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ORIGINAL RESEARCH ARTICLE

Slowing Progression of Cardiovascular Calcification With SNF472 in Patients on Hemodialysis

Results of a Randomized Phase 2b Study

Editorial, see p 740

Paolo Raggi, MD
Antonio Bellasi, MD, PhD
David Bushinsky, MD
Jordi Bover, MD, PhD
Mariano Rodriguez, MD, PhD
Markus Ketteler, MD
Smeeta Sinha, MD
Carolina Salcedo, PhD
Kristen Gillotti, BA, BSN
Claire Padgett, PhD
Rekha Garg, MD
Alex Gold, MD
Joan Perelló, PhD
Glenn M. Chertow, MD

BACKGROUND: The high cardiovascular morbidity and mortality in patients with end-stage kidney disease could be partially caused by extensive cardiovascular calcification. SNF472, intravenous myo-inositol hexaphosphate, selectively inhibits the formation and growth of hydroxyapatite.

METHODS: This double-blind, placebo-controlled phase 2b trial compared progression of coronary artery calcium volume score and other measurements of cardiovascular calcification by computed tomography scan during 52 weeks of treatment with SNF472 or placebo, in addition to standard therapy, in adult patients with end-stage kidney disease receiving hemodialysis. Patients were randomized 1:1:1 to SNF472 300 mg (n=92), SNF472 600 mg (n=91), or placebo (n=91) by infusion in the hemodialysis lines thrice weekly during hemodialysis sessions. The primary end point was change in log coronary artery calcium volume score from baseline to week 52. The primary efficacy analysis combined the SNF472 treatment groups and included all patients who received at least 1 dose of SNF472 or placebo and had an evaluable computed tomography scan after randomization.

RESULTS: The mean change in coronary artery calcium volume score was 11% (95% CI, 7–15) for the combined SNF472 dose group and 20% (95% CI, 14–26) for the placebo group (P=0.016). SNF472 compared with placebo attenuated progression of calcium volume score in the aortic valve (14% [95% CI, 5–24] versus 98% [95% CI, 77–123]; P<0.001) but not in the thoracic aorta (23% [95% CI, 16–30] versus 28% [95% CI, 19–38]; P=0.40). Death occurred in 7 patients (4%) who received SNF472 and 5 patients (6%) who received placebo. At least 1 treatment-emergent adverse event occurred in 86%, 92%, and 87% of patients treated with SNF472 300 mg, SNF472 600 mg, and placebo, respectively. Most adverse events were mild. Adverse events resulted in discontinuation of SNF472 300 mg, SNF472 600 mg, and placebo for 14%, 29%, and 20% of patients, respectively.

CONCLUSIONS: Compared with placebo, SNF472 significantly attenuated the progression of coronary artery calcium and aortic valve calcification in patients with end-stage kidney disease receiving hemodialysis in addition to standard care. Future studies are needed to determine the effects of SNF472 on cardiovascular events.

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Clinical Perspective

What Is New?

- Patients with end-stage kidney disease receiving hemodialysis have very high cardiovascular morbidity and mortality rates.
- Part of their excess risk is explained by extensive calcification of the cardiovascular system that is caused by a combination of atherosclerosis and mineralization of the arterial media.
- SNF472, a selective inhibitor of hydroxyapatite formation and growth, attenuated the progression of cardiovascular calcification in a phase 2b trial in patients receiving long-term hemodialysis.

What Are the Clinical Implications?

- Meta-analytical data suggest that slowing the progression of calcification may improve survival.
- Future research is needed to determine whether SNF472 reduces cardiovascular morbidity and mortality in patients receiving long-term hemodialysis.
- SNF472 is administered thrice weekly as an infusion during hemodialysis, ensuring high compliance.

Among patients with end-stage kidney disease (ESKD) requiring dialysis, the relative risk of death resulting from cardiovascular causes is 5 to 30 times higher than in the general population.[1] Although traditional risk factors such as diabetes mellitus and hypertension are highly prevalent in patients with chronic kidney disease,[2] they account for only a portion of the increased cardiovascular risk. In clinical practice, at least 80% of patients who receive maintenance hemodialysis have evidence of cardiovascular calcification.[3,4] This marker of vasculopathy has been linked to morbidity and mortality in the general population[5,6] and in patients receiving maintenance hemodialysis.[7–9]

In patients with advanced chronic kidney disease, cardiovascular calcification is likely secondary to a combination of accelerated atherosclerosis and perhaps more so to arteriosclerosis related to derangements of mineral metabolism.[10,11] Cardiovascular calcification is a highly regulated process that resembles bone formation and ultimately depends on hydroxyapatite nucleation and crystal growth. Patients with chronic kidney disease and cardiovascular calcification have increased morbidity and mortality through several pathways, including coronary atherosclerosis,[12] arterial stiffness,[13,14] left ventricular hypertrophy,[15] myocardial ischemia,[16] and electrocardiographic abnormalities.[14]

There is evidence that attenuating the progression of vascular calcification in chronic kidney disease is associated with a reduction in mortality.[17] The phosphate binder sevelamer[18] and the calcimimetic cinacalcet,[19] used to treat hyperphosphatemia and secondary hyperparathyroidism, respectively, may reduce the progression of vascular calcification in ESKD, but they do not fully address the complex biology responsible for this pathological phenomenon. SNF472, an intravenous formulation of myo-inositol hexaphosphate, acts through a novel pathway to selectively and directly inhibit the formation and growth of hydroxyapatite crystals,[20,21] the final common step in the pathophysiology of vascular calcification. Infusing SNF472 during each dialysis session achieves therapeutic levels,[22] ensuring treatment adherence without additional burden to the patient. A phase 1 clinical trial showed that in patients receiving maintenance hemodialysis, administration of a single dose of SNF472 at 9 mg/kg inhibited hydroxyapatite crystallization potential by 80% compared with 9% with placebo.[23]

CaLIPSO (Cal for calcium and ipso meaning the item itself) is the first multicenter, randomized, double-blind placebo-controlled clinical trial to test the hypothesis that SNF472 attenuates the progression of cardiovascular calcification compared with placebo in patients receiving maintenance hemodialysis and contemporary adjunct therapies, including non–calcium-containing phosphate binders and cinacalcet. In this report, we describe the primary and secondary efficacy end points and the safety results of the CaLIPSO trial.

