Phase II pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mCRPC) patients with limited progression on abiraterone plus prednisone (SWITCH study)

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BACKGROUND: Despite most metastatic castration-resistant prostate cancer (mCRPC) patients benefit from abiraterone acetate plus prednisone 5 mg bid (AA + P), resistance eventually occurs. Long-term use of prednisone has been suggested as one of the mechanisms driving resistance, which may be reversed by switching to another steroid.

METHODS: SWITCH was a single-arm, open-label, single-stage phase II study. The primary objective was to evaluate the antitumour activity of abiraterone acetate plus dexamethasone 0.5 mg daily (AA + D) in mCRPC patients progressing to AA + P. Clinically stable mCRPC patients who had prostate-specific antigen (PSA) and/or limited radiographic progression after at least 12 weeks on AA + P, were eligible. The primary endpoint was measured as the proportion of patients achieving a PSA decline of ≥30% (PSA30) from baseline after 6 weeks on AA + D. Secondary endpoints included: PSA50 response rate at 12 weeks, time to biochemical and radiological progression, overall survival, safety profile evaluation, benefit from subsequent treatment lines and the identification of biomarkers of response (AR copy number, TMPRSS2-ERG status and PTEN expression).

RESULTS: Twenty-six patients were enrolled. PSA30 and PSA50 were 46.2% and 34.6%, respectively. Median time to biochemical and radiographical progression were 5.3 and 11.8 months, respectively. Two radiological responses were observed. Median overall survival was 20.9 months. Patients with AR gain detected in plasma circulating tumour DNA did not respond to switch, whereas patients with AR normal status benefited the most. No significant toxicities were observed and PSA50 response rate to subsequent taxane was 50%.

CONCLUSIONS: In selected clinical stable mCRPC patients with limited disease progression on AA + P, a steroid switch from prednisone to dexamethasone can lead to PSA and radiological responses.

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INTRODUCTION
Although novel therapeutic options are being developed for metastatic castration-resistant prostate cancer (mCRPC), new rational-based strategies may optimise the benefit from currently available therapies such as abiraterone acetate (AA)1,2.

AA inhibits androgen synthesis through blockade of CYP17 17α-hydroxylase and 17,20-lyase functions. Continuous CYP17 inhibition may result in rising adrenocorticotropic hormone levels and increased steroid levels upstream of CYP17, which may not only prevent adrenocortical insufficiency but also could result in a secondary mineralocorticoid excess characterised by fluid retention, hypertension and/or hypokalemia3. To prevent these, AA is administered in combination with prednisone 5 mg twice daily1,2.
Nonetheless, prednisone has not been the only concomitant steroid used with AA. In the initial phase I/II trial, AA was administered without steroids, and dexamethasone 0.5 mg od was only added to single AA after biochemical progression. This strategy led to a prostate-specific antigen (PSA) decline > 50% (PSA50) in 33% of patients, suggesting a reversal of resistance to AA. In the first reported post-docetaxel phase II trial of AA, Reid et al. also used dexamethasone 0.5 mg od. This study showed a

