Clinical Study Report Synopsis	
Drug Substance	Verinurad / RDEA3170
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A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled Study of Verinurad and Allopurinol in Patients with Chronic Kidney Disease and Hyperuricaemia (SAPPHIRE)

Study dates: First subject enrolled: 28 August 2019
Last subject last visit: 22 November 2021
The analyses presented in this report are based on a clinical data lock date of 17 December 2021

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

205 study centres across 12 countries, including sites in Czech Republic, France, Hungary, Israel, Italy, Mexico, Poland, Romania, Slovakia, South Africa, Spain, and United States of America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoint/variable:
Primary objective:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on uACR at 6 months	Change from baseline in uACR at 6 months (V8)
Secondary objectives:	
To assess the effects of treatment with verinurad and allopurinol, allopurinol alone, and placebo on uACR at 12 months	Change from baseline in uACR at 12 months (V10)
To assess the effects of verinurad and allopurinol, allopurinol alone, and placebo on sUA	Change from baseline in sUA at 6 months (V8) and 12 months (V10)
To estimate the dose-response relationship among 3 doses of verinurad and allopurinol and placebo on uACR and sUA	Change from baseline in uACR and sUA at 6 months (V8)
To assess the effects of verinurad and allopurinol versus placebo on kidney function	Change from baseline in estimated glomerular filtration rate at 6 months (V8) and 12 months (V10) Change from baseline in creatinine at 6 months (V8) and 12 months (V10) Change from baseline in cystatin-C at 6 months (V8) and 12 months (V10)
Safety objective:	
To assess the safety and tolerability of intensive UA lowering therapy with verinurad and allopurinol	Rates of AEs and SAEs, including CV events Changes in vital signs, electrocardiograms, and clinical laboratory parameters

AEs adverse events; CV cardiovascular; SAE serious adverse event; sUA serum uric acid; UA uric acid; uACR urinary albumin to creatinine ratio.

Study design

This was a randomised, double-blind, placebo-controlled, parallel, global, dose-finding, Phase 2b study to assess the efficacy and safety of verinurad and allopurinol in patients with chronic kidney disease and hyperuricaemia. Patients who met the eligibility criteria were

randomised in a 1:1:1:1:1 ratio to high, intermediate or low dose of verinurad plus allopurinol, allopurinol, or placebo. CCI [redacted]

As of Protocol Version 5.0 (PA5) and following a pre-specified interim analysis in September 2020, the study design was modified to include a new dosing regimen. Patients previously allocated to the low dose verinurad plus allopurinol group were to switch to treatment with 24 mg verinurad plus 300 mg allopurinol. As a consequence of PA5, the study population could receive the following nominal treatment:

1 High dose: verinurad 12 mg plus allopurinol 300 mg
2 Intermediate dose (Inter. dose): verinurad 7.5 mg plus allopurinol 300 mg
3 Low dose: verinurad 3 mg plus allopurinol 300 mg
4 Switch dose (Switch dose PA5): verinurad 3 mg plus allopurinol 300 mg up to V9 then verinurad 24 mg plus allopurinol 300 mg
5 Allopurinol alone (Allopurinol): 300 mg
6 Placebo.

Target population and sample size

Patients with chronic kidney disease (CKD). Chronic kidney disease as defined in the Kidney Disease: Improving Global Outcomes guidelines as abnormalities in kidney structure or function present for >3 months. Patients should have received background standard of care treatment for albuminuria and/or type 2 diabetes mellitus (T2DM) and been treated according to locally recognised guidelines, as appropriate, and met the following criteria:

7 Serum uric acid (sUA) $\geq$ 6.0 mg/dL at screening
8 Estimated glomerular filtration rate (eGFR) $\geq$ 25 mL/min/1.73 m^2 (CKD-EPI formula) at screening
9 Mean urinary albumin to creatinine ratio (uACR) between 30 mg/g and 5000 mg/g inclusive.

The estimated sample size of 145 patients per arm (initial dosing regimen) yielded 80% power to detect a 25% reduction in uACR for the high dose of verinurad + allopurinol compared to placebo (treatment difference of approximately -0.29 on the natural log scale) at the 2-sided alpha level of 0.1, assuming a standard deviation of 1.0 on the natural log-scale.

