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Does GnRHa co-treatment cost height? Two-year net effect and near-adult settlement in children receiving growth hormone

Keywords: Central precocious puberty; Gonadotropin-releasing hormone analogue; Growth hormone; Bone age; Near-adult height

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Abstract

Background: GnRH-analogue (GnRHa) co-treatment delays bone-age (BA) progression in GH-treated children, but whether the time gained converts into height, and whether the interim velocity loss is repaid at final height, are unclear.

Methods: Single-centre cohort: 82 children receiving combined treatment versus matched GH-only controls for BA progression, height velocity and height-SDS gain (years 1–2), and near-adult height (girls ≥15, boys ≥16 years); Bayley–Pinneau predicted adult height (PAH) was computed at baseline and year 1.

Results: GnRHa reduced BA progression from 2.05 to 0.77 BA-years per year and height velocity from 10.0 to 5.1 cm per year (both $p = 0.004$). By year 2 it had suppressed 0.35 more BA-years but gained 0.33 SDS less height ($p = 0.058$). At near-adult height, the combined group was not shorter than controls (160.0 vs. 157.5 cm; adjusted difference −0.08 SDS; −0.57 to +0.41); the year-1 dose–response penalty had disappeared (β = +0.02, $p = 0.98$). Baseline PAH was lower in combined children (153.4 vs. 164.9 cm),

but at near-adult height both groups exceeded their baseline predictions by a median of 5.5 cm (adjusted difference −1.0 cm; −4.5 to +2.5).

Conclusion: In the first 2 years GnRHa buys bone-age time at a roughly equal interim price in height, but the price is repaid: near-adult height is not reduced, early BA suppression no longer predicts it, and in predicted-height terms both groups overshot their baseline predictions by a median of 5.5 cm.

Introduction

Children with central precocious puberty (CPP) grow quickly, but skeletal maturation outpaces linear growth. GnRH analogues (GnRHa) suppress the pubertal axis and slow bone-age (BA) progression, thereby preserving growth potential [1–4]; on average, treated children gain roughly 2.7 cm of adult height relative to untreated children [5]. Because GnRHa also suppresses height velocity, growth hormone (GH) is frequently added, and combined treatment improves predicted adult height [6–8]. Two questions nevertheless remain unsettled: whether the bone-age delay achieved by GnRHa is converted into proportionally greater height, or merely buys time that is never cashed in; and whether the interim loss of height velocity is recovered once final height is reached. Recent evidence leaves both questions open. Meta-analyses show that adding GH to GnRHa improves growth velocity and predicted adult height without consistently improving final adult height [6, 7], real-world series report similar final heights across regimens [8–10], and the 2026 Endocrine Society guideline advises against routine GH add-on in CPP [1].

Addressing these questions requires separating two effects of GnRHa that act in opposite directions, namely the gain in growth potential through BA suppression and the loss of growth rate through velocity suppression, and then following both to final height. We used three complementary designs in a real-world registry, extended by follow-up of final or current heights. A propensity-score-matched comparison of combined treatment against GH alone estimated the adjusted two-year differences in BA progression and height gain. An interrupted time-series design, in children who had received GH monotherapy before GnRHa initiation, measured within-patient changes at the moment GnRHa was added. A within-cohort

dose–response analysis related the degree of achieved BA suppression to height gain at years 1 and 2, and later to near-adult height. Finally, combined treatment was compared with GnRHa monotherapy to test whether adding GH restores the velocity lost to GnRHa.

Methods

Setting and data source

This retrospective cohort study used the prospectively maintained registry of the Pediatric Growth and Development Clinic of the First Affiliated Hospital of University of South China (Hengyang, Hunan, China), January 2018 to March 2026. Each child's longitudinal form records visit dates, height, weight, bone age, laboratory rechecks and drug prescriptions. Data-quality rules excluded implausible height-for-age values (|height SDS| > 5) and per-interval height velocities above 15 cm/year. The study is reported according to the STROBE statement.

Participants and exposure

The combined-treatment group comprised children receiving GH plus GnRHa with a baseline bone age between 5 and 12.5 years and a height measurement at 9–15 months. The GH-only pool comprised children receiving GH without any GnRHa exposure and the same data requirements. Treatment start was the first recorded GH (or GnRHa) administration. Children receiving GnRHa alone formed a secondary comparison group. Diagnoses were taken from clinical records.

Measurements

Height SDS (HtSDS) was calculated using WHO LMS standards [11, 12], and bone age was assessed by the Greulich–Pyle method [13]. Predicted adult height (PAH) was calculated by the Bayley–Pinneau method from height and Greulich–Pyle bone age, using the standard average-maturation tables [14]; PAH gain was defined as near-adult height minus baseline PAH, and year-1 ΔPAH as year-1 PAH minus baseline PAH. Children with a baseline bone age below the table floor (girls <6.0, boys <7.0 years) were excluded from PAH analyses. BA−CA denotes bone age minus chronological age. Height-for-bone-age

SDS (HtSDS_BA), which standardizes height to the child's bone age, served as an index of growth potential. Outcomes were extracted within windows relative to treatment start: baseline (−6 to +6 months), year 1 (9–15 months) and year 2 (21–27 months), using the value closest to the window midpoint. ΔBA/ΔCA was computed from the first and last bone-age assessments at least 6 months apart. Height velocity (HV) was the per-patient median of consecutive interval velocities.

Near-adult height follow-up

In October 2026, the families of all 82 combined-treatment children and the 58 matched GH-only controls were contacted by telephone, and the final height, or the current height for children still growing, was recorded. Follow-up heights were converted to SDS with the WHO reference [11, 12] at the child's current age (capped at 19 years). Near-adult height was defined as girls aged 15.0 years or older and boys aged 16.0 years or older at follow-up; a sensitivity analysis used 14.0 years for girls and 15.0 years for boys. Outcomes were near-adult height (cm), near-adult height SDS, the total height-SDS gain from baseline to near-adult height, and the change in HtSDS from year 2 to near-adult height.

Statistical analysis

Matched cohort. A propensity score for combined treatment was estimated by logistic regression on age, bone age and sex. Combined children were matched 1:2 to GH-only controls without replacement, using nearest-neighbour matching with a caliper of 0.6 SD of the logit [15, 16]; sensitivity analyses used calipers of 0.2 and 1.0. Balance was assessed with standardized mean differences (SMD). Outcomes were compared by linear regression with adjustment for age, bone age, baseline HtSDS, baseline BA−CA and sex, using cluster-robust standard errors by matched set.

