**Appendices**

**Cost analysis of use of GH before and after puberty onset**

Somatotropin costs between **€22**/mg (Humatrope) and **€29**/mg (Genotropin). At the lowest recommended GH dose (23mcg/kg/day; 0.16mg/kg/week) this would cost between **€0.51**/kg/day or **€3.57**/kg/week (for Humatrope) and **€0.66**/kg/day or **€4.64**/kg/week (for Genotropin). At the highest recommended GH dose (39mcg/kg/day; 0.27mg/kg/week) this would cost between **€0.87**/kg/day or **€6.13**/kg/week (for Humatrope) and **€1.12**/kg/day or **€7.83**/kg/week (for Genotropin).

Thus for a 40kg male child (mean weight of boys at puberty in our study population) the lowest dose annual cost of GH would be between **€7519** and **€9670** (mean value **€8594**), whilst the highest dose annual cost would be between **€12,756** and **€16,281** (mean value **€14,519**), with a difference in mean values of **€5925**/year. For a 35kg female child (mean weight of girls at puberty in our study population) the lowest dose annual cost of GH would be between **€6566** and **€8462** (mean value **€7513**), whilst the highest dose annual cost would be between **€11,161** and **€14,247** (mean value **€12,704**), with a difference in mean values of **€5191**/year.

Cost analysis for male patient

Using the multilevel model equations above we can calculate the expected annual increase in height SDS for an example male patient of (mean) 40kg, with chronological age of puberty at 13 years, number of injections per week = 7, isolated hormone deficiency and mean weight SDS -0.44 (see table 1).

Expected increase in annual height SDS in the pre-pubertal period on the lowest recommended dose of GH (0.16mg/kg/week):

Change in height SDS/ year = 0.36 (95% CI: 0.15,0.56) + (1.17(0.70,1.63) x 0.16[wtddos]) + (-0.04(-0.10,0.02) x 2[gender]) + (-0.04(-0.06,-0.02) x -0.44[wtSDS]) + (-0.03(-0.04,-0.01) x 13[cap]) =>

= 0.26 SDS/yr (95% CI -0.43,0.74) - approximates to mean of 1.60cm/year above baseline growth

Expected increase in annual height SDS in the pre-pubertal on the highest recommended dose of GH (0.27mg/kg/week):

Change in height SDS/year = 0.36 (95% CI: 0.15,0.56) + (1.17(0.70,1.63) x 0.27[wtddos]) + (-0.04(-0.10,0.02) x 2[gender]) + (-0.04(-0.06,-0.02) x -0.44[wtSDS]) + (-0.03(-0.04,-0.01) x 13[cap]) =>

= 0.39 SDS/yr (95% CI -0.36,0.84) - approximates to mean of 2.40cm/year above baseline growth

Therefore, for a mean increase in cost from lowest to highest recommended dose of GH in the pre-pubertal period of **€5925**/year, for a 40kg ‘average’ boy, we would expect to an annual difference in height gain of approximately 0.80cm (above baseline growth).

In contrast, expected increase in annual height SDS in the post-pubertal onset period on the lowest recommenced dose of GH (0.16mg/kg/week):

Change in height SDS/ year = -0.87 (95% CI: -1.1,-0.66) + (0.20(-0.02,0.6) x 0.16[wtddos]) + (-0.11(-0.17,-0.05) x 2[gender]) + (0.03(0.02,0.04) x 7[noi]) + (0.08(0.06,0.09) x 13[cap]) =>

= 0.19 SDS/yr (95% CI: -0.52,0.79) - approximates to mean of 1.40cm/year above baseline growth

Expected increase in annual height SDS post-pubertal onset on the highest recommended dose of GH (0.27mg/kg/week):

Change in height SDS/year = -0.87(95% CI: -1.1,-0.66) + (0.20(-0.02,0.6) x 0.27[wtddos]) + (-0.11(-0.17,-0.05) x 2[gender]) + (0.03(0.02,0.04) x 7[noi]) + (0.08(0.06,0.09) x 13[cap]) =>

= 0.21 SDS/yr (95% CI: -0.57,0.85) - approximates to mean of 1.60cm/year above baseline growth

 Therefore, for a mean increase in cost from lowest to highest recommended dose of GH in the post-pubertal onset period of **€5925**/year, for a 40kg ‘average’ boy, we could expect to see an annual difference in height gain of approximately 0.20cm.