METHODS

Study Design and Participants

The design and overall baseline patient characteristics of the CaLIPSO trial (NCT02966028) have been reported previously.[24] The full data, methods used in the analyses, and materials used to conduct the research are not available at this time for the purposes of reproducing the results or replicating the procedure. Briefly, CaLIPSO is a multinational, randomized, placebo-controlled, double-blind phase 2b trial among adult patients (18–80 years of age) receiving hemodialysis for ≥6 months who had a coronary artery calcium (CAC) Agatston score between 100 and 3500 units at trial entry, as measured on a non-contrast multidetector computed tomography (CT) scanner. Initially, the trial recruited patients with a CAC Agatston score between 100 and 2000 units; however, an amendment to the protocol increased the upper limit for CAC Agatston score to 3500 units, which is more fully representative (and inclusive) of this complex patient population. Calcium Agatston scores were used for study eligibility because they are commonly used for risk stratification in clinical practice. Younger patients (18–54 years of age) were also required to have a history of diabetes mellitus (either type 1 or type 2). Key exclusion criteria were scheduled kidney transplantation, weight >136 kg, recent (within 3 months) hospitalization for cardiovascular events (unstable angina, myocardial infarction, stroke, transient ischemic attack, amputation, peripheral or coronary bypass surgery, or unstable heart failure), hypocalcemia (serum calcium <8.0 mg/dL [2.0 mmol/L]), extreme elevation in serum phosphate (>10 mg/dL [3.23 mmol/L] within the last 2 months), uncontrolled hypertension (≥2 consecutive

postdialysis diastolic blood pressure values >100 mm Hg within the last 2 months), or expected survival of <2 years per the investigator.

After screening, eligible patients were randomized 1:1:1 to receive SNF472 300 mg, SNF472 600 mg, or placebo 3 times weekly, infused over 2.5±0.5 hours during each hemodialysis session for 52 weeks. To maintain blinding, randomization was performed with a centralized electronic randomization system, and the study drug was packaged in identical vials containing either SNF472 or physiological saline. Randomization was stratified by baseline CAC Agatston score (100–399, 400–1000, or >1000 units). Investigators managed blood pressure, calcium, phosphate, parathyroid hormone, lipids, and anemia according to current guidelines or standard practices at their centers.

At screening and week 52 (or at the time of early discontinuation), imaging of the coronary arteries, aortic valve, and thoracic aorta was performed with multidetector CT, with a minimum of 64 slices. A central expert who was blinded to the patient's assigned treatment group reviewed each scan and quantified each calcified area using both the volume[25] and Agatston score.[26] A postrandomization scan was considered evaluable if the expert image reviewer considered it of sufficient quality to be compared with the baseline scan and could calculate a CAC volume score without being hampered by artifact. Patients who discontinued before week 52 without withdrawal of consent were asked to undergo CT scanning for assessment of efficacy to pursue maximal available follow-up and to minimize missing data.

An external, independent Data and Safety Monitoring Board monitored subject safety and data integrity. Ethics approval was obtained from an institutional review board for each study site, in accordance with the local/national processes for each study site. Participants provided written informed consent before enrollment, and the trial was conducted according to the principles of the Declaration of Helsinki. Enrollment began in December 2016 and continued through July 2018. Follow-up ended in August 2019.

End Points

The primary efficacy end point was the change from baseline to week 52 in log CAC volume score, which has a known lower variability than the Agatston score.[25] The primary efficacy analysis combined the 2 SNF472 treatment groups compared with placebo. Secondary efficacy end points described in this report include change from baseline to week 52 for log CAC Agatston score and changes from baseline to week 52 for log calcium volume score and log calcium Agatston score at the aortic valve and the thoracic aorta level, as well as the proportion of patients with <15% progression in CAC Agatston score at week 52.[27] Each end point was analyzed for the combined SNF472 dose groups versus placebo and for each SNF472 dose group versus placebo. Other end points included a composite safety end point for cardiovascular outcomes (death resulting from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or heart failure), all-cause mortality, incidence of adverse events (overall, serious, or leading to study drug discontinuation), and changes from baseline to week 52 for clinical laboratory tests.

Statistical Analysis

Analyses were conducted with SAS version 9.4. The safety population included all randomized patients who received at least 1 dose of SNF472 or placebo. The modified intention-to-treat (mITT) analysis population, which was used for efficacy analyses, consisted of all randomized patients who received at least 1 dose of SNF472 or placebo and had a postrandomization CT scan with a CAC volume score. The mITT excluded patients who did not have an evaluable follow-up scan. For the primary analyses of calcification progression at week 52, we used the last observation (the postrandomization scan) carried forward (LOCF) in the mITT population.

The primary efficacy analysis model was an ANCOVA with the change in log score (log[week 52]–log[baseline]) as the dependent variable, a fixed-effect term for randomized treatment group, and log(baseline) as covariates; the model was stratified by baseline CAC Agatston score. The primary comparison of interest was the SNF472 combined dosing groups versus placebo; supportive comparisons examined differences between each dose and placebo. Geometric least squares means and 95% CIs were estimated and back-transformed before presentation to provide the mean percent change from baseline to week 52. For each comparison between SNF472 and placebo, geometric least squares mean and 95% CIs for treatment differences were calculated. We considered 2-tailed values of $P<0.05$ as statistically significant. For secondary efficacy end points, we used similar ANCOVA models to compare SNF472 combined dosing groups with placebo and SNF472 300 and 600 mg doses with placebo individually. Zero calcium scores for the aortic valve and thoracic aorta were imputed with the next smallest value in the relevant treatment arm.

We also analyzed progression of calcification and the proportion of patients with <15% progression in CAC Agatston score at week 52 in the per-protocol population of patients who met all inclusion/exclusion criteria, had an evaluable baseline CT scan, received 80% of scheduled treatment, completed the study and the week 52 dosing visit, and had a week 52 evaluable CT scan (up to 120 days after the last dose of study drug).