A total of 725 patients (145 patients per arm [initial dosing regimen]) were planned to be randomised.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Verinurad or matching placebo capsules: 3, 7.5, or 12 mg to be taken, once daily. Patients from 3 mg dose who were switched to 24 mg dose received 24 mg as two 12-mg capsules.
Manufacturer: AstraZeneca AB.
Batch numbers:

a. Verinurad 3 mg: CCI [redacted]
b. Verinurad 7.5 mg: CCI [redacted]
c. Verinurad 12 mg: CCI [redacted]
d. Verinurad placebo: CCI [redacted]

Allopurinol (100 and 200 mg for up-titration, or 300 mg) or matching placebo oral tablet: once daily. Manufacturer: CCI [redacted]
Batch numbers:

e. Allopurinol 100 mg: CCI [redacted]
f. Allopurinol 300 mg: CCI [redacted]
g. Allopurinol placebo for 100 mg: CCI [redacted]
h. Allopurinol placebo for 300 mg: CCI [redacted]

Duration of treatment

Before Protocol Version 5.0:

Initially planned to be 108 weeks. During the first 3 months, study treatments were up-titrated as described in the table below:

	Step 1 - titration (verinurad/allopurinol)	Step 2 - titration (verinurad/allopurinol)	Step 3 - target dose (verinurad/allopurinol)
High Dose (mg)	3/100	7.5/200	12/300
Inter. Dose (mg)	3/100	7.5/200	7.5/300
Low Dose (mg)	3/100	3/200	3/300
Allopurinol alone (mg)	0/100	0/200	0/300
Placebo (mg)	0/0	0/0	0/0

After Protocol Version 5.0:
Following the implementation of the amendment, all patients discontinued therapy after 60 weeks (Visit 10).

Statistical methods

In the main analysis of UACR at V8, a repeated measures mixed model (MMRM) was applied, where log(uACR) depended on the fixed categorical effects of randomised treatment, visit, diabetes mellitus status (yes/no) at baseline, albuminuria status at baseline, N-terminal

natriuretic peptide status at baseline, use of sodium-glucose transport protein 2 inhibitor (yes/no) at baseline, and treatment-by-visit interaction, as well as the continuous fixed covariate of baseline log(uACR) and its baseline-log(uACR)-by-visit interaction. The least squares mean (LSMean) change from baseline to 6 months (V8) in the log (uACR) was calculated by treatment (High dose and Placebo) with its 95% confidence interval (CI). The LSMeans difference between the 2 treatments (High dose vs Placebo) was calculated with its 95% CI. A p-value for a test of no the treatment difference between High dose and Placebo was calculated. The above LSMeans change from baseline (and the 95% CI) for each of the 2 treatments was exponentiated to yield the geometric mean ratio from baseline for each treatment with its 95% CI at the original scale of uACR. Percent change from baseline with 95% CI for each of the 2 treatments was in turn to be derived from the geometric estimated mean ratio, and CI. The LSMeans difference between High dose and Placebo (and it's 95% CI) was also exponentiated to yield the geometric mean ratio between the two treatments at V8 and its 95% CI at the original scale of uACR.

A sensitivity analysis was conducted using a multiple-imputation analysis with an assumption of an unconditional jump to placebo arm for off-treatment subjects.

Each of the 7 other analyses (High dose and Inter. dose combined vs Allopurinol alone, Inter. dose vs Placebo, Low dose vs Placebo, High dose vs Allopurinol, Inter. dose vs Allopurinol, Low dose vs Allopurinol, and Allopurinol vs Placebo) were to be carried out exactly as the main analysis.

Study population

A total of 1149 patients were enrolled in 205 study centres across 12 countries.

Eight hundred and sixty-one patients were randomised to receive treatment: 172 patients, in each of the High dose and Inter. dose groups, 173 patients (out of which 37 later switched to double-capsule regimen and formed the Switch dose PA5 group) in the Low dose group, 171 patients in the Allopurinol group, and 173 patients in the Placebo group.

Details on disposition are given in the table below:

Table S2 Subject disposition (All subjects)

	Number (%) of subjects						
	High dose	Inter. dose	Low dose[c]	Switch dose PA5[d]	Allopurinol	Placebo	Total
Subjects pre-screened[a]							2219
Subjects screened/enrolled							1149
Subjects who screen failed							271
Subjects randomised	172 (100.0)	172 (100.0)	173 (100.0)	37 (100.0)	171 (100.0)	173 (100.0)	861 (100.0)
Subjects who were randomised and not treated	0	0	1 (0.6)	0	0	0	1 (0.1)
Subjects who were randomised and treated	172 (100.0)	172 (100.0)	172 (99.4)	37 (100.0)	171 (100.0)	173 (100.0)	860 (99.9)
Subjects who signed informed consent for PA5	49 (28.5)	55 (32.0)	47 (27.2)	37 (100.0)	49 (28.7)	52 (30.1)	252 (29.3)
Subjects who received treatment under PA5	40 (23.3)	46 (26.7)	37 (21.4)	37 (100.0)	36 (21.1)	42 (24.3)	201 (23.3)
Subjects who completed treatment	119 (69.2)	123 (71.5)	118 (68.2)	36 (97.3)	118 (69.0)	122 (70.5)	600 (69.7)
Subjects who did not complete treatment	53 (30.8)	49 (28.5)	54 (31.2)	1 (2.7)	53 (31.0)	51 (29.5)	260 (30.2)
Subjects who completed study	137 (79.7)	143 (83.1)	131 (75.7)	34 (91.9)	145 (84.8)	147 (85.0)	703 (81.6)

