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# Men's Sexual Health Questionnaire score changes vs spontaneous sexual adverse event reporting in men treated with dutasteride/tamsulosin combination therapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia: A post hoc analysis of a prospective, randomised, placebo-controlled study

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## Summary

**Aim:** To assess the impact of baseline characteristics on Men's Sexual Health Questionnaire (MSHQ) total scores and to evaluate the clinical relevance of MSHQ changes and their association with spontaneously reported sexual adverse events (SexAEs) in patients with benign prostatic hyperplasia.

**Methods:** This was a post hoc analysis of the Phase 4 FDC116115 study, in which patients aged ≥50 years were randomised 1:1 to receive a fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg (DUT-TAM FDC), or placebo. End-points included: change in MSHQ total scores by baseline characteristics and SexAEs; cumulative distribution function for change from baseline to month 12 in MSHQ total score and the ejaculation, erection, satisfaction and sexual desire (libido) domain scores; and relationship between changes in MSHQ scores and SexAEs.

**Results:** The intent-to-treat population comprised 489 patients (DUT-TAM FDC, n = 243; placebo, n = 246). The mean reduction in total MSHQ score was greater in patients with SexAEs across both groups, compared with patients without SexAEs. Most patients reporting any SexAE (86% DUT-TAM FDC, 67% placebo) had a worsening of the MSHQ total score at month 12 compared with baseline. Specifically, 90% (DUT-TAM FDC) and 75% (placebo) of patients reporting an ejaculation SexAE and 73% (DUT-TAM FDC) and 87% (placebo) of patients reporting an erection SexAE had a worsening of MSHQ ejaculation and erection domain scores, respectively, at month 12. A threshold effect for incident SexAE was observed; patients showing a decrease of approximately 6-10 points in the total MSHQ score were more likely to report SexAEs.

**Conclusion:** Findings support the clinical utility of the MSHQ tool in assessing the impact of DUT-TAM on sexual function by linking numerical changes in MSHQ scores

to spontaneously reported SexAEs for the first time. The threshold effect for incidence of SexAEs warrants further investigation to determine its clinical relevance.

**What's known**

- A randomised, placebo-controlled trial reported a significant decrease (worsening) in total Male Sexual Health Questionnaire (MSHQ) scores in patients with benign prostatic hyperplasia treated with dutasteride-tamsulosin fixed-dose combination therapy (DUT-TAM FDC) compared with placebo.
- Changes in MSHQ scores at month 12 were driven by changes in the ejaculation domain, with no significant changes reported in the erection domain, and modest impairments in the satisfaction, sexual activity and desire domains.

**What's new**

- This post hoc analysis showed that spontaneous reporting of sexual, ejaculation and impotence adverse events (SexAEs) was associated with a worsening of MSHQ total, ejaculation and erection domain scores, respectively, in patients receiving DUT-TAM FDC and those receiving placebo.
- A threshold effect for incident SexAEs was observed; patients showing a decrease of approximately 6-10 points in the total MSHQ score were more likely to report SexAEs.

## 1 | INTRODUCTION

The fixed-dose combination (FDC) of the 5-alpha reductase inhibitor (5ARI), dutasteride and the alpha-1 adrenoceptor antagonist, tamsulosin (DUT-TAM) is recommended as first-line therapy in men with moderate to severe lower urinary tract symptoms (LUTS), secondary to benign prostatic hyperplasia (BPH), who are at risk of disease progression.[1,2] The effects of 5ARIs and α-blockers on sexual function are published in clinical trials, but these lack baseline assessments of sexual function. In addition, the mechanisms underlying these effects have not been fully elucidated.[3,4] Our current knowledge of the clinical effects of 5ARIs and α-blockers on sexual function is largely based on the spontaneous reporting of adverse events (AEs) in clinical trials and postmarketing studies as opposed to a quantitative, validated score of sexual dysfunction.[1,5-7]

A validated scale, the Male Sexual Health Questionnaire (MSHQ), was developed for assessing specific aspects of male sexual dysfunction in patients from a BPH registry,[8] and is a valuable, freely available tool for assessing the impact of BPH treatment on sexual function. Use of the MSHQ is expected to be advantageous compared with spontaneous reporting of sexual AEs (SexAEs) as it provides an opportunity for quantitative, validated and detailed prospective data collection, and can be administered prospectively to assess patient-reported changes in sexual function related to BPH. This 25-item questionnaire comprises three core domains of sexual outcome: erection, ejaculation and satisfaction, with additional items relating to sexual activity, sexual desire and bother.[9,10]

