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Sponsor: Sanofi **Drug substance(s):** SAR407899A	**Study Identifiers:** U1111-1123-5699, NCT01485900, 2011-003793-83 **Study code:** TDR12446
Title of the study: A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and hemodynamics of ascending repeated oral doses of SAR407899A in patients with moderate chronic kidney disease on stable angiotensin converting enzyme-inhibitor (ACE-I) treatment	
Study center(s): 2 centers in Europe (1 center each in Romania and Moldova)	
Study period: Date first participant enrolled: 21/Nov/2011 Date last participant:completed: 14/Aug/2012 Study Status: Completed	
Phase of development: Phase 1	
Objectives: Primary objective: • To assess the tolerability and safety of ascending repeated oral doses of SAR407899A in patients with moderate chronic kidney disease (CKD) on stable ACE-I. Secondary objectives: To assess in patients with moderate CKD: • The effect of concomitant multiple doses of SAR407899A and ACE-Is on office and 24-hour ambulatory blood pressure (BP) and heart rate (HR) • The effect of repeated multiple doses of SAR407899A on the pharmacodynamic response to ACE-Is (AcSDKP, a hemoregulatory tetrapeptide of the composition N-Acetyl-Ser-Asp-Lys-Pro) • The pharmacokinetic (PK) profile of repeated oral administration of SAR407899A during co-administration of ACE-Is	
Methodology: Multi-center, double-blind, randomized, placebo-controlled, sequential 20-day repeated ascending oral dose study in patients with moderate CKD, at 2 dose levels of SAR407899A.	

Number of participants:

Planned: 20

Randomized: 20

Treated: 20

Evaluated:

Safety: 20

Pharmacodynamics: 20

Pharmacokinetics: 15

Diagnosis and criteria for inclusion:

Male or female patients between 18 and 79 years of age inclusive, with stage 3 CKD as defined by Kidney Disease Outcome Quality Initiative; receiving stable ACE-I treatment for at least 2 months prior to screening; body mass index between 18.0 and 35.0 kg/m^2 inclusive; estimated glomerular filtration rate (eGFR) ≤59 but >30 mL/min/1.73 m^2; resting supine BP of 120 mmHg < systolic BP (SBP) <160 mmHg and 80 mmHg < diastolic BP (DBP) <100 mmHg; hepatic enzymes (alanine aminotransferase, aspartate aminotransferase) and bilirubin levels <2 x upper limit of normal range; female patients had to be postmenopausal or surgically sterilized.

Study products

Investigational medicinal product(s): SAR407899A

Formulation: 5 and 10 mg strength capsules (same size and appearance)

Route(s) of administration: Oral, with 240 mL of noncarbonated water, taken with or without food

Dose regimen:

1st dose group: patients received 5 mg SAR407899A (base) once daily (QD) for 3 days followed by 10 mg SAR407899A (base) QD for 3 days. From Day 7 to Day 20 patients were treated with the maintenance dose of 20 mg SAR407899A (base) QD.

2nd dose group: patients received 5 mg SAR407899A (base) QD for 6 days. From Day 7 to Day 20 patients were treated with the maintenance dose of 10 mg SAR407899A (base) QD. Originally planned: 10 mg SAR407899A QD for 3 days followed by 20 mg SAR407899A QD for 3 days. From Day 7 to Day 20 it was planned to treat the patients with the maintenance dose of 30 mg SAR407899A.

Investigational medicinal product(s): Placebo

Formulation: capsules (same size and appearance as SAR407899A capsules)

Route(s) of administration: oral, with 240 mL of noncarbonated water, taken with or without food

Dose regimen: 0 mg QD

Duration of treatment/participation: 20 days

Duration of observation: Approximately 8 weeks (including screening, study period, and end-of-study [EOS] visit)

Criteria for evaluation:

Pharmacodynamics:

- Standing and supine SBP, DBP, and HR.
- Ambulatory BP monitoring (ABPM): 24-hour ABPM measures (SBP, DBP, mean arterial pressure [MAP], HR). Individual mean systolic/diastolic day and nighttime BP obtained from 24-hour ABPM.
- Area under the concentration versus time curve calculated using the trapezoidal method from 0 to 12 hours (AUC0-12) of AcSDKP in plasma following 14-day multiple dosing of 20 or 10 mg SAR407899A or matching placebo on top of standard treatment with ACE-Is.
- Explorative urine proteomics.