Low Dose: Verinurad 3 mg + Allopurinol 300 mg; Inter. Dose: Verinurad 7.5 mg + Allopurinol 300 mg;
High Dose: Verinurad 12 mg + Allopurinol 300 mg; Allopurinol: Allopurinol 300 mg;
Switch Dose PA5: Verinurad 24 mg + Allopurinol 300 mg.

[a] Signed the pre-screening informed consent.

[b] Signed the screening informed consent.

[c] Contains all subjects randomized to the low dose group including those that later switched to Verinurad 24 mg + Allopurinol 300 mg.

[d] Contains all subjects randomized to the low dose group that later switched to Verinurad 24 mg + Allopurinol 300 mg.

PPD discontinued treatment and did not come in for future visits after April 2021. The reason for treatment discontinuation was recorded as lost to follow-up. This subject was later contacted by phone in October 2021 and per monitor decision, reason for study discontinuation was recorded as non-compliance with study drug.

PPD was recorded as discontinuing treatment with reason lost to follow-up. This subject was later contacted in December 2020 and the reason for study discontinuation was recorded as other, known to be alive. PA5 Protocol amendment 5.

The demographics were representative of the intended study patient population as defined by protocol eligibility criteria and were generally balanced between randomised treatment groups. Mean age (SD) was 65.3 years (10.8). Sixty-seven point zero percent of patients were male, and, 72.2% were White.

In general, the disease characteristics were well balanced across the treatment groups with no clinically meaningful differences between groups in terms of CKD etiology.

Overall, 82.1% of the population had T2DM, 79.2% of the population had an eGFR < 60 ml/min/1.73m^2 and median uACR was 217.0 mg/g (range: 7 to 7767 mg/g).

Summary of efficacy results

Primary endpoints:

The first test of the multiple testing procedure performed on the change from baseline in uACR for High dose vs Placebo reached statistical significance on level 0.1 (p = 0.0648). The second test of the High dose and Inter. dose vs Allopurinol, p = 0.6296, did not. As a consequence, the last comparison, Allopurinol vs Placebo, is not statistically significant even if the p-value (p = 0.0263) is well below 0.1.

At Visit 8, changes from baseline in uACR were 13.99% (95% CI: -3.35, 34.44) in the High dose group compared to 37.34% (95% CI: 16.59, 61.79) in the Placebo group. The geometric mean ratio for the comparison between group was 0.8300 (95% CI: 0.6810, 1.012), in favour of the High dose group, compared with the Placebo group. At the pre-specified significance level of 0.1, the difference between treatments was statistically significant (p = 0.0648).

The results of the sensitivity analysis of uACR change from baseline at 6 months were consistent with those of the primary analysis, with a geometric mean ratio for the comparison between group of 0.8558 (95% CI: 0.6980,1.049) vs 0.8300 (95% CI: 0.6810, 1.012) in the main analysis.

Change from baseline in uACR at Visit 8 - Comparisons vs Placebo

The percent change in uACR from baseline in the Placebo group was 37.34% (95% CI: 16.59, 61.79). In the active groups the following changes from baseline in uACR at Visit 8 were observed: 14.95% (95% CI: -1.85, 34.62) in the Inter. dose group, 16.72% (95% CI: -0.62, 37.10) in the Low dose group, and 9.89% (95% CI: -6.64, 29.36) in the Allopurinol group. The geometric mean ratios were 0.8369 (95% CI: 0.6887, 1.017) for the Inter. dose vs Placebo comparison (p = 0.0735), 0.8499 (95% CI: 0.6984, 1.034) for the Low dose vs Placebo comparison (p = 0.1041), and 0.8001 (95% CI: 0.6573, 0.9739) for the Allopurinol vs Placebo comparison (p = 0.0263).

