## Supplementary

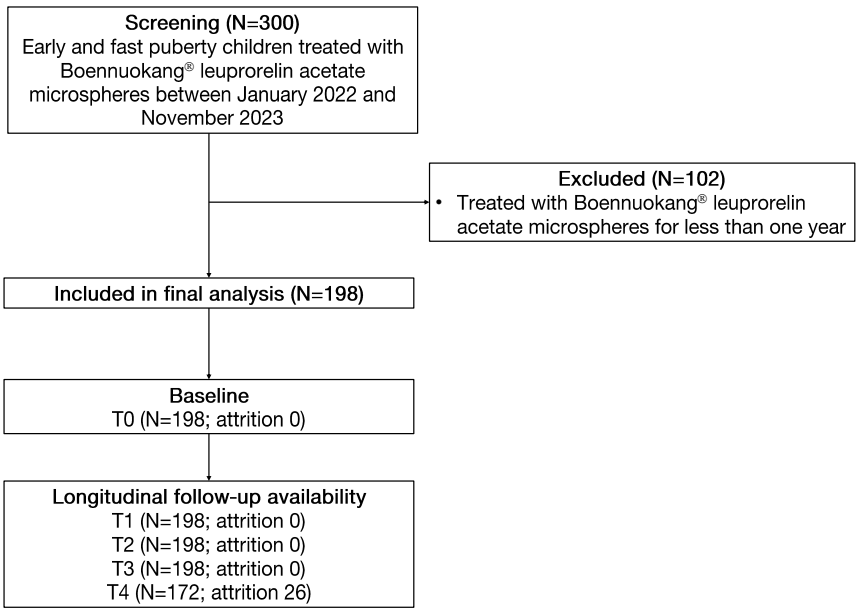


**Figure S1** Study flow.

**Table S1** Number of children with available data at each time point across variables

| Items | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|
| LH | 198 | 198 | 198 | 198 | 170 |
| FSH | 198 | 198 | 197 | 198 | 170 |
| Estradiol | 198 | 198 | 198 | 198 | 172 |
| PAH | 198 | 198 | 193 | 198 | 170 |
| GTH minus PAH | 198 | 198 | 193 | 198 | 170 |
| BMI | 198 | 198 | 198 | 198 | 170 |
| BA/CA ratio | 198 | – | 195 | 198 | 170 |
| Growth velocity | 198 | – | 198 | 198 | 170 |
| Tanner stage | 198 | 198 | 198 | 198 | 168 |
| Length of uterus change | 198 | – | 195 | 195 | 167 |

T0, before the first administration; T1, 3 months after the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMI, body mass index; BA, bone age; CA, chronological age; B, breast; PAH, predicted adult height; GTH, genetic target height.


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**Table S2** LH, FSH, and estradiol change over time in different age stratification

