SUPPLEMENTARY MATERIALS

Supplementary Methods

Full eligibility criteria:

Inclusion criteria

1) Personally submitted written voluntary informed consent to participate in the study;

2) Aged ≥18 years at the time of consent (the cut-off age depends on the local law);

3) Stable chronic renal failure treated with hemodialysis three times weekly for at least 12 weeks before screening;

4) IPTH level (centrally measured) of >300 pg/ml at screening; and

5) Corrected serum Ca level (centrally measured) of ≥9.0 mg/dl at screening.

Exclusion criteria

1) Treatment with cinacalcet hydrochloride within 2 weeks before screening;

2) Change in dose or dosing regimen of an activated vitamin D drug or its derivative, phosphate binder, or Ca preparation within 2 weeks before screening; or start of treatment with such drugs within 2 weeks before screening;

3) Change in prescribed conditions of dialysis (dialysate Ca concentration, prescribed dialysis time, and prescribed number of dialysis sessions per week) within 2 weeks before screening;

4) Treatment with bisphosphonates, denosumab, or teriparatide within 24 weeks before screening;

5) Parathyroidectomy and/or parathyroid intervention within 24 weeks before screening;

6) Severe heart disease (e.g., ≥Class III per New York Heart Association classification, see Appendix 1 of the protocol);

7) Severe hepatic dysfunction (e.g., treatment with antiviral therapy);

8) Uncontrolled hypertension and/or diabetes mellitus;

9) Pregnant, lactating, possibly pregnant women (women of childbearing potential with a positive pregnancy test at screening or with negative pregnancy test but not using any contraceptive methods), or unwilling to use the adequate contraceptive method(s) according to the physician's instructions. Amenorrhea for ≥12 months after the last menstrual period without an alternative medical cause is considered as non-childbearing potential.

10) History of serious drug allergy. History of or current drug or alcohol dependence;

11) History of drug allergy to cinacalcet hydrochloride;

12) History of diagnosis and treatment of malignant tumor within 5 years before screening (excluding basal cell carcinoma or surgically resected intraepithelial carcinoma of the uterine cervix);

13) Treatment with an investigational product (drug or medical device) in a clinical study or any study equivalent to a clinical study within 12 weeks before screening;

14) Exposure to an investigational product in a prior clinical study of evocalcet;

15) Primary hyperparathyroidism;

16) Other conditions unfit for participation in this study at the discretion of the investigator or subinvestigator.

Prohibited concomitant medications and therapies

Concomitant use of the following medications and therapies will be prohibited. The use will be prohibited during the period between 2 weeks before screening and Week 52 (or early termination) for (1), between 24 weeks before screening and Week 52 (or early termination) for (2) to (5), and between 12 weeks before screening and Week 52 (or early termination) for (6).

(1) Cinacalcet hydrochloride (excluding the comparator cinacalcet hydrochloride)

(2) Bisphosphonates

(3) Denosumab

(4) Teriparatide

(5) PTx and parathyroid intervention

(6) Peritoneal dialysis

Concomitant medications allowed with restrictions

1) Active Vitamin D Preparations and Derivatives

If the subject is receiving any active vitamin D preparation or its derivative, the preparation and its dose and dosing regimen must not be changed during the period between 2 weeks before screening and Week 52 (or early termination). Treatment with active vitamin D preparations and derivatives must not be started during this period for subjects who are currently not receiving these preparations. However, dose reduction or discontinuation of active vitamin D preparations and derivatives will be allowed if corrected serum Ca level exceeds 11.0 mg/dL after the start of study treatment. The dose may be returned to the previous dose, after reduction or discontinuation. The dose of active vitamin D preparations and derivatives may be increased, or treatment with these preparations may be newly started, if it seems difficult to improve low corrected serum Ca level (≤7.5 mg/dL) or hypocalcemia symptoms after dose increase or the start of a Ca preparation.

2) Phosphate Binders and Ca Preparations

If the subject is receiving any phosphate binder, Ca preparation, or food having a phosphate binding effect, the preparation (or food) and its dose and dosing regimen must not be changed during the period between 2 weeks before screening and Week 0. Use of phosphate binders, Ca preparations, and food having a phosphate binding effect must not be started during this period for subjects who are not taking these preparations or food.

Concomitant therapies allowed with restrictions

Changes in prescribed conditions of dialysis (dialysate Ca concentration, prescribe dialysis time,

and prescribed number of dialysis per week) will be prohibited during the period between 2 weeks before screening and Week 52 (or early termination).

