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Quality of life outcomes from the PATCH trial evaluating LHRH agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer

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Abstract

Objectives: To compare quality of life (QoL) outcomes at 6 months between men with advanced prostate cancer (PCa) receiving either transdermal oestradiol (tE2) or LHRH agonists (LHRHa) for androgen deprivation therapy (ADT).

Patients and methods: Men with locally advanced or metastatic PCa participating in an ongoing randomised, multi-centre UK trial comparing tE2 versus LHRHa for ADT were enrolled into a QoL sub-study. tE2 was delivered via 3 or 4 transcutaneous patches containing 100mcg of oestradiol/24 hours. LHRHa was administered as per local practice. Patients completed questionnaires based on EORTC QLQ-C30 with prostate-specific module QLQ PR25. The primary outcome measure was global QoL score at 6 months, compared between randomised arms.

Results: 727 men were enrolled between August 2007 and 5 October 2015 (412 tE2, 315 LHRHa) with QoL questionnaires completed at both baseline and 6 months. Baseline clinical characteristics were similar between arms: median age 74 years (interquartile range [IQR] 68-79), median PSA 44 ng/ml (IQR 19-119), and 40% (294/727) had metastatic disease. At 6 months, patients on tE2 reported higher global QoL than LHRHa (mean difference +4.2, 95% CI 1.2 to 7.1, p=0.006), less fatigue and improved physical function. Men in the tE2 arm were less likely to experience hot flushes (8% vs 46%), and report a lack of sexual interest (59% vs 74%) and sexual activity, but had higher rates of significant gynecomastia (37% vs 5%). The higher incidence of hot flushes among LHRHa patients appear to account for both the reduced global QoL and increased fatigue in the LHRHa arm compared to tE2 arm.

Conclusion: Patients receiving tE2 for ADT had better 6-month self-reported QoL outcomes compared to those on LHRHa, but increased likelihood of gynecomastia. The ongoing trial will evaluate clinical efficacy, and longer term QoL. These findings are also potentially relevant for short-term neoadjuvant ADT.

Introduction

Prostate cancer (PCa) is the most frequent cancer diagnosis in men in the developed world and responsible for 11,000 deaths per year in the UK and 26,000 in the US(1, 2). PCa cell growth is driven by androgen signalling, and androgen deprivation therapy (ADT) forms a cornerstone of treatment. Evidence supports the use of ADT in conjunction with radiotherapy in localised(3, 4) and locally-advanced disease(5, 6), and as first-line therapy in the metastatic setting(7).

ADT, usually achieved using luteinising hormone-releasing hormone agonists (LHRHa) in contemporary practice, is associated with numerous side-effects(8, 9). Specifically, these include declining bone health(10, 11), weight gain and metabolic syndrome(12), sexual dysfunction(13-15), hot flushes(16, 17), mental and cognitive decline(18-22), and physical deterioration and fatigue(23-26). LHRHa increase the risk of depression in men with PCa(27), reportedly driven by the loss of sexual function(28). Recent data suggest an increased risk of subsequent Alzheimer's disease(29). An association with increased cardiac events is described but remains controversial(30). Whereas a number of interventions have been demonstrated to ameliorate the toxicities of LHRHa to a

greater or lesser extent(8), further efforts are required to maintain the highest possible quality of life (QoL) for these patients.

PATCH (Prostate Adenocarcinoma: TransCutaneous Hormones, MRC PR09) is an ongoing randomised controlled trial comparing transdermal oestradiol (tE2) delivered via transcutaneous patches versus LHRHa in men with advanced PCa. LHRHa act through the hypothalamic-pituitary axis to suppress testosterone production by the testes. Endogenous oestradiol (E2) in men is derived from testosterone through aromatase. Thus, it is also suppressed by, and consequently contributes to, the toxicity profile of LHRHa(9). Exogenous administration of E2 inhibits the hypothalamic-pituitary axis (thereby suppressing testosterone) as well but maintains oestradiol levels and hence mitigates some of the toxicity of LHRHa. Administration of exogenous E2 via oral or intravenous routes is associated with risk of thrombosis and adverse cardiovascular (CVS) events(31). However, tE2 avoids the hepatic first-pass effects mediating these risks, as supported by previous results from PATCH (n=254) showing similar rates of CVS events in both tE2 and LHRHa arms after a median follow-up of 19 months(32). Among this initial cohort, castration rates were similar in both arms.