| Time point | ≥8–<9 years (n=20) | | ≥9–<11 years (n=127) | | ≥11 years (n=51) | | P value[$] |
|---|---|---|---|---|---|---|---|
| | Median (IQR) | P value* | Median (IQR) | P value* | Median (IQR) | P value* | |
| LH (mIU/mL) | | | | | | | |
| T0 | 2.59 (1.80–4.92) | – | 2.80 (2.23–3.51) | – | 2.52 (2.26–3.51) | – | 0.913 |
| T1 | 0.71 (0.59–1.55) | <0.001 | 0.87 (0.63–1.65) | <0.001 | 0.84 (0.61–1.50) | <0.001 | 0.893 |
| T2 | 0.74 (0.51–1.45) | <0.001 | 0.72 (0.51–1.21) | <0.001 | 0.75 (0.51–1.16) | <0.001 | 0.810 |
| T3 | 0.91 (0.66–1.40) | <0.001 | 0.65 (0.45–1.32) | <0.001 | 0.76 (0.52–1.12) | <0.001 | 0.082 |
| T4 | 0.76 (0.66–1.53) | <0.001 | 0.65 (0.45–1.33) | <0.001 | 0.66 (0.51–1.05) | <0.001 | 0.124 |
| P value[#] | <0.001 | | <0.001 | | <0.001 | | |
| FSH (mIU/mL) | | | | | | | |
| T0 | 5.84 (5.12–6.54) | – | 5.33 (5.11–6.09) | – | 5.11 (4.71–5.64) | – | <0.001 |
| T1 | 2.25 (1.85–4.67) | <0.001 | 2.81 (1.89–3.75) | <0.001 | 2.89 (2.33–3.51) | <0.001 | 0.696 |
| T2 | 2.13 (1.63–2.95) | <0.001 | 2.11 (1.52–2.65) | <0.001 | 2.21 (1.87–2.76) | <0.001 | 0.120 |
| T3 | 2.12 (1.55–2.84) | <0.001 | 2.12 (1.51–2.61) | <0.001 | 2.13 (1.67–2.45) | <0.001 | 0.652 |
| T4 | 2.28 (1.63–2.64) | <0.001 | 1.96 (1.56–2.37) | <0.001 | 2.16 (1.57–2.41) | <0.001 | 0.260 |
| P value[#] | <0.001 | | <0.001 | | <0.001 | | |
| Estradiol (pmol/L) | | | | | | | |
| T0 | 193.00 (138.00–250.75) | – | 146.00 (121.00–194.00) | – | 166.00 (132.00–180.00) | – | 0.045 |
| T1 | 38.20 (36.70–57.65) | <0.001 | 44.00 (36.70–70.00) | <0.001 | 44.00 (36.70–71.00) | <0.001 | 0.528 |
| T2 | 36.70 (36.70–40.68) | <0.001 | 36.70 (36.70–42.10) | <0.001 | 36.70 (36.70–40.00) | <0.001 | 0.845 |
| T3 | 36.70 (36.70–36.70) | <0.001 | 36.70 (36.70–36.70) | <0.001 | 36.70 (36.70–36.70) | <0.001 | 0.453 |
| T4 | 36.70 (36.70–36.70) | <0.001 | 36.70 (36.70–36.70) | <0.001 | 36.70 (36.70–36.70) | <0.001 | 0.263 |
| P value[#] | <0.001 | | <0.001 | | <0.001 | | |

Specific statement: P value* was determined via a Wilcoxon signed-rank test, which compared each individual time point with T0. P value[#] was determined via the Friedman test, which compared the LH, FSH, and estradiol at T0 to T4 over time. P value [$] was determined via the Kruskal-Wallis test, which compared the LH, FSH, and estradiol among three groups at T0 to T4. LH, luteinizing hormone; FSH, follicle-stimulating hormone; IQR, interquartile range; T0, before the first administration; T1, 3 months after the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration.


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**Table S3** Tanner stage (breast) change over time in different age stratification

| Time point | ≥8–<9 years (n=20) | | | | | | ≥9–<11 years (n=127) | | | | | | ≥11 years (n=51) | | | | | | P value [$] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tanner stage, n (%) | | | | | P value* | Tanner stage, n (%) | | | | | P value* | Tanner stage, n (%) | | | | | P value* | |
| | B1 | B2 | B3 | B4 | B5 | | B1 | B2 | B3 | B4 | B5 | | B1 | B2 | B3 | B4 | B5 | | |
| T0 | 0 (0.00) | 1 (5.00) | 5 (25.00) | 8 (40.00) | 6 (30.00) | – | 0 (0.00) | 4 (3.15) | 25 (19.69) | 81 (63.78) | 17 (13.39) | – | 0 (0.00) | 0 (0.00) | 13 (25.49) | 24 (47.06) | 14 (27.45) | – | 0.526 |
| T1 | 0 (0.00) | 0 (0.00) | 4 (20.00) | 13 (65.00) | 3 (15.00) | <0.001 | 0 (0.00) | 5 (3.94) | 24 (18.90) | 91 (71.65) | 7 (5.51) | <0.001 | 0 (0.00) | 0 (0.00) | 10 (19.61) | 30 (58.82) | 11 (21.57) | <0.001 | 0.106 |
| T2 | 0 (0.00) | 0 (0.00) | 6 (30.00) | 11 (55.00) | 3 (15.00) | 0.480 | 1 (0.79) | 3 (2.36) | 37 (29.13) | 76 (59.84) | 10 (7.87) | <0.001 | 0 (0.00) | 0 (0.00) | 9 (17.65) | 34 (66.67) | 8 (15.69) | 0.593 | 0.067 |
| T3 | 0 (0.00) | 1 (5.00) | 4 (20.00) | 12 (60.00) | 3 (15.00) | 0.480 | 0 (0.00) | 3 (2.36) | 33 (25.98) | 85 (66.93) | 6 (4.72) | 0.004 | 0 (0.00) | 0 (0.00) | 9 (17.65) | 35 (68.63) | 7 (13.73) | 0.366 | 0.094 |
| T4 | 0 (0.00) | 0 (0.00) | 4 (20.00) | 9 (45.00) | 3 (15.00) | 0.480 | 0 (0.00) | 3 (2.36) | 32 (25.20) | 66 (51.97) | 8 (6.30) | 0.021 | 0 (0.00) | 0 (0.00) | 10 (19.61) | 26 (50.98) | 7 (13.73) | 0.257 | 0.187 |
| P value[#] | | | 0.473 | | | | | | <0.001 | | | | | | 0.513 | | | | |

