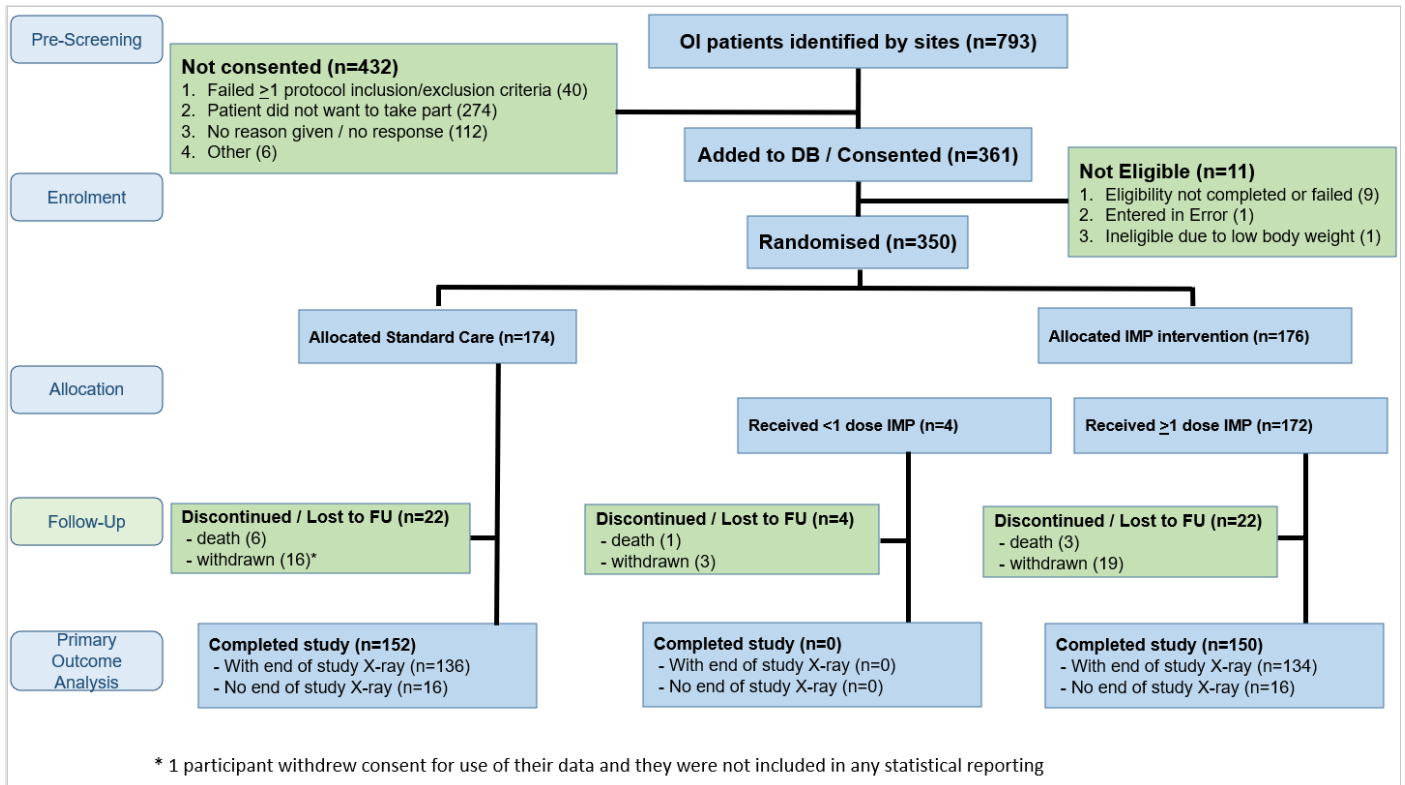


## Participant Flow



**Table 1: Clinical, genetic and biochemical characteristics of the study population**

Variable	TPTD / ZA	Standard Care
Number of participants	176	173
Age	43.6 ± 14.1	43.8 ± 13.9
Female	95 (54.0%)	93 (53.8%)
Body Mass Index (Kg/M <sup>2</sup> )	27.8 ± 6.4	29.6 ± 7.6
<i>Subtype of OI</i>		
Type I	135 (76.7%)	131 (75.7%)
Type III	12 (6.8%)	7 (4.1%)
Type IV	26 (14.8%)	29 (16.8%)
Not classified	3 (1.7%)	6 (3.5%)
<i>Clinical features of OI</i>		
Blue Sclera	149 (84.7%)	133 (76.9%)
Dentinogenesis imperfecta	64 (36.4%)	61 (35.3%)
Bone Deformity	115 (65.3%)	105 (60.7%)
<i>Genetic analysis</i>		
Pathogenic variant <i>COL1A1/ COL1A2</i>	153 (86.9%)	148 (85.5%)
Pathogenic variant in other genes <sup>1</sup>	4 (2.3%)	4 (2.3%)
Qualitative variants	55 (31.3%)	54 (31.2%)
Quantitative variants	77 (43.8%)	69 (39.9%)
Splice site variants	26 (14.8%)	29 (16.8%)
No pathogenic variant or VUS <sup>2</sup>	18 (10.2%)	20 (11.6%)
<i>Bone Mineral Density</i>		
Lumbar spine BMD (g/cm <sup>2</sup> )	0.862 ± 0.172	0.849 ± 0.201
Lumbar spine T-score	-2.18 ± 1.57	-2.11 ± 1.92
Femoral neck BMD (g/cm <sup>2</sup> )	0.741 ± 0.144	0.740 ± 0.151
Femoral neck T-score	-1.55 ± 1.22	-1.41 ± 1.30
Total hip BMD (g/cm <sup>2</sup> )	0.824 ± 0.142	0.830 ± 0.149
Total hip T-score	-1.33 ± 1.21	-1.12 ± 1.26
<i>Participants with previous fractures</i>		
Fractures within previous two years	83 (47.2%)	80 (46.2%)
Vertebral fracture at baseline	94 (53.4%)	83 (48.5%)
Bisphosphonates within previous two years	48 (27.3%)	50 (28.9%)
<i>Biochemistry</i>		
Serum 25(OH)D <sub>3</sub> (nmol/L)	63.0 ± 27.0	66.0 ± 33.0
Serum PINP µg/L	32.0 [22.2-44.4]	33.0 [21.3-45.5]
Serum CTX µg/L	0.18 [0.12- 0.26]	0.18 [0.12-0.26]