Safety:

- Adverse events (AEs) reported by the patients or noted by the Investigators
- Physical examination including weight
- Tympanic body temperature
- Clinical laboratory evaluations including hematology, biochemistry, coagulation, and urinalysis
- Standard 12-lead electrocardiogram (ECG)
- Urine and blood renal function marker panel (urea, creatinine, cystatin C)

Pharmacokinetics:

- Plasma concentrations of SAR407899 were used to determine the following PK parameters on Day 20: maximum observed concentration (Cmax), (first) time to reach the maximum concentration (tmax), area under the concentration versus time curve calculated using the trapezoidal method during a dosing interval (AUC0-24), terminal half-life (t1/2z), apparent total body clearance at steady state (CLss/F), and apparent volume of distribution at steady state (Vss/F). Plasma concentration observed just before SAR407899A administration during repeated dosing (Ctrough) on Day 2 to Day 10, Day 14, Day 19, and Day 20.
- Urine concentrations of SAR407899 were used to determine the following PK parameters on Day 20: renal clearance (CLR), cumulated amount excreted in urine from time 0 to 24 hours after the drug administration (Ae0-24), and fraction of the dose excreted in urine from time 0 to 24 hours (Fe0-24).
- Plasma concentrations of the metabolite SAR407899-M3 were used to determine the following PK parameters on Day 20: Cmax, tmax, AUC0-24, t1/2z, and the metabolic ratio of SAR407899-M3 to SAR407899, Rmet. Plasma concentration of SAR407899-M3 observed just before SAR407899A administration during repeated dosing (Ctrough) on Day 2 to Day 10, Day 14, Day 19, and Day 20.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Samples were collected at the following time points for AcSDKP:

- -24, -22, -20, -18, -16, and -12 hours on Day -1
- 0, 2, 4, 6, 8, and 12 hours on Day 20

Plasma assays of AcSDKP were determined by a validated enzyme immunoassay with a lower limit quantification (LLOQ) of 0.585 nM.

Explorative urine proteomic samples were collected in the morning of Day -2 and Day 21.

Samples were collected at the following time points for the determination of SAR407899 and SAR407899-M3 plasma concentrations:

- Predose on Days 1 to 10, Day 14, and Day 19
- Day 20 at predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose and EOS

Plasma concentrations of SAR407899 were determined by a validated liquid chromatography with tandem mass spectrometry method with a LLOQ of 1 ng/mL, and plasma concentrations of SAR407899-M3 by an exploratory liquid chromatography with tandem mass spectrometry method with a LLOQ of 2 ng/mL.

Urine samples were collected at the following time points for the determination of SAR407899 concentrations:

- Day -1: -24 to 0 hours
- Day 20: 0 to 24 hours postdose

Urine assays of SAR407899 were determined by a validated liquid chromatography tandem mass spectrometry method with a LLOQ of 10 ng/mL.

Statistical methods:

Safety:

The safety evaluation was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots). The on-treatment phase was defined as the time from the first dose of investigational medicinal product administration up to the EOS visit (inclusive).

The safety analysis was conducted on all patients who received at least one dose of study drug. For AEs, frequencies of treatment-emergent adverse events (TEAEs) classified by the Medical Dictionary for Regulatory Activities (Version 15.0) system organ class and preferred term were tabulated by treatment. All AEs were listed. Potentially Clinically Significant Abnormalities (PCSAs; company definition for Phase 2/3 studies, version dated 14 September 2009) for clinical laboratory, vital sign, and ECG data, and out-of-normal range values for clinical laboratory data were flagged and summarized in frequency tables by treatment. In addition, raw data and changes from baseline in ECG and renal function parameters (creatinine, urea, cystatin C) were summarized in descriptive statistics.

Pharmacodynamics:

Mean BP and HR from ABPM and from office vital signs assessments were summarized, along with their changes from baseline, by position, treatment group, day, and time. Mean profile plots of raw data and change from baseline were also provided.