Change from baseline in uACR at Visit 8 - Comparisons vs Allopurinol

The percent change from baseline in the Allopurinol group was 9.89% (95% CI: -6.64, 29.36). The geometric mean ratios were 1.037 (95% CI: 0.8506, 1.265) for the High dose vs Allopurinol comparison (p = 0.7174), 1.046 (95% CI: 0.8603, 1.272) for the Inter. dose vs Allopurinol comparison (p = 0.6517), and 1.062 (95% CI: 0.8725, 1.293) for the Low dose vs Allopurinol comparison (p = 0.5474). One additional comparison was performed by pooling High and Inter. dose groups resulting in a geometric mean ratio of 1.043 (95% CI: 0.8793, 1.237) for the High and Inter. dose vs Allopurinol comparison (p = 0.6296). Results for pooled High and Inter. dose groups were then similar to High dose group results.

Secondary endpoints:

At Visit 10, an increase from baseline in uACR was observed in both Switch dose PA5 and Placebo groups (Placebo group being comprised of patients who switched to double capsule placebo): 17.26% (95% CI: -9.85,52.52) in the Switch dose PA5 group compared to 15.42% (95% CI: -6.07,41.83) in the Placebo group. The geometric mean ratio for the comparison between group was 1.016 (95% CI: 0.7437,1.388), showing a greater worsening in the Switch dose PA5 group compared to the Placebo group.

At Visit 8, the percent change from baseline in sUA was -2.52% (95% CI: -8.54, 3.91) in the Placebo group. In the active groups, the following decreases from baseline in sUA were observed: -50.30% (95% CI: -53.38, -47.02) in the High dose group, -43.36% (95% CI: -46.76, -39.75) in the Inter. dose group, -40.57% (95% CI: -44.18, -36.73) in the Low dose group. The geometric mean ratios were 0.5098 (95% CI: 0.4701, 0.5528) for the High dose vs Placebo comparison, 0.5810 (95% CI: 0.5362, 0.6295) for the Inter. dose vs Placebo comparison, and 0.6096 (95% CI: 0.5623, 0.6609) for the Low dose vs Placebo comparison. All nominal p-values for these comparisons were < 0.0001.

At Visit 8, the percent change from baseline in sUA was - 39.27% (95% CI: -43.01, -35.29) in the Allopurinol group. Both High dose and Inter. dose groups had a numerically greater decrease from baseline in sUA compared to the decrease observed for Allopurinol group: -50.30% (95% CI: -53.38, -47.02) in the High dose group and -43.36% (95% CI: -46.76, -39.75) in the Inter. dose group. The geometric mean ratios were 0.8184 (95% CI: 0.7544, 0.8878) for the High dose vs Allopurinol comparison (p <0.0001) and 0.9327 (95% CI: 0.8604, 1.011) for the Inter. dose vs Allopurinol comparison (p = 0.0901). Low dose induced a similar decrease from baseline in sUA (-40.57% [95% CI: -44.18, -36.73]) compared to Allopurinol. The geometric mean ratio was 0.9786 (95% CI: 0.9024, 1.061) (p = 0.6003). A decrease in sUA was greater in the Allopurinol group than in the Placebo group. The geometric mean ratio was 0.6229 (95% CI: 0.5744, 0.6755) (p <0.0001).

At Visit 10, a numerically greater decrease from baseline in sUA was observed in the Switch dose PA5 group compared to the Placebo group: -48.39% (95% CI: -53.96, -42.15) in the Switch dose PA5 group compared to -6.85% (95% CI: -14.61,1.61) in the Placebo group. The geometric mean ratio for the comparison between group was 0.5540 (95% CI: 0.4825, 0.6362), showing a greater improvement in the Switch dose PA5 group over the Placebo group.

No relationship between uACR reduction from baseline at Visit 8 and verinurad dose was observed whereas sUA reduction from baseline was observed to be greater following higher doses of verinurad: -40.57% (95% CI: -44.18, -36.73), -43.36% (95% CI: -46.76, -39.75) and -50.30% (95% CI: -53.38, -47.02) reductions were observed following low, iInter. and high dose, respectively.

There were no obvious effects or differences in any comparison for change from baseline in eGFR at Visit 8 and Visit 10. No changes from baseline at Visit 8 and Visit 10 were reported for S-creatinine.

At Visit 8, a greater increase from baseline in P-cystatin C was observed in the Inter. dose group compared to the Placebo group: 5.28% (95% CI: 2.50, 8.14) in the Inter. dose group compared to 1.40% (95% CI: -1.39, 4.28) in the Placebo group. The geometric mean ratio for the comparison between Inter. dose and Placebo groups was 1.038 (95% CI: 1.005, 1.073), p = 0.0238. There were no differences in any of the other comparisons at Visit 8. At Visit 10, there were no differences in any group compared to baseline.