Interrupted time series. In combined-treatment children with at least 3 months of GH monotherapy before GnRHa, the BA progression slope (BA-years per year) and HV were computed for the 12 months before and the 15 months after GnRHa initiation and compared with paired Wilcoxon tests [17].

Dose–response within the combined cohort. The achieved BA suppression was quantified as the first- (or second-) year change in BA−CA. Its association with concurrent ΔHtSDS, and at follow-up with the total

ΔHtSDS from baseline to near-adult height, was estimated by linear regression with robust errors, adjusting for age, baseline BA−CA, baseline HtSDS and sex; suppression was also categorized in tertiles.

Near-adult height. Group comparisons used Mann–Whitney tests and linear regression adjusting for baseline HtSDS and BA−CA (with a sensitivity model additionally adjusting for age, bone age and sex), using cluster-robust standard errors by matched set in the matched-cohort subset. Near-adult height SDS was compared with the population mean (0) by Wilcoxon signed-rank tests. In a supplementary analysis, the latest height SDS of all followed children was compared between groups with age- and baseline-adjusted linear regression. PAH gain, baseline PAH and year-1 ΔPAH were analysed in the same way, and baseline PAH was validated against near-adult height by Spearman correlation and mean prediction error.

Analyses were performed in Python 3.14 (NumPy, SciPy, scikit-learn, statsmodels). Continuous data are presented as median (IQR). Two-sided *p* values below 0.05 were considered significant.

Results

Matched cohort

Of 142 children receiving combined treatment and 618 receiving GH alone in the registry, 82 and 222 respectively met the matched-cohort entry criteria. With a 0.6-SD caliper, 29 combined children (all girls) were matched to 58 GH-only controls. Baseline age (SMD −0.12) and bone age (0.09) were well balanced, whereas baseline HtSDS (−0.39 vs. −1.20, SMD 0.83) and BA−CA (+0.58 vs. +0.02, SMD 0.44) reflected the different indications; these were retained as covariates in all outcome models (Table 1). Strict (0.2-SD, 21 sets) and permissive (1.0-SD, 37 sets) calipers gave qualitatively identical results.

Over year 1, combined treatment produced no significant adjusted difference from GH alone in BA−CA change (−0.01, 95% CI −0.31 to +0.28), ΔHtSDS (+0.02, −0.15 to +0.19) or HV (−0.61 cm/year, −1.37 to +0.16). By year 2, however, the combined group had suppressed 0.35 more BA-years (−0.35, −0.73 to +0.04, $p = 0.079$) while gaining 0.33 SDS less height (−0.33, −0.67 to +0.01, $p = 0.058$); with the 1.0-SD caliper these differences were −0.33 BA-years ($p = 0.082$) and −0.31 SDS ($p = 0.050$) (Table 2, Fig. 1).

Height-for-bone-age SDS did not differ at year 1 (−0.08, −0.34 to +0.18); the group trajectories over the treatment period are shown in Fig. 2.

Interrupted time series at GnRHa initiation

Seventeen combined-treatment children had received at least 3 months of GH monotherapy before GnRHa (median lead-in 7.1 months); 9 had sufficient bone-age data for the paired analysis. GnRHa initiation reduced the BA progression slope from a median of 2.05 BA-years per year (pubertal acceleration) to 0.77 (p = 0.004, Wilcoxon), while HV fell in parallel from 10.0 to 5.1 cm per year (p = 0.004) (Fig. 3). BA suppression and velocity loss therefore occurred together, in the same children, at the same time.

Dose–response within the combined cohort

Among 60 combined children with year-1 data, each BA−CA year suppressed was associated with 0.38 SDS less first-year height gain (adjusted β = +0.38 per BA−CA year, 95% CI 0.14–0.62, p = 0.002); the year-2 association was stronger (β = +0.69, 0.38–1.00, $p < 0.001$, n = 36). Suppression tertiles showed a monotonic gradient: children with weak suppression gained +0.42 SDS in year 1, those with moderate suppression +0.20 SDS, and those with strong suppression −0.08 SDS (p = 0.004) (Fig. 4). Over the first two years, in other words, the children whose BA was delayed most by GnRHa were precisely those who grew least.

Combined treatment versus GnRHa alone

Compared with 44 children receiving GnRHa alone (matched 1:2 on age, bone age and sex; 21 sets), combined treatment produced similar year-1 BA−CA change (−0.12 vs. −0.23 years, p = 0.59), similar ΔHtSDS (+0.08 vs. +0.04, p = 0.70) and similar HV (5.2 vs. 5.1 cm/year, p = 0.22) (Table 3). In the unadjusted comparison across the full groups, HV was higher with combined treatment (6.0 vs. 5.2 cm/year, p = 0.006), but this difference disappeared after matching, indicating that it reflected baseline differences rather than a year-1 effect of added GH.

Sensitivity analyses

Results were consistent across calipers (0.2/0.6/1.0 SD) and in a comparison restricted to GH-only controls with relatively advanced bone age (BA−CA > −0.5, n = 66). In that comparison, combined treatment showed more BA suppression (−0.13 vs. +0.07 BA−CA years, $p = 0.018$) but less height gain (+0.16 vs. +0.59 ΔHtSDS, $p < 0.001$) and lower velocity (6.0 vs. 8.0 cm/year, $p < 0.001$) at year 1 (online suppl. Table S1).

Near-adult height follow-up

Follow-up heights were obtained for 83 of 140 children (59%): 56 of 82 combined (68%) and 27 of 58 GH-only controls (47%). Twenty-four children had reached near-adult height, 16 in the combined group (13 girls, 3 boys) and 8 GH-only controls (all girls), at a median of 7.1 years after treatment start and at a median age of 16.5 versus 17.1 years (Table 4). None of the 17 interrupted time-series children had yet reached near-adult height (median current age 11.4 years), so the within-patient account has not yet been settled for that subgroup.