For office vital signs assessments, descriptive statistics of maximal decrease (for BP) or increase (for HR) from baseline (Emax), as well as the corresponding timepoints (Etmax), were provided by position, treatment group, and day , using the vital signs assessments (supine and orthostatic only) on Day 14 and Day 19. For each parameter (SBP, DBP, and HR) and position (supine and orthostatic), Emax treatment difference point estimates and 90% confidence intervals (CI) for each dose versus placebo were computed on Day 14 and Day 19 separately using a linear mixed effects model.

AcSDKP AUC0-12 values and change from baseline were summarized by treatment group and day using descriptive statistics. Mean and individual time profiles plots for AcSDKP values were provided on each day. AcSDKP AUC0-12 ratio point estimate and 90% CI for each dose versus placebo on Day 20 were computed using a linear fixed effects model on the log-scale.

Pharmacokinetics:

Pharmacokinetic parameters were summarized using descriptive statistics. The occurrence of steady-state was assessed by visual inspection of mean Ctrough values over time. Dose proportionality was assessed by estimating the dose ratio using a fixed effect model on log-transformed Cmax and AUC0-24 on Day 20. For t1/2z on Day 20, the dose effect was assessed with a linear fixed effect model.

Summary Results:

Population characteristics:

Initially it was planned to randomize a total of 24 CKD-3 patients. However, dose Cohort 1 (maintenance dose of 20 mg) was stopped prematurely because 2/8 patients experienced orthostatic hypotension (OH) which met the criteria given in the "guidance for stopping rules" of the study protocol (defined by a decrease in SBP ≥30 mmHg within 3 minutes when changing from supine to standing position). Following the "guidance for stopping rules", the double blind was broken by the Sponsor for the concerned patients 2 patients. Since both patients were given SAR407899A, study drug administration was stopped in Cohort 1. It was decided to proceed to the Cohort 2 with reduction of the maintenance dose to 10 mg and a prolongation of the titration phase at 5 mg from 3 to 6 days as shown in the table below:

Table 1 - Dose levels - planned and actual

	Cohort 1	Cohort 2	
Days	planned and actual dose	planned dose	actual dose
1 to 3	5 mg	10 mg	5 mg
4 to 6	10 mg	20 mg	5 mg
7 to 20	20 mg	30 mg	10 mg

A total of 20 CKD-3 patients (14 male and 6 female) were randomized and exposed to study treatment (Cohort 1: 6 active and 2 placebo; Cohort 2: 9 active and 3 placebo), with 18 patients completing the study. Demographics and mean eGFR at baseline were generally similar across the treatment groups with the exception of gender: in Cohort 2 only 1/9 patients exposed to SAR407899A were female compared to 3/6 patients in Cohort 1 and 2/5 patients in the placebo group.

Dosage and duration

Not all patients received the planned dose levels as outlined in Table 1. Due to safety concerns (recurrent episodes of symptomatic or asymptomatic OH) the titration phase was prolonged for some patients. In order not to exceed the overall treatment duration of 20 days, the maintenance dose was shortened accordingly in these patients as follows:

Placebo group:

- Subject 1: the titration phase was prolonged from 6 to 10 days and the maintenance phase shorted from 14 days to 10 days (total treatment duration 20 days as planned).

Cohort 1:

- Subject 1: received SAR407899 5 mg from Day 1 to Day 4 and 10 mg from Day 5 to Day 7, followed by SAR407899 20 mg from Day 8 to Day 20.
- Subject 2: received SAR407899 5 mg from Day 1 to Day 4. The subject was then up-titrated to SAR407899 10 mg from Day 5 to Day 8 and up-titrated again to the targeted dose of 20 mg on Day 9 and Day 10. Due to the occurrence of OH on Day 10, the dose was reduced to 10 mg on Day 11 and this dose was kept until the patient was withdrawn from the study on Day 15.

- Subject 3: received the intended doses of SAR407899 on Day 1 to Day 10 but was then withdrawn due to the Sponsor's decision to stop dosing the first cohort.

Cohort 2:

- Subject 1: received the intended SAR407899 5 mg doses on Day 1 to Day 6 and was then up titrated to SAR407899 10 mg on Day 7 as planned. Due to recurrent episodes of symptomatic and asymptomatic OH, the subject received SAR407899 5 mg for the remaining 13 days of treatment.