Summary of safety results

There were minor differences in the duration of exposure between groups, with median duration of exposure ranging from 417.0 days in the High dose group to 421.0 days in the Placebo group. In the Low dose group (Switchers included), the median duration of exposure was slightly inferior (339.5 days), due to the fact that low dose duration was measured up until the time of switching doses for patients randomised to the Switch dose PA5 group. For the Switch dose PA5 group, the duration was measured starting from the date the patients switched doses. Due to the shorter duration of observation (13 weeks), the exposure in days was lower than in the other groups (median: 92.0 days).

When looking at the safety results, and some efficacy results (eg, CCI [redacted] and incidence of subjects reaching a 40% reduction in eGFR), reported in this clinical study report, one should bear in mind the shorter duration of exposure for the Switch dose PA5 group, and to a lesser extent, for the Low dose group.

No new safety concerns were identified during the study. A summary of adverse events (AE) by category is presented below:

Table S3 Number of Subjects with Adverse Events in Any Category, In-Study (Safety Analysis Set)

	Number (%) of subjects[a]					
AE category	High Dose (N=172)	Inter. Dose (N=172)	Low Dose[b] (N=172)	Switch Dose PA5[c] (N=37)	Allopurinol (N=171)	Placebo (N=173)
Any AE	124 (72.1)	125 (72.7)	121 (70.3)	9 (24.3)	123 (71.9)	128 (74.0)
Any SAE (including events with outcome = death)	36 (20.9)	39 (22.7)	40 (23.3)	4 (10.8)	42 (24.6)	35 (20.2)
Any AE with outcome = death	14 (8.1)	8 (4.7)	13 (7.6)	1 (2.7)	10 (5.8)	11 (6.4)
Any AE leading to discontinuation of IP	27 (15.7)	25 (14.5)	23 (13.4)	0	30 (17.5)	25 (14.5)
Any AE leading to dose reduction	1 (0.6)	3 (1.7)	1 (0.6)	0	3 (1.8)	1 (0.6)

Low Dose: verinurad 3 mg + allopurinol 300 mg

Inter. Dose: verinurad 7.5 mg + allopurinol 300 mg
High Dose: verinurad 12 mg + allopurinol 300 mg
Allopurinol: allopurinol 300 mg; Switch Dose PA5: verinurad 24 mg + allopurinol 300 mg.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[b] Contains events for all subjects randomized to the low dose group while on the low dose (i.e. prior to switching or if never switching).
[c] Contains events for all subjects randomized to the low dose group occurring after switching to Verinurad 24 mg + Allopurinol 300 mg.
This table includes adverse events with an onset date on or after date of visit 3 until the day of last attended sched uled visit.
Percentages are based on the total numbers of subjects in the treatment group (N).
AE Adverse event; IP Investigational product;
N Number of subjects in treatment group; PA5 Protocol amendment 5; SAE Serious AE.

The proportion of patients with AEs and serious adverse events (SAEs) was balanced between the treatment groups, except in the Switch PA5 group (13 weeks of exposure). The Allopurinol group presented the highest incidence of SAEs, AEs leading to investigational product discontinuation, and AEs leading to dose reduction.

The percentage of AEs with an outcome of death ranged from 4.7% in the Inter. dose group to 8.1% of the patients in the High dose group. In the Low dose (while on a single-capsule regimen) and Switch dose PA5 groups, AEs with an outcome of death occurred in 7.6% and 2.7% of patients, respectively.

The incidence of AEs leading to discontinuation of either study treatment was similar across the following groups: 15.7% of the patients in the High dose group, 14.5% in the Inter. Dose group, 17.5% in the Allopurinol group, and 14.5% in the Placebo group. In the Low dose (while on a single-capsule regimen) and Switch dose PA5 groups, AEs leading to discontinuation of either study treatment occurred in 13.4% and 0.0% (none) of patients, respectively.

Conclusions

- In the current study, verinurad was exclusively administered in combination with allopurinol. No new safety concerns were identified in the study.
- At a level of 0.1, a statistically significant difference between the High dose group and the Placebo group was observed in change from baseline in uACR at 6 months (V8) but that significant difference could be explained by a momentary, transient increase in uACR in the Placebo group at 6 months (V8). No differences were observed between any of the Verinurad groups and Allopurinol group.

All active treatment groups showed a greater decrease of sUA compared to placebo at 6 months (V8). Higher doses of verinurad resulted in greater sUA reductions at 6 months (V8).