Overall survival with relacorilant and nab-paclitaxel in patients with platinum-resistant ovarian cancer (ROSELLA): a phase 3 randomised controlled trial

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Summary

Background Relacorilant is a selective glucocorticoid receptor antagonist that increases the sensitivity of many cancer cell types to chemotherapy. The efficacy and safety of relacorilant plus nab-paclitaxel were assessed in the phase 3 ROSELLA (GOG-3073, ENGOT-ov72, APGOT-Ov10, and LACOG-0223) trial; the combination showed significant improvement in progression-free survival among patients with platinum-resistant ovarian cancer compared with nab-paclitaxel monotherapy. Results of the final overall survival analysis are reported here.

Methods In this open-label phase 3 trial, patients were randomly assigned 1:1 to receive relacorilant (150 mg orally the day before, day of, and day after nab-paclitaxel infusion) plus nab-paclitaxel (80 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle) or nab-paclitaxel monotherapy (100 mg/m² intravenously on the aforementioned schedule). Patients, aged 18 years or older, with one to three lines of previous anticancer therapy and platinum-resistant disease (progression <6 months from their last dose of platinum) were eligible. The trial was conducted at 117 hospitals and community oncology centres in 14 countries across Australia, Europe, Latin America, North America, and South Korea. Progression-free survival, assessed by blinded independent central review, and overall survival (time from randomisation to death from any cause) were dual primary endpoints. Additional prespecified endpoints included safety, second progression-free survival (time from randomisation to disease progression on subsequent anticancer therapy or death due to any cause, whichever occurred first), and patient-reported outcomes. This trial is registered at ClinicalTrials.gov, NCT05257408, and is ongoing.

Findings Between Jan 5, 2023, and April 8, 2024, 381 patients were randomly assigned to the relacorilant combination group (n=188) or the nab-paclitaxel monotherapy group (n=193). All patients had received bevacizumab; 167 (44%) had received three previous lines of therapy, and 234 (61%) had received a poly(ADP-ribose) polymerase inhibitor. At a median follow-up of 24·8 months (95% CI 23·6–25·7), the addition of relacorilant to nab-paclitaxel resulted in a statistically and clinically significant improvement in overall survival compared with nab-paclitaxel monotherapy (hazard ratio for death 0·65 [95% CI 0·51–0·83]; p=0·0004); 18-month overall survival was 46% and 27%, respectively. The median overall survival in the relacorilant combination group was extended by 4·1 months compared with the nab-paclitaxel monotherapy group (16·0 [95% CI 13·0–18·3] *vs* 11·9 months [10·0–13·8]). Subsequent anticancer treatments were similar across study groups. Adverse events were similar in both groups when adjusted for duration of study treatment. Neutropenia (121 [64%]), anaemia (115 [61%]), fatigue (101 [54%]), and nausea (82 [44%]) were the most common adverse events in the relacorilant combination group. No new safety signals were observed with additional follow-up since the primary analysis.

Interpretation The addition of relacorilant to nab-paclitaxel led to significantly longer overall survival in patients with platinum-resistant ovarian cancer, without the need for biomarker selection. The findings support relacorilant plus nab-paclitaxel as a potential new standard treatment option for patients with platinum-resistant ovarian cancer.

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Introduction

Platinum-resistant ovarian cancer is a leading cause of gynaecological cancer-related mortality worldwide;[1,2] median overall survival estimates in clinical trials range from 10 months to 17 months.[3–5] Treatment options in this setting are limited to single-agent chemotherapy with or

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Research in context

Evidence before this study

In a search of PubMed for articles published up to Jan 27, 2026, using the search terms "selective" AND "glucocorticoid receptor" AND ("cancer" or "carcinoma") with no language restrictions, we found that data have been published on selective glucocorticoid receptor antagonism in ovarian cancer for only four clinical trials, three with the selective glucocorticoid receptor antagonist relacorilant and one with the less selective ORIC-101. The first trial (NCT02762981) was a phase 1/2 study to determine the recommended phase 2 dose of relacorilant plus nab-paclitaxel in patients with advanced solid tumours. The second and third trials (NCT03776812 and NCT05257408) were a randomised phase 2 study, and the primary results of the phase 3 study described herein, evaluating the combination of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer. The fourth trial (NCT03928314) was a phase 1 dose escalation and expansion study to determine the recommended phase 2 dose of ORIC-101 in combination with nab-paclitaxel in patients with advanced solid tumours.

Added value of this study

The positive results for final overall survival, a dual primary endpoint of the ROSELLA (GOG-3073, ENGOT-ov72, APGOT-Ov10, and LACOG-0223) study, confirm the previously reported data for the other dual primary endpoint, progression-free survival, and are consistent with the findings from the phase 2 study. In a patient population that is receiving single-agent chemotherapy with a median life expectancy of 1 year, overall survival results are the most impactful efficacy endpoint. This study provides a robust analysis that is mature, has considerable follow-up, was conducted per the prespecified statistical analysis plan, and is based on a complete dataset. In addition, positive data for second progression-free survival confirm that the treatment benefit of relacorilant provides durable disease control beyond first progression. The study also provides patient-reported outcome data and updated safety data to support a complete benefit–risk determination.