Specific statement: P value* was determined via a Wilcoxon signed-rank test, which compared each individual time point with T0. P value[#] was determined via the Friedman test, which compared the Tanner stage (breast) at T0 to T4 over time. P value [$] was determined via the Kruskal-Wallis test, which compared the Tanner stage (breast) among three groups at T0 to T4. B, breast; T0, before the first administration; T1, 3 months after the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration.


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**Table S4** Length of uterus change over time in different age stratification

| Time point | ≥8–<9 years (n=20) | | ≥9–<11 years (n=127) | | ≥11 years (n=51) | | P value [$] |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | P value* | Mean ± SD | P value* | Mean ± SD | P value* | |
| T0 | 35.40±8.07 | – | 31.77±6.16 | – | 31.13±6.56 | – | 0.039 |
| T2 | 22.18±4.35 | <0.001 | 21.43±4.02 | <0.001 | 21.32±4.84 | <0.001 | 0.733 |
| T3 | 20.06±3.91 | <0.001 | 20.03±3.65 | <0.001 | 19.27±3.84 | <0.001 | 0.459 |
| T4 | 18.73±3.29 | <0.001 | 18.88±3.33 | <0.001 | 18.35±3.98 | <0.001 | 0.705 |
| P value[#] | <0.001 | | <0.001 | | <0.001 | | |

Specific statement: P value* was determined via a paired t-test, which compared each individual time point with T0. P value[#] was determined via the repeated-measure ANOVA, which compared the Length of uterus at T0 to T4 over time. P value [$] was determined via the ANOVA, which compared the Length of uterus among three groups at T0 to T4. SD, standard deviation; T0, before the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration.


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**Table S5** BA, BA/CA ratio, PAH, and loss in growth potential (GTH minus PAH) change over time in different age stratification