In prespecified sensitivity analyses, multiple imputation was implemented to explore the effect of missing data. In multiple imputation 1, we imputed missing data in each group using distribution implied by the nonmissing patient data for that treatment group. In multiple imputation 2, we imputed missing data for all groups using distribution implied by the nonmissing patient data in the placebo arm. We did not adjust for multiple comparisons.

For the composite safety end point, we used proportional hazards (Cox) regression to compare SNF472 with placebo, stratified by baseline CAC Agatston score.

The planned sample size of 270 patients provided 80% power to test the hypothesis that the log-transformed true difference in progression between the SNF472 combined dosing groups and the placebo group was 0.130, corresponding to a true ratio of 1.139, or 18.5% progression for the SNF472 combined dosing groups and 35% progression for the placebo group. These assumptions were based on results from the ADVANCE study (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects With Chronic

Kidney Disease Receiving Hemodialysis), a similarly designed 52-week study in patients with cardiovascular calcification receiving hemodialysis.[19]

Role of the Funding Source

Sanifit Therapeutics provided financial support and study treatment for the trial. Coauthors of this work included employees of Sanifit Therapeutics who participated in the trial design, data analysis, data interpretation, and writing of the article. All authors had full access to all the data and final responsibility for the decision to submit for publication.

RESULTS

Enrollment and Disposition

Of 645 patients who were screened for enrollment from 65 centers in 3 countries (United States, Spain, and United Kingdom; see Appendix A in the online-only Data Supplement), 274 patients were randomized to 1 of the 3 treatment groups: SNF472 300 mg (n=92), SNF472 600 mg (n=91), or placebo (n=91). Patient disposition was similar across the treatment groups (Table I in the online-only Data Supplement). Safety evaluations included 92, 91, and 90 patients in the SNF472 300 mg, SNF472 600 mg, and placebo groups, respectively, who received at least 1 dose of study drug (Figure 1). Follow-up CT scans were available for evaluation of calcium volume score progression in the mITT population for 142 patients in the SNF472 combined dosing groups and 77 patients in the placebo group.

Baseline Characteristics

A previous report described the baseline characteristics for all randomized patients combined.[24] After the randomization codes were unblinded for this analysis, patient demographics and clinical characteristics at baseline were shown to be similar across the 3 treatment groups (Table 1). At baseline, geometric mean scores in the SNF472 300 mg, SNF472 600 mg, and placebo groups were 621, 636, and 634 units, respectively, for CAC Agatston scores, and 573, 583, and 584, respectively, for CAC volume scores. Baseline calcium scores for the coronary arteries, aortic valve, and thoracic aorta are summarized by treatment group in Table 2. A sample image of a patient with extensive calcification of the coronary arteries at baseline is provided in Figure I in the online-only Data Supplement.

Coronary Artery

For the primary end point, SNF472 (combined dosing groups) significantly attenuated the progression

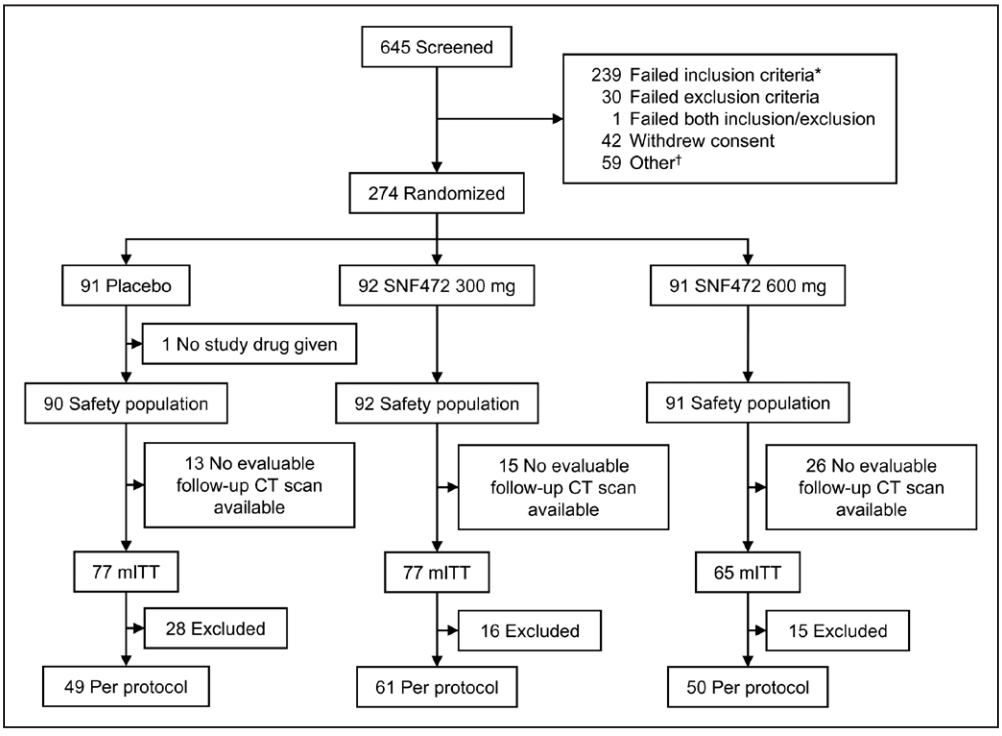

Figure 1. Patient disposition.
Modified intention-to-treat population (mITT) indicates at least 1 dose of study drug and postbaseline evaluable scan; per-protocol population includes patients who met entry criteria, completed the week 52 visit, had a week 52 evaluable scan, and had at least 80% exposure to study drug. *Two hundred thirty-one patients did not have a coronary artery calcium score in the required range at screening. †Other reasons for screening failure included computed tomography (CT) scan not completed/not evaluable, kidney transplantation, or screening/enrollment closed.