At near-adult height, the combined group did not fall short of the GH-only controls: median height was 160.0 cm versus 157.5 cm ($p = 0.23$), height SDS −0.46 versus −0.75 ($p = 0.45$), and total SDS gain from baseline −0.03 versus +0.48 ($p = 0.12$). In the matched-cohort subset (11 combined, 8 GH-only), the adjusted difference was −0.08 SDS (95% CI −0.57 to +0.41, $p = 0.75$) for height SDS and +1.97 cm (−4.69 to +8.64, $p = 0.56$) for absolute height (Table 4, Fig. 1, Fig. 5A). Near-adult height SDS remained below the population mean in both groups ($p = 0.005$ and $p = 0.039$). A sensitivity analysis with a more permissive age cut-off (girls ≥14, boys ≥15 years; 19 vs. 12 children) showed an unadjusted ΔHtSDS difference of −0.01 versus +0.58 SDS ($p = 0.024$), which disappeared after adjustment for baseline HtSDS and BA−CA (+0.01 SDS, 95% CI −0.53 to +0.54, $p = 0.98$). The raw difference reflected the controls' lower baseline height, not slower growth during treatment.

Within the combined group, the dose–response penalty documented at years 1 and 2 had vanished by final height. Among 13 near-adult children with year-1 BA data, BA suppression showed no association with

total height-SDS gain (β = +0.02 per BA−CA year, 95% CI −1.24 to +1.28, p = 0.98) (Fig. 5B). Suppression tertiles (cohort-derived cut-offs; Table 3) likewise showed no gradient: total ΔHtSDS was +0.25 (weak), −0.14 (moderate) and +0.21 (strong; p = 0.46), and near-adult height SDS was highest in the strongly suppressed group (−0.13 vs. −0.49 for weak suppression) (Table 3). First-year BA suppression correlated with final height SDS in the favourable direction, although not significantly (Spearman ρ = −0.42, p = 0.16): the children whose BA was suppressed most ended no shorter, and if anything slightly taller.

Between year 2 and near-adulthood, height-for-age SDS declined in the seven combined children with both measurements (median, from +0.57 to −0.43; p = 0.03) but changed little in the six GH-only children (from −0.70 to −0.82; p = 0.56). Because these children stopped growing earlier than their age-matched peers, this convergence in SDS rank did not translate into lower absolute final height (160.0 vs. 157.5 cm; Fig. 5C). In the supplementary comparison of the latest height SDS among all 83 followed children, the age- and baseline-adjusted difference was +0.02 SDS (95% CI −0.32 to +0.36, p = 0.91) (online suppl. Table S2).

Predicted adult height

At baseline, Bayley–Pinneau PAH was substantially lower in the combined group than in the GH-only pool (153.4 [149.7–157.4] vs. 164.9 [154.8–172.5] cm, p < 0.001), reflecting the advanced bone age that indicated GnRHa in the first place; in the matched cohort the adjusted baseline difference was −0.09 cm (95% CI −2.42 to +2.25, p = 0.94). During year 1, PAH rose less in combined children than in matched GH-only controls (+1.8 [−0.3 to +6.0] vs. +5.1 [+1.6 to +6.7] cm, p = 0.16), but this difference disappeared after adjustment (+0.06 cm, 95% CI −2.21 to +2.32, p = 0.96): in predicted-height terms the interim price of GnRHa is barely visible, because the method credits the bone-age slowdown it purchases (Table 2). At near-adult height, both groups had overshot their baseline predictions to the same degree: median PAH gain was +5.5 cm (combined) versus +5.7 cm (GH alone, p = 0.79), and the adjusted difference in the matched subset was −1.0 cm (95% CI −4.5 to +2.5, p = 0.56) (Table 4, Fig. 6). Baseline

PAH predicted the rank order of near-adult height moderately well overall (Spearman $\rho = 0.49$, $p = 0.014$; combined $\rho = 0.43$, $p = 0.095$; GH alone $\rho = 0.77$, $p = 0.025$) but underestimated achieved height by a median of 5.5 cm (Fig. 6A). Within the combined group, first-year BA suppression showed no association with PAH gain at settlement (adjusted $\beta = +3.0$ cm per BA−CA year, 95% CI −3.1 to +9.1, $p = 0.33$; Spearman $\rho = -0.24$, $p = 0.43$), confirming in predicted-height terms that the early dose–response penalty does not survive to final height.

Discussion

The two effects of GnRHa are well known individually; what this study adds is the exchange rate between them, and what happens when the account is settled. During the first two years of combined treatment the slowing of bone-age progression and the fall in height velocity appeared together in the same children at the moment GnRHa was introduced, at a ratio of roughly one for one: by year 2 the combined group had gained about 0.35 bone-age years relative to matched GH-only controls while losing about 0.33 SDS of height. This coupling is what one would expect if both changes share a single mechanism, suppression of the pubertal axis, and it means that during treatment the drug appears to cost height while actually deferring it [18]. The follow-up supports that reading. At a median of 7.1 years after treatment start, the children who had reached near-adult height showed no deficit, and the dose–response relationship that made the interim price visible at years 1 and 2 predicted nothing at final height; the children whose bone age had been suppressed most strongly ended, if anything, tallest. The velocity loss during treatment is therefore the mechanism of the treatment rather than a side effect to be corrected.

The same pattern holds when the comparison is made in predicted adult height (PAH), the metric actually recorded in the chart when treatment begins. Baseline Bayley–Pinneau predictions underestimated achieved near-adult height by a median of about 5.5 cm in both groups, and PAH gain did not differ between groups after adjustment. The apparent year-1 PAH advantage of the GH-only controls disappeared entirely once baseline characteristics were accounted for, which suggests that in PAH terms the interim price of GnRHa is largely invisible: the method already credits the bone-age slowdown that the

drug produces. Jin et al. recently reported that recalibrated Bayley–Pinneau predictions validated poorly against near-final height in their GnRHa-treated cohort [22]. Our data point to an explanation. In treated children the prediction error is not random but systematically positive, because treatment lifts achieved height above the untreated expectation embedded in the tables. The prediction nevertheless retained its rank information (Spearman correlation about 0.5), which is presumably why clinicians continue to use it for monitoring even though they cannot rely on it for absolute forecasts.

The literature on this question looks contradictory only if the observation window is ignored. Short-term series consistently find that adding GH to GnRHa restores growth velocity and improves predicted adult height [19, 23], whereas studies with final-height outcomes find no consistent advantage [8, 24], and the 2026 Endocrine Society guideline now recommends against routine GH add-on [1]. A contemporaneous single-centre cohort likewise found the on-treatment advantage of added GH substantially attenuated at near-final height once predicted adult height was accounted for [22]; anchored instead to GH alone, our design isolates the net effect of GnRHa itself. These findings are compatible if the early height deficit is regarded as a loan that later growth repays. Comparisons made during treatment then measure the price, while comparisons made at final height can find nothing to measure. The same logic explains our negative result for added GH in the first year: any benefit, like the benefit of GnRHa itself, would only be booked against growth that occurs after the observation window [6, 9].