Sample size

The target sample size was 400 patients, with 200 patients per group. This would provide greater than 90% power to detect the non-inferiority of evocalcet vs cinacalcet in the mean percentage change in iPTH level from baseline, assuming there was no difference between the evocalcet and cinacalcet groups in the mean percentage change in iPTH level from baseline, with a non-inferiority margin of 15%, a standard deviation (SD) of 41%, a one-sided significance level of 2.5%, and a drop-out rate of 10%.

Supplementary Table

Supplementary Table S1. Mean percentage change from baseline in intact PTH during evaluation period by multiple imputation by subgroup (FAS)

	Evocalcet (n = 199) N mean (SD)	**Cinacalcet (n = 196)** N mean (SD)	**p-value**
Age, years			
<65	159 −34.53 (40.503)	162 −29.90 (39.330)	0.000
≥65 years, n (%)	40 −35.23 (34.040)	34 −31.89 (30.831)	0.049
Sex			
Male	125 −34.42 (40.096)	127 −27.08 (37.478)	0.000
Female	74 −35.08 (37.931)	69 −36.07 (38.335)	0.051
Baseline iPTH (pg/ml)			
<500	53 −20.39 (48.129)	65 −20.76 (36.293)	0.095
500–1000	98 −36.81 (33.464)	79 −33.53 (37.390)	0.003
≥1000	48 −46.07 (35.081)	52 −37.13 (39.112)	0.002
Baseline corrected serum Ca (mg/dl)			

<9.5	64 −34.19 (30.716)	76 −28.76 (37.265)	0.004
≥9.5	134 −34.94 (42.912)	120 −31.19 (38.468)	0.000
Baseline serum P level (mg/dl)			
<5.5	61 −32.41 (37.489)	67 −24.52 (40.999)	0.004
≥5.5	138 −35.67 (40.039)	128 −33.38 (36.140)	0.000
Use of cinacalcet hydrochloride			
Yes	111 −37.42 (33.852)	111 −30.40 (41.093)	0.000
No	88 −31.20 (45.035)	85 −30.05 (33.589)	0.019
Use of active vitamin-D preparations			
Yes	119 −37.29 (42.008)	122 −31.76 (36.259)	0.000
No	80 −30.77 (34.520)	74 −27.76 (40.664)	0.007
Presence or absence of underlying diabetic nephropathy			

Yes	17 −43.73 (26.988)	21 −32.36 (43.636)	0.062
No	182 −33.82 (40.112)	175 −30.00 (37.319)	0.000
Dialysis history (years)			
<10	123 −34.56 (42.601)	114 −30.01 (37.039)	0.000
≥10	76 −34.84 (33.265)	81 −30.43 (39.577)	0.003
Ca concentration in dialysis solution (mEq/l)			
2.5	49 −37.77 (31.366)	52 −35.13 (36.719)	0.025
2.75	0 - (-)	0 - (-)	-
3.0	143 −33.12 (41.957)	138 −28.04 (38.111)	0.000
Dialysis type			
HD	120 −29.67 (41.396)	110 −30.47 (36.361)	0.016
HDF	13 −41.18 (35.734)	6 −42.29 (39.477)	0.473
Other	66 −42.49 (34.546)	80 −29.04 (40.194)	0.000
Initial dose of study drug			

Evocalcet 1 mg	62 −25.61 (35.525)	65 −20.81 (38.898)	0.011
Evocalcet 2 mg	137 −38.77 (40.223)	131 −34.93 (36.693)	0.000
Region			
China (including Hong Kong SAR)	138 −34.44 (43.007)	136 −28.38 (40.351)	0.000
South Korea	22 −29.23 (31.325)	19 −31.10 (28.026)	0.281
Taiwan	39 −38.55 (27.699)	41 −36.06 (33.428)	0.039

Ca, calcium; FAS, full analysis set; HD, hemodialysis; HDF, hemodiafiltration; P, phosphorus; PTH, parathyroid hormone; SD, standard deviation; SAR, Special Administrative Region.