Table 1. Baseline Patient Characteristics

	Placebo (n=90)	SNF472 300 mg (n=92)	SNF472 600 mg (n=91)
Age, y	64.1±8.2	63.0±9.5	63.6±8.9
Sex, n (%)			
Male	57 (63.3)	54 (58.7)	55 (60.4)
Female	33 (36.7)	38 (41.3)	36 (39.6)
Race, n (%)			
White	62 (68.9)	59 (64.1)	67 (73.6)
Black or African American	19 (21.1)	27 (29.3)	15 (16.5)
Asian	4 (4.4)	2 (2.2)	4 (4.4)
Other	0	2 (2.2)	1 (1.1)
Not reported	5 (5.6)	3 (3.3)	4 (4.4)
Hispanic or Latino ethnicity, n (%)	32 (35.6)	31 (33.7)	36 (39.6)
Dialysis duration, mo*	34.5 (6–263)	48.5 (7–521)	40.0 (7–339)
Time receiving dialysis, n (%)			
<2 y	31 (34.4)	26 (28.3)	30 (33.0)
2–< 5 y	37 (41.1)	27 (29.3)	31 (34.1)
≥5 y	22 (24.4)	39 (42.4)	30 (33.0)
Blood pressure, mm Hg			
Systolic	135.3±22.6	140.4±26.3	135.8±24.9
Diastolic	68.1±13.2	70.2±13.8	68.3±12.7
Medical history, n (%)			
Hypertension	87 (96.7)	88 (95.7)	83 (91.2)
Diabetes mellitus	60 (66.7)	60 (65.2)	54 (59.3)
Coronary artery disease	23 (25.6)	29 (31.5)	17 (18.7)
Peripheral vascular disease	22 (24.4)	11 (12.0)	17 (18.7)
Stroke	12 (13.3)	11 (12.0)	15 (16.5)
Myocardial infarction	10 (11.1)	13 (14.1)	9 (9.9)
Heart failure	19 (21.1)	26 (28.3)	15 (16.5)
Baseline medications, n (%)			
Calcimimetic	26 (28.9)	39 (42.4)	21 (23.1)
Sevelamer	42 (46.7)	48 (52.2)	47 (51.6)
Lanthanum	5 (5.6)	7 (7.6)	8 (8.8)
Iron-based phosphate binder	16 (17.8)	8 (8.7)	9 (9.9)
Non–calcium-based phosphate binder†	55 (61.1)	57 (62.0)	62 (68.1)
Calcium-based phosphate binder	26 (28.9)	26 (28.3)	29 (31.9)
Statin	53 (58.9)	56 (60.9)	59 (64.8)
Warfarin	5 (5.6)	8 (8.7)	5 (5.5)
Activated vitamin D	47 (52.2)	53 (57.6)	44 (48.4)

Data are expressed as mean±SD or number (percent) for the safety population.
*Dialysis duration is expressed as median (range).
†Includes sevelamer, lanthanum, and iron-based phosphate binders.

of CAC compared with placebo; the mean change in CAC volume score from baseline to week 52 was 11% (95% CI, 7–15) and 20% (95% CI, 14–26), respectively (*P*=0.016; Figure 2A). The mean change from baseline to week 52 in CAC volume score was 12% (95% CI, 6–18) for the 300-mg dose group (*P*=0.052 versus placebo) and 10% (95% CI, 4–17) for the 600-mg dose group (*P*=0.029 versus placebo; Figure IIA in the online-only Data Supplement).

Corresponding results using the CAC Agatston score were a mean change of 11% (95% CI, 6–17) for the SNF472 combined dosing groups and 20% (95% CI, 12–28) for placebo (*P*=0.075; Figure 2B). The mean change in CAC Agatston score was 10% (95% CI,

Table 2. Baseline Calcium Scores (Volume and Agatston)

	Placebo (n=77)	SNF472 300 mg (n=77)	SNF472 600 mg (n=65)
Coronary artery calcium score			
Volume	584±0.88	573±0.83	583±0.89
Agatston score, units	634±0.96	621±0.91	636±0.98
Aortic valve calcium score			
Volume	15.3±1.94	27.9±2.04	15.5±1.90
Agatston score, units	8.1±2.47	17.5±2.56	8.5±2.44
Thoracic aorta calcium score			
Volume	1138±1.82	1095±1.87	981±1.91
Agatston score, units	1276±2.00	1210±2.08	1096±2.14

Data are expressed as geometric mean±log(SD) for the modified intention-to-treat population.

3–17) for the 300-mg dose group (*P*=0.055 versus placebo) and 13% (95% CI, 6–22) for the 600-mg dose group (*P*=0.24 versus placebo; Figure IIB in the online-only Data Supplement).

Similar results for progression of calcium volume and Agatston scores were obtained in the per-protocol population of patients who completed 52 weeks of treatment (Figure 3A and 3B) and in sensitivity analyses that used multiple imputation for missing data in the mITT population (Figure IIIA and IIIB in the online-only Data Supplement).

The proportion of patients with <15% progression in CAC Agatston score at week 52 was 61% for the SNF472 combined dosing groups and 48% for the placebo group in the mITT population (*P*=0.030; Figure 4A) and 64% and 43%, respectively, in the per-protocol population (*P*=0.002; Figure 4B).

Aortic Valve

Changes from baseline to week 52 in calcium volume scores in the aortic valve were 14% (95% CI, 5–24) for the SNF472 combined dosing groups and 98% (95% CI, 77–123) for placebo (*P*<0.001; Figure 2C). The mean change from baseline to week 52 was 28% (95% CI, 14–43) for the 300-mg dose group (*P*<0.001 versus placebo) and 1% (95% CI, −10 to 14) for the 600-mg dose group (*P*<0.001 versus placebo; Figure IIC in the online-only Data Supplement).

Corresponding results for calcium Agatston scores were 14% (95% CI, 2–28) for the SNF472 combined dosing groups and 186% (95% CI, 145–235) for the placebo group (*P*<0.001; Figure 2D). The mean change from baseline to week 52 was 33% (95% CI, 14–54) for the 300-mg dose group (*P*<0.001 versus placebo) and −2% (95% CI, −16 to 16) for the 600-mg dose group (*P*<0.001 versus placebo; Figure IID in the online-only Data Supplement).

Similar results for progression of calcium volume and Agatston scores were obtained in the per-protocol population of patients who completed 52 weeks of treatment (Figure 3C and 3D) and in sensitivity analyses that used multiple imputation for missing data in the mITT population (Figure IIIC and IIID in the online-only Data Supplement).