Two practical messages follow. First, families can be told in advance that height velocity typically falls by roughly half, to about 5 cm per year, during combined treatment, that this slowing is expected and even desirable, and that in the children followed here the two-year deficit was not carried into final height. Second, monitoring can stay simple. The bone-age progression slope, height velocity and height-for-bone-age SDS together show whether treatment is working; a child whose bone age is not slowing ($\Delta BA/\Delta CA$ near 1) or whose height-for-bone-age SDS is not stabilizing deserves closer attention [2]. Our data also argue against reducing GnRHa dose intensity out of fear of the interim velocity loss, since strong early bone-age suppression did not predict lower final height, and they fit with the real-world observation that

baseline bone-age advancement, the very indication for suppression, is the strongest predictor of height gain [10, 20].

The main strengths are the three complementary designs, which approach the same quantity from different angles and give the same answer, the within-patient interrupted time series, which is free of between-group confounding, and the near-adult height follow-up that the original two-year window lacked. The limitations should be read against those strengths. Only 24 of 140 children (17%) had reached near-adult height, and the interrupted time-series children, the cleanest counterfactual, have not matured, so the adjusted near-adult differences remain wide and equivalence is demonstrated imprecisely rather than definitively. Matching rested on 21–37 sets because the two treatment populations differ inherently in baseline height and skeletal advancement, and residual confounding by indication cannot be excluded. Follow-up heights were parent-reported by telephone for a subset (59%) and could not be verified against closure of the growth plates; some children classified as near-adult may retain small residual growth, and children lost to follow-up may differ from those followed. The interrupted time series comprises nine children, and adherence, dose intensity and visit irregularity are imperfectly captured [21]. PAH was calculated with the average-maturation Bayley–Pinneau tables for all children, and children with baseline bone age below the table floor were excluded. A definitive answer will require final heights for the full cohort and for the within-patient subgroup, and this registry is well positioned to provide them.

Conclusion

During the first two years of combined treatment GnRHa buys bone-age time at an approximately one-for-one price in height. At near-adult height, that price has been repaid: the combined group shows no height deficit relative to GH alone, and the extent of early BA suppression no longer predicts final height. The trade-off quantified here provides a benchmark against which the eventual adult-height outcome of this cohort, and of combined treatment generally, can be measured.

Abbreviations

BA: bone age; BA−CA: bone age minus chronological age; CI: confidence interval; CPP: central precocious puberty; GH: growth hormone; GnRHa: gonadotropin-releasing hormone analogue; HtSDS: height standard deviation score; HtSDS_BA: height standard deviation score for bone age; HV: height velocity; IQR: interquartile range; SDS: standard deviation score; SMD: standardized mean difference; WHO: World Health Organization

Declarations

Ethics approval and consent to participate. This study protocol was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of University of South China (approval no. 2026LL1013004). The need for informed consent was waived by the Ethics Committee because the study was a retrospective analysis of routinely collected, anonymized data.

Consent for publication. Not applicable.

Competing interests. The authors declare that they have no competing interests.

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Availability of data and materials. The datasets generated and/or analysed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Authors' contributions. Peng Xiang: Data curation, Formal analysis, Writing – original draft. Huihui Tao: Data curation, Investigation. Kaipeng Liang: Data curation, Investigation. Chunhong Yin: Investigation. Xin Guo: Conceptualization, Methodology, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of the matched cohort (caliper 0.6 SD; all matched children were girls)

Characteristic	Combined GH + GnRHa (n = 29)	GH alone (n = 58)	SMD after
Age at start, years	8.77 (7.88–10.34)	9.61 (7.62–10.50)	−0.12
Bone age at start, years	9.00 (8.20–11.30)	9.50 (8.07–10.95)	0.09
Baseline HtSDS	−0.39 (−1.04 to 0.46)	−1.20 (−1.62 to −0.75)	0.83
Baseline BA − CA, years	0.58 (0.03–1.00)	0.02 (−0.46 to 0.49)	0.44
Baseline HtSDS for bone age	−0.98 (−1.19 to −0.41)	−1.22 (−1.70 to −0.87)	0.60

Data are median (IQR). SMD, standardized mean difference after matching. In the unmatched pool (82 combined vs. 222 GH-only children), SMDs were −0.76 (age), 0.62 (bone age), 2.05 (HtSDS), 2.32 (BA−CA), −0.39 (HtSDS for bone age) and 1.42 (sex).

Table 2. Outcomes at 1 and 2 years: combined treatment vs. matched GH-only controls (caliper 0.6 SD, 29 matched sets)

Outcome	Combined, median (IQR)	GH alone, median (IQR)	Adjusted difference (95% CI)	*p*
Year 1				
Δ(BA − CA), years	+0.03 (−0.37 to +0.60); n = 21	+0.04 (−0.24 to +0.38); n = 46	−0.01 (−0.31 to +0.28)	0.92
ΔHtSDS	+0.38 (+0.16 to +0.67); n = 29	+0.58 (+0.44 to +0.78); n = 58	+0.02 (−0.15 to +0.19)	0.79
Height velocity, cm/year	6.50 (5.30–7.83)	7.80 (6.51–9.13)	−0.61 (−1.37 to +0.16)	0.12
ΔHtSDS for bone age	+0.21 (+0.10 to +0.68); n = 21	+0.48 (+0.25 to +0.90); n = 46	−0.08 (−0.34 to +0.18)	0.56
ΔPAH, cm	+1.8 (−0.3 to +6.0); n = 20	+5.1 (+1.6 to +6.7); n = 40	+0.06 (−2.21 to +2.32)	0.96
Year 2				
Δ(BA − CA), years	+0.04 (−0.46 to +0.43); n = 15	+0.44 (+0.01 to +0.82); n = 26	−0.35 (−0.73 to +0.04)	0.079
ΔHtSDS	+0.49 (+0.01 to +0.57); n = 17	+0.95 (+0.69 to +1.19); n = 33	−0.33 (−0.67 to +0.01)	0.058

Adjusted differences from linear regression with cluster-robust standard errors by matched set, adjusting for age, bone age, baseline HtSDS, baseline BA−CA and sex. With the 1.0-SD caliper (37 sets), year-2 adjusted differences were −0.33 BA−CA years ($p = 0.082$) and −0.31 SDS ($p = 0.050$); with the 0.2-SD caliper (21 sets), −0.30 BA−CA years ($p = 0.19$) and −0.32 SDS ($p = 0.061$).