### Table 1. Baseline characteristics of 26 patients included in the study

| Characteristics                     | All (n=26) | AA + D pre-chemo (n=14) | AA + D post chemo (n=12) |
|-------------------------------------|------------|-------------------------|--------------------------|
| **Age**                             |            |                         |                          |
| Median (range)                      | 73.0 years (60–85) | 72.5 years (60–85) | 73 years (66–78)  |
| **Baseline PSA**                    |            |                         |                          |
| Median (range)                      | 36.1 (4.46–965.2) | 20.6 ng/mL (4.5–367.0) | 39.9 ng/mL (6.9–1880) |
| **Gleason**                         |            |                         |                          |
| 6                                   | 4 (15%)   | 2 (14%)                 | 2 (17%)                 |
| 7                                   | 7 (27%)   | 3 (21%)                 | 4 (33%)                 |
| 8–10                                | 14 (54%)  | 8 (57%)                 | 6 (50%)                 |
| **ECOG**                            |            |                         |                          |
| 0                                   | 10 (38%)  | 6 (43%)                 | 4 (33%)                 |
| 1                                   | 15 (58%)  | 7 (50%)                 | 8 (67%)                 |
| 2                                   | 1 (4%)    | 1 (7%)                  | –                        |
| **Time to CRPC**                    |            |                         |                          |
| Median (range)                      | 24.3 months (6.2–145.1) | 23.3 months (6.2–145.1) | 34.8 months (19.1–107.5) |
| **Previous steroids to AA**         |            |                         |                          |
| Monotherapy                         | 3 (12%)   | 3 (21%)                 | –                        |
| Docetaxel                           | 12 (46%)  | –                       | 12 (100%)               |
| Cabazitaxel                         | 1 (4%)    | –                       | 1 (8%)                  |
| > 6 months                          | 11 (42%)  | 2 (14%)                 | 9 (75%)                 |
| < 6 months                          | 4 (15%)   | 1 (7%)                  | 3 (25%)                 |
| **Metastasis**                      |            |                         |                          |
| Bone                                | 24 (92%)  | 12 (86%)                | 12 (100%)               |
| Nodes                               | 12 (46%)  | 8 (57%)                 | 4 (33%)                 |
| Visceral                            | 4 (15%)   | 1 (7%)                  | 3 (25%)                 |
| **Progression to AA + PRED**        |            |                         |                          |
| Biochemical (PSA)                   | 26 (100%) | 14 (100%)               | 12 (100%)               |
| Radiological (new)§                 | 8 (31%)   | 4 (29%)                 | 4 (33%)                 |
| Radiological (size)§                | 4 (15%)   | 2 (14%)                 | 2 (17%)                 |
| **LDH**                             |            |                         |                          |
| Normal                              | 14 (54%)  | 8 (57%)                 | 6 (50%)                 |
| High                                | 12 (46%)  | 6 (43%)                 | 6 (50%)                 |
| **Alkaline phosphatase**            |            |                         |                          |
| Normal                              | 19 (73%)  | 4 (29%)                 | 9 (75%)                 |
| High                                | 7 (27%)   | 10 (71%)                | 3 (25%)                 |
| **Haemoglobin**                     |            |                         |                          |
| > 10 g/dL                           | 23 (88%)  | 13 (93%)                | 10 (83%)                |
| ≤ 10 g/dL                           | 3 (12%)   | 1 (7%)                  | 2 (17%)                 |
| **Albumin**                         |            |                         |                          |
| ≥ 35 g/L                            | 19 (73%)  | 11 (79%)                | 8 (67%)                 |
| < 35 g/L                            | 5 (19%)   | 2 (14%)                 | 3 (25%)                 |
| **AA + PRED cycles (28 days)**      |            |                         |                          |
| Median (range)                      | 6.2 (3.0–31.3) | 5.8 (3.0–28.1) | 6.4 (3.0–31.3) |
| **PSA response to AA + PRED**       |            |                         |                          |
| PSA decrease ≥ 50%                  | 12 (46%)  | 6 (43%)                 | 6 (50%)                 |
| PSA decrease ≥ 30% and < 50%        | 1 (4%)    | –                      | 1 (8%)                  |
| No response                         | 13 (50%)  | 8 (57%)                 | 5 (42%)                 |

§Three new bone metastasis in bone scan and/or an increase of target lesions <40%. AA Abiraterone acetate, P prednisone, D dexamethasone
PSA50 response rate of 51%, whereas a contemporaneous phase II trial with AA plus prednisone 5 mg bid observed a PSA50 response rate of 39%.

A potential difference in the activity of AA in combination with prednisone and dexamethasone may also be supported by the superiority of dexamethasone in monotherapy over prednisone in terms of PSA response (47% vs 24%, \( p = 0.05 \)) and median time to PSA progression (9.7 vs 5.1 months) as demonstrated in a randomised phase II trial in mCRPC patients. In this study, crossover to dexamethasone in patients progressing to prednisone was associated with 37% biochemical responses.