Thoracic Aorta

Changes from baseline to week 52 in calcium volume scores in the thoracic aorta were 23% (95% CI, 16–30) for the SNF472 combined dosing groups and 28% (95% CI, 19–38) for the placebo group (*P*=0.40; Figure 2E). The mean change from baseline to week 52 was 25% (95% CI, 16–35) for the 300-mg dose group (*P*=0.63 versus placebo) and 21% (95% CI, 11–32) for the 600-mg dose group (*P*=0.34 versus placebo; Figure IIE in the online-only Data Supplement).

Corresponding results for calcium Agatston scores were 29% (95% CI, 20–38) for the SNF472 combined dosing groups and 32% (95% CI, 21–45) for the placebo group (*P*=0.66; Figure 2F). The mean change from baseline to week 52 was 30% (95% CI, 19–43) for the 300-mg dose group (*P*=0.82 versus placebo) and 28% (95% CI, 15–42) for the 600-mg dose group (*P*=0.61 versus placebo; Figure IIF in the online-only Data Supplement).

Similar results for progression of calcium volume and Agatston scores were obtained in the per-protocol population of patients who completed 52 weeks of treatment (Figure 3E and 3F) and in sensitivity analyses that used multiple imputation for missing data in the mITT population (Figure IIIE and IIIF in the online-only Data Supplement).

Composite Safety End Point

The incidence of the composite safety end point in the SNF472 300 mg, SNF472 600 mg, and placebo groups was 8%, 7%, and 11%, respectively (Table 3). The hazard ratio for the composite safety end point for the SNF472 combined dosing groups versus placebo was 0.60 (95% CI, 0.26–1.37; *P*=0.22).

Adverse Events

Adverse events occurred in 79 of 92 patients (86%) in the SNF472 300 mg group, 84 of 91 patients (92%) in the SNF472 600 mg group, and 78 of 90 patients (87%) in the placebo group (Table 4). Serious adverse events occurred in 38 patients (41%) in the SNF472 300 mg group, 55 patients (60%) in the SNF472 600 mg group, and 49 patients (54%) in the placebo group. An investigator considered 1 serious adverse event (acute hepatic failure in the SNF472 300 mg group) to

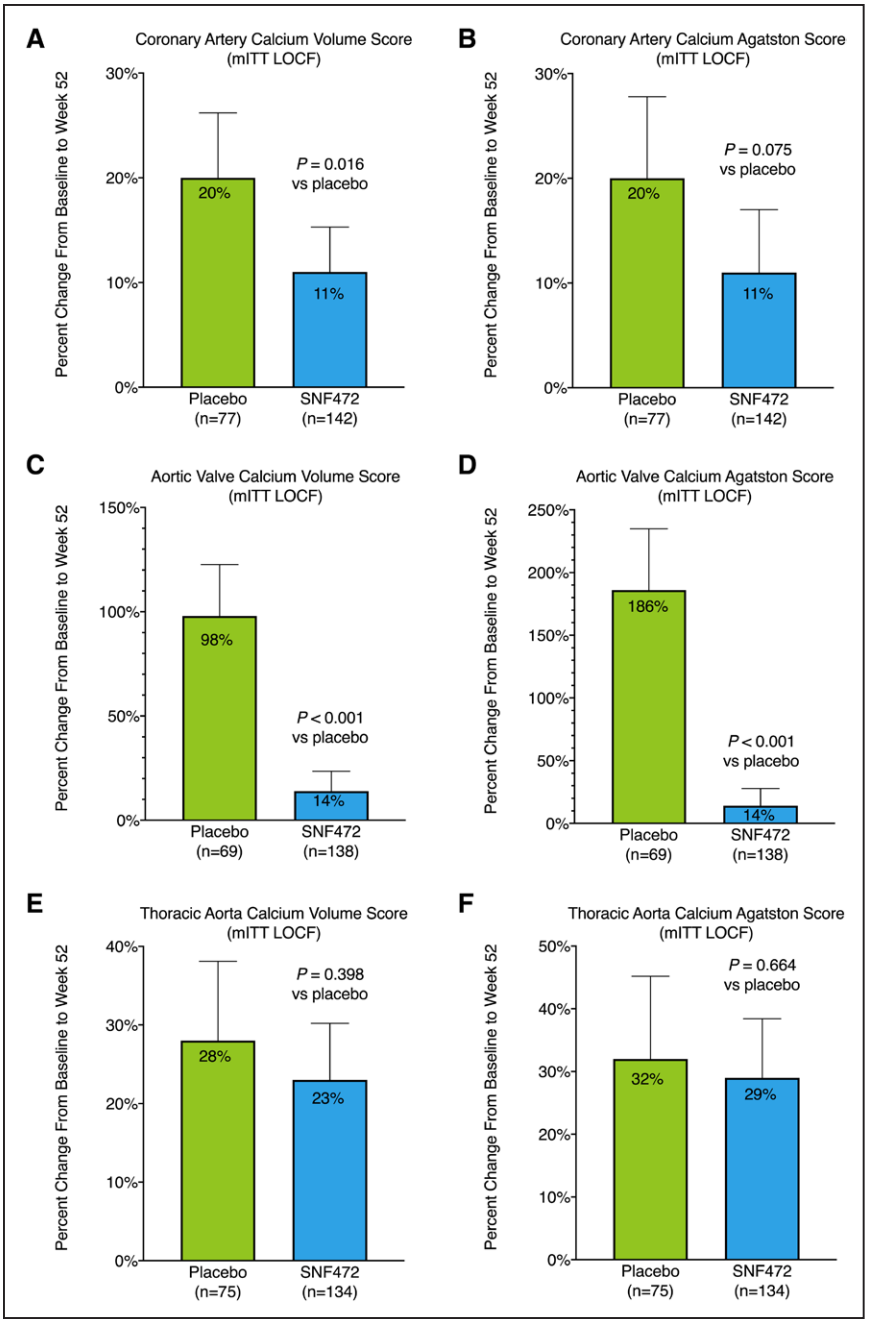

Figure 2. Mean (95% CI) change from baseline to week 52 for calcium scores in the SNF472 combined dosing groups vs placebo.
Modified intention-to-treat population with last observation carried forward (mITT LOCF). **A**, Coronary artery calcium volume score. **B**, Coronary artery calcium Agatston score. **C**, Aortic valve calcium volume score. **D**, Aortic valve calcium Agatston score. **E**, Thoracic aorta calcium volume score. **F**, Thoracic aorta calcium Agatston score.

be related to study drug. The patient had a history of HIV and multiple comorbidities. The event resolved, and the patient completed the week 52 visit. The Data and Safety Monitoring Board reviewed the event and considered it to be unrelated to study drug.