Table 3. Within-patient, dose–response and near-adult settlement analyses

Analysis	Before / weaker	After / stronger	*p*
Interrupted time series (n = 9)			
BA progression, BA-years/year	2.05 (1.31–2.49)	0.77 (0.57–0.91)	0.004
Height velocity, cm/year	10.0 (8.2–12.1)	5.1 (4.4–5.4)	0.004
BA suppression tertiles (n = 60), year 1			
Δ(BA − CA), years	+0.45 (weak) / −0.13 (moderate)	−0.51 (strong)	—
ΔHtSDS	+0.42 (weak) / +0.20 (moderate)	−0.08 (strong)	0.004
Dose–response (adjusted β per BA−CA year suppressed)			
ΔHtSDS year 1 (n = 60)	β = +0.38 (95% CI 0.14–0.62)		0.002
ΔHtSDS year 2 (n = 36)	β = +0.69 (95% CI 0.38–1.00)		<0.001
ΔHtSDS, baseline to near-adult height (n = 13)	β = +0.02 (95% CI −1.24 to +1.28)		0.98
PAH gain, baseline to near-adult height (n = 13)	β = +3.0 cm per BA−CA year (95% CI −3.1 to +9.1)		0.33
Suppression tertiles at near-adult height (n = 13)			
ΔHtSDS, baseline to near-adult	+0.25 (weak, n = 3) / −0.14 (moderate, n = 5)	+0.21 (strong, n = 5)	0.46

Near-adult height SDS	−0.49 (weak) / −0.43 (moderate)	−0.13 (strong)	—
Combined vs. GnRHa alone (matched 1:2, 21 sets)	Combined	GnRHa alone	*p*
Δ(BA − CA) year 1, years	−0.12	−0.23	0.59
ΔHtSDS year 1	+0.08	+0.04	0.70
Height velocity, cm/year	5.2	5.1	0.22

Values are medians (IQR) or adjusted estimates as indicated. *p* values from paired Wilcoxon tests (time series), Kruskal–Wallis tests (tertiles) or Mann–Whitney U tests (group comparisons). At near-adult height, first-year BA suppression no longer predicted lower total height gain; the Spearman correlation between year-1 BA suppression and near-adult height SDS was $\rho = -0.42$ ($p = 0.16$), i.e. stronger suppression tended toward higher final height SDS.

Table 4. Near-adult height outcomes after extended follow-up (October 2026)

Follow-up characteristic / outcome	Combined GH + GnRHa	GH alone	*p*
Height obtained at follow-up, n/N (%)	56/82 (68)	27/58 (47)	—
Reached near-adult height (girls ≥15 y, boys ≥16 y), n	16	8	—
Age at near-adult assessment, years	16.5 (16.0–18.1)	17.1 (16.5–17.5)	0.67
Years since treatment start	7.1 (6.2–9.1)	7.0 (6.2–7.5)	—
Near-adult height, cm	160.0 (157.8–163.8)	157.5 (156.8–159.5)	0.23
Near-adult height SDS (WHO)	−0.46 (−0.80 to −0.12)	−0.75 (−0.92 to −0.45)	0.45
ΔHtSDS, baseline to near-adult	−0.03 (−0.37 to +0.43)	+0.48 (+0.08 to +1.18)	0.12
Baseline PAH, cm	152.2 (149.9–156.8)	153.0 (149.8–153.6)	0.70
PAH gain (near-adult height − baseline PAH), cm	+5.5 (+2.8 to +10.4)	+5.7 (+4.4 to +7.9)	0.79
Matched-cohort subset (all girls)	n = 11	n = 8	—
Adjusted difference (95% CI), near-adult height, cm	+1.97 (−4.69 to +8.64)	ref	0.56
Adjusted difference (95% CI), near-adult height SDS	−0.08 (−0.57 to +0.41)	ref	0.75
Adjusted difference (95% CI), ΔHtSDS baseline to near-adult	−0.08 (−0.57 to +0.41)	ref	0.75

Adjusted difference (95% CI), PAH gain, cm	−1.04 (−4.55 to +2.46)	ref	0.56

Data are median (IQR) unless stated. Adjusted differences from linear regression with cluster-robust standard errors by matched set in the matched-cohort subset (11 combined, 8 GH-only), adjusting for baseline HtSDS and BA−CA; results with the full covariate set (age, bone age, sex) were similar. Near-adult height SDS was below the population mean in both groups (p = 0.005 and p = 0.039, Wilcoxon signed-rank). Sensitivity with a permissive cut-off (girls ≥14 y, boys ≥15 y; 19 vs. 12 children): unadjusted ΔHtSDS −0.01 vs. +0.58 (p = 0.024), adjusted difference +0.01 SDS (95% CI −0.53 to +0.54, p = 0.98). Among children with year-2 data, height-for-age SDS fell from +0.57 to −0.43 by near-adulthood in the combined group (n = 7, p = 0.03) and changed little in GH-only controls (−0.70 to −0.82; n = 6, p = 0.56), reflecting earlier growth cessation relative to age-matched peers rather than lower absolute height.

Figure Legends

Fig. 1. Net effect of GnRHa co-treatment over years 1–2 and at near-adult height. Adjusted differences (combined minus GH alone) with 95% CIs from the caliper-0.6-SD matched cohort: Δ(BA−CA) and ΔHtSDS at years 1 and 2, height velocity (29 matched sets, all girls), and ΔHtSDS from baseline to near-adult height (11 vs. 8 children, cluster-robust by matched set). Blue points indicate $p < 0.05$; grey points indicate $p \geq 0.05$.