Safety results:

No serious adverse events were reported during the study. Two patients in Cohort 1 at the SAR407899A 20 mg maintenance dose discontinued the study treatment. One patient discontinued the study due to several episodes of symptomatic and asymptomatic OH and the second patient's discontinuation was due to the Sponsor's decision to stop dosing the first cohort as the stopping rules defined in the study protocol were met. Overall, TEAEs were more frequent in patients receiving SAR407899A (12/15 [80%]) than in patients receiving placebo (3/5 [60%]). The most frequently reported TEAEs were OH, nasopharyngitis, postural dizziness, hyperkalemia, and blood creatinine increased. All TEAEs were either mild or moderate in intensity.

Orthostatic hypotension was reported as an AE in 2/5 placebo patients (4 episodes), in 3/6 patients in Cohort 1 (7 episodes), and in 2/9 patients in Cohort 2 (3 episodes). In the placebo treatment group all events of OH were asymptomatic, whereas in the cohorts receiving active drug, 5 out of 10 episodes of OH were symptomatic.

The individual maximum decrease in SBP was 49 mmHg (supine 109 mmHg, standing 60 mmHg) with a parallel decrease in DBP of 18 mmHg (supine 62 mmHg, standing 44 mmHg) and an increase in HR of 29 bpm (supine 72 bpm, standing 101 bpm) on Day 7, 2 hours after administration of SAR407899A 10 mg to 1 subject (who was finally withdrawn from the study due to recurrent episodes of OH). Postural dizziness was only reported in SAR407899A treatment groups: in 1 patient in Cohort 1 during the titration phase and in 2 patients in Cohort 2 during the titration and maintenance phase. The majority of episodes of OH or postural dizziness occurred around 2 hours after study drug administration.

All 3 events of hyperkalemia occurred in Cohort 2 during the maintenance dose phase. Treatment-emergent AEs of blood creatinine increased were reported in 1/5, 1/6, and 2/9 patients in the placebo group, Cohort 1, and Cohort 2, respectively.

For laboratory parameters, PCSAs were observed occasionally in the placebo and SAR407899A treatment groups. No PCSAs were reported for any liver function parameters. Abnormal potassium (≥5.5 mmol/L) was observed in 1/6 and 5/9 patients in Cohort 1 and Cohort 2, respectively. Increases in serum creatinine ≥30% change from baseline were observed in 1/5, 1/6, and 2/9 patients in the placebo group, Cohort 1, and Cohort 2, respectively. The maximum change in Cohort 1 was 44.5% on Day 10 (baseline: 129 µmmol/L, Day 10: 187 µmmol/L, EOS: 139 µmmol/L), in Cohort 2 a maximum change of 37.9% was observed on Day 14 (baseline: 103 µmmol/L, Day 14: 141 µmmol/L, EOS: 105 µmmol/L) and on Day 10 (baseline: 128 µmmol/L, Day 10: 177 µmmol/L, EOS: 150 µmmol/L), and under placebo the maximum change was 40.5% (baseline: 149 µmmol/L, Day 10: 209 µmmol/L, EOS: 140 µmmol/L). Two patients had an increase in cystatin C ≥30%: in Cohort 1 on Day 10 (30.5%) and in Cohort 2 on Day 14 (35.8%), compared to no patients given placebo.

No PCSAs were observed for HR in patients given SAR407899A. Patients with PCSAs for SBP ≤95 mmHg with a decrease from baseline ≥20 mmHg were more frequent in Cohort 1 (4/6 patients), than in Cohort 2 (2/9 patnts) or the placebo group (0/5 patients). No clear dose effect could be seen for orthostatic SBP and DBP following SAR407899A treatment as the numbers of PCSAs in Cohort 1 (20 mg maintenance dose) were comparable to placebo.

There were a few PCSAs for ECG parameters in the SAR407899A treatment groups, without any dose-incidence relationship. Two patients experienced QRS prolongation, 1 in each of the SAR407899 treatment groups. PR prolongation ≥220 ms was observed in 2/5 patients in the placebo treatment group and only in 1/9 patients in Cohort 2.