Adverse events led to study drug discontinuation for 13 patients (14%) in the SNF472 300 mg group, 26 patients (29%) in the SNF472 600 mg group, and 18 patients (20%) in the placebo group. A majority of these study drug discontinuations were for kidney transplantation in 27 patients overall (6 [7%] SNF472 300 mg, 12 [13%] SNF472 600 mg, and 9 [10%] placebo). No other event led to study drug withdrawal for >2 patients.

No clinically significant abnormalities were identified from analyses of clinical laboratory values (hematology and chemistry) with SNF472 compared with placebo (Table II in the online-only Data Supplement).

Death occurred in 1 patient in the SNF472 300 mg group (multiple organ dysfunction syndrome), 6 patients in the SNF472 600 mg group (1 each resulting from aortic stenosis, arteriosclerosis, hypotension, cardiac arrest, septic shock, and epilepsy), and 5 patients in the placebo group (1 each resulting from congestive heart failure, multiple organ dysfunction syndrome, sepsis, postprocedural complication, and renal transplantation). Investigators considered none of the deaths to be

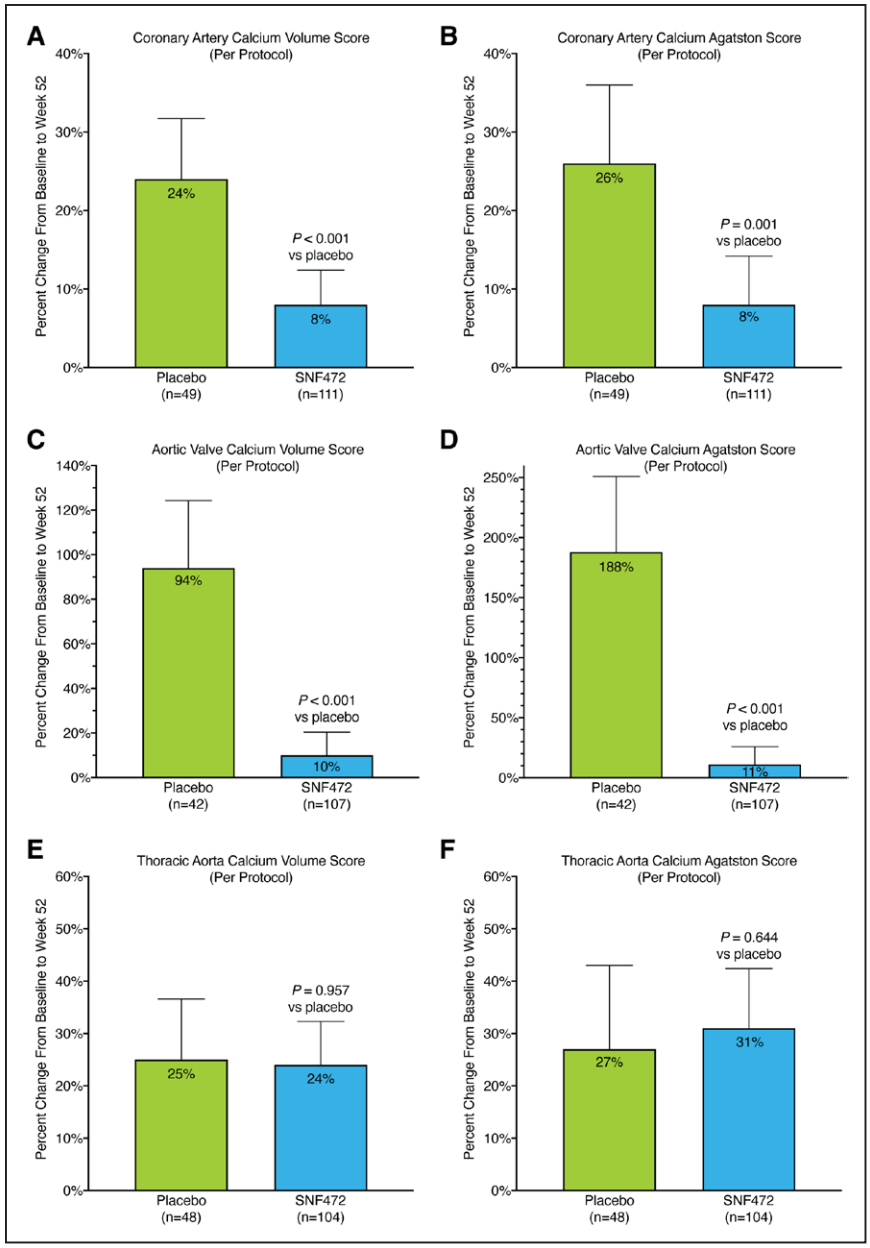

Figure 3. Per-protocol analyses of mean (95% CI) change from baseline to week 52 for calcium scores in the SNF472 combined dosing groups vs placebo.
Per-protocol population without data imputation. **A**, Coronary artery calcium volume score. **B**, Coronary artery calcium Agatston score. **C**, Aortic valve calcium volume score. **D**, Aortic valve calcium Agatston score. **E**, Thoracic aorta calcium volume score. **F**, Thoracic aorta calcium Agatston score.

related to study drug. The Data and Safety Monitoring Board did not identify any safety signals.

