**Supplementary Tables:**

**Table 1. Study visit schedule**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Screening** | **1st infusion** | **3 months** | **6 months** | **12 months** | **18 months** | **24 months** |
| **Visit no #** | **Visit 1** | **Visit 2\*** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** |
| **Length of visit** | **2.5 hrs** | **2 hrs** | **2 hrs** | **2 hrs** | **2.5 hrs** | **2 hrs** | **2.5 hrs** |
| Medical check-up | • | • | • | • | • | • | • |
| Dental check-up**\*** | • |  |  |  |  |  |  |
| Zoledronic acid infusion\*  |  | • | • | • | • | • |  |
| Blood test | • | • | • | • | • | • | • |
| DXA scan  | • |  |  |  | • |  | • |
| pQCT scan | • |  |  |  | • |  | • |
| Bone age x-ray | • |  |  |  | • |  | • |
| Lateral spine x-ray | • |  |  |  | • |  | • |
| Wong-Baker FACES pain scale | • | • | • | • | • | • | • |
| 6 minute walk test | • |  |  |  | • |  | • |

*\*Applicable to participants randomised to the active intervention arm (ZA) only*

**Table 2. Changes and percentage changes of DXA outcomes from baseline to 12 months and 24 months.**

|  |  |  |
| --- | --- | --- |
|  | **Control** | **ZA**  |
|  | **N=31** | **N=31** |
| **LSBMD Z score** |  |  |
| change at 12 months | -0.3 (0.73) | 0.8 (0.70) |
| change at 24 months | -0.6 (0.86) | 1.0 (1.14) |
| **Height adjusted LSBMD Z score** |  |
| change at 12 months | -0.1 (0.84) | 1.2 (0.71) |
| change at 24 months | -0.3 (1.05) | 1.1 (1.34) |
| **LSBMD** |  |  |
| %change at 12 months | 1.48 (10.12) | 20.04 (8.47) |
| %change at 24 months | 4.91 (11.18) | 31.22 (18.60) |
| **LSBMC** |  |  |
| %change at 12 months | 4.44 (8.28) | 25.15 (18.02) |
| %change at 24 months | 10.68 (13.70) | 39.45 (29.24) |
| **TBBMC** |  |  |
| %change at 12 months | 4.22 (18.75) | 13.40 (13.03) |
| %change at 24 months | 13.46 (19.44) | 28.98 (17.05) |