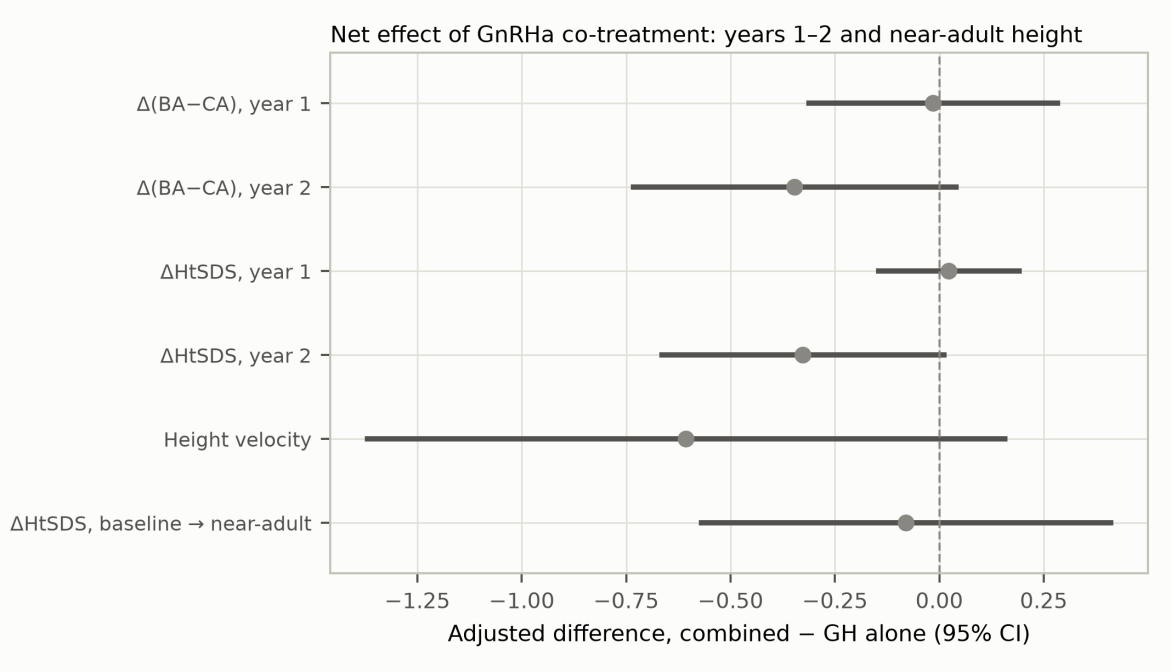
Fig. 2. Group trajectories in the matched cohort. Binned medians of (A) bone age minus chronological age and (B) height SDS over treatment time for combined treatment versus matched GH-only controls.

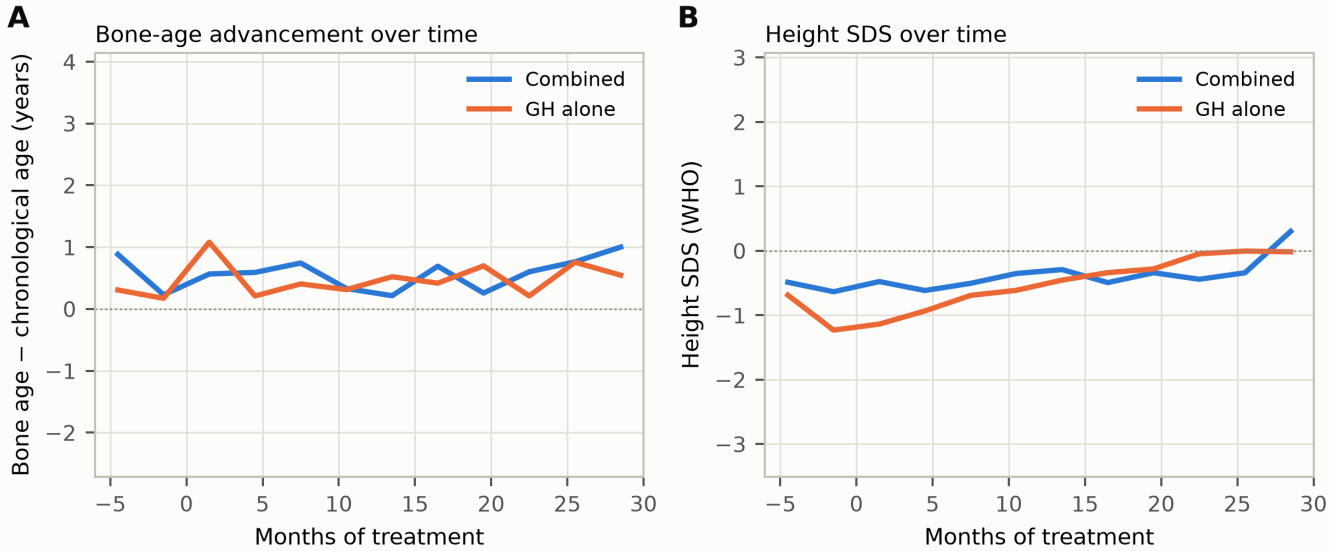
Fig. 3. Within-patient changes at GnRHa initiation (interrupted time series, n = 9). Paired values for (A) bone-age progression slope and (B) height velocity before (GH monotherapy) and after (combined treatment) GnRHa initiation; thick black lines connect medians. *p* values from paired Wilcoxon tests.