In this report, we compare QoL outcomes at 6 months from randomisation between the two hormonal treatments, based on data available from approximately 700 patients.

Methods

Patients

The study design for the PATCH trial has previously been described(32). Briefly, patients from participating UK centres were eligible for recruitment if they had locally advanced or metastatic PCa, and a treatment plan for indefinite ADT in the metastatic setting or ≥3 years for locally advanced disease. National regulatory and ethics committees approved the protocol, and participating hospitals obtained the appropriate local approvals. Participants provided written informed consent.

Men were randomly allocated (in 2:1 ratio before February 2011 and then 1:1) to receive tE2 or LHRHa (open-label). This was done centrally according to a computer-based minimisation algorithm with a random element (80%), balanced for the following factors: disease stage, age, smoking status, personal or family history of heart disease, which LHRHa agent was to be used, PSA, intent to give radical radiotherapy, and centre.

Patients in the tE2 arm received, after a dose regimen change in August 2007(33), 4 FemSeven patches (100mcg/24hours), which were self-administered and changed twice weekly during the first 4 weeks. This was reduced to 3 patches changed twice weekly, provided testosterone levels were <1.7 nmol/l. LHRHa was administered as per local practice.

Quality of life data collection

Patients received a specific patient information sheet for the QoL study and provided separate consent to participate in this component of the study. QoL information was collected on paper questionnaires utilizing EORTC QLQ-C30 and the prostate specific module QLQ-PR25. These were self-completed by participants, who were instructed to record responses without discussion with site staff, friends or relatives. Data were collected pre-randomisation, then at 4, 8 and 12 weeks, and subsequently every 3 months up to 2 years post-randomisation. QLQ-C30 includes a range of domains which are either multi-item scales or single-item measures: a global health status/QoL scale, five function scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). QLQ-PR25 contains 25 items designed to assess QoL in PCa patients, including urinary, bowel and sexual symptoms and functioning, and hormone-related symptoms.

The Independent Data Monitoring Committee (IDMC) permitted release of the QoL data during the first 6 months from randomisation for patients already enrolled whilst the main trial continues.

Statistical Analysis

For each multi-item QoL domain (eg. global QoL), a summary score was derived according to the EORTC QLQ C-30 scoring manual(34), with range 0-100. For example, the summary global QoL score is a standardised average of the patients' scores from the questions "How would you rate your overall health

during the past week?" and "How would you rate your overall quality of life?". These scores were considered as continuous variables. A higher score corresponds to improved outcomes for global QoL and function scales, but indicates more symptoms (hence poorer outcomes) for symptoms scales. Single-item domains (e.g. sexual interest) were analysed based on reported responses on the questionnaires (not at all, a little, quite a bit, or very much).

The primary outcome was global QoL score at 6 months, as differences in hormone-related symptoms potentially impacting on QoL were expected to be apparent by then(17, 20, 25, 26, 32). The following domains were secondary outcomes: sexual interest, sexual activity, whether feeling less masculine as result of illness or treatment, cognitive functioning, physical functioning, fatigue, and selected hormone-related symptoms which were hot flushes, gynecomastia and weight gain. Gynecomastia was reported as sore or enlarged nipples or breasts.

Patients were considered to have baseline QoL data, if they completed their first QoL questionnaire either by the date of randomisation or 1 week after, but before starting trial treatment. Information on QoL outcomes at 6 months was based on the questionnaire completed nearest to this time point, within ±3 months window. Multi-item QoL domains at 6 months were compared between randomised arms using Tobit regression models (to account for scores being bounded by 0 and 100)(35), adjusting for baseline score. Single-item domains were categorised according to pre-defined binary outcomes for comparison between arms (for ease of clinical interpretation); for example, hot flushes were analysed as "quite a

bit"/"very much" versus "not at all"/"a little". These were compared between arms using logistic regression models, adjusting for baseline response.