The hypothesis that the switch of prednisone to dexamethasone in patients with biochemical progression to AA plus prednisone would achieve secondary responses has been explored in a retrospective post-docetaxel cohort. Biochemical responses were observed in 40% of the cases included in this series. Here, we present the data of a prospective phase II study of mCRPC patients treated with AA 1000 mg od plus dexamethasone 0.5 mg od (AA + D) after biochemical and/or limited radiographic progression to AA 1000 mg od plus prednisone 5 mg bid (AA + P) pre- and post-docetaxel.

**MATERIALS AND METHODS**

**Patient population**

The SWITCH study (NCT02928432) was a prospective multicentre study conducted at four university hospitals in Spain. Castrate (serum testosterone ≤ 50 ng/dL) metastatic prostate cancer patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 who had a histological diagnosis of prostate adenocarcinoma, a PSA > 2 ng/mL, and confirmed biochemical progression as defined by PCWG2 criteria after at least 12 weeks of AA 1000 mg od and prednisone 5 mg bid were eligible. Patients with limited radiological progression on AA + P (as defined by: i. ≤ 3 new asymptomatic metastasis in bone scan, ii. no new soft tissue lesions, and iii. < 40% increase in the size of target lesions according to RECIST1.11) were allowed in the study. Patients had to be asymptomatic or present stable symptoms without any worsening in grade. A complete list of eligibility criteria is provided as Supplementary Appendix. Eligible patients were enrolled in the study after providing informed consent. The study was approved by the institutional ethics review committees of all participating centres and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation/WHO Good Clinical Practice standards.

**Study design and response assessment**

This was a single-arm, open-label, single-stage phase II study. The primary objective was to evaluate the antitumour activity of AA + D in patients with mCRPC who had biochemical progression (with or without limited radiological progression as described above). The primary endpoint was measured as the proportion of patients achieving a PSA decline of ≥30% (PSA30) from baseline after 6 weeks on AA + D, and confirmed by a second PSA value ≥2-weeks later. The proportion of patients achieving PSA50 response after ≥12 weeks on AA + D was also reported as secondary endpoint as per PCWG2 recommendation. Time to PSA progression was defined as the date that a ≥25% increase in PSA with an absolute increase of ≥2 ng/mL above the nadir occurred. Confirmation by a second PSA value ≥2-weeks later was required. Measurable disease response rate using RECIST1.1 and PCWG2 criteria was assessed at least 12 weeks after AA + D initiation.
Patients with biochemical progression were allowed to continue on AA + D until radiographic or clinical progression, whichever occurred first.

Treatment and procedures
Four tablets (250 mg each) of AA and one capsule (0.5 mg) of dexamethasone were administered daily, continuously, in 28-day cycles. All patients underwent a standard evaluation that included prior medical history, physical examination, and laboratory tests (PSA, haematology, biochemistry, liver and renal function studies) at baseline and at 2-weeks intervals for the first 8 weeks and then in 4 weeks intervals. AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. Baseline high-resolution computed tomography scans and bone-scans were performed and repeated every 12 weeks.

Biomarker studies
Available archival prostate cancer formalin-fixed paraffin-embedded samples and optional plasma samples at progression to abiraterone and prednisone within 4 weeks prior to first dose of dexamethasone were collected. PTEN protein expression was determined by immunohistochemistry as previously described. TMPRSS2-ERG fusion was assessed by fluorescent in-situ hybridisation using a modified three-colour assay based on the ERG break-apart assay described by Attard et al. Plasma was obtained by centrifugation of 10 mL of blood collected in ethylenediaminetetraacetic acid tubes within 2 hours from blood-drawn and stored at −80 °C. DNA was extracted from 2 mL of plasma and AR status in plasma was determined by digital drop PCR (ddPCR) using the QX200 ddPCR system (Bio-Rad), for AR copy number as described previously, and for AR mutations (supplementary appendix S2).