| Time point | ≥8–<9 years (n=20) | | ≥9–<11 years (n=127) | | ≥11 years (n=51) | | P value[ic] |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | P value* | Mean ± SD | P value* | Mean ± SD | P value* | |
| BA (years) | | | | | | | |
| T0 | 11.50±1.19 | – | 12.00±0.76 | – | 12.53±0.56 | – | <0.001 |
| T2 | 11.58±1.21 | 0.163 | 12.06±0.78 | 0.069 | 12.50±0.55 | 0.533 | <0.001 |
| T3 | 11.92±1.08 | <0.001 | 12.35±0.74 | <0.001 | 12.73±0.50 | <0.001 | <0.001 |
| T4 | 12.41±0.90 | <0.001 | 12.71±0.68 | <0.001 | 13.03±0.52 | <0.001 | 0.002 |
| P value# | <0.001 | | <0.001 | | <0.001 | | |
| BA/CA ratio | | | | | | | |
| T0 | 1.44±0.15 | – | 1.27±0.10 | – | 1.14±0.05 | – | <0.001 |
| T2 | 1.45±0.15 | 0.163 | 1.28±0.10 | 0.086 | 1.13±0.05 | 0.533 | <0.001 |
| T3 | 1.33±0.12 | <0.001 | 1.18±0.08 | <0.001 | 1.06±0.04 | <0.001 | <0.001 |
| T4 | 1.38±0.10 | 0.001 | 1.22±0.08 | <0.001 | 1.08±0.04 | <0.001 | <0.001 |
| P value# | <0.001 | | <0.001 | | <0.001 | | |
| PAH (cm) | | | | | | | |
| T0 | 150.10±5.59 | – | 151.29±3.96 | – | 151.78±2.90 | – | 0.271 |
| T1 | 152.05±4.97 | 0.002 | 153.00±3.36 | <0.001 | 153.55±2.41 | <0.001 | 0.232 |
| T2 | 152.84±4.97 | <0.001 | 154.08±3.23 | <0.001 | 154.73±2.65 | <0.001 | 0.109 |
| T3 | 154.35±4.40 | <0.001 | 155.76±3.34 | <0.001 | 156.45±2.85 | <0.001 | 0.059 |
| T4 | 154.94±3.55 | <0.001 | 157.59±3.39 | <0.001 | 157.70±2.74 | <0.001 | 0.008 |
| P value# | <0.001 | | <0.001 | | <0.001 | | |
| Loss in growth potential (GTH minus PAH) (cm) | | | | | | | |
| T0 | 6.15±5.27 | – | 6.78±4.46 | – | 5.80±6.04 | – | 0.482 |
| T1 | 4.20±4.58 | 0.002 | 5.07±4.48 | <0.001 | 4.03±5.54 | <0.001 | 0.376 |
| T2 | 3.53±4.80 | <0.001 | 4.00±4.48 | <0.001 | 2.84±5.82 | <0.001 | 0.377 |
| T3 | 1.90±4.82 | <0.001 | 2.31±4.44 | <0.001 | 1.13±5.86 | <0.001 | 0.344 |
| T4 | 2.37±4.82 | 0.035 | –0.54±5.94 | <0.001 | 1.59±3.00 | <0.001 | 0.019 |
| P value# | 0.029 | | <0.001 | | <0.001 | | |

Specific statement: P value* was determined via a paired t-test, which compared each individual time point with T0. P value# was determined via the repeated-measure ANOVA, which compared the BA, BA/CA ratio, PAH, and loss in growth potential (GTH minus PAH) at T0 to T4 over time. P value[ic] was determined via the ANOVA, which compared the BA, BA/CA ratio, PAH, and loss in growth potential (GTH minus PAH) among three groups at T0 to T4. BA, bone age; CA, chronological age; PAH, predicted adult height; GTH, genetic target height; SD, standard deviation; T0, before the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration; T1, 3 months after the first administration.


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**Table S6** LH, FSH, and estradiol change over time in children giving a day–15 booster dose

| Time point | Median (IQR) | P value* |
|---|---|---|
| LH (mIU/mL) | | |
| T0 | 2.41 (2.17–3.51) | – |
| T1 | 0.62 (0.53–0.87) | <0.001 |
| T2 | 0.55 (0.45–0.95) | <0.001 |
| T3 | 0.62 (0.42–0.91) | <0.001 |
| T4 | 0.56 (0.45–0.76) | <0.001 |
| P value# | <0.001 | |
| FSH (mIU/mL) | | |
| T0 | 5.27 (5.12–5.54) | – |
| T1 | 2.28 (1.83–3.33) | <0.001 |
| T2 | 2.05 (1.47–2.23) | <0.001 |
| T3 | 0.62 (0.42–0.91) | <0.001 |
| T4 | 0.56 (0.45–0.76) | <0.001 |
| P value# | <0.001 | |
| Estradiol (pmol/L) | | |
| T0 | 166.00 (145.50–220.50) | – |
| T1 | 36.70 (36.70–43.00) | <0.001 |
| T2 | 36.70 (36.70–38.85) | <0.001 |
| T3 | 36.70 (36.70–36.70) | <0.001 |
| T4 | 36.70 (36.70–36.70) | <0.001 |
| P value# | <0.001 | |

Specific statement: P value* was determined via a Wilcoxon signed-rank test, which compared each individual time point with T0. P value# was determined via the Friedman test, which compared the LH, FSH, and estradiol at T0 to T4 over time. LH, luteinizing hormone; FSH, follicle-stimulating hormone; IQR, interquartile range; T0, before the first administration; T1, 3 months after the first administration; T2, 6 months after the first administration; T3, 12 months after the first administration; T4, 18 months after the first administration.


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