All models were further adjusted for the following pre-defined baseline factors: age, calendar year (partly to account for the change in allocation ratio), smoking status, stage of disease (M0/M1), and whether patient was newly diagnosed or relapsing. All comparisons between arms were based on the original allocated treatment, and included patients randomised after the change in patch dose regimen(33) who had data on the relevant QoL domains at both baseline and 6 months. A significance level of 0.05 was chosen *a priori*, without adjustment for multiple statistical testing. Additional exploratory analyses were undertaken to investigate associations between global QoL and other domains.

Statistical analyses were performed using Stata version 14 (Stata Corporation, College Station, Texas, USA).

Results

Between 14 August 2007 and 5 October 2015, 875 men were recruited under the revised patch dose regime, 480 allocated to tE2 and 395 to LHRHa. Within the tE2 arm, 468 patients enrolled on the QoL sub-study, of whom 412 (86% of 480) completed QoL questionnaires at both baseline and 6 months. For the LHRHa group, 385 participated in the QoL sub study, with 315 (80% of 395) having both baseline and 6-month QoL data available (Figure 1). Baseline clinical characteristics were similar between arms for the 727 patients included in the 6-month QoL analyses (Table 1). Overall median age was 74 years (interquartile

[IQR] range 68-79), median PSA 44 ng/ml (19-119), and 40% (294/727) had metastatic disease. There were no differences in baseline global QoL by age nor testosterone level, but men with T4 tumours had worse global QoL compared with other T-stages, and patients with metastatic disease had worse baseline QoL than M0 patients.

Rates of castration were equivalent between the LHRHa and tE2 arms at both 3 and 6 months; the proportion of patients with testosterone concentrations ≤1.7 nmol/l was 93.6% for LHRHa and 93.7% for tE2 at 3 months, and 89.8% and 92.2% at 6 months respectively).

At 6 months, global QoL declined from baseline in both arms (Table 2), but to a lesser extent in the tE2 patients (mean change -2.8) compared to those on LHRHa (-5.0). The estimated mean difference in 6-month global QoL between arms was +4.2 (95% confidence interval (CI) 1.2 to 7.1, p=0.006) in favour of tE2. There was no evidence that the treatment effect on global QoL at 6 months differed by age (≤70 versus >70 years); test for interaction p=0.56.

In addition, there was less decline in physical function among tE2 patients (mean change -2.8 vs -5.7), with mean difference in 6-month score +5.8 (2.8 to 8.8, p<0.001) between arms. In addition, tE2 patients had less fatigue at 6 months, mean difference between arms -4.3 (-8.1 to -0.6, p=0.02) favouring the patches. There was, however, no difference in reported decline in cognitive function between arms.

Analysis of specific domains linked with testosterone suppression (Table 3) showed that tE2 patients were less likely than LHRHa patients to report having no interest in sex (59% vs 74%, odds ratio [OR] 0.42 (95% CI 0.28 to 0.62, p<0.001)) and being “not at all” sexually active (78% vs 87%, OR 0.51 (0.32 to 0.82, p=0.005)). Interestingly, there was weak evidence that the negative effect of LHRHa compared to tE2 on interest in sex was more pronounced in patients aged ≤70 years than those >70 years (t-test for interaction p=0.06).

The likelihood of experiencing “quite a bit” or “very much” hot flushes was significantly lower in the tE2 group (8% vs 46%, OR 0.10 (0.07 to 0.16, p<0.001)). However, as expected, patients in the tE2 arm were much more likely to report “quite a bit” or “very much” gynecomastia than those receiving LHRHa (37% vs 5%, OR 12.70 (7.14 to 22.60, p<0.001)). There was no difference between arms in patients who reported feeling “quite a bit” or “very much less” masculine (as a result of their illness or treatment) or experiencing “quite a bit” or “very much” weight gain.

An association between hot flushes and deterioration in global QoL was observed in both arms at 6 months, with patients who experienced more severe symptoms reporting lower scores (Table 4, p<0.001). The relationship between gynecomastia and global QoL was assessed in the tE2 arm only, owing to few LHRHa patients reporting symptoms. Gynecomastia was associated with poorer global QoL at 6 months (Table 5, p=0.004), though the adverse effect was only seen in patients reporting “very much” gynecomastia (corresponding to 8% of the group with data available). Other QoL domains associated with lower global QoL

score were: poorer cognitive and physical function, increased fatigue, weight gain, and feeling less masculine (data not shown).