Implications of all the available evidence

Combined with the evidence from previous studies, these positive overall survival data support relacorilant plus nab-paclitaxel as a potential new standard treatment option for patients with platinum-resistant ovarian cancer, without the need for biomarker selection. This study is the first positive clinical trial conducted with registrational intent for a selective glucocorticoid receptor antagonist in patients with cancer. The data supports the ongoing evaluation of relacorilant in other solid tumour indications and in combination with other classes of anticancer agents. In the AURELIA trial, the VEGF inhibitor bevacizumab also extends progression-free survival in combination with chemotherapy in this setting but has not shown a statistically significant overall survival benefit—probably owing, in part, to crossover to the investigational group at progression—and is predominantly used in earlier lines of therapy for patients with ovarian cancer. Furthermore, mirvetuximab soravtansine has shown an overall survival benefit in a third of patients with high-grade serous folate receptor α–positive ovarian cancer. The addition of pembrolizumab to weekly paclitaxel (with or without bevacizumab) has reported an overall survival benefit in a less pre-treated population. Additional studies will be needed to determine the appropriate sequencing of these agents.

without bevacizumab, mirvetuximab soravtansine for approximately 33% of high-grade serous cancers that are folate receptor α-positive,[5] trastuzumab deruxtecan for approximately 5% of ovarian cancers that have a *HER2* immunohistochemistry score of 3 or greater,[6,7] and clinical trials.[8]

Acting through the glucocorticoid receptor, cortisol provides survival signals to cancer cells, increasing the expression of anti-apoptotic proteins. Relacorilant is a first-in-class selective glucocorticoid receptor antagonist that inhibits cortisol survival signals and increases the sensitivity of tumours to several classes of cytotoxic chemotherapy.[9–11]

The international, randomised, controlled, open-label, phase 3 ROSELLA trial assessed the efficacy and safety of relacorilant plus nab-paclitaxel compared with nab-paclitaxel alone in patients with platinum-resistant ovarian cancer. At the primary analysis, the relacorilant combination group showed superior progression-free survival to those receiving nab-paclitaxel monotherapy (hazard ratio [HR] for disease progression or death 0·70; p=0·0076).[12] In the planned interim overall survival analysis at the time of primary progression-free survival analysis (50% maturity; median follow-up, 13·9 months), patients in the relacorilant combination group showed a 31% reduction in the risk of death (HR 0·69 [95% CI 0·52–0·92]; p=0·012; conducted at an α=0·0001 significance level, constituting the α spending function) and a 4·5 month improvement in median overall survival compared with those receiving nab-paclitaxel monotherapy.[12] The combination of relacorilant plus nab-paclitaxel was well tolerated, with a safety profile similar to nab-paclitaxel monotherapy when adjusted for the duration of study treatment. Here, we report the protocol-specified final overall survival analysis, subsequent treatments, second progression-free survival, and patient-reported outcomes.

Methods

Study design

Full details regarding the ROSELLA trial have been published previously[12] and are provided in the trial protocol in the appendix. In this randomised, controlled, parallel

group, open-label, superiority, phase 3 trial, approximately 360 patients were planned to be randomly assigned 1:1 to receive relacorilant plus nab-paclitaxel or nab-paclitaxel monotherapy. The trial was conducted at 117 sites (an additional 12 sites were considered but did not open) in 14 countries, including hospital outpatient clinics and community oncology treatment centres across Australia, Europe, Latin America, North America, and South Korea. Criteria for site selection included experience conducting registrational phase 3 ovarian cancer trials, anticipated volume of eligible patients, ability to comply with the protocol, research staff resourcing, and likelihood of activation within the anticipated enrolment timeframe of the study. The trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines as defined by the International Council for Harmonisation, applicable regulatory requirements, and the bioethics policy of the trial sponsor. The trial was approved by the Institutional Review Board or Ethics Committee of all participating centres (appendix pp 2–10). An Independent Data Safety Monitoring Committee had access to unblinded data and evaluated safety data at regular intervals in all dosed patients. To ensure the integrity of the data and to minimise the potential for bias, the sponsor was blinded to aggregate efficacy and safety data by treatment group until the primary analysis of progression-free survival and was blinded to additional accumulated aggregate efficacy and safety data until the final analysis of overall survival. There was no patient or public involvement in the design or conduct of this trial. The sponsor continues to engage with patients and patient advocacy groups on the analysis, interpretation, and dissemination of these trial results. This trial was registered at ClinicalTrials.gov, NCT05257408, and is ongoing.

Participants

Adult (aged ≥18 years) women with platinum-resistant (defined as progression <6 months after their last dose of platinum), high-grade, epithelial ovarian, primary peritoneal, or fallopian-tube cancer who had received one to three lines of prior systemic anticancer therapy, had previous treatment with bevacizumab, and had measurable disease were eligible. Patients were excluded if they had not responded to their initial platinum-containing regimen or had disease progression within 1 month of their last dose of first-line platinum therapy. Full eligibility criteria are provided in the trial protocol in the appendix. Race and ethnicity were self-reported by patients using Clinical Data Interchange Standards Consortium standards, where permissible by local laws and regulations. All patients provided written informed consent.

Randomisation and masking

Patients were enrolled by trial sites and randomly assigned (1:1) to receive relacorilant plus nab-paclitaxel or nab-paclitaxel monotherapy. A permuted block randomisation method with block size of four was used. The random allocation sequence was developed by an independent contract research organisation. Randomisation was centrally assigned using the Interactive Response Technology System (IRT). The sponsor study team, investigators, and site staff did not have access to the live randomisation schedule in the IRT. Region (North America *vs* Europe *vs* South Korea, Australia, and Latin America) and previous lines of therapy (one *vs* more than one) were stratification factors.

Procedures

Patients in the relacorilant combination group received 150 mg of relacorilant administered orally the day before, day of, and day after nab-paclitaxel infusion, in combination with 80 mg/m² nab-paclitaxel administered intravenously on days 1, 8, and 15 of each 28-day cycle. Patients in the control group received 100 mg/m² of nab-paclitaxel monotherapy administered intravenously on the aforementioned schedule. In the combination group, the dose of nab-paclitaxel was reduced because relacorilant is an inhibitor of CYP3A4,[13] which is a minor pathway of elimination for nab-paclitaxel (the major pathway of elimination is CYP2C8, which is not affected by relacorilant in humans). Pharmacokinetic data from the relacorilant phase 2 trial showed that the lower dose of nab-paclitaxel in the relacorilant combination group provides a comparable exposure to the nab-paclitaxel monotherapy group,[11] and exposure–response analyses showed that higher nab-paclitaxel exposures were not associated with improved efficacy in the phase 2 study.[14] Publication of complete exposure–response analyses for nab-paclitaxel and relacorilant in the phase 2 study and ROSELLA are planned in a peer-reviewed journal.