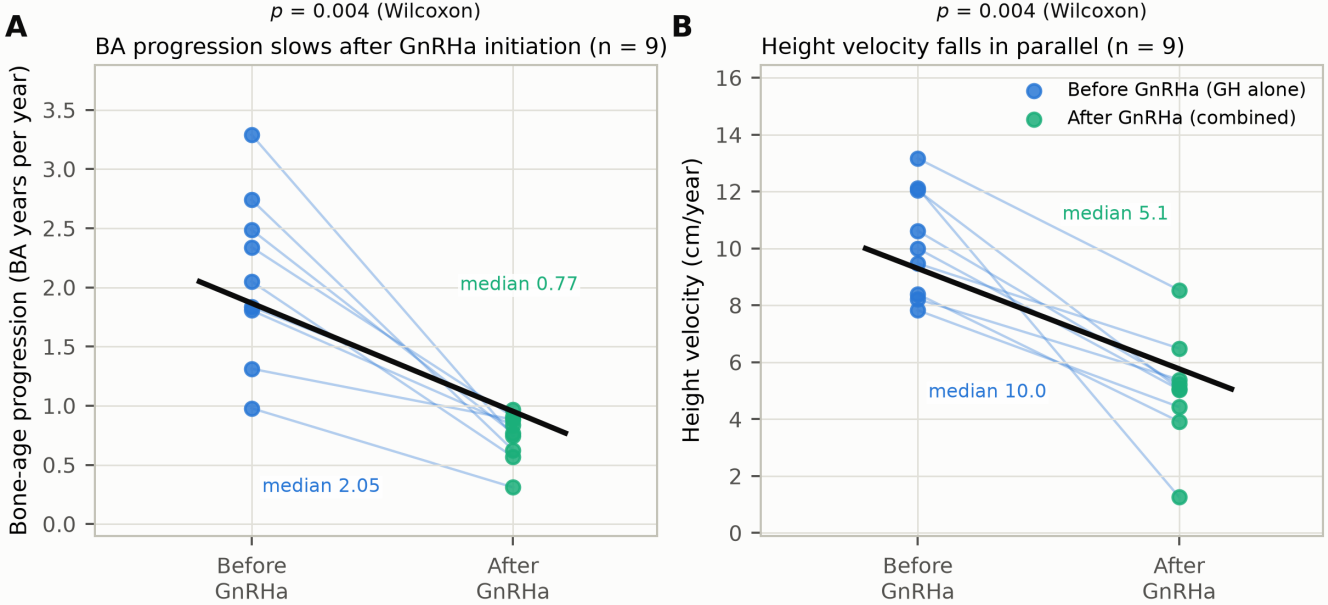
Fig. 4. Dose–response between achieved bone-age suppression and concurrent height gain within the combined cohort at years 1 and 2. Scatter plots of ΔHtSDS against first-year (A) and second-year (B) Δ(BA−CA); solid lines are adjusted regression slopes (β = +0.38 and +0.69 SDS per BA−CA year).

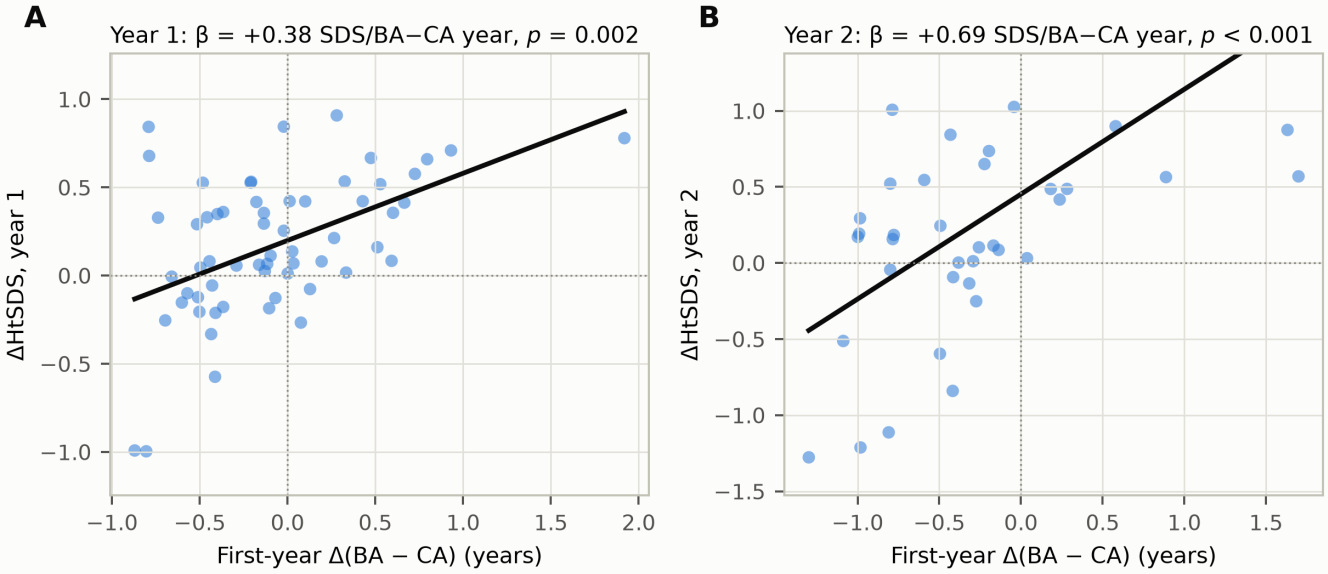
Fig. 5. Near-adult height settlement. (A) Total height-SDS change from baseline to near-adult height for 16 combined and 8 GH-only children; horizontal lines mark medians. (B) Within the combined cohort, the steep year-1 dose–response between first-year Δ(BA−CA) and year-1 height-SDS gain (grey, n = 60; β = +0.38) is absent when the same children are judged at near-adult height (blue, n = 13; β = +0.02). (C) Median height-SDS trajectories from treatment start to near-adult height, showing converging outcomes from different baselines.

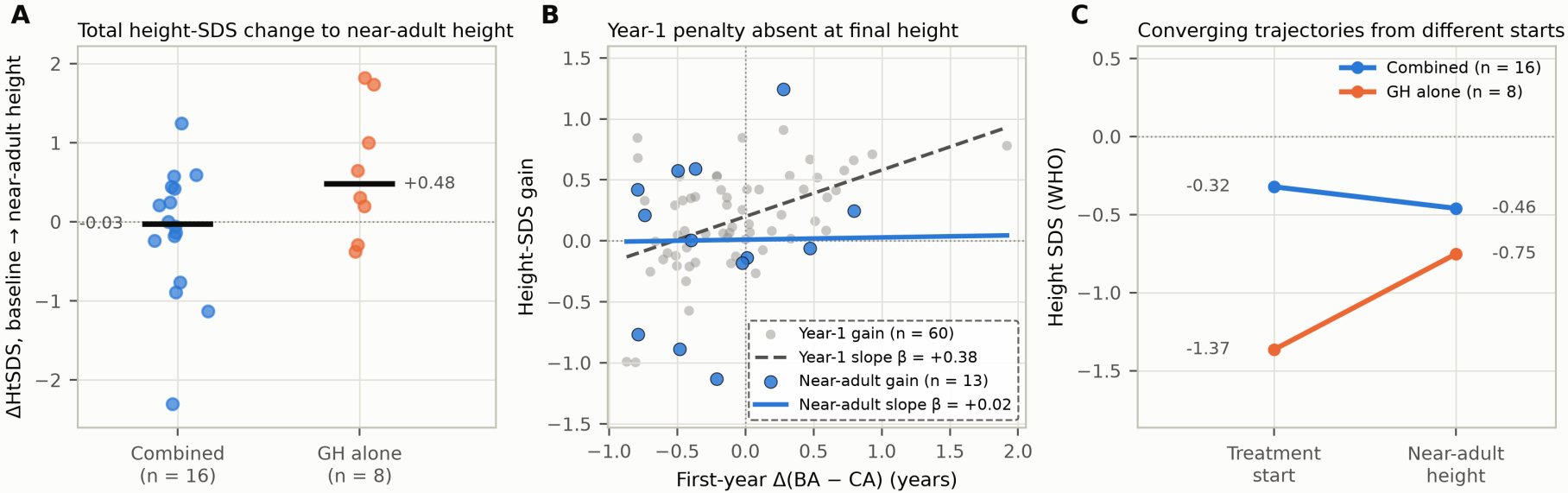
Fig. 6. Predicted adult height audit and settlement. (A) Baseline Bayley–Pinneau PAH versus achieved near-adult height for 16 combined and 8 GH-only children; the dashed line marks identity, and points above it indicate height gained relative to prediction. (B) PAH gain (near-adult height minus baseline PAH) by group; thick black lines mark medians (+5.5 vs. +5.7 cm, $p = 0.79$).