After accounting for hot flushes, there was little difference in the 6-month global QoL score observed between arms (estimated mean difference -0.4 (95% CI -3.8 to 3.0, p=0.80) comparing tE2 vs LHRHa patients). In comparison, the difference between arms remained after other QoL domains were individually adjusted for (data not shown). This suggests a significant component of the effect of treatment arm on global QoL could potentially be attributable to the higher incidence of hot flushes in LHRHa patients.

In addition, there was an association between severity of hot flushes and fatigue at 6 months in both arms (data not shown), which may potentially account for the increased fatigue in the LHRHa versus tE2 arm; after adjusting for hot flushes, there was little difference in the 6-month fatigue score between arms (mean difference comparing tE2 vs LHRHa 0.0 (95% CI -4.3 to 4.4, p=0.98)). Further post-hoc analyses showed a relationship between hot flushes and sleep disturbance within both arms; 72% (124/172) of patients reporting “quite a bit” or “very much” hot flushes had trouble sleeping compared to 43% (232/534) of those with “not at all” or “a little” hot flushes (p<0.001, with similar results by arm).

Patients experiencing gynecomastia were more likely to report feeling less masculine at 6 months, with 24% (36/148) of men who reported “quite a bit” or ”very much” gynecomastia feeling “quite a bit” or ”very much” less masculine compared to 7% (17/247) of those reporting “not at all” or “a little” gynecomastia

(p<0.001). The protocol explicitly allowed prophylactic breast bud radiotherapy and 5% of patients on tE2 received this treatment as opposed to no patients on LHRHa. Two patients underwent surgical treatment for gynaecomastia who were both on tE2, corresponding to 0.4% (2/480) of the overall tE2 arm cohort enrolled to date.

Discussion

In this study, we found better overall QoL after 6 months of androgen deprivation with tE2 compared to LHRHa, as well as less fatigue and improved physical function. While the magnitude of the QoL effects was modest(36), a number of additional differences are important to note. Men treated with LHRHa were more likely to report lack of sexual interest (74% vs 59%) and being not sexually active (87% vs 78%)[20]. In addition, tE2 patients had lower rates of hot flushes but more gynecomastia, consistent with earlier findings from the trial(32).

Significant hot flushes were reported by 8% of men on tE2 compared to 44% of those on LHRHa. Interestingly, there was a suggestion that hot flushes mediated the treatment effect on global QoL, potentially accounting for both the reduced global QoL and increased fatigue in the LHRHa compared to tE2 arm. Conversely, 37% men on tE2 reported significant gynecomastia compared with 5% on LHRHa, though gynecomastia was only seen to adversely affect global QoL if the patient reported “very much” symptoms (which corresponded to less than 10% of the tE2 cohort). It is noteworthy that men may vary significantly in how bothersome gynecomastia is on an individual basis (37). In addition, data from the main PATCH trial suggest no association between oestradiol levels and clinical gynaecomastia (data not shown).

LHRHa therapy can severely impact on physical well-being and other QoL outcomes(15, 16, 27). Hot flushes, reported by 40-80% of men on LHRHa(17, 38, 39), are linked to sleep disturbance and psychological distress(16, 39). In our study, patients with hot flushes had more trouble sleeping, which may account for the effect of hot flushes on increased fatigue and reduced QoL. tE2 appeared to be effective in reducing the severity of hot flushes in men on ADT in a prior study, consistent with our findings(40). The adverse effects of LHRHa on sexual outcomes, which can have significant psychological impact on both patients and their partners, have also been well-documented(13, 15, 27). Data from men castrated for reasons other than PCa suggest exogenous oestrogen can help maintain sexual interest(41, 42). Other potential benefits of tE2 reported include protective effects on cognition(43), though we did not find a difference in cognitive function between arms within our study, possibly because the short-term outcomes analysed and/or limitations of the questionnaires used for assessing the cognitive domain.