Outcomes

The dual primary endpoints in the trial were progression-free survival (defined as the time from randomisation to disease progression or death due to any cause, whichever occurred first) assessed by blinded independent central review and overall survival (defined as the time from randomisation to death due to any cause). Safety was a secondary endpoint. Second progression-free survival (time from randomisation to progression on subsequent anticancer therapy or death due to any cause, whichever occurred first) and patient-reported outcomes were prespecified exploratory endpoints.

The intention-to-treat population included all randomised patients, analysed according to the randomised treatment group. This population was used for the analysis of the dual primary endpoints of progression-free survival assessed by blinded independent central review and overall survival, as well as the exploratory endpoint of second progression-free survival (assessed by the investigator). Overall survival and disease status were evaluated every 8 weeks for the

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See **Online** for appendix

first 40 weeks, then every 12 weeks. Patients who discontinued treatment for any reason were followed for survival and subsequent treatments until death, the patient was lost to follow-up, or other study exit criteria were met. Where permissible, public records for survival status were consulted if the patient was lost to follow-up. All efforts to reach the patient, including at least three documented attempts, had to be exhausted before a patient was deemed lost to follow-up. Cross-over was not permitted and could not occur outside of the trial as relacorilant was not commercially available. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 and assessed in the safety population (all randomised patients who received at least one dose of the assigned treatment).

Patient-reported outcomes were assessed in the safety population at the time of the primary analysis (data cutoff Feb 24, 2025), using the European Organisation for Research and Treatment of Cancer (EORTC) ovarian cancer–specific quality-of-life questionnaire 28 (QLQ-OV28), and the EORTC non-specific cancer quality-of-life questionnaire core 30 (QLQ-C30) on the first day of each cycle.[15,16]

Statistical analysis

A group sequential weighted Holm procedure was used for the dual primary endpoints, progression-free and overall survival, in the intention-to-treat population. Progression-free survival was tested at a two-sided $\alpha=0\cdot04$ level of significance using a stratified log-rank test. The primary endpoint of overall survival was allocated a two-sided $\alpha=0\cdot01$ level of significance for the stratified log-rank test. If the null hypothesis for progression-free survival by blinded independent central review was rejected, then, per the Holm procedure, overall survival would be tested at $\alpha=0\cdot05$, using a stratified log-rank test. The interim overall survival analysis was conducted at an $\alpha=0\cdot0001$ significance level (the α spending function). The final analysis of overall survival was conducted at an $\alpha=0\cdot0499$ significance level using a two-sided stratified log-rank test because progression-free survival was significant. With 1:1 randomisation, approximately 292 events provided 80% power to detect a 50% increase in progression-free survival (HR 0·66) with a log-rank test at a two-sided $\alpha=0\cdot01$ significance level. Assuming an exponential distribution of overall survival, this corresponds to an increase in median overall survival from 13 months (benchmarked to phase 2 data) to 19·4 months.[11] All other secondary efficacy endpoints were tested at a nominal two-sided $\alpha=0\cdot05$ level of significance, with no additional adjustment for multiplicity. The Kaplan–Meier method was used for all time-to-event endpoints to generate the survival curves and to estimate the medians. The HRs were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomisation as covariates. The second progression-free survival analysis was also performed in the intention-to-treat population using similar methods to those used for the primary endpoints; patients alive and for whom a second disease progression had not been reported were censored at the time they were last known to be alive without second disease progression. Descriptive statistics are provided for safety endpoints; statistical methods for exposure-adjusted incidence rates are provided in the appendix (pp 11–12).

For EORTC QLQ-OV28 and EORTC QLQ-C30 data, descriptive statistics (mean, SD, 95% CI, median, and range) of the observed scores at each visit and change from baseline were summarised at each timepoint by treatment group, for each scale and overall. In a prespecified analysis, the number of patients achieving at least a 15-point absolute improvement at week 8 or week 9 in the abdominal or gastrointestinal scale of the QLQ-OV28 questionnaire was summarised by treatment group along with the 95% CI (computed using an exact binomial method). Similarly, the number of patients achieving at least a 10-point absolute improvement at week 8 or week 9 in the abdominal or gastrointestinal scale was summarised as a sensitivity analysis. A stratified Cochran–Mantel–Haenszel test was used to test differences in 15-point and 10-point absolute improvements in the abdominal or gastrointestinal scale of the QLQ-OV28 between treatment groups. Mean change in linear transformed scores between the groups was assessed, using a linear mixed model for repeated measures analysis that included the scores at each assessment point up to the cycle 6, day 1 assessment. Least-square means for change from baseline to cycle 6, day 1, within groups and between groups, are reported based on this model. When a patient had missing QLQ-OV28 or QLQ-C30 data from a scheduled assessment, it was imputed with data from an unscheduled or end of treatment assessment if these assessments were completed within one month of the scheduled assessment timepoint. Data from all other unscheduled assessments were not included.

Role of the funding source

The trial was designed by the principal investigators and the sponsor. The sponsor supported trial conduct, patient enrolment, and drug supply. The first draft of the manuscript was written by the authors, with medical writing support funded by the sponsor.

Results

From Jan 5, 2023, to April 8, 2024, a total of 381 patients underwent randomisation with 188 participants allocated to the relacorilant combination group and 193 to the nab-paclitaxel monotherapy group (figure 1). All patients in the relacorilant combination group and 190 patients in the nab-paclitaxel monotherapy group received at least one dose of the assigned treatment. As

reported previously, baseline demographic and disease characteristics were well balanced among the trial groups (appendix pp 15–16).[12] Patients were heavily pretreated: all had received bevacizumab; 167 (44%) had received three prior lines of therapy, 234 (61%) had received a poly(ADP-ribose) polymerase inhibitor. 47 (12%) of 381 patients had *BRCA*-mutant ovarian cancer, which is consistent with other published global phase 3 studies in patients with platinum-resistant ovarian cancer.[5,17]