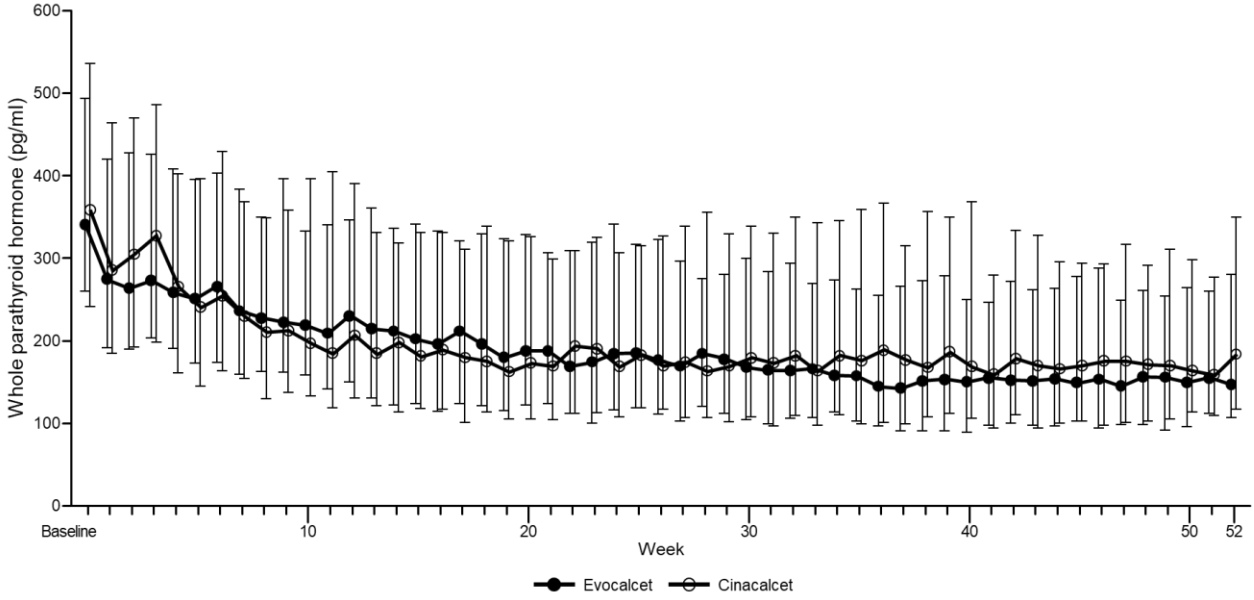
The p-values were calculated by t-test.

Supplementary Table S2. Mean dosage at last observation period by baseline iPTH subgroup (FAS)

	Evocalcet (n = 199) N mean (SD)	**Cinacalcet (n = 196)** N mean (SD)
Baseline iPTH (pg/ml)		
<500	53 1.89 (2.07)	65 25.0 (23.0)
500–1000	98 3.77 (2.87)	79 46.5 (36.0)

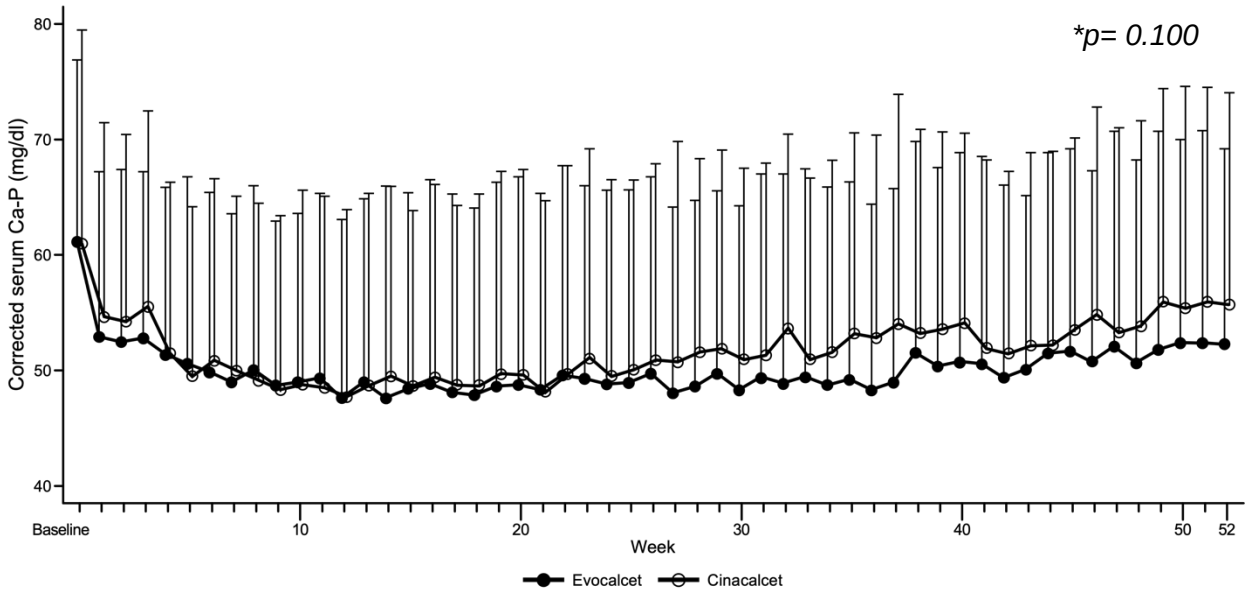
≥1000	48 5.58 (3.93)	52 56.7 (37.4)