A number of strategies have been investigated in an attempt to mitigate the adverse effects LHRHa therapy(8). Randomised trials have demonstrated some benefit to medoxyprogesterone, venlafaxine and gabapentin in reducing hot flushes associated with LHRHa and exercise may improve levels of fatigue and overall QoL(44-46). Agents which can potentially preserve bone health during treatment with LHRHa include bisphosphonates, denosumab or toremifine(8). Importantly however, data from PATCH recently showed that patients on tE2 avoid the loss in bone mineral density seen with LHRHa administration(47). The data presented here suggest tE2 as an alternative to LHRHa might limit the

requirement for additional treatments to allay the side-effects of LHRHa over and above bone health. Alternatively a low dose of tE2 in addition to LHRHa could be investigated in the future as a treatment for bothersome hot flushes.

Alternatively, an intermittent approach to ADT has been assessed for clinical efficacy and potential QoL benefits. In the non-metastatic setting, intermittent ADT appears to be non-inferior to continuous therapy in terms of overall survival, with some potential benefits with respect to hot flushes, libido and possibly fatigue, but not global health(48). However, a randomised trial by Hussain et *al*. including 1535 men with metastatic PCa failed to show non-inferiority for intermittent ADT based on overall survival. Although small improvements were initially observed for sexual function and mental health(49), older men assigned to intermittent ADT had no apparent reduction in bone, endocrine, or cognitive events and experienced an increased incidence of ischemic and thrombotic events(50).

It is increasingly apparent across a number of QoL domains that there are important differences in the unintended consequences of ADT depending upon the method chosen to achieve castrate levels of testosterone(51, 52). Here, we have shown that at 6 months of treatment, tE2 improves patients' QoL in a number of domains compared to LHRH— i.e. fewer hot flushes, less fatigue, improved physical functioning, sexual interest and sexual activity— but at a cost of increased incidences of gynecomastia. This can be viewed in addition to the beneficial effects on tE2 on bone mineral density previously reported within PATCH (47), also noting the lack of any excess cardiovascular or

thromboembolic effects from tE2 (32). From our data, hot flushes appear to potentially account for the increased fatigue and reduced global QoL among patients on LHRHa.

We acknowledge the relatively short-term outcomes assessed and presented here. However, ADT is often used for periods as short as 6 months when administered as neoadjuvant therapy along with radiotherapy to treat localised disease. As such, our 6 months QoL data are clinically pertinent, given short-term neoadjuvant ADT has been shown to be associated with impaired QoL(53). Further data from the ongoing trial will inform whether the differences between arms persist long term. Although it is premature to suggest a fundamental change in practice when it comes to starting patients on ADT, comprehensive analysis of comparative efficacy and toxicity within PATCH will allow men and their partners to optimise treatment choices.

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APPENDIX

PATCH Trial Committees:

Trial Management Group (in alphabetical order): Paul Abel (Chief Investigator), Abdulla A Alhasso, Anna Bara, Robin Carpenter, Noel W Clarke, David Dearnaley, Trinh Duong, Duncan Gilbert, Ian F Godsland, Gordana Jovic, Ruth E Langley , Howard G Kynaston, Roger Kockelbergh, Mahesh KB Parmar, Michael Philips (patient representative), Stuart D Rosen, Andrew Welland.

Trial Steering Committee: David Guthrie (chair), John Chester, and Richard Cowan

Independent Data Monitoring Committee: Peter Hoskin (chair), Philip Smith, and Laurence Collette.

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Figure 1: CONSORT diagram of patient inclusion in the analysis of 6-month quality of life data

Abbreviations: QoL, quality of life; LHRHa, LHRH agonists; tE2, transdermal oestradiol.

[a] The allocation ratio was 1:2 LHRHa: tE2 before 21/02/2011 and 1:1 thereafter.

[b] Patients were considered to have baseline QoL data if they had completed their first QoL questionnaire either by the date of randomisation or within 1 week after but before starting trial treatment.

[c] Since overall survival is a co-primary outcome measure in the ongoing trial, the number of patients who have died before completing 6-month QoL questionnaire is not provided.