DISCUSSION

In this international, multicenter, randomized, double-blind placebo-controlled clinical trial, we showed that SNF472, a selective inhibitor of the formation and growth of hydroxyapatite crystals, when infused during each hemodialysis session for 1 year, attenuated the progression of coronary artery and aortic valve calcification relative to placebo. These results are remarkable in view of the concomitant use of drugs shown in previous studies to potentially attenuate CAC such as the non–calcium-based phosphate binder sevelamer and the calcimimetic cinacalcet.[19,28,29] In those previous studies, patients receiving hemodialysis assigned placebo demonstrated a 35% to 40% average rate of progression of CAC per year, nearly double the rate of progression seen in placebo-treated patients in this study. Our power calculations assumed a CAC volume score progression of 18.5% for SNF472-treated patients and 35% for placebo-treated patients (a 47% relative difference in progression). These assumptions were based on previous published rates of progression. Although the observed progression of CAC in placebo-treated patients in CaLIPSO was slower than expected, in part because of the use of non–calcium-based phosphate binders and calcimimetics in many patients, the relative difference of 45% was very close to what we expected.

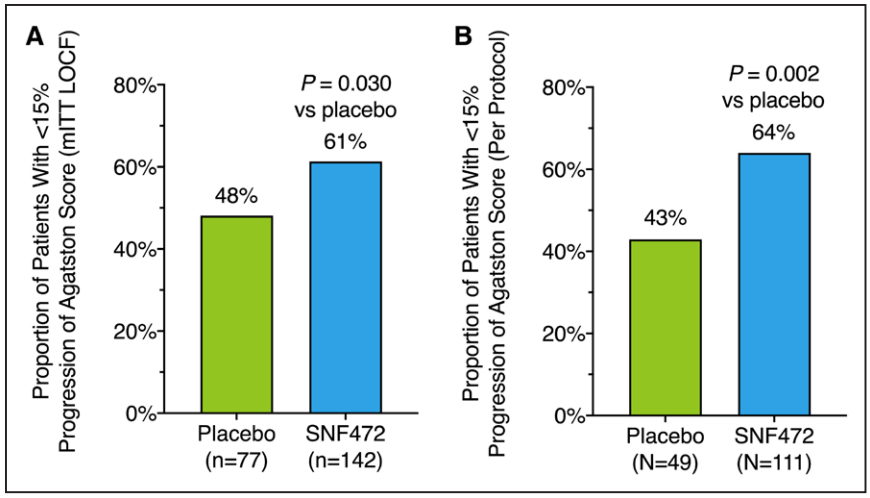

Figure 4. Proportion of patients with <15% progression from baseline to week 52 in coronary artery calcium Agatston score. **A**, Modified intention-to-treat population with last observation carried forward (mITT LOCF). **B**, Per-protocol population.

At baseline, all patients had coronary calcium with CAC Agatston scores between 100 and 3500 units. In addition, 57% of patients had calcification of the aortic valve, and 96% had calcification of the thoracic aorta.[24] Because the primary aim of the study was to show that SNF472 effectively inhibits progression of coronary calcification, we enrolled patients with moderate to high CAC scores who generally show a faster progression. These results should be seen in the context of the current knowledge of cardiovascular calcification and clinical practice.

Previous meta-analyses showed that the prescription of non–calcium-based phosphate binders is associated with attenuation of the progression of cardiovascular calcification and improved survival.[17,18] The association between cardiovascular calcification and morbidity and mortality has been shown in the general population in numerous previous publications.[6,30–32] As a result, CAC has been recognized as a risk-modifying marker in the most recent guidelines from the American Heart Association and American College of Cardiology for the primary prevention of atherosclerotic cardiovascular disease.[33] The evidence is less extensive but nonetheless convincing in patients with ESKD. Both CAC measured on CT[8,9,34–36] and simple measures of calcification such as radial and femoral artery, as well as aortic calcification seen on planar x-rays,[37–42] have been shown to be strongly associated with adverse events in ESKD.

Table 3. Composite Safety End Point

	Placebo (n=90), n (%)	SNF472 300 mg (n=92), n (%)	SNF472 600 mg (n=91), n (%)
Any composite safety end-point event	10 (11.1)	7 (7.6)	6 (6.6)
Cardiovascular death	0	0	1 (1.1)
Nonfatal myocardial infarction	4 (4.4)	4 (4.3)	1 (1.1)
Nonfatal stroke	2 (2.2)	1 (1.1)	0
Heart failure	4 (4.4)	1 (1.1)	2 (2.2)
Nonfatal cardiac arrest	0	1 (1.1)	2 (2.2)

Data are expressed as number (percent) of patients for the safety population.

It is well established that patients with ESKD develop cardiovascular calcifications well in excess of patients with normal or near-normal kidney function and that there are 2 distinct sites of arterial calcification in these patients: intimal and medial. The former is linked to traditional risk factors for atherosclerosis and inflammation, whereas the latter is found mostly (if not exclusively) in arteries of medium and large caliber and is more closely associated with the mineral and bone disorder typical of ESKD.[43] Calcification of medium and large arterial conduits is responsible for reduced vascular compliance, which can induce left ventricular hypertrophy and systolic/diastolic dysfunction in the long term. Reduced compliance, as measured by increased pulse pressure velocity, can result in reduced diastolic filling of the coronary arteries with a state of relative ischemia of the myocardium even in the absence of obstructive luminal disease.[44–46] Hence, arterial calcification in ESKD should be interpreted as a harbinger of severe complications and therefore worth pursuing as a target of therapy. Equally important is the impact of valvular calcification in ESKD,[47] particularly calcification of the aortic valve. Numerous patients have severe calcification of the left-sided cardiac valves with subsequent regurgitation or restriction of the mobility of the valve leaflets. These conditions in turn are associated with progressive left ventricular fibrosis, left ventricular hypertrophy, and dysfunction, as well as endocarditis and severe conduction abnormalities. In addition, surgical and interventional treatments proven efficacious in the general population may not exert a similar benefit in patients with ESKD. The reduction in progression of calcification of the aortic valve seen in this study is therefore encouraging.