The protocol-specified final analysis of overall survival was conducted after 288 deaths had been reported (76% maturity). At the data cutoff (Jan 8, 2026), 129 (69%) patients in the relacorilant combination group and 159 (82%) patients in the nab-paclitaxel monotherapy group had died. The addition of relacorilant to nab-paclitaxel resulted in a statistically significant improvement in overall survival (HR 0·65 [95% CI 0·51–0·83]; two-sided stratified log-rank p=0·0004; figure 2A, appendix p 17). With a median follow-up of 24·8 months (95% CI 23·6–25·7), median overall survival in the relacorilant combination group was extended by 4·1 months compared with nab-paclitaxel alone (16·0 months [95% CI 13·0–18·3] *vs* 11·9 months [10·0–13·8], respectively). A higher proportion of patients who received relacorilant plus nab-paclitaxel were alive at 18 months compared with those who received nab-paclitaxel monotherapy (46% *vs* 27%, respectively). The Kaplan–Meier curves remain well separated and increasingly divergent throughout the follow-up period, suggesting the addition of relacorilant offers a long-term benefit. The addition of relacorilant to nab-paclitaxel improved overall survival across all prespecified subgroups (figure 2B). The proportional hazards assumption was not violated (supremum test p=0·25). The restricted mean overall survival time at 30 months was 16·6 months (95% CI 15·0–18·1) in the relacorilant combination group and 13·4 months (95% CI 11·7–15·0) in the nab-paclitaxel monotherapy group, a difference of 3·2 months (95% CI 0·9–5·5; two-sided test of equality nominal p=0·0059).

In total, 127 (68%) of 188 patients from the relacorilant combination group and 139 (72%) of 193 patients from the nab-paclitaxel monotherapy group received subsequent systemic anticancer treatment, and 128 (68%) of 188 patients from the relacorilant combination group and 140 (73%) of 193 patients from the nab-paclitaxel monotherapy group received subsequent anticancer treatment when radiotherapy is included. The median time to start the first subsequent anticancer treatment was 6·2 months (range 1·1–23·7) in the relacorilant combination group versus 5·6 months (range 0·9–21·6) in the nab-paclitaxel monotherapy group. First and all subsequent anticancer treatments were similar in both treatment groups. The most common classes of agents in the first subsequent regimen were chemotherapy (182 [48%]), investigational therapy (40 [11%]), chemotherapy plus bevacizumab (13 [3%]), and mirvetuximab soravtansine (13 [3%]; figure 3). Among all subsequent systemic anticancer regimens, gemcitabine (128 [34%]), pegylated liposomal doxorubicin (84 [22%]), investigational therapies (56 [15%]), and carboplatin (53 [14%]) were administered the most (appendix p 18). Investigator-assessed second progression-free survival demonstrated a statistically significant improvement for the combination group compared with the nab-paclitaxel monotherapy group: HR 0·73 (95% CI 0·58–0·90); two-sided stratified log-rank nominal p=0·0037 (appendix p 14).

Patient-reported outcomes baseline questionnaire data and completion rates are summarised in the appendix (pp 19–20). The least-squares mean of the difference between treatment groups for the QLQ-C30 and the QLQ-OV28 scales was less than five (ie, less than the minimally important difference) for 20 of 22 questionnaire scales and symptom measures. Only

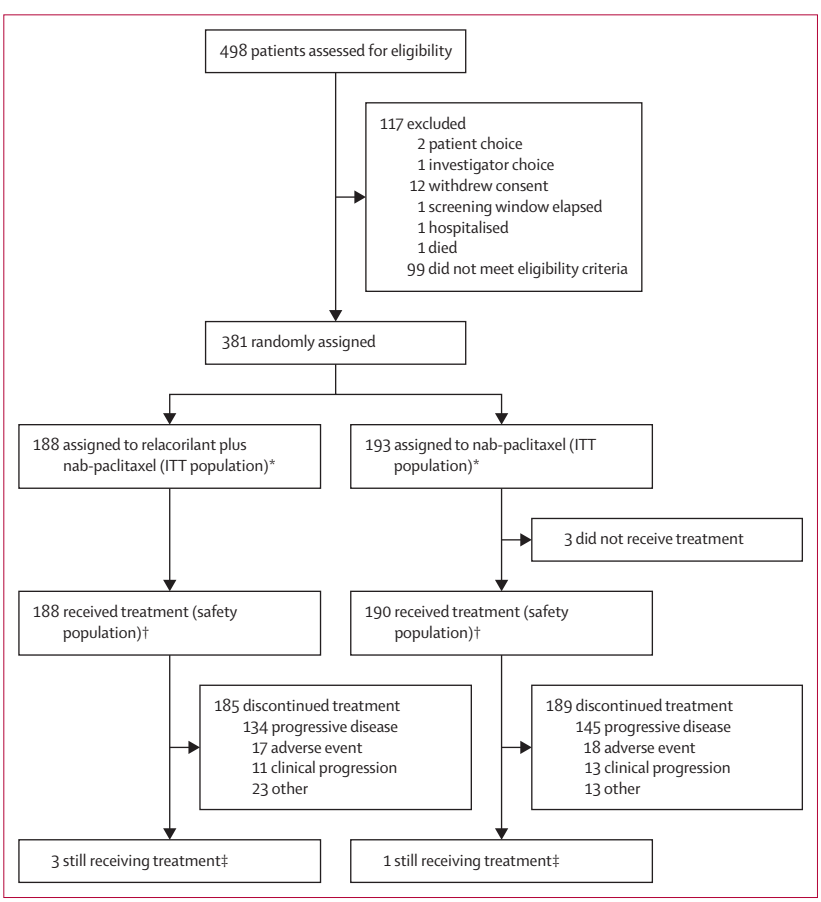

Figure 1: **Trial profile**
Three patients in the nab-paclitaxel monotherapy group withdrew consent and did not receive treatment. ITT=intention-to-treat. *All randomly assigned patients were analysed according to the randomised treatment group. †All randomly assigned patients who received at least one dose of study treatment (ie, relacorilant plus nab-paclitaxel or nab-paclitaxel monotherapy). ‡Refers to patients on nab-paclitaxel at the data cutoff of Jan 8, 2026.