Table 1: Patient characteristics for those with both baseline and 6-month quality of life questionnaires completed (N=727)

	LHRHa (n=315)	tE2 (n=412)
Age at randomisation (years)		
<70	99 (31%)	128 (31%)
70-79	146 (46%)	202 (49%)
≥80	70 (22%)	82 (20%)
Median (IQR)	74 (67-79)	73 (68-79)
Metastatic disease	133 (42%)	161 (39%)
Bone metastases (% of those with metastatic disease)	120 (90%)	148 (92%)
PSA concentration (ng/ml)		
<50	173 (55%)	214 (52%)
50-<500	121 (39%)	163 (40%)
≥500	19 (6%)	35 (9%)
Median (IQR)	43 (22-115)	45 (18-119)
Tumour status		
T0/1/2	19 (6%)	27 (7%)
T3	220 (70%)	296 (72%)
T4	52 (17%)	64 (16%)
TX	24 (8%)	25 (6%)
N category		
N0	118 (37%)	145 (35%)
N+	87 (28%)	102 (25%)
NX	110 (35%)	165 (40%)
Gleason sum score		
4-6	28 (10%)	28 (8%)
7	89 (31%)	137 (37%)
8-10	171 (59%)	207 (56%)
Smoking status		
Never smoked	119 (38%)	167 (41%)
Previous smoker	162 (51%)	204 (50%)
Current smoker	34 (11%)	41 (10%)
WHO performance status		
Normal activity	209 (66%)	293 (71%)
Avoid strenuous activity	92 (29%)	102 (25%)
Up and about >50%	14 (4%)	17 (4%)
Year of randomisation		
2007/08	30 (10%)	69 (17%)
2009/10	40 (13%)	75 (18%)
2011/12	141 (45%)	156 (38%)
2013/15	104 (33%)	112 (27%)

Abbreviations: LHRHa, LHRH agonists; tE2, transdermal oestradiol; IQR, interquartile range

Table 2: Quality of life multi-item domains: scores at 6 months by treatment arm[a]

Outcome	Arm	Number of patients	Mean score at baseline (95% CI)	Mean score at 6-month (95% CI)	Mean change in 6-month score from baseline (95% CI)	Mean difference in 6-month score between arms (95% CI)	P-value comparing arms
Global QoL score	LHRHa	308	75.1 (72.7,77.4)	70.1 (67.7,72.4)	-5.0 (-7.4,-2.7)		
	tE2	403	78.0 (76.1,80.0)	75.2 (73.3,77.2)	-2.8 (-4.7,-0.8)	+4.2 (1.2,7.1)	0.006
Cognitive function	LHRHa	309	86.9 (84.8,89.0)	82.8 (80.7,84.9)	-4.1 (-6.2,-2.0)		
	tE2	403	87.5 (85.7,89.3)	84.0 (82.2,85.9)	-3.5 (-5.3,-1.6)	+1.9 (-1.8,5.5)	0.32
Physical function	LHRHa	307	87.6 (85.4,89.8)	81.8 (79.6,84.1)	-5.7 (-7.9,-3.5)		
	tE2	399	89.0 (87.2,90.9)	86.2 (84.3,88.1)	-2.8 (-4.7,-1.0)	+5.8 (2.8,8.8)	<0.001
Fatigue	LHRHa	304	18.9 (16.4,21.4)	27.2 (24.7,29.7)	8.3 (5.8,10.8)		
	tE2	400	17.1 (14.8,19.4)	23.0 (20.8,25.3)	6.0 (3.7,8.2)	-4.3 (-8.1,-0.6)	0.02

Abbreviations: QoL, quality of life; LHRHa, LHRH agonists; tE2, transdermal oestradiol; CI, confidence interval.

[a] For global QoL, cognitive function and physical function, a higher score corresponds to a better outcome. For fatigue, a higher score corresponds to more fatigue.