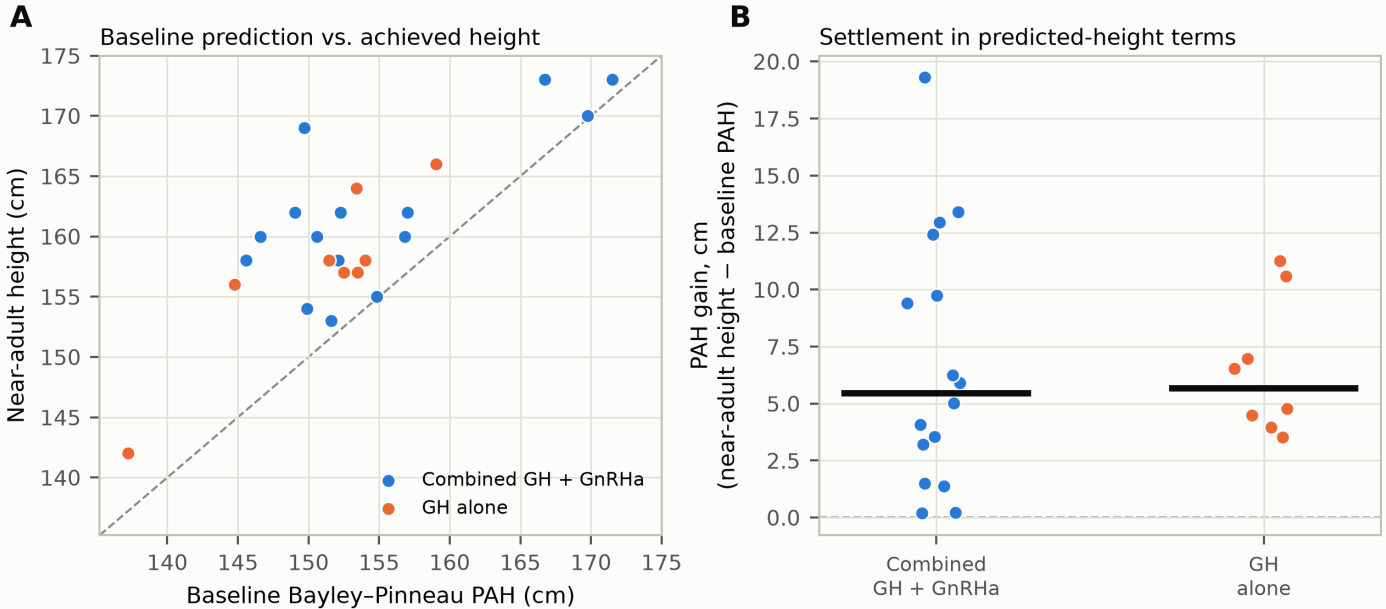

Net effect of GnRHa co-treatment: years 1–2 and near-adult height
Δ(BA−CA), year 1
Δ(BA−CA), year 2
ΔHtSDS, year 1
ΔHtSDS, year 2
Height velocity
ΔHtSDS, baseline → near-adult
−1.25
−1.00
−0.75
−0.50
−0.25
0.00
0.25
Adjusted difference, combined − GH alone (95% CI)


A
Bone-age advancement over time
Bone age − chronological age (years)
Combined
GH alone
Months of treatment
B
Height SDS over time
Height SDS (WHO)
Combined
GH alone
Months of treatment


A
p = 0.004 (Wilcoxon)
BA progression slows after GnRHa initiation (n = 9)
Bone-age progression (BA years per year)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
median 0.77
median 2.05
Before GnRHa
After GnRHa
B
p = 0.004 (Wilcoxon)
Height velocity falls in parallel (n = 9)
Height velocity (cm/year)
16
14
12
10
8
6
4
2
0
Before GnRHa (GH alone)
After GnRHa (combined)
median 5.1
median 10.0
Before GnRHa
After GnRHa


A
Year 1: β = +0.38 SDS/BA−CA year, p = 0.002
ΔHtSDS, year 1
First-year Δ(BA − CA) (years)
B
Year 2: β = +0.69 SDS/BA−CA year, p < 0.001
ΔHtSDS, year 2
First-year Δ(BA − CA) (years)


A
Total height-SDS change to near-adult height
ΔHtSDS, baseline → near-adult height
2
1
0
−1
−2
-0.03
+0.48
Combined
(n = 16)
GH alone
(n = 8)
B
Year-1 penalty absent at final height
Height-SDS gain
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0
First-year Δ(BA − CA) (years)
Year-1 gain (n = 60)
Year-1 slope β = +0.38
Near-adult gain (n = 13)
Near-adult slope β = +0.02
C
Converging trajectories from different starts
Height SDS (WHO)
0.5
0.0
−0.5
−1.0
−1.5
Combined (n = 16)
GH alone (n = 8)
-0.32
-0.46
-1.37
-0.75
Treatment
start
Near-adult
height


A
Baseline prediction vs. achieved height
Near-adult height (cm)
Baseline Bayley–Pinneau PAH (cm)
Combined GH + GnRHa
GH alone
B
Settlement in predicted-height terms
PAH gain, cm
(near-adult height − baseline PAH)
Combined
GH + GnRHa
GH
alone

Supplementary Files

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- SupplementaryMaterialIJOP.docx