%) |
| Craniopharyngioma | 3 (0.1%) | 3 (0.2%) | 4 (0.4%) |
| Pyrexia | 3 (0.1%) | - | - |
| Sinusitis | 3 (0.1%) | 1 (0.1%) | 1 (0.1%) |
| Scoliosis | 3 (0.1%) | - | - |
| Headache | 2 (<0.1%) | 3 (0.2%) | 2 (0.2%) |
| Hypoglycaemia | 2 (<0.1%) | 2 (0.1%) | 3 (0.3%) |
| Vomiting | 2 (<0.1%) | 1 (0.1%) | 3 (0.3%) |
| Fall | - | 1 (0.1%) | 3 (0.3%) |
| **SGA** |  |  |  |
| Patients evaluable for safety | 353 | 221 | 266 |
| Patients with ≥1 SAE | 8 (2.3%) | 5 (2.3%) | 5 (1.9%) |
| **Turner syndrome** |  |  |  |
| Patients evaluable for safety | 737 | 267 | 114 |
| Patients with ≥1 SAE | 22 (3.0%) | 16 (6.0%) | 13 (11.4%) |
| Most common SAEsa |  |  |  |
| Pneumonia | 3 (0.4%) | - | - |
| Tonsillar hypertrophy | - | - | 3 (2.6%) |
| **SHOX deficiency** |  |  |  |
| Patients evaluable for safety | 61 | 215 | 185 |
| Patients with ≥1 SAE | 1 (1.6%) | 5 (2.3%) | 8 (4.3%) |

aAny SAE that was reported for at least 3 children in any of the three countries.

Note no individual SAEs were seen in ≥3 children for SGA and SHOX deficiency.

Abbreviations: GH=growth hormone, GHD=growth hormone deficiency, SAE=serious adverse event, SGA=small for gestational age, *SHOX*=short-stature homeobox containing gene.

**Supplementary Figure 1.** Height SDS and delta height SDS during 4 years of GH treatment by diagnostic group for patients in the USA, Germany (GE) and France (FR); data shown are mean (95% confidence interval)

Abbreviations: GH=growth hormone, GHD=GH deficiency, SGA=small for gestational age, SDS=standard deviation score, *SHOX*=short-stature homeobox containing gene.