Supplementary Figures



Supplementary Figure S1. Whole Parathyroid Hormone Levels Over Time (Median [Q1–Q3]) (FAS)

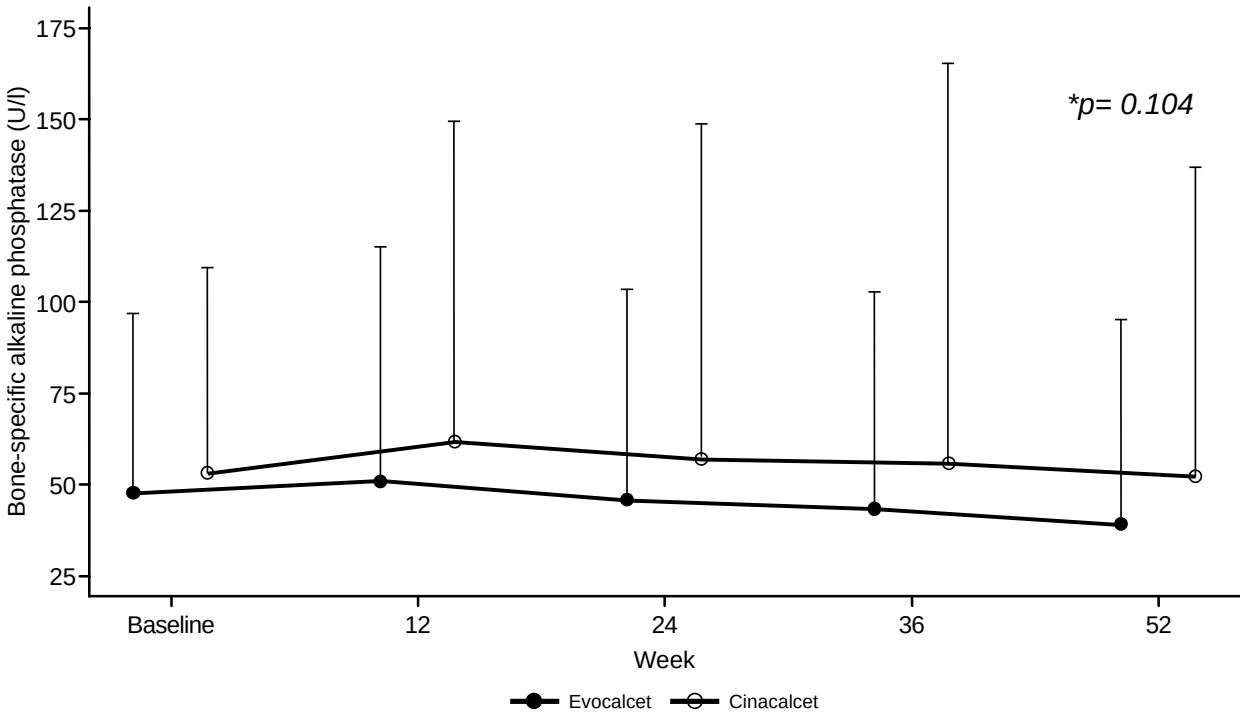
FAS, full analysis set; Q, quartile



Supplementary Figure S2. Corrected Serum Ca–P Product Over Time (Mean + SD) (FAS)

Ca–P, calcium–phosphorus; SD, standard deviation; FAS, full analysis set.