**Table 3. pQCT results of 4% and 65% radius at baseline, 12 months and 24 months, compared between arms.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  | **Mean differences (adjusted)** |
|  |  | **Control** | **ZA Intervention** | **MD adj****(ZA-control)** | **95% CI** | **p** |
| **4% Radius** |  |  |  |  |  |  |
| total BMC | Baseline  | 51.31 (11.76) | 52.06 (16.89) |  |  |  |
| (mg/mm) | 12 months | 55.97 (14.46) | 77.60 (35.95) | 19.87 | (5.14 ; 34.60) |  0.008 |
|  | 24 months | 54.44 (12.30) | 86.07 (35.51) | 27.80 | (13.20 ; 42.41) |  <0.001 |
| total BMC  | Baseline  | -1.95 (1.34) | -1.77 (1.93) |  |  |  |
| Z score | 12 months | -1.99 (2.01) | -0.26 (2.74) |  1.34 | (0.22 ; 2.45) |  0.019 |
|  | 24 months | -2.41 (1.58) | -0.30 (3.20) |  2.08 | (1.00 ; 3.17) |  <0.001 |
| trab vBMD | Baseline  | 143.33 (35.24) | 174.36 (64.39) |  |  |  |
| (mg/cm3) | 12 months | 157.90 (62.96) | 237.97 (115.72) | 63.47 | (13.00 ; 113.94) |  0.014 |
|  | 24 months | 138.31 (46.64) | 272.23 (152.08) | 85.89 | (28.71 ; 143.08) |  0.003 |
| trab vBMD Z | Baseline  | -2.7 (2.13) | -1.3 (2.38) |  |  |  |
|  | 12 months | -2.5 (3.27) | 0.5 (3.53) |  2.1 | (0.38 ; 3.74) |  0.017 |
|  | 24 months | -3.3 (3.04) | 0.9 (4.77) |  2.8 | (0.77 ; 4.83) |  0.007 |
| **65% Radius** |  |  |  |  |  |  |
| cort BMC | Baseline  | 39.50 (9.87) | 38.43 (11.19) |  |  |  |
| (mg/mm) | 12 months | 39.10 (11.87) | 47.31 (12.52) |  4.84 | (-0.24 ; 9.91) |  0.062 |
|  | 24 months | 46.00 (11.76) | 44.05 (11.81) |  0.50 | (-7.61 ; 8.61) |  0.903 |
| cort BMC  | Baseline  | -3.9 (1.60) | -3.9 (2.51) |  |  |  |
| Z score | 12 months | -4.2 (1.76) | -3.1 (1.90) |  0.8 | (-0.04 ; 1.56) |  0.063 |
|  | 24 months | -3.6 (1.84) | -4.0 (3.71) | -0.2 | (-2.04 ; 1.70) |  0.860 |
| cort thickness | Baseline  | 1.60 (0.32) | 1.61 (0.34) |  |  |  |
| (mm) | 12 months | 1.61 (0.35) | 1.91 (0.46) |  0.10 | (-0.05 ; 0.25) |  0.200 |
|  | 24 months | 1.81 (0.37) | 1.81 (0.41) |  0.07 | (-0.18 ; 0.32) |  0.579 |
| cort thickness  | Baseline  | -0.8 (1.19) | -0.6 (1.44) |  |  |  |
| Z score | 12 months | -1.0 (1.38) | -0.0 (1.35) |  0.3 | (-0.19 ; 0.79) |  0.229 |