Statistical analyses
The primary aim of the study was to demonstrate the rate of patients that showed a ≥30% decline in PSA at 6 weeks. A single-stage A’Hern phase II trial design used to estimate the sample size. By using a response rate of 10% for the null hypothesis versus an alternative hypothesis response rate of 30%, an alpha-error of 0.05 and a power of 0.80, 25 patients were to be recruited. The null hypothesis would be rejected if at least six patients had a PSA decline ≥30%. Biomarker studies were exploratory and descriptive statistics were used.

RESULTS
Patient characteristics
Twenty-six mCRPC patients were enrolled in this Phase II trial between June 2013 and March 2016 (CONSORT diagram supplementary appendix S3). Median age was 72.6 years (range 60.2–85.8), median PSA 36.1 ng/mL (range 4.5–1880) and 96% were ECOG 0–1. Excluding AA + P, the median number of prior treatment lines for mCRPC was 1 (range 0–3). Fourteen patients (53.8%) were chemotherapy-naive at the initiation of AA + P. Median time on AA + P was 6.2 months (range 3.0–31.3). All patients had PSA progression and 12 (46.2%), also presented a biochemical (PSA) progression-free survival (bPFS) with AA and 21.4%, respectively. In this series, median biochemical progression-free survival (bPFS) from AA was 11.8 months (95% CI 6.6–17.1), Fig. 2a. In the pre- and post-docetaxel settings median rPFS was 13.6 and 11.8 months, respectively. According to RECIST1.1 criteria, two objective partial response rates at 12 patients (46.2%) presented a PSA30 response. PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response. PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response rates were 41.7%, 12 patients (46.2%) presented a PSA50 response.
responses were observed in a patient with liver metastasis (Fig. 3a–d) and in a second patient with measurable nodal disease (Fig. 3e, f).

Overall survival and effect of SWITCH on subsequent therapies
Median OS since AA+D initiation was 20.9 months (95%CI 10.0–31.7), Fig. 2b. Effect of subsequent therapies for mCRPC was evaluated in 20 out of 23 patients with clinical and/or radiological progression who had started a new treatment line after AA+D at the time of data collection cutoff. Docetaxel (40%), Ra-223 (30%) and enzalutamide (15%) were the most-frequent subsequent-line after AA+D, see supplementary appendix S5.

Twelve patients received at least 1 taxane (11 docetaxel, 1 cabazitaxel) as first-chemotherapy following AA+D (9 immediately after AA+D, 2 after Ra-223, and 1 after enzalutamide). PSA50 response rate to taxanes at ≥12 weeks in these 12 patients was 50%.

Safety evaluation
Eight patients (31%) presented at least one grade 1–2 related adverse events (AEs) after switch to AA+D. No grade 3–4 related AEs were reported. The commonest AA+D related AEs were muscle weakness (n = 3, 12%), hypertension (n = 2, 8%) and hyperglycaemia (n = 2, 8%). An episode of orthostatic...
Table 2. Treatment-related adverse events

|                      | AA + Prednisone | AA + Dexamethasone |
|----------------------|-----------------|-------------------|
|                      | Grade P         | Grade A           | Grade P         | Grade A         |
|                      | Grade 1         | Grade 2           | Grade 3/4       | Grade 1         | Grade 2           | Grade 3/4       |
| Hypertension         | 1               | 2                 | 0               | 1               | 1                 | 0               |
| Hypokalaemia         | 2               | 0                 | 0               | 2               | 0                 | 2               |
| Oedema               | 1               | 0                 | 0               | 0               | 0                 | 0               |
| Hyperglycaemia       | 1               | 0                 | 0               | 1               | 1                 | 0               |
| Hypertension         | 1               | 0                 | 0               | 0               | 0                 | 0               |
| Muscle weakness      | 0               | 0                 | 0               | 0               | 0                 | 0               |
| Total events         | 6               | 2                 | 0               | 6               | 2                 | 0               |

The SWITCH trial was a proof of concept study that, for the first time, prospectively evaluated the antitumour activity of a steroid switch from prednisone 5 mg bid to dexamethasone 0.5 mg od concomitant to AA 1000 mg od. We report durable PSA declines, two objective radiological responses and several prolonged disease stabilisations in clinically stable patients progressing to AA + P. This extension of time on therapy associated to a clinical benefit is a meaningful therapeutic objective. Activity was seen in both pre- and post-docetaxel settings. Importantly, AA + D switch in this study did not add any significant toxicities to AA + P and did not compromise subsequent treatment with taxanes.