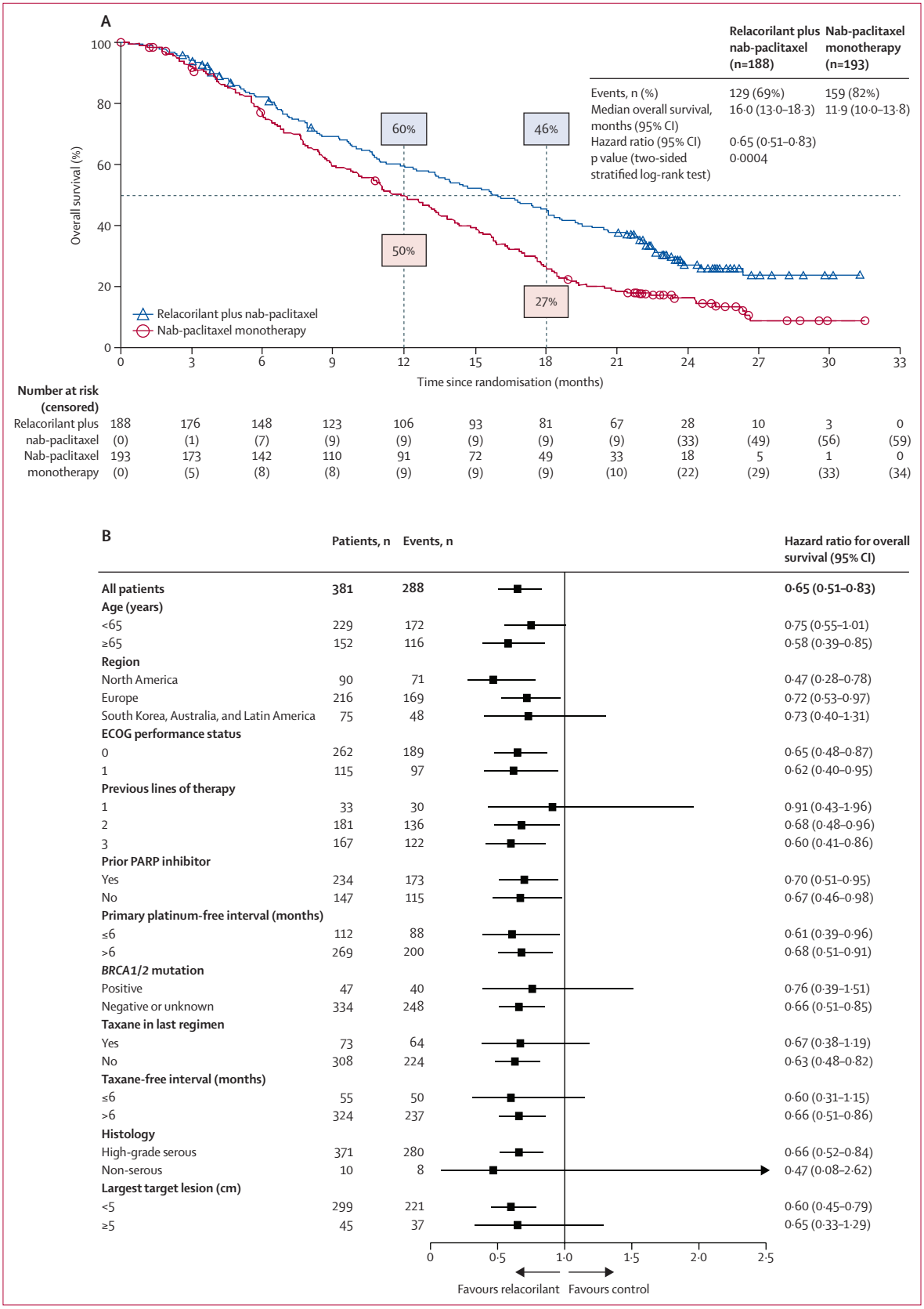

Figure 2: **Overall survival**
(A) Kaplan–Meier estimates of overall survival (time from randomisation to death from any cause) among patients who received relacorilant plus nab-paclitaxel and those who received nab-paclitaxel monotherapy. (B) Results of exploratory subgroup analyses of overall survival in the intention-to-treat population represented as forest plots. The HRs reported throughout the figure are based on a Cox proportional hazards model, stratified according to the randomisation factors that were collected in the interactive response technology system, except when the randomisation factor was the subgroup under analysis; in which case, only a single stratification variable was used. Under the assumption of proportional hazards, a HR of less than 1 indicates a reduction in the hazard in favour of the combination group. Circles and triangles indicate censored data. *BRCA*=breast cancer gene. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. PARP=poly(ADP-ribose) polymerase.

two items reached the minimally important difference threshold, favouring the nab-paclitaxel monotherapy group: nausea and vomiting (least-squares mean of difference 5·32, 95% CI 2·25–8·39; nominal p=0·0007) and appetite loss (least-squares mean of difference 7·75, 95% CI 3·18–12·32; p=0·0009); both were under the clinically meaningful threshold of a 10-point difference in the least-square mean of the difference (appendix p 21).

In an evaluation of at least 15-point and at least 10-point improvements in the abdominal or gastrointestinal symptoms scale of the EORTC QLQ-OV28 at week 8 or week 9, neither showed significant differences between treatment groups (two-sided stratified Cochran–Mantel–Haenszel test nominal p=0·10 and nominal p=0·20; appendix p 22).