|  | 24 months | -0.6 (1.32) | -0.6 (1.77) |  0.1 | (-0.89 ; 1.02) |  0.895 |
| cort CSA | Baseline  | 40.19 (9.76) | 36.71 (9.30) |  |  |  |
| (mm2) | 12 months | 38.74 (9.94) | 44.50 (10.65) |  5.53 | (1.42 ; 9.64) |  0.008 |
|  | 24 months | 43.44 (8.61) | 41.73 (10.08) |  1.16 | (-6.05 ; 8.36) |  0.753 |
| cort CSA  | Baseline  | -1.7 (1.13) | -2.0 (1.56) |  |  |  |
| Z score | 12 months | -2.2 (1.13) | -1.3 (1.27) |  0.7 | ( 0.17 ; 1.14) |  0.008 |
|  | 24 months | -2.0 (1.35) | -2.1 (2.47) |  0.2 | (-1.06 ; 1.41) |  0.784 |
| total CSA | Baseline  | 74.30 (22.93) | 62.84 (15.06) |  |  |  |
| (mm2) | 12 months | 70.38 (23.77) | 70.44 (14.52) |  7.59 | ( 0.65 ; 14.52) |  0.032 |
|  | 24 months | 72.43 (16.61) | 66.83 (14.22) |  1.25 | (-8.83 ; 11.34) |  0.807 |
| total CSA  | Baseline  | -1.9 (1.44) | -2.5 (1.31) |  |  |  |
| Z score | 12 months | -2.5 (1.49) | -2.2 (1.16) |  0.6 | ( 0.04 ; 1.23) |  0.035 |
|  | 24 months | -2.5 (1.41) | -2.7 (2.16) |  0.0 | (-0.97 ; 1.02) |  0.964 |
| pSSI Z score | Baseline  | -2.51 (1.33) | -2.62 (1.37) |  |  |  |
|  | 12 months | -2.95 (1.24) | -2.38 (1.16) |  0.25 | (-0.08 ; 0.57) |  0.135 |
|  | 24 months | -3.23 (1.42) | -2.66 (1.58) |  0.35 | (-0.15 ; 0.85) |  0.174 |
| cort vBMD | Baseline  | 985.9 (98.36) | 1039.7 (71.81) |  |  |  |
| (mg/cm3) | 12 months | 1003.7 (117.26) | 1058.9 (78.61) | -4.7 | (-53.00 ; 43.64) |  0.849 |
|  | 24 months | 1054.6 (132.46) | 1052.3 (83.33) | -16.0 | (-71.51 ; 39.49) |  0.572 |
| cort vBMD  | Baseline  | -1.0 (3.02) | 0.7 (1.72) |  |  |  |
| Z score | 12 months | -0.6 (3.63) | 0.9 (2.12) | -0.3 | (-1.62 ; 1.05) |  0.676 |
|  | 24 months | 0.6 (4.22) | 0.5 (2.21) | -0.5 | (-2.18 ; 1.14) |  0.540 |
| total vBMD | Baseline  | 621.04 (143.57) | 689.95 (121.58) |  |  |  |
| (mg/cm3) | 12 months | 659.76 (172.39) | 751.38 (156.97) | -43.94 | (-95.55 ; 7.67) |  0.095 |
|  | 24 months | 720.80 (171.84) | 733.74 (141.12) |  0.48 | (-64.50 ; 65.46) |  0.988 |
| total vBMD Z score | Baseline  | 0.1 (2.42) | 1.2 (1.94) |  |  |  |
| 12 months | 0.4 (2.94) | 1.7 (2.19) | -0.3 | (-1.27 ; 0.67) |  0.546 |
| 24 months | 1.2 (2.89) | 1.4 (1.72) |  0.1 | (-1.09 ; 1.23) |  0.905 |

