# Supplemental methods

## Inclusion and exclusion criteria

The 29 participants in this study were recruited from the patient populations at 14 medical centers, and scanned at 13 HR-pQCT imaging sites in North America and Europe as part of the ASTEROID Phase 2b, multinational, randomized, double-blind, dose-finding study in adults with OI. Inclusion criteria included male and female patients with a clinical diagnosis of OI Type I, III or IV with a *COL1A1*/*COL1A2* defect confirmed by genetic testing, age greater than 18 years, and one or more non-traumatic long bone, rib, hand/feet and/or vertebral fracture(s) in the past five years. Female participants were ineligible if pregnant, breastfeeding, or following contraceptive guidance. Patients were ineligible to participate if they were greater than 75 years of age, or had a history of the following: skeletal malignancies/bone metastases; neural foraminal stenosis; uncontrolled diseases affecting bone metabolism; skeletal conditions leading to long bone deformities or increased fracture risk other than OI; bisphosphonate treatment 3 months prior to baseline; teriparatide, denosumab or other anabolic or anti-resorptive medication within 6 months prior to baseline; myocardial infarction, agina pectoris, ischaemic stroke, or transient ischaemic attack; alcohol or drug abuse in 12 months prior to dosing; significant psychiatric or medical disorder affecting compliance to study protocol; history of external radiation; participation in any clinical investigation within 4 weeks or 5 half-lives of the drug prior to dosing; or allergy to the study drug.

## Imaging

***Imaging phantoms****.* The quality control phantom (QC1, SCANCO Medical AG) consists of four cylinders with varying densities (approximately 800, 400, 200, 100 mgHA/ccm) embedded in water-equivalent resin (**Fig 1A**). The European Forearm Phantom (EFP, QRM GmbH) mimics the macroscopic morphology of the forearm with two hollow rods (**Fig 1B**). The rod, representing the radius has four bone mimicking (BM) sections, imitating cortical and trabecular bone macro-architecture through varying diameter (28.0, 19.8, 14.0, 10.0 mm), thickness (1.2, 0.6, 1.2, 2.5 mm), and density (corticalBM volumetric bone mineral density [vBMD]: 800 mgHA/ccm; trabecularBM vBMD: 200, 100, 50 mgHA/ccm, water-equivalent resin).

***Micro-computed tomography of the different EFP compartments*.** The EFP phantom was scanned with microcomputed tomography (µCT; SkyScan1276, Bruker, Kontich, Belgium) to investigate cortical and trabecular bone-mimic structural parameters. The following scanning parameters were used: isotropic voxel size of 10.6 µm, peak voltage of 100 kVp, Aluminium-Copper filter, source current of 100 µA, 0.3° rotational steps for full 360°, and frame averaging of 5. All EFP sections were binarized using a global threshold of 450 mgHA/cm3, the same threshold used in XCT2 scans. Measured outcome parameters included(24): volumetric BMD inside each trabecular bone mimicking region, Tb.vBMDBM (mgHA/cm3); trabecular area, Tb.ArBM (mm2); cortical thickness, Ct.ThBM (mm); cortical porosity, Ct.PoBM (mm3/ mm3); cortical area, Ct.ArBM (mm2); cortical perimeter, Ct.PmBM (mm); volumetric BMD inside each cortical bone mimicking region, Ct.vBMDBM (mgHA/cm3); and total area, Tt.ArBM (mm2). Trabecular microstructural parameters were not measured because the trabecular bone mimic portion is nearly homogenous and displays a lack of microstructure.