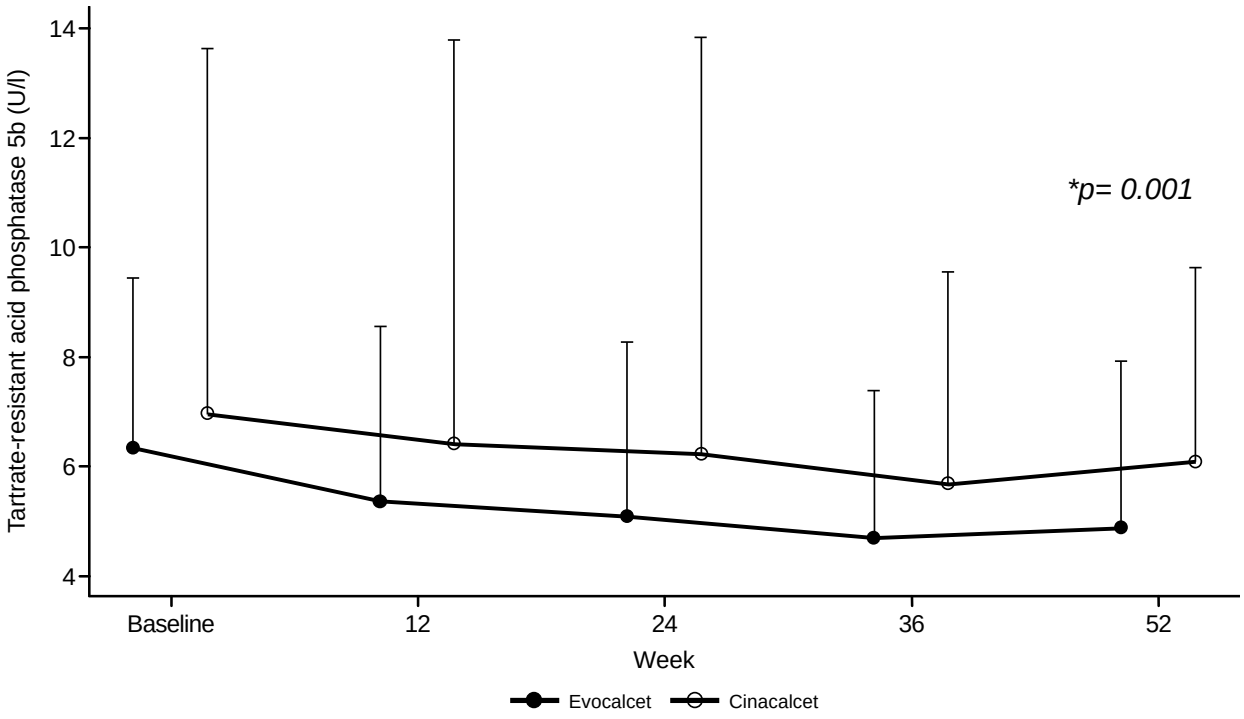
*The p-value was based on t-test at week 52.



Supplementary Figure S3. BAP Levels Over Time (Mean + SD) (FAS)

BAP, bone-specific alkaline phosphatase; SD, standard deviation; FAS, full analysis set.

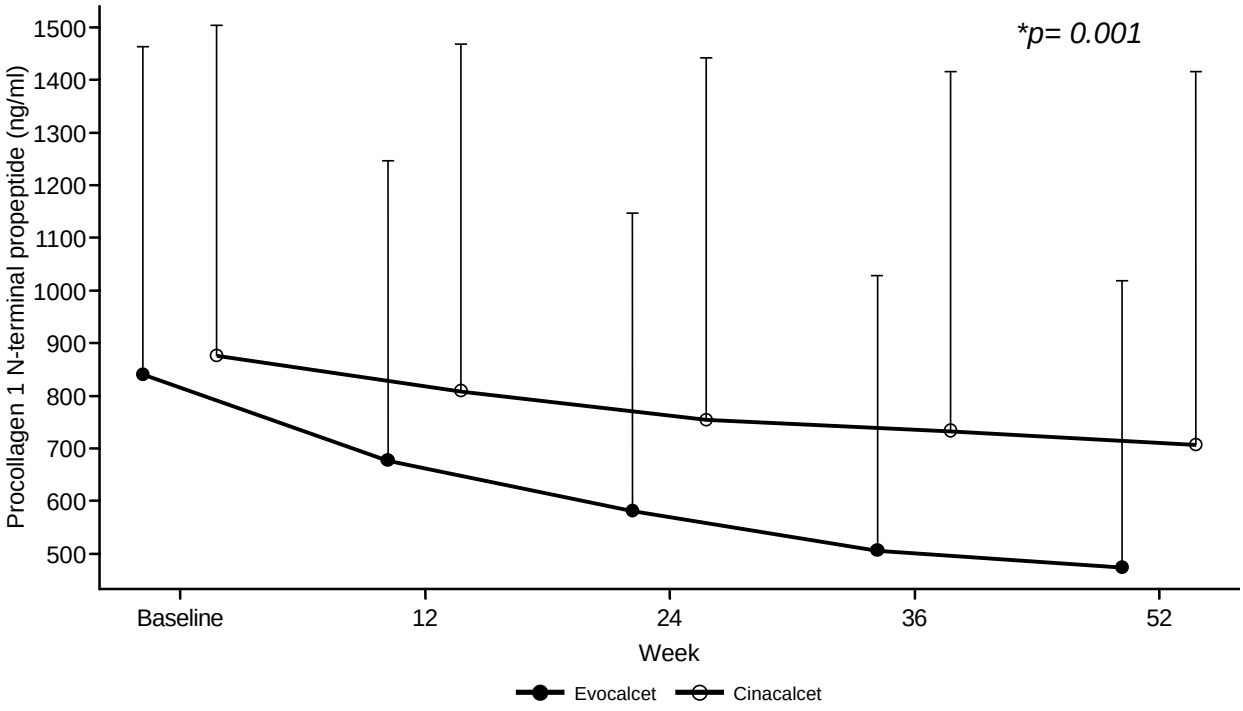
*The p-value was based on t-test at week 52.