Independently of the pathophysiology of cardiovascular calcification, the final step entails the formation of crystals of hydroxyapatite through active processes mimicking bone assembly. SNF472 is a selective inhibitor of hydroxyapatite crystallization and was effective at

Table 4. Adverse Events

	Placebo (n=90), n (%)	SNF472 300 mg (n=92), n (%)	SNF472 600 mg (n=91), n (%)
Any adverse event	78 (86.7)	79 (85.9)	84 (92.3)
Adverse events in >5% of patients in any group			
Renal transplantation	9 (10.0)	6 (6.5)	14 (15.4)
Diarrhea	10 (11.1)	7 (7.6)	12 (13.2)
Abdominal pain upper	2 (2.2)	11 (12.0)	2 (2.2)
Cough	8 (8.9)	10 (10.9)	9 (9.9)
Arteriovenous fistula site complication	8 (8.9)	7 (7.6)	9 (9.9)
Chest pain	9 (10.0)	2 (2.2)	3 (3.3)
Pneumonia	8 (8.9)	5 (5.4)	4 (4.4)
Pain in extremity	8 (8.9)	7 (7.6)	8 (8.8)
Dyspnea	8 (8.9)	5 (5.4)	7 (7.7)
Vomiting	4 (4.4)	1 (1.1)	8 (8.8)
Musculoskeletal pain	5 (5.6)	3 (3.3)	7 (7.7)
Hyperphosphatemia	0	0	7 (7.7)
Atrial fibrillation	2 (2.2)	5 (5.4)	7 (7.7)
Upper respiratory tract infection	6 (6.7)	2 (2.2)	4 (4.4)
Fluid overload	6 (6.7)	4 (4.3)	3 (3.3)
Nasopharyngitis	6 (6.7)	3 (3.3)	1 (1.1)
Fall	6 (6.7)	6 (6.5)	3 (3.3)
Bronchitis	5 (5.6)	1 (1.1)	4 (4.4)
Hypoglycemia	1 (1.1)	6 (6.5)	6 (6.6)
Arthralgia	4 (4.4)	6 (6.5)	2 (2.2)
Back pain	4 (4.4)	6 (6.5)	2 (2.2)
Dizziness	4 (4.4)	6 (6.5)	5 (5.5)
Hyperkalemia	3 (3.3)	6 (6.5)	5 (5.5)
Pain	5 (5.6)	4 (4.3)	3 (3.3)
Headache	5 (5.6)	3 (3.3)	3 (3.3)
Nausea	4 (4.4)	2 (2.2)	5 (5.5)
Gastrointestinal hemorrhage	0	0	5 (5.5)
Hypertension	4 (4.4)	3 (3.3)	5 (5.5)
Bradycardia	3 (3.3)	5 (5.4)	0
Any serious adverse event	49 (54.4)	38 (41.3)	55 (60.4)
Any adverse event leading to study drug withdrawal	18 (20.0)	13 (14.1)	26 (28.6)
Any adverse event leading to study discontinuation	10 (11.1)	7 (7.6)	13 (14.3)
Any grade ≥3 adverse event	41 (45.6)	38 (41.3)	48 (52.7)

Data are expressed as number (percent) of patients for the safety population.

delaying the progression of coronary artery and aortic valve calcification. Although the effects on calcification in the thoracic aorta were directionally consistent, between-group changes were not statistically significant. The thoracic aortas of patients included in the study were generally heavily calcified at baseline, and it may be difficult to delay further calcification at a late and very advanced stage of disease. The mere size of the arterial territory to be imaged may cause an increased measurement error with reduced reproducibility compared with the smaller coronary arteries and aortic valve.

Healthy bone continually undergoes quantitatively matched resorption and formation of its principal mineral phase hydroxyapatite.[48,49] An agent such as SNF472, which inhibits the growth of hydroxyapatite crystals, has the potential to affect bone formation and bone mineral density. Further studies of sufficient size and duration are necessary to determine whether SNF472 significantly reduces bone density or modifies the risk of fracture.

A small difference in calcification progression was evident between the 2 doses of SNF472. However, the study was not powered to address the efficacy difference between 300 and 600 mg of SNF472.

A few limitations in the CaLIPSO trial limit the direct extension of our findings to patients with ESKD with different baseline characteristics and the general population. By restricting inclusion to patients with preexisting CAC, we could not determine whether SNF472 prevents the initial development of CAC. The study sample was relatively small but on par with previous trials addressing the progression of cardiovascular calcification in patients with ESKD. The trial was not designed to test whether SNF472 reduced the frequency of cardiovascular events. Therefore, although the reported rates of events in the CaLIPSO trial support the safety of SNF472, its efficacy in preventing cardiovascular events needs to be tested in future trials. The study results are remarkable because the comparison was performed on top of standard of care for the management of cardiovascular disease and disorders of mineral metabolism.

Conclusions

Compared with placebo, 52 weeks of treatment with SNF472 significantly attenuated the progression of coronary artery and aortic valve calcification in patients with ESKD receiving hemodialysis. These results were obtained on a background of contemporary management of mineral metabolism disorder in patients receiving hemodialysis, including drugs with the potential to attenuate, at least partially, the progression of cardiovascular calcification in patients with ESKD. Further studies are needed to determine the effects of SNF472 on cardiovascular events.

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Correspondence

Paolo Raggi, MD, Professor of Medicine, Division of Cardiology, University of Alberta 5A9-014, 11220 83rd Ave NW, Edmonton, AB T6G 2B7, Canada. Email raggip@gmail.com

Affiliations

Department of Medicine, Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Canada (P.R.). Research, Innovation and Brand Reputation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy (A.B.). Department of Medicine, University of Rochester Medical Center, NY (D.B.). Department of Nephrology, Fundació Puigvert and Universitat Autònoma, IIB Sant Pau, REDinREN, Barcelona, Spain (J.B.). Nephrology Unit, Hospital Universitario Reina Sofia, IMIBIC, REDinREN, Córdoba, Spain (M.R.). Department of General Internal Medicine and Nephrology, Robert-Bosch-Krankenhaus, Stuttgart, Germany (M.K.). Department of Renal Medicine, Salford Royal NHS Foundation Trust, UK (S.S.). Research and Development, Sanifit Therapeutics, Palma, Spain (C.S., J.P.). Research and Development, Sanifit Therapeutics, San Diego, CA (K.G., C.P. R.G., A.G.). Department of Medicine, Stanford University, Palo Alto, CA (A.G., G.M.C.). University of the Balearic Islands, Palma, Spain (J.P.).

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