4% radius data available in control arm: baseline 18 boys, 12 months 20 boys, 24 months 13 boys; in ZA intervention arm: 19, 19, 23 , respectively. 65% radius data available in control arm: baseline 17 boys, 12 months 16 boys, 24 months 10 boys; in ZA intervention arm: 16, 20, 14 , respectively. BMC: bone mineral content; vBMD: volumetric bone mineral density; CSA: cross-sectional area; Z: Z score; Trab: trabecular; cort: cortical; prop: proportion; pSSI: polar stress strain index; endo: endosteal; peri: periosteal; circ: circumference.

Notes: Group comparisons estimated using a mixed model applied to data from all 3 time points simultaneously adjusted for age and site of recruitment

**Table 4. pQCT results of 4% and 66% tibia at baseline, 12 months and 24 months, compared between arms**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  | **mixed model (adjusted)** |
|  |  | **Control** | **ZA Intervention** | **MD (ZA-control)** | **95% CI** | **p** |
| **4% Tibia** |  |  |  |  |  |  |
| total BMC | Baseline  | 134.12 (35.25) | 137.13 (37.14) |  |  |  |
| (mg/mm) | 12 months | 147.37 (36.03) | 206.83 (76.71) | 54.61 | (25.39 ; 83.83) |  <0.001 |
|  | 24 months | 151.95 (40.53) | 175.43 (72.37) | 27.64 | (-6.55 ; 61.83) |  0.113 |
| trab vBMD | Baseline  | 158.69 (46.68) | 172.74 (50.97) |  |  |  |
| (mg/cm3) | 12 months | 170.15 (66.96) | 265.31 (125.28) | 78.64 | (27.42 ; 129.86) |  0.003 |
|  | 24 months | 179.45 (76.64) | 201.10 (128.76) | 26.50 | (-32.94 ; 85.95) |  0.382 |
| trab vBMD  | Baseline  | -1.8 (0.93) | -1.5 (1.01) |  |  |  |
| Z score | 12 months | -1.6 (1.34) | 0.3 (2.46) |  1.5 | (0.54 ; 2.54) |  0.003 |
|  | 24 months | -1.4 (1.55) | -1.0 (2.53) |  0.5 | (-0.62 ; 1.68) |  0.370 |
| **66% Tibia** |  |  |  |  |  |  |
| cort BMC  | Baseline  | 119.22 (38.30) | 122.96 (30.65) |  |  |  |
| (mg/mm) | 12 months | 131.59 (30.62) | 131.33 (29.60) |  7.71 | (-0.42 ; 15.85) |  0.063 |
|  | 24 months | 129.22 (32.24) | 140.49 (36.45) | 13.19 | (1.64 ; 24.73) |  0.025 |
| cort BMC  | Baseline  | -2.9 (2.07) | -2.8 (2.78) |  |  |  |
| Z score | 12 months | -3.8 (2.88) | -3.0 (2.74) |  0.3 | (-0.25 ; 0.83) |  0.290 |
|  | 24 months | -4.0 (2.79) | -4.1 (3.29) |  0.5 | (-0.26 ; 1.23) |  0.202 |
| cort thickness | Baseline  | 2.45 (0.80) | 2.64 (0.62) |  |  |  |
| (mm) | 12 months | 2.68 (0.69) | 2.62 (0.57) |  0.12 | (-0.04 ; 0.28) |  0.132 |
|  | 24 months | 2.67 (0.63) | 2.82 (0.76) |  0.17 | (-0.10 ; 0.44) |  0.218 |
| cort thickness  | Baseline  | -1.3 (1.29) | -0.9 (1.19) |  |  |  |
| Z score | 12 months | -1.4 (1.58) | -1.2 (1.28) |  0.1 | (-0.24 ; 0.45) |  0.560 |
|  | 24 months | -1.5 (1.35) | -1.4 (1.57) |  0.1 | (-0.36 ; 0.60) |  0.623 |
| cort CSA | Baseline  | 107.29 (30.50) | 111.51 (26.60) |  |  |  |
| (mm2) | 12 months | 116.85 (25.29) | 117.45 (25.22) |  4.68 | (-1.94 ; 11.31) |  0.166 |
|  | 24 months | 115.78 (24.68) | 124.62 (32.07) |  8.07 | (-1.10 ; 17.24) |  0.084 |
| cort CSA  | Baseline  | -3.7 (2.23) | -3.5 (2.94) |  |  |  |
| Z score | 12 months | -4.7 (2.94) | -3.8 (2.75) |  0.2 | (-0.26 ; 0.67) |  0.391 |
|  | 24 months | -4.8 (2.83) | -4.9 (3.26) |  0.4 | (-0.32 ; 1.08) |  0.286 |
| total CSA | Baseline  | 230.46 (70.65) | 207.53 (40.32) |  |  |  |
| (mm2) | 12 months | 226.77 (49.67) | 230.74 (55.70) |  3.99 | (-7.74 ; 15.72) |  0.505 |
|  | 24 months | 225.13 (59.21) | 231.03 (54.24) | 16.39 | (-6.57 ; 39.35) |  0.162 |
| total CSA  | Baseline  | -3.5 (2.98) | -3.9 (2.81) |  |  |  |
| Z score | 12 months | -4.9 (2.59) | -3.8 (2.31) |  0.2 | (-0.16 ; 0.61) |  0.251 |
|  | 24 months | -4.9 (2.98) | -5.1 (2.65) |  0.5 | (-0.27 ; 1.17) |  0.221 |
| pSSI  | Baseline  | -2.9 (2.53) | -3.19 (3.32) |  |  |  |
| Z score | 12 months | -4.4 (3.20) | -3.21 (3.05) |  0.2 | (-0.17 ; 0.63) |  0.255 |
|  | 24 months | -4.5 (3.48) | -4.88 (3.65) |  0.5 | (-0.14 ; 1.17) |  0.126 |
| cort vBMD | Baseline  | 1094.98 (81.64) | 1099.65 (45.33) |  |  |  |
| (mg/cm3) | 12 months | 1122.32 (37.72) | 1116.49 (48.96) | 15.36 | (-0.83 ; 31.55) |  0.063 |
|  | 24 months | 1107.06 (69.74) | 1126.95 (44.81) | 28.13 | (-1.77 ; 58.03) |  0.065 |
| cort vBMD  | Baseline  | 2.4 (2.08) | 2.47 (1.06) |  |  |  |
| Z score | 12 months | 2.9 (1.02) | 2.72 (1.29) |  0.3 | (-0.13 ; 0.73) |  0.176 |
|  | 24 months | 2.4 (1.72) | 2.68 (1.17) |  0.6 | (-0.21 ; 1.34) |  0.153 |
| total vBMD | Baseline  | 620.12 (147.52) | 660.59 (113.75) |  |  |  |
| (mg/cm3) | 12 months | 660.71 (151.10) | 640.81 (114.98) | 20.74 | (-9.00 ; 50.48) |  0.172 |
|  | 24 months | 660.08 (148.96) | 666.32 (129.09) |  5.90 | (-51.39 ; 63.18) |  0.840 |