Our study met its primary endpoint by proving that the steroid switch could induce a PSA decrease ≥ 30% in at > 30% of patients (46.2%). A PSA30 response rate at 6 weeks was chosen as a}

**DISCUSSION**

The SWITCH trial was a proof of concept study that, for the first time, prospectively evaluated the antitumour activity of a steroid switch from prednisone 5 mg bid to dexamethasone 0.5 mg od concomitant to AA 1000 mg od. We report durable PSA declines, two objective radiological responses and several prolonged disease stabilisations in clinically stable patients progressing to AA + P. This extension of time on therapy associated to a clinical benefit is a meaningful therapeutic objective. Activity was seen in both pre- and post-docetaxel settings. Importantly, AA + D switch in this study did not add any significant toxicities to AA + P and did not compromise subsequent treatment with taxanes.

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-hypotension without other symptoms of adrenocortical insufficiency during a concurrent episode of acute gastroenteritis was reported as possibly related to AA + D. Prior study enrolment, three patients on AA + P had been started on eplerenone 25–50 mg od due to mineralocorticoid excess syndrome (oedema, hypertension and/or hypokalaemia). A fourth patient was started on oral antidiabetics due to AA + P related hyperglycaemia. These side-effects were controlled in all the four patients at time of switch to AA + D and did not require treatment adjustment, whereas on dexamethasone. Related AEs on study are summarised in Table 2.

**Biomarker studies**

AR copy number, T877A and L702H mutation status in plasma ctDNA at AA + D baseline, as well as PTEN and ERG rearrangement status in tissue were determined in patients with available samples (supplementary appendix S6). The best PSA change at any time after 12 weeks according to AR status in plasma ctDNA and other biomarkers is presented in Fig. 4a. PSA30 and PSA50 response rates in patients with AR normal were 100% and 50%, respectively. None of the five patients with AR gain had a PSA response and compared with AR normal patients showed significantly shorter bPFS (2.8 vs 8.3 months, p = 0.001) and rPFS (7.9 vs 19.5 months, p = 0.002), Fig. 4b. AR T877A mutation was detected in six patients at switch, PSA30 and PSA50 response rates were 67% and 50%, respectively. Median bPFS and rPFS for this group were 5.3 and 11.8 months, respectively, which did not differ significantly from AR gain. TMPRSS2-ERG rearrangement was present in 9 (52.9%) patients. PSA30 response rates were 11.1% and 50% in patients with or without ERG rearrangement, respectively, but not significant differences in bPFS or rPFS were seen.

**Fig. 4**

**a** Waterfall plot representing PSA best response according to PCWG2 criteria (y-axis) and patients (x-axis). Each individual bar represents a patient, ordered by the magnitude of PSA response. Patients’ ID at the bottom match those in Fig. 1 (swimmer-plot). Each bar is coloured according to AR status determined in ctDNA: navy-blue for AR gain, medium-blue for AR T877A mutation, sky-blue for AR normal, grey for unknown status due to lack of sample available, or low ctDNA isolated. Panel at the bottom summarises pre- or post-docetaxel status, TMPRSS2-ERG (TE) fusion and PTEN status in archived diagnostic biopsies/prostatectomy.

**b** Kaplan–Meier radiographic progression-free survival (rPFS) curves according to AR status in ctDNA: blue represents patients with AR normal status, orange for patients harbouring an AR T877A mutation, and red for patients with AR gain detected, respectively. The exploratory long rank-test suggests that rPFS is significantly prolonged in AR normal compared with AR gain (p = 0.002). The differences observed between AR normal and AR T877A (p = 0.117) or AR T877A and AR gain (p = 0.092) were not significant.
primary endpoint in the trial in order to minimise the patients’ exposition to a potentially ineffective strategy while maximising the possibility of identifying significant antitumour activity. Despite the fact, this is not a standard definition as per PCWG criteria\(^1\), recent analyses support the potential utility of a PSA30 response rate endpoint: PSA30 has been associated with improved survival in patients treated with taxanes\(^1\) and abiraterone\(^2\). On the other hand, PSA50 response rates at 12 weeks were concordant with PSA30 responses at 6 weeks, further supporting our alternative hypothesis.