Four patients had a prolonged QTc interval (1 patient in the placebo group and 3/9 patients in Cohort 2). No patient had a prolonged QTc interval of ≥500 ms. Four out of 15 patients who received SAR407899A (2 in each dose cohort) had a borderline increase in QTc from baseline (30 to 60 ms) compared to no patients who received placebo. No patients had a QTc increase from baseline >60 ms.

Pharmacodynamic results:

Results of the ABPM showed treatment with SAR407899A 20 mg (Cohort 1) decreased mean 24-hour SBP and DBP on Day 15 and Day 20, compared to placebo (Table presented below). These effects were even more pronounced during daytime measurements. Mean 24-hour MAP results were similar to those for SBP and DBP.

Table 3 - ABPM - summary of changes from baseline for mean 24-hour data

Treatment	Mean 24-hr HR (bpm ± SD)	Mean 24-hr SBP (mmHg ± SD)	Mean 24-hr DBP (mmHg ± SD)	Mean 24-hour MAP (mmHg ± SD)
Placebo				
- Day 15	-2.6 ± 2.3	-5.2 ± 17.3	-3.4 ± 8.4	-3.8 ± 11.3
- Day 20	-5.6 ± 1.5	-2.0 ± 17.5	-2.0 ± 8.1	-1.8 ± 10.7
Cohort 1				
- Day 15	2.8 ± 3.3	-8.6 ± 19.6	-8.0 ± 11.3	-8.4 ± 13.8
- Day 20	2.8 ± 3.4	-8.3 ± 19.6	-7.8 ± 11.3	-8.0 ± 14.1
Cohort 2				
- Day 15	0.9 ± 4.8	-6.8 ± 10.6	-4.0 ± 8.3	-4.7 ± 8.9
- Day 20	0.1 ± 3.7	-5.0 ± 11.2	-3.4 ± 6.9	-3.9 ± 8.2

Cohort 1: 5 mg SAR407899A from D1 to D3, followed by 10 mg from D4 to D6. From D7 to D20 patients were treated with the maintenance dose of 20 mg SAR407899A.

Cohort 2: 5 mg SAR407899A from D1 to D6. From D7 to D20 patients were treated with the maintenance dose of 10 mg SAR407899A.

Results of the office vital sign assessments showed a clear decrease in the supine DBP Emax value observed on Day 14 and Day 19 in both Cohort 1 and Cohort 2, compared to placebo. Supine SBP measurements should be interpreted with caution due to the large variability observed in Cohort 1.

Table 4 - E_{max} mean ± SD supine and orthostatic vital sign parameters

Treatment	HR (bpm)	SBP (mmHg)	DBP (mmHg)	Orthostatic HR (bpm)	Orthostatic SBP (mmHg)	Orthostatic DBP (mmHg)
Placebo						
- Day 14	18.4 ± 16.3	-32.2 ± 19.3	-17.2 ± 10.0	12.6 ± 9.3	-23.4 ± 10.0	-21.8 ± 6.3
- Day 19	12.2 ± 12.5	-22.2 ± 20.9	-11.8 ± 7.2	10.4 ± 8.9	-19.0 ± 13.0	-15.4 ± 9.0
Cohort 1						
- Day 14	14.2 ± 6.5	-34.8 ± 28.8	-24.6 ± 16.6	14.2 ± 9.0	-25.8 ± 8.7	-24.4 ± 9.6
- Day 19	18.5 ± 7.4	-34.3 ± 32.0	-29.0 ± 26.0	15.3 ± 9.4	-18.3 ± 4.8	-24.0 ± 13.7
Cohort 2						
- Day 14	11.2 ± 6.3	-27.6 ± 16.0	-22.7 ± 17.9	22.2 ± 23.4	-21.0 ± 9.1	-18.3 ± 8.7
- Day 19	11.6 ± 5.7	-21.7 ± 14.3	-19.0 ± 9.1	17.0 ± 21.6	-14.3 ± 10.6	-13.4 ± 3.6