At the time of the final overall survival analysis, the safety profile of the relacorilant combination was consistent with the safety profile at the time of the primary analysis. Neutropenia (121 [64%]), anaemia (115 [61%]), fatigue (101 [54%]), and nausea (82 [44%]) were the most common treatment-emergent adverse events in the relacorilant combination group. The overall incidence of any grade and grade 3 or higher treatment-emergent adverse events (table 1), and treatment-emergent serious adverse events (table 1; appendix p 23) were similar to those reported in the primary analysis. The overall frequencies of grade 3 or worse adverse events (141 [75%] *vs* 113 [59%]), all serious adverse events (66 [35%] *vs* 45 [24%]), and grade 3 or worse neutropenia (82 [44%] *vs* 48 [25%]), anaemia (34 [18%] *vs* 17 [9%]), and fatigue (17 [9%] *vs* 3 [2%]) were numerically higher in the combination group, which had a 30% longer median treatment duration with nab-paclitaxel compared with the nab-paclitaxel monotherapy group, respectively (4·52 months [range 0·0–23·6] *vs* 3·48 months [0·0–25·2]; appendix p 13). No further serious adverse events of febrile neutropenia or sepsis, or deaths on treatment were reported with additional follow-up since the primary analysis of progression-free survival (appendix p 23). White blood cell growth factor use was at the discretion of the investigator and did not change with additional follow-up; growth factor use was more frequent in the combination group (84 [45%] patients; 52 [28%] as prophylaxis and 50 [27%] for adverse events) than in the nab-paclitaxel monotherapy group (41 [22%] patients; 29 [15%] as prophylaxis and 31 [16%] for adverse events). The confidence intervals for exposure-adjusted incidence rate differences between groups overlapped zero for all serious adverse events, including febrile neutropenia, and for the treatment-emergent adverse events of neutropenia and anaemia

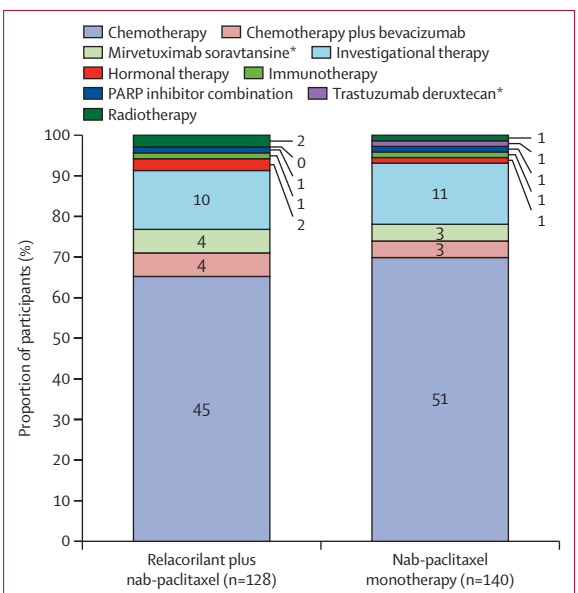

Figure 3: **First subsequent anticancer therapies**
First subsequent therapy received by 128 (68%) of 188 patients from the relacorilant combination group and 140 (73%) of 193 patients from the nab-paclitaxel monotherapy group who discontinued their assigned trial treatment and received subsequent therapy. Chemotherapy included both monotherapy and combination regimens. The most-used chemotherapy agents in the first subsequent regimen in the relacorilant combination group (n=188) versus the nab-paclitaxel monotherapy group (n=193) were gemcitabine (34 [18%] *vs* 38 [20%]), pegylated liposomal doxorubicin (31 [17%] *vs* 31 [16%]), carboplatin (eight [4%] *vs* 11 [6%]), and topotecan (four [2%] *vs* ten [5%]). PARP=poly(ADP-ribose) polymerase. *Monotherapy or combination therapy.

	Relacorilant plus nab-paclitaxel (n=188)		Nab-paclitaxel monotherapy (n=190)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	188 (100%)	141 (75%)	189 (99%)	113 (59%)
Any serious adverse event	66 (35%)	60 (32%)	45 (24%)	39 (21%)
Any adverse event resulting in death	4 (2%)*	..	..	..
Any adverse event leading to relacorilant discontinuation	19 (10%)	..	..	..
Any adverse event leading to nab-paclitaxel discontinuation	18 (10%)	..	15 (8%)	..
Adverse events reported in ≥20% of the patients in either group (by preferred term)				
Neutropenia†	121 (64%)	82 (44%)	93 (49%)	48 (25%)
Anaemia‡	115 (61%)	34 (18%)	106 (56%)	17 (9%)
Fatigue§	101 (54%)	17 (9%)	85 (45%)	3 (2%)
Nausea	82 (44%)	7 (4%)	68 (36%)	6 (3%)
Diarrhoea	74 (39%)	7 (4%)	52 (27%)	3 (2%)
Alopecia	72 (38%)	1 (1%)	59 (31%)	0
Constipation	62 (33%)	1 (1%)	51 (27%)	0
Abdominal pain	55 (29%)	4 (2%)	54 (28%)	2 (1%)
Vomiting	49 (26%)	5 (3%)	43 (23%)	3 (2%)
Decreased appetite	41 (22%)	3 (2%)	22 (12%)	1 (1%)
Hypomagnesaemia	40 (21%)	3 (2%)	36 (19%)	2 (1%)

*There were four deaths on study treatment (or within 30 days of the last dose of study drug) due to adverse events, all in the combination group (one each due to cardiac arrest, intestinal perforation, ischaemic stroke, and septic shock). One death (septic shock, on study day 87 in a patient with febrile neutropenia) was considered related to nab-paclitaxel by the investigator, and none of the deaths were related to relacorilant. The cause of death for the other three patients was attributed to their advanced ovarian cancer. †Combined term including neutropenia, decreased neutrophil count, and febrile neutropenia. ‡Combined term including anaemia, decreased haemoglobin, and decreased red blood cell count. §Combined term including fatigue and asthenia.

Table 1: **Adverse events in the safety population**

	Relacorilant plus nab-paclitaxel (n=188)	Nab-paclitaxel monotherapy (n=190)
Alanine aminotransferase or aspartate aminotransferase increase		
>3–5 × ULN	3 (2%)	13 (7%)
>5–8 × ULN	4 (2%)	3 (2%)
>8–10 × ULN	2 (1%)	0
>10 × ULN	1 (1%)	2 (1%)
Total bilirubin increase		
>2 × ULN	3 (2%)	4 (2%)
Alkaline phosphatase increase		
>2 × ULN	16 (9%)	24 (13%)
Hy's law* criteria met	0	0

ULN=upper limit of normal. *Hy's Law is a clinical rule stating that a drug is likely to cause serious liver injury when a patient develops alanine aminotransferase or aspartate aminotransferase 3 × or greater the upper limit of normal together with total bilirubin greater than 2 × the upper limit of normal, without evidence of cholestasis or another explanation.