Current guidelines recommend the maintenance of AA+P beyond PSA rise until clinical and/or radiological progression occurs\(^2\). In our study, all patients experienced PSA progression to AA+P, and approximately half of them (14/26) presented radiographic progression. Median rPFS from the AA+D switch was, approximately, 11.8 months, which is longer than the median 5.4 months that was observed from biochemical to radiographic progression in the abiraterone arm of the COU-302 trial\(^2\). Our results also compare favourably (rPFS 11.8 months, PSA response: 34.6%) to a recently presented phase IV study in which a highly selected population of patients who had disease progression after ≥ 24 weeks on treatment with AA+P received enzalutamide. In this study, median rPFS was 8.1 months with an unconfirmed PSA response rate of 27%\(^1\). Furthermore, switching steroids on progression to AA+P was recognised as a valid therapeutic option in the recent St. Gallen Advanced Prostate Cancer Consensus Conference, where 72% of panellists recommended a steroid switch in selected patients\(^2\) despite the lack of prospective evidence available at the time and which we provide for the first time.

Noteworthy, time to bPFS and rPFS were shorter in patients with AR gain compared with AR normal. In addition, none of the patients with AR gain responded by PSA to AA+D, whereas all AR normal presented a decline > 30%. The poor outcomes observed in patients harbouring AR aberrations are consistent with previous reports of primary resistance to AA+P\(^2\). Interestingly, a majority of the patients with detected T878A mutation had a PSA decline following switch, although median bPFS and rPFS were shorter than AR normal patients. T878A mutation is activated by 21-carbon-steroids, such as progesterone\(^2\), and its levels are increased by abiraterone\(^2\) but suppressed by continuous low-dose dexamethasone\(^2\). Confirmation of our results in additional cohorts would allow the selection of patients likely to benefit from the steroid switch\(^2\). We have also analysed ERG rearrangements and PTEN expression (variants suggested as potential biomarkers of AA+P benefit\(^2\)). However, in our small series the absence of ERG rearrangements seemed related to PSA responses but not to rPFS.

We acknowledge that our study has some limitations. First, the lack of a control arm makes it impossible to establish the exact clinical benefit that can be obtained with a steroid switch, beyond PSA responses; a future randomised phase II study should include a control group in which AA+P is continued until radiographic progression. A second limitation is that molecular analyses did not include other potential predictive biomarkers such as AR-V7 or the glucocorticoid receptor (GR). Although AR splicing variants have been linked to resistance to AA+P\(^2\), GR has been suggested to lead to the cross-stimulation of AR target genes in the absence of androgens\(^2\).

CONCLUSION

Our study provides prospective evidence that a steroid switch is a feasible and safe manoeuvre that can induce responses in clinically stable patients progressing on abiraterone. We also present hypothesis-generating evidence of the role of AR amplifications, AR mutations and ERG rearrangements as potential predictive biomarkers. Nonetheless, these findings require further validation, ideally in a prospective, randomised clinical trial.

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ADDITIONAL INFORMATION

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Competing interests: RL, GA, EC and DO have received research funding from Janssen. NRL, FLC, MIS, AM, BH, JCL, DL, GA, EC and DO have received speaker fees from Janssen. GA, EC and DO have received consulting fees from Janssen. AJ and GA are employees of The ICR, who developed abiraterone, and therefore have a commercial interest in this agent. GA is on the ICR list of rewards to inventors for abiraterone.

Ethics approval and consent to participate: The study was approved by the institutional ethics review committees of all participating centres and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation/WHO Good Clinical Practice standards. All patients provided informed consent to enter the study at the time of enrolment.

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