Values are mean ± SD, numbers (%), or median [interquartile range] for fractures, serum PINP and serum CTX.<sup>1</sup>Pathogenic variants were also found *FKBP10* (n=3), *IFITM5* (n=3), *P3H1* (n=1), *SERPINF1* (n=1), and *BMP1* (n=1).  
<sup>1</sup>VUS = Variants of uncertain significance. Genetic analysis was missing in one participant from the standard care group.

**Table 2. Effects of TPTD /ZA and standard care on fractures**

	TPTD / ZA	Standard Care	Treatment effect <sup>1</sup> and statistical significance
Participants with incident fractures <sup>2</sup>	65 (36.9%)	63 (36.4%)	HR 0.97 [0.68-1.38], p=0.872
Months to new incident fracture	27.1 [17-58]	23.9 [10-49]	
<i>Number of confirmed incident fractures:</i>			
1 fracture	22 (12.5%)	21 (12.5%)	IRR 1.03 [0.64-1.65], p=0.911
2 fractures	10 (5.7%)	7 (4.0%)	
3 fractures	5 (2.8%)	6 (3.5%)	
4 fractures	1 (0.6%)	2 (1.2%)	
5 fractures	1 (0.6%)	0 (0%)	
Total incident fractures	66	61	
<i>Number of confirmed incident vertebral fractures<sup>3</sup></i>			
<i>Thoracic spine</i>	85	49	
<i>Lumbar spine</i>	40	36	
<i>Total vertebral fractures</i>	125	85	IRR 1.36 [0.78-2.36], p=0.280
Total confirmed fracture number <sup>4</sup>	191	146	
Participants reporting fractures, not confirmed by imaging	131 (74.4%)	131 (75.5%)	IRR 0.94 [0.76-1.18], p=0.601
Total number of fractures reported by participants not confirmed by imaging	860	932	
Number of fractures reported by participants, not confirmed by imaging	3.0 [1-8]	3.0 [1-8]	

Values are frequency and (%) or median [interquartile range]. For statistical significance point estimates are Hazard Ratio (HR) [95% confidence intervals] or Incidence Rate Ratios (IRR) [95% confidence intervals] calculated by Poisson regression, adjusting for minimisation variables.

<sup>1</sup>TPTD/ZA vs Standard care. Values less than one indicate benefit of TPTD vs. SC

<sup>2</sup> Primary outcome

<sup>3</sup> Includes new vertebral fractures and vertebral fractures worsening from baseline.

<sup>4</sup> Incident fractures occurring during follow up and new or worsening vertebral fractures identified by spine x-rays at the end of study

**Table 3: Sites of primary outcome fractures in treatment groups**

Variable	TPTD / ZA	Standard Care
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Serum PINP µg/L	32.0 [22.2-44.4]	33.0 [21.9-44.6]
Serum CTX µg/L	0.18 [0.12- 0.26]	0.18 [0.121-0.26]

**Table 4. Adverse Events and serious adverse events**

	<b>TPTD / ZA (n=177)</b>	<b>Standard Care (n=172)</b>
Participants with an adverse event	144 (81.4%)	146 (84.9%)
Participants with a serious adverse event	39 (22.2%)	41 (23.3%)
Total number of adverse events	936	716
Gastrointestinal disorders	64 (6.8%)	36 (5.0%)
General & administration disorders	54 (5.8%)	16 (2.2%)
Infections & infestations	143 (15.3%)	124 (17.3%)
Injury & procedural complications	89 (9.5%)	102 (14.2%)
Musculoskeletal disorders	264 (28.2%)	194 (27.1%)
Nervous system disorders	60 (6.4%)	20 (2.8%)

Values for any adverse event and serious adverse events refer to the number and percentage of participants that experienced them. For individual categories, numbers of adverse events are shown only for categories where the percentages were at least 5% of the total number of adverse events.