Table 2: **Summary of liver function test abnormalities in the safety population**

(appendix p 24). There were no reported cases of adrenal insufficiency or any cases with signs and symptoms indicative of adrenal insufficiency. The frequency of liver function test abnormalities was low and similar across treatment groups (table 2); no cases met Hy's Law criteria.[18]

Discussion

The phase 3 ROSELLA trial met its dual primary endpoints: the addition of relacorilant to nab-paclitaxel for patients with platinum-resistant ovarian cancer resulted in a statistically and clinically significant improvement in progression-free survival (HR 0·70; p=0·0076)[12] and overall survival (HR 0·65; p=0·0004). This was a robust analysis: the median follow-up exceeds the median overall survival in each study group by more than 8 months, the overall survival data is mature (76%), the dataset is complete (only 5% of patients did not have a documented vital status at the final analysis data cutoff [Jan 8, 2026]), the proportional hazards assumption was not violated, and subsequent therapies were well balanced across study groups. The nab-paclitaxel monotherapy group performed as expected for single-agent chemotherapy in this setting, with a median overall survival of 11·9 months versus a range of 11·1 to 14·4 months in contemporaneous trials.[3,4,11,17,19–24] Moreover, overall survival analyses consistently favoured the relacorilant combination group in all prespecified subgroups, including in poor prognosis populations. The efficacy results from ROSELLA confirm the progression-free survival (HR 0·66) and overall survival (HR 0·67) benefit observed in the randomised controlled phase 2 study (NCT03776812), and position selective glucocorticoid receptor antagonism as a promising novel mechanism of action in many applicable oncology settings.[11]

A significant improvement in second progression-free survival suggests that the treatment benefit from the addition of relacorilant to nab-paclitaxel extends into subsequent lines of treatment. Although a significant improvement was not observed for exploratory patient-reported outcome endpoints, the absence of a clinically meaningful detriment for the relacorilant combination group supports the conclusion that this regimen is manageable by patients.

The final overall survival results for relacorilant plus nab-paclitaxel compare well with the results from other contemporaneous phase 3 trials such as MIRASOL, which compared mirvetuximab soravtansine to investigator's choice chemotherapy.[25] Clinical outcome data for relacorilant and nab-paclitaxel in patients with folate receptor α-positive platinum-resistant ovarian cancer could help to support treatment decisions and appropriate sequencing of relacorilant plus nab-paclitaxel and mirvetuximab soravtansine in an evidence-based paradigm. In the absence of head-to-head data comparing these agents in a population with folate receptor α-positive disease, their order of use will depend on patient preference for their distinct safety profiles and the practicality of waiting for biomarker testing results in patients whose disease is progressing rapidly.

The addition of bevacizumab to chemotherapy in the AURELIA trial showed a significant improvement in progression-free survival but did not result in a significant improvement in the key secondary endpoint of overall survival, probably due, in part, to crossover to the investigational group at progression.[4,22] Moreover, in the current era, bevacizumab is predominantly used to treat patients in the front line and those with recurrent platinum-sensitive ovarian cancer,[26] and there is no evidence from prospective trials to support bevacizumab rechallenge in patients with platinum-resistant disease. All patients in the ROSELLA trial had previously received bevacizumab, a key distinction from AURELIA, and relevant to current clinical practice. Subgroup analyses for overall survival in the phase 2 study of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer showed a benefit in both bevacizumab-exposed and bevacizumab-naive populations,[11] suggesting that this combination regimen is an appropriate choice irrespective of previous bevacizumab treatment. Moreover, given the potential for additive benefit, the combination of bevacizumab with relacorilant plus nab-paclitaxel is being explored in an ongoing study (NCT06906341).

Anti-PD(L)1 therapy has been extensively evaluated in patients with ovarian cancer. To date, 12 randomised controlled phase 3 trials of anti-PD(L)1 agents have been completed,[23,27–37] including four in patients with platinum-resistant ovarian cancer.[23,35–37] Of these four trials, one, KEYNOTE-B96, reported a significant overall survival benefit (HR 0·76) in the prespecified PDL1 combined positive score of 1 or greater primary analysis population,[36] which has a relatively good prognosis.[38] Final overall survival data and peer-reviewed publication will inform the benefit–risk of the KEYNOTE-B96 regimen in the

overall and biomarker-selected populations and among different histological subtypes.[39] The choice between these regimens probably reflects tissue availability, biomarker testing timelines and status, the number of previous lines of therapy, preferences for an oral and intravenous combination versus three intravenous therapies, and patient preference between the distinct adverse event profiles. These new treatments with diverse mechanisms of action provide much needed options for patients with advanced ovarian cancer; additional work to determine the optimal patient selection for these therapies will help to maximise the benefit in routine clinical practice.

Nab-paclitaxel is a rational combination partner for a trial investigating relacorilant—a selective, competitive, reversible glucocorticoid receptor antagonist—as it does not require pretreatment with corticosteroids that agonise the glucocorticoid receptor. To delineate the contribution of components in the investigational group, weekly nab-paclitaxel at a dose of 100 mg/m² was chosen as the control group chemotherapy. Although nab-paclitaxel is not currently approved for use in patients with ovarian cancer by the FDA or EMA, this choice was supported by a National Comprehensive Cancer Network Compendia evidence category 2A assessment of nab-paclitaxel for the treatment of patients with platinum-resistant ovarian cancer.[8] Moreover, phase 2 data from Coleman and colleagues[40] and the relacorilant development programme[11] showed similar safety and efficacy for this dose and schedule of nab-paclitaxel to published data for weekly paclitaxel (an approved taxane therapy) in patients with platinum-resistant ovarian cancer. Real-world evidence also shows similar outcomes for nab-paclitaxel and paclitaxel monotherapy in this population.[41] In ROSELLA, the nab-paclitaxel monotherapy control group showed a median progression-free survival of 5·5 months,[12] a median overall survival of 11·9 months, and an adverse event profile that is consistent with data for weekly paclitaxel in recent phase 3 studies[17,19] in this setting. These data support weekly nab-paclitaxel monotherapy as an appropriate comparator for a randomised controlled trial in patients with platinum-resistant ovarian cancer.