Cohort 1: 5 mg SAR407899A from D1 to D3, followed by 10 mg from D4 to D6. From D7 to D20 patients will be treated with the maintenance dose of 20 mg SAR407899A. Cohort 2: 5 mg SAR407899A from D1 to D6. From D7 to D20 patients will be treated with the maintenance dose of 10 mg SAR407899A.
Emax = Maximal change from baseline (decrease for DBP and SBP, increase for HR)
Only planned values, without time deviations (time deviations: <8 min in supine or not 2, 3 or 4 min in standing position), will be taken into account for the calculation. Orthostatic = standing after 3 minutes – supine after 10 minutes

For the supine trough vital sign assessments, there was a clear decrease in the mean changes from baseline in Cohort 1 for supine SBP and DBP and a parallel increase in HR, compared to placebo (placebo: SBP: -9.4 mmHg, DBP: -2.0 mmHg, HR: -0.8 bpm; Cohort 1: SBP: -20.75 mmHg; DBP: -15.50 mmHg; HR: 8.75 bpm). For Cohort 2, there was no clear difference in the change from baseline in SBP, DBP, and HR compared to placebo (SBP: -4.78 mmHg, DBP: -6.67 mmHg, HR: 0.44 bpm).

The mean change from baseline in AUC0-12 of AcSDKP was comparable between the placebo and the SAR407899A treatment groups, indicating a lack of an effect of multiple dosing of SAR407899A on the pharmacodynamic effect of ACE-Is.

Pharmacokinetic results:

For the PK results, SAR407899 20 mg (targeted) and SAR407899 10 mg (targeted) refer to the titration phase and the maintenance phase with maintenance doses of 20 mg and 10 mg, respectively.

Following repeated oral administration of maintenance doses of 20 mg or 10 mg SAR407899 to patients with moderate CKD and on treatment with ACE-Is, steady state was reached on Day 20. SAR407899 appeared rapidly in plasma, with a median t_{max} of 2 to 3 hours. Exposures, C_{max}, and AUC_{0-24}, generally increased in a more than dose proportional manner. The geometric mean C_{max} increased by 2.93-fold [90% CI: (2.17; 3.94)] for a 2-fold increase in dose. Similarly, AUC_{0-24} increased by 2.66-fold [90% CI: (1.96, 3.60)]. Variability as assessed by CV% was moderate to low being <32% for C_{max} and <30% for AUC_{0-24}. The pooled estimate for the geometric mean of $t_{1/2z}$ was 38.3 hours; there was no trend with dose.

Table 5 - Pharmacokinetic Parameters. Descriptive statistics for SAR407899 in plasma

Mean ± SD (Geometric Mean) [CV%]	**Plasma SAR407899**	
	SAR407899 20 mg (targeted)*	SAR407899 10 mg (targeted)*
	Day 20	Day 20
N	4	8
Cmax (ng/mL)	79.4 ± 24.5 (76.5) [30.9]	26.8 ± 5.81 (26.1) [21.7]
tmaxa	2.02	2.75
(h)	(1.50 - 2.50)	(1.50 - 4.00)
AUC0-24	1000 ± 154 (993) [15.3]	389 ± 114 (374) [29.3]
(ng•h/mL)	38.9 ± 5.08	38.6 ± 7.84
t1/2z		
(h) CLss/F	(38.7) [13.1]	(37.9) [20.3]
(L/h)	20.3 ± 3.13 (20.1) [15.4]	27.9 ± 9.04 (26.8) [32.4]
Vss/F	989 ± 353	1220 ± 231
(L)	(944) [35.7]	(1200) [18.9]

[a] Median
(Min - Max)
Profile of 1 subject, SAR407899 10 mg (targeted), was excluded
Source = PKS Study : TDR12446; Scenario: P-D-A-EV-OD, Version 1
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*All patients in the PK analysis received the targeted dose for 14 days except 1 patient in the 20 mg cohort and 1 patient in the 10 mg cohort. As the titration phase was prolonged in 1 Patient on the 20mg cohort, this patient received the maintenance dose for only 13 days (planned 14 days). One Patient in the 10 mg cohort who did not receive the targeted maintenance dose of 10 mg was excluded from PK analysis.

On Day 20, mean urinary excretion of unchanged SAR407899 within 24 hours after dosing ranged from 47.1% to 48.9% of the administered dose.

On Day 20, the mean metabolic ratio of SAR407899-M3 to SAR407899 in plasma ranged from 0.364 to 0.449.

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