***Repeated scans of OI participants*** Repeated scans of OI participants were used to assess short-term reproducibility. Scans were performed at the non-dominant radius/tibia, unless there was a history of prior fractures, surgery, or implants producing metal artifacts. The radius length was estimated from the ulnar length, measured from the ulnar styloid process to the olecranon process, while the tibial length was measured from the tibial plateau to the distal edge of the medial malleolus. For each participant, the radius and tibia lengths were measured once and the measured values were used in the acquisition of both repeated scans. The reference line was positioned by the technician at the medial proximal margin of the radial articular surface for radius scans and at the tibial plateau for tibia scans. The mid-point of the scanned volume of interest was located at a distance of 4% (radius) and 7% (tibia) of total bone length from the reference line(25,26). The standard scan region was 110 slices at 82 μm isotropic voxel size for XCT and 168 slices at 60.7 μm isotropic voxel size for XCT2. All scans were acquired according to the manufacturer's standard *in vivo* acquisition protocol for each respective generation of the scanner. For the XCT, the acquisition protocol is as follows: energy: 59.4 kVp, current: 900 μA, field of view: 12.6 cm, integration time: 100 ms, scan time: 2.8 min, stack length: 9.020 mm. For the XCT2, the acquisition protocol is as follows: 68.0 kVp, current: 1470 μA, field of view: 14.0 cm, integration time: 43 ms, scan time: 2.0 min, stack length: 10.197 mm.

## Precision Errors

***Short-term multi-site (STMS) precision errors*** were computed as:

and as:

E.g., ( EFP, , Tb.vBMDBM, , and ) is the short-term multi-site precision error of EFP-derived () Tb.vBMDBM () estimated by pooling scans from all sites () and computing PEs for each EFP section () at each timepoint ().

***Longitudinal single-site (LTSS) precision errors*** were computed as:

and as:

where is the set of timepoints that spans baseline to intermediate-term or baseline to long-term. E.g., ( EFP, , Ct.ArBM, , and ) is the long-term single-site precision error of EFP-derived () Ct.ArBM () estimated by pooling baseline and long-term scans () and computing PEs for each EFP section () at each XCT scanner site ().

Finally, ***longitudinal multi-site*** ***(LTMS) precision errors*** were computed as:

and as:

where is the set of timepoints that spans baseline to intermediate-term or baseline to long-term. E.g., ( QC1, , Tt.vBMDBM, , and ) is the intermediate-term multi-site precision error of QC1-derived () Tt.vBMDBM () estimated by pooling baseline and intermediate-term scans () across all sites () and computing PEs for each QC1 section ().

***Least significant change***. For each precision error calculated, we also report the least significant change (LSC), which is the smallest difference between two measurements that can be deemed significant at a 95% confidence level(8,33):

where or .

# Abbreviations

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| **Abbreviation** | **Description** |
| BM | Bone mimicking |
| CI | Confidence interval |
| CSA | Cross-sectional area |
| Ct.Ar | Cortical area |
| Ct.Pm | Cortical perimeter |
| Ct.Po | Cortical porosity |
| Ct.Th | Cortical thickness |
| Ct.vBMD | Cortical volumetric bone mineral density |
| CV | Coefficient of variation |
| DXA | Dual-energy X-ray absorptiometry |
| EFP | European forearm phantom |
| HR-pQCT | High-resolution peripheral quantitative tomography |
| ISCD | International society for clinical densitometry |
| LSC | Least significant change |
| LTMS | Longitudinal multi-site |
| LTSS | Longitudinal single-site |
| µCT | Micro-computed tomography |
| MA | Motion artefact |
| Med | Median |
| Meta/Inn | Peripheral to medullary trabecular bone density ratio |
| MSE | Mean squared error |
| OI | Osteogenesis imperfecta |
| PE | Precision error |
| RMS | Root mean square |
| SD | Standard deviation |
| SE | Standard error |
| STMS | Short-term multi-site |
| STSS | Short-term single-site |
| Tb.1/N.SD | Inhomogeneity of trabecular network |
| Tb.Ar | Trabecular area |
| Tb.Sp | Trabecular separation |
| Tb.Th | Trabecular thickness |
| Tb.vBMD | Trabecular volumetric bone mineral density |
| Tt.Ar | Total area |
| Tt.vBMD | Total volumetric bone mineral density |
| VOI | Volume of interest |
| XCT | XtremeCT (first generation scanner) |
| XCT2 | XtremeCT2 (second generation scanner) |