Relacorilant selectively antagonises the glucocorticoid receptor, providing a new and unique mechanism to improve survival outcomes. Unlike folate receptor α and immune checkpoints, the glucocorticoid receptor is expressed by the tumour cells of more than 95% of epithelial ovarian cancers.[42] In the relacorilant phase 2 study (NCT03776812),[42] the level of tumour cell glucocorticoid receptor expression was evaluated by immunohistochemistry in patients with available tissue. Exploratory analyses showed a similar progression-free survival benefit from the addition of relacorilant to nab-paclitaxel in each tertile of glucocorticoid receptor expression.[42] These phase 2 glucocorticoid receptor biomarker data support the all-comers ROSELLA design and can be further validated by analyses of glucocorticoid receptor expression in tumour and immune cells, diurnal cortisol levels, and markers of glucocorticoid receptor pathway activation in future clinical trials.

ROSELLA study limitations include the open-label design and the applicability of these results to patients with greater than three lines of anticancer therapy. The limitations of an open-label design are mitigated by the objectivity of the dual primary endpoints (blinded independent central review for progression-free survival and overall survival), the consistency of the benefit across primary and secondary efficacy endpoints, and the prespecified statistical analysis plan. A consistent progression-free and overall survival benefit was observed in subgroups of patients who had received one, two, and three previous lines of anticancer therapy.[12] In the phase 2 study, which permitted the enrolment of patients with up to four previous lines of anticancer therapy,[11] a similar benefit from the addition of relacorilant to nab-paclitaxel was observed. Additional clinical studies might prove the utility of relacorilant and nab-paclitaxel in more heavily pretreated patients. Although both ROSELLA and the phase 2 study enrolled patients with non-serous high-grade histologies, the numbers of patients with these rarer ovarian cancers were too few to allow meaningful conclusions to be drawn among different histological subtypes. An additional limitation of the ROSELLA study design is that patient-reported outcomes were only collected until the end of treatment visit. Continued collection of these data after the end of study treatment might have increased the potential to discriminate between study groups, but might also have been confounded by the impact of subsequent treatments.

The participants in ROSELLA were enrolled globally in 14 countries across Australia, Europe, Latin America, North America, and South Korea. Consistent with disease distribution among ethnicities, White people were the most highly represented group in the study. The proportion of Black or African American and Hispanic participants was low (five [1%] and 33 [9%], respectively). However, there was a higher proportion of Asian participants (48 [13%]). Of note, 57 (15%) participants did not report their race or ethnicity.

Relacorilant showed a consistent safety profile; no new safety signals were identified with longer follow-up since the primary analysis. The nature of the adverse events reported with relacorilant plus nab-paclitaxel is consistent with the established nab-paclitaxel monotherapy safety profile. Higher rates of grade 3 or worse neutropenia and anaemia were observed for the combination group but were similar following adjustment for the duration of study drug treatment, were well managed with standard supportive care, and did not add to the patient safety burden. Glucocorticoids do not stimulate granulopoiesis,[43] and neutropenia has not been reported for relacorilant monotherapy.[44–46] Therefore, the increased frequency of

neutropenia is most probably due to prolonged duration of treatment with nab-paclitaxel in the combination group, and pharmacodynamic synergy between relacorilant and nab-paclitaxel, increasing apoptosis of myeloid progenitor cells. However, the glucocorticoid receptor regulates erythropoietin and increases the sensitivity of erythroid progenitors to erythropoietin.[47–51] Low-grade anaemia has been reported for relacorilant monotherapy,[52] suggesting that the increased rates of anaemia could reflect both an additive effect and prolonged duration of treatment with nab-paclitaxel in the combination group. Nab-paclitaxel is a known cause of transaminitis;[53] the frequency observed in ROSELLA is consistent with the reported literature and was not increased with the addition of relacorilant.

In summary, the addition of relacorilant to nab-paclitaxel showed a progression-free and overall survival benefit in patients with platinum-resistant ovarian cancer. These outcomes—a 35% reduction of the risk of death from any cause and a median overall survival improvement of 4·1 months—position relacorilant plus nab-paclitaxel as a new standard treatment option for patients with platinum-resistant ovarian cancer, without the need for biomarker selection.

Contributors

All authors provided resources, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. All authors were given the opportunity to access the data in the study and agreed to submit for publication. DL, DMO, BJM, LKD, ICT, and ABO conceptualised the study. ICT curated the data, used data software, and performed data validation. AK-H, ICT, and AMJ were involved with formal analyses and visualisation. LKD, AK-H, ICT, and AMJ were involved with study methodology. Project administration was led by DL, DMO, J-WK, LM, BJM, LKD, AK-H, ICT, AMJ, and ABO. DL, DMO, J-WK, LM, LKD, ICT, AMJ, and ABO provided supervision. DL, LGl, J-WK, GG, AF, LGi, LM, SQ, EH, YJL, AO, MS, B-GK, AC, CP, CD, AB, ALL, VS, BJM, PF, EM, VC, BS, EG, MCC, LGa, AD, PS, GS, CC, GA, TVG, AS, LKD, AK-H, ICT, AMJ, NC, and ABO were involved with the study investigation. DL, LGl, SQ, AO, BJM, TVG, LKD, AK-H, ICT, AMJ, and ABO were involved with writing of the original draft.

Declaration of interests

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Data sharing

De-identified datasets for the results reported in this publication can be made available to qualified researchers following submission of a methodologically sound proposal to datarequests@corcept.com. Data will be made available for such requests following the online publication of the Article and for 1 year thereafter in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation. Data will be provided by Corcept Therapeutics.

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