Thus, for an annual mean increase cost of **€5925**, the expected height gain after puberty onset would be only 0.20cm/year above baseline growth, compared to an expected height gain of 0.80cm/year in the pre-pubertal period, if GH is increased from the low to high end of the recommended dose range.

Cost analysis for a female patient

Using the multilevel model equations above we can calculate the expected annual increase in height SDS for an example female patient of (mean) 35kg, with chronological age of puberty at 11.5 years, number of injections per week = 7, isolated hormone deficiency and mean weight SDS -0.24 (see table 1).

Expected increase in annual height SDS in the pre-pubertal period on the lowest recommended dose of GH (0.16mg/kg/week):

Change in height SDS/ year = 0.36 (95% CI: 0.15,0.56) + (1.17(0.70,1.63) x 0.16[wtddos]) + (-0.04(-0.10,0.02) x 1[gender]) + (-0.04(-0.06,-0.02) x -0.24[wtSDS]) + (-0.03(-0.04,-0.01) x 11.5[cap]) =>

= 0.17 SDS/yr (95% CI -0.28,0.73) - approximates to mean of 1.10cm/year above baseline growth

Expected increase in annual height SDS in the pre-pubertal on the highest recommended dose of GH (0.27mg/kg/week):

Change in height SDS/year = 0.36 (95% CI: 0.15,0.56) + (1.17(0.70,1.63) x 0.27[wtddos]) + (-0.04(-0.10,0.02) x 1[gender]) + (-0.04(-0.06,-0.02) x -0.24[wtSDS]) + (-0.03(-0.04,-0.01) x 11.5[cap]) =>

= 0.30 SDS/yr (95% CI -0.21,0.90) - approximates to mean of 1.95cm/year above baseline growth

Therefore, for a mean increase in cost from lowest to highest recommended dose of GH in the pre-pubertal period of **€5191**/year, for a 35kg ‘average’ girl, we would expect to an annual difference in height gain of approximately 0.85cm.

In contrast, expected increase in annual height SDS in the post-pubertal onset period on the lowest recommenced dose of GH (0.16mg/kg/week):

Change in height SDS/ year = -0.87 (95% CI: -1.1,-0.66) + (0.20(-0.02,0.6) x 0.16[wtddos]) + (-0.11(-0.17,-0.05) x 1[gender]) + (0.03(0.02,0.04) x 7[noi]) + (0.08(0.06,0.09) x 11.5[cap]) =>

= 0.18 SDS/yr (95% CI: -0.44,0.70) - approximates to mean of 1.3 cm/year above baseline growth

Expected increase in annual height SDS post-pubertal onset on the highest recommended dose of GH (0.27mg/kg/week):

Change in height SDS/year = -0.87(95% CI: -1.1,-0.66) + (0.20(-0.02,0.6) x 0.27[wtddos]) + (-0.11(-0.17,-0.05) x 1[gender]) + (0.03(0.02,0.04) x 7[noi]) + (0.08(0.06,0.09) x 11.5[cap]) =>

= 0.20 SDS/yr (95% CI: -0.45,0.77) - approximates to mean of 1.45cm/year

Therefore, for a mean increase in cost from lowest to highest recommended dose of GH in the post-pubertal onset period of **€5191**/year, for a 35kg ‘average’ girl, we could expect to see an annual difference in height gain of approximately 0.15cm.

Thus, for an annual mean increase cost of **€5191**, the expected height gain after puberty onset would be only 0.15cm/year, compared to an expected height gain of 0.85cm/year in the pre-pubertal period, if GH is increased from the low to high end of the recommended dose range.

Figure 1(S) - Year-by-year regression analysis of the relationship between GH dose and change in height SDS (-3,-2,-1 years pre-pubertal onset, at pubertal onset (0), and +1,+2,+3,+4 years post-pubertal onset)