4% tibia data available in control arm: baseline 25 boys, 12 months 27 boys, 24 months 18 boys; in ZA intervention arm: 24, 20, 18, respectively. 66% tibia data available in control arm: baseline 25 boys, 12 months 24 boys, 24 months 18 boys; in ZA intervention arm: 22, 21, 19, respectively. BMC: bone mineral content; vBMD: volumetric bone mineral density; CSA: cross-sectional area; Z: Z score; Trab: trabecular; cort: cortical; prop: proportion; pSSI: polar stress strain index; endo: endosteal; peri: periosteal; circ: circumference.

Notes: Group comparisons estimated using a mixed model applied to data from all 3 time points simultaneously adjusted for age and site of recruitment

**Table 5. Blood test results at baseline, 12 months and 24 months (results expressed as mean (SD), n). Also, mean differences (MD) of changes of blood test results from baseline at 12 months and 24 months compared between arms using a mixed model analysis adjusted for age and site of recruitment.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Control** | **ZA Intervention** | **mixed model (adjusted)** |
|  |  | **N=31** | **N=31** | **MD (ZA-control)** | **95% CI** | **p** |
| **ALP** | Baseline  | 82.1 (17.8), 28 | 85.9 (24.8), 29 |  |  |  |
| **U/L** | 12 months | 76.3 (21.0), 28 | 74.2 (23.1), 27 | -5.37 | (-13.49 ; 2.76) |  0.195 |
|  | 24 months | 76.1 (28.7), 22 | 67.9 (20.7), 26 | -10.93 | (-23.62 ; 1.76) |  0.091 |
| **Calcium** | Baseline  | 2.42 (0.08), 30 | 2.41 (0.09), 30 |  |  |  |
| **mmol/L** | 12 months | 2.45 (0.13), 28 | 2.42 (0.11), 28 | -0.03 | (-0.09 ; 0.03) |  0.298 |
|  | 24 months | 2.45 (0.11), 23 | 2.47 (0.14), 26 |  0.02 | (-0.04 ; 0.09) |  0.445 |
| **PTH** | Baseline  | 2.70 (0.82), 26 | 3.04 (1.08), 28 |  |  |  |
| **pmol/L** | 12 months | 2.45 (0.96), 24 | 2.23 (0.91), 21 | -0.35 | (-0.84 ; 0.14) |  0.160 |
|  | 24 months | 2.62 (0.92), 21 | 2.72 (1.27), 25 | -0.06 | (-0.68 ; 0.56) |  0.846 |
| **25(OH)D**  | Baseline  | 61.7 (24.1), 30 | 54.1 (22.0), 31 |  |  |  |
| **nmol/L** | 12 months | 61.7 (17.7), 26 | 58.1 (15.8), 27 | -1.10 | (-9.88 ; 7.68) |  0.806 |
|  | 24 months | 65.6 (18.0), 22 | 58.1 (15.8), 25 | -3.29 | (-11.70 ; 5.11) |  0.442 |

ALP: Alkaline phosphatase. PTH: Parathyroid hormone. ZA: Zoledronic Acid. 25(OH)D: Vitamin D