Table 3: Quality of life single item domains: proportion of patients with pre-defined outcomes at 6-months by treatment arm

Outcome	Arm	Number of patients	Number (%) of patients with outcome at baseline	Number (%) of patients with outcome at 6 months	Odds ratio (95% CI)	P-value comparing arms
Felt quite a bit/very much less masculine	LHRHa	292	16 (5%)	41 (14%)		
	tE2	381	18 (5%)	53 (14%)	0.92 (0.57,1.48)	0.73
Not at all interested in sex	LHRHa	268	118 (44%)	199 (74%)		
	tE2	350	155 (44%)	208 (59%)	0.42 (0.28,0.62)	<0.001
Not at all sexually active	LHRHa	266	168 (63%)	231 (87%)		
	tE2	348	214 (61%)	271 (78%)	0.51 (0.32,0.82)	0.005
Quite a bit/very much gynecomastia	LHRHa	293	4 (1%)	14 (5%)		
	tE2	386	2 (1%)	144 (37%)	12.70 (7.14,22.60)	<0.001
Quite a bit/very much hot flushes	LHRHa	291	6 (2%)	135 (46%)		
	tE2	390	9 (2%)	32 (8%)	0.10 (0.07,0.16)	<0.001
Quite a bit/very much weight gain	LHRHa	296	13 (4%)	21 (7%)		.
	tE2	379	13 (3%)	27 (7%)	1.06 (0.56,2.00)	0.87

Abbreviations: LHRHa, LHRH agonists; tE2, transdermal oestradiol; CI, confidence interval.

Table 4: Global quality of life score at 6 months in both treatment arms, by patients' experience of hot flushes.

Whether experienced hot flushes at 6 months	LHRHa arm			tE2 arm			Mean difference in 6-month score (95% CI), both arms combined[a]
	Number of patients (% of total)	Mean score at 6 months (95% CI)	Mean change in 6-month score from baseline (95% CI)	Number of patients (% of total)	Mean score at 6 months (95% CI)	Mean change in 6-month score from baseline (95% CI)	
Not at all	77 (26%)	75.1 (70.4,79.8)	-0.9 (-5.6,3.9)	288 (73%)	78.6 (76.4,80.8)	-1.8 (-4.0,0.4)	Reference group
A little	83 (28%)	74.0 (69.9,78.1)	-4.0 (-8.1,0.1)	75 (19%)	65.1 (60.6,69.6)	-5.9 (-10.4,-1.4)	-6.8 (-10.6,-3.1)
Quite a bit	92 (31%)	65.6 (61.1,70.1)	-8.1 (-12.6,-3.5)	23 (6%)	67.4 (58.0,76.7)	-5.8 (-15.1,3.6)	-10.4 (-15.0,-5.9)
Very much	47 (16%)	62.4 (56.6,68.2)	-7.6 (-13.4,-1.9)	10 (3%)	65.0 (52.7,77.4)	-2.5 (-14.8,9.9)	-11.8 (-17.6,-6.0)
							P-value <0.001

Abbreviations: LHRHa, LHRH agonists; tE2, transdermal oestradiol; CI, confidence interval.

[a] Estimated from Tobit regression models, adjusted for treatment arms, baseline global quality of life score and other pre-defined baseline factors. There was no evidence that the effect of hot flushes on 6-month global quality of life score differed by treatment arm (p for interaction=0.20).

Table 5: Global quality of life score at 6 months in the tE2 arm, by whether patient reported to have experienced gynecomastia[a]

Whether experienced sore or enlarged nipples or breasts	Number of patients (% of total)	Mean score at baseline (95% CI)	Mean score at 6 months (95% CI)	Mean change in 6-month score from baseline (95% CI)	Mean difference in 6-month score[b] (95% CI)
Not at all	55 (14%)	78.6 (73.0,84.3)	73.3 (67.9,78.7)	-5.3 (-10.7,0.1)	Reference group
A little	190 (49%)	80.0 (77.2,82.7)	78.0 (75.2,80.9)	-1.9 (-4.8,0.9)	4.8 (-0.8,10.4)
Quite a bit	114 (29%)	74.4 (70.9,78.0)	73.8 (70.5,77.0)	-0.7 (-3.9,2.6)	3.3 (-2.7,9.3)
Very much	32 (8%)	74.5 (66.7,82.2)	63.8 (56.1,71.5)	-10.7 (-18.4,-3.0)	-7.6 (-15.6,0.4)
					P-value= 0.004

Abbreviations: CI, confidence interval

[a] This association was not assessed in the LHRHa arm owing to few patients reporting symptoms.

[b] Estimated from Tobit regression models, adjusted for baseline global quality of life score and other pre-defined baseline factors.