Supplementary Figure S4. TRACP-5b Levels Over Time (Mean + SD) (FAS)

TRACP-5b, tartrate-resistant acid phosphatase; SD, standard deviation; FAS, full analysis set.

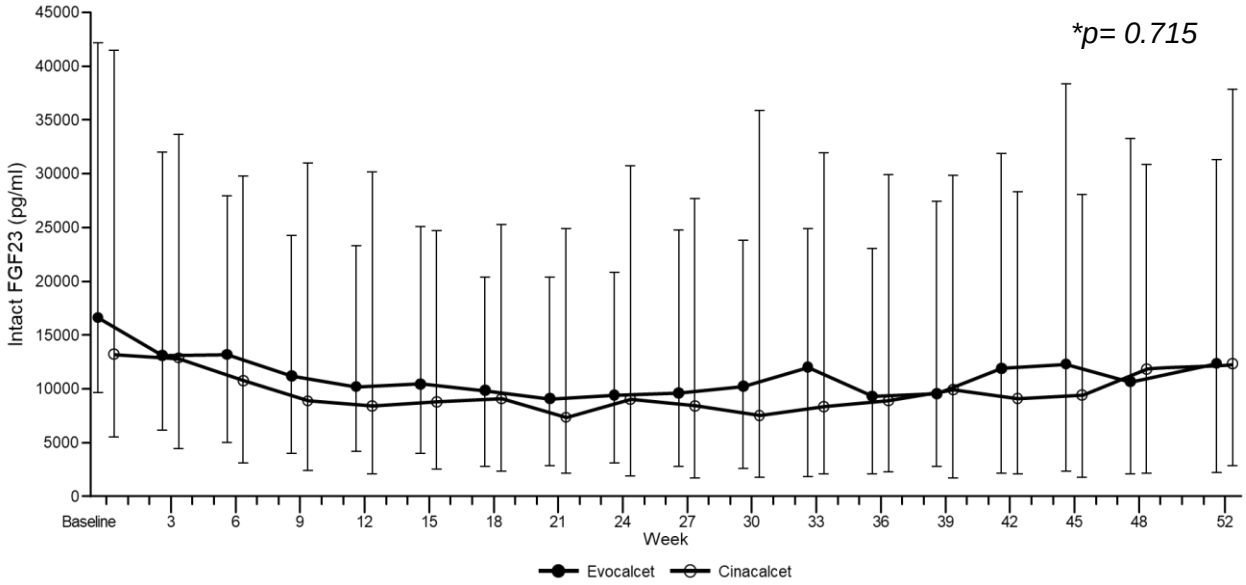
*The p-value was based on t-test at week 52.



Supplementary Figure S5. P1NP Levels Over Time (Mean + SD) (FAS)

P1NP, total N-terminal propeptide of type 1 procollagen; SD, standard deviation; FAS, full analysis set.

*The p-value was based on t-test at week 52.



Supplementary Figure S6. Intact FGF23 Over Time (Median [Q1–Q3])

FGF23, fibroblast growth factor 23.

*The p-value was based on generalized Wilcoxon test at week 52.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	n/a
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4–5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5–6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6–7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8–9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a

Sample size	7a	How sample size was determined	9, supplementary methods
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11–12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11–12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12–13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13–15
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.