We have recently reported findings from the first domain-specific quantitative evaluation of DUT-TAM FDC therapy on the MSHQ total score and three core domains (erection, ejaculation and satisfaction) in sexually active males with LUTS secondary to BPH. In this primary analysis, the total MSHQ score was calculated based on the sum of scores for the erection, ejaculation and satisfaction domains. The study showed a significant decrease (worsening) in the total MSHQ scores in patients treated with DUT-TAM FDC vs placebo.[11] The impact on libido, as assessed by the items relating to sexual activity and sexual desire, has been explored further in a separate post hoc analysis.[10] The observed changes in the MSHQ with DUT-TAM FDC therapy after 1 year of treatment were primarily driven by changes in the ejaculation domain, with no significant changes reported in the erection domain, and modest impairments in the satisfaction, sexual activity and sexual desire domains, which is unlikely to be of clinical relevance.[10,11]

This article presents a post hoc analysis of the primary study.[11] The aim of this post hoc analysis was: to investigate the impact of baseline characteristics on the MSHQ total score; and assess the clinical relevance of changes in both the MSHQ total score and the scores for the individual domains of the MSHQ (ejaculation, erection, sexual desire and satisfaction) by correlating numerical changes in MSHQ scores with spontaneously reported SexAEs.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design

This was a post hoc analysis of a European and Australian double-blind, placebo-controlled, parallel-group, multicentre study comparing DUT-TAM FDC therapy (DUT 0.5 mg and TAM 0.4 mg; one capsule daily) with placebo (FDC116115; NCT01777269). The study was conducted at 51 centres between 18 February 2013 and 5 April 2016. Patients were randomised (1:1) to DUT-TAM FDC therapy or placebo for 12 months following a 4-week placebo run-in period. Details of the study design have been described previously.[11]

The first objective of this analysis was to determine the impact of baseline characteristics on the MSHQ total score. The second objective was to assess the clinical relevance of changes in MSHQ total and domain scores and their association with the spontaneous reporting of SexAEs relating to sexual dysfunction. The study was approved by appropriate regulatory and ethics committees and performed in accordance with the Declaration of Helsinki 2008 and Good Clinical Practice guidelines. Written

informed consent was obtained from each patient prior to study participation.

## 2.2 | Patients

Patients included in the primary study (FDC116115) had to be sexually active males (ie engaged in sexual activity with a partner during the past 4 weeks and planning to be active during the next 4 weeks), aged ≥50 years, with a confirmed clinical diagnosis of BPH, an International Prostate Symptom Score (IPSS) of ≥12 at screening, a prostate volume (PVol) of ≥30 cc (assessed using transrectal ultrasonography) and a total serum prostate-specific antigen (PSA) concentration of ≥1.5 ng/mL at screening. These criteria ensured that all patients were at risk of BPH progression.[1] Prior use of BPH therapy was permitted, with the exception of 5ARIs.

Patients with a total serum PSA of >10.0 ng/mL at screening were excluded, as were those with a history or evidence of prostate cancer and/or used prohibited medications. Full inclusion and exclusion criteria have previously been described.[11]

## 2.3 | End-points

### 2.3.1 | Primary study

The primary end-point of the FDC116115 study was the change in sexual function from baseline to month 12, measured by the change in total MSHQ score (calculated based on 16 items of the 25-item MSHQ[11]). The English-language version of the MSHQ was used for this study along with the Greek, Dutch, German, Hungarian, Spanish and French versions, which were obtained from the Mapi Research Trust.[12] Secondary end-points included the change in total MSHQ score from baseline at 1, 3, 6 and 9 months, and the change from baseline at 1, 3, 6, 9 and 12 months in MSHQ erection (questions 1-3; range 0-15), ejaculation (questions 5-11; range 1-35) and satisfaction (questions 13-18; range 6-30) domain scores. Higher scores indicate better sexual function.[8]

Safety evaluations included the incidence of AEs, serious AEs, drug-related AEs, serious drug-related AEs, AEs leading to withdrawal or discontinuation of study medication and adverse events of special interest (AESIs). AESIs included cardiovascular events (ie acute coronary syndrome, ischaemic cerebrovascular events cardiac failure, ischaemic coronary artery disorders/atherosclerosis or cardiac arrhythmias). In addition, SexAEs were assessed, which included breast disorders (ie breast enlargement and breast tenderness), altered (decreased) libido, impotence and ejaculation disorders) and prostate cancer.

### 2.3.2 | Post hoc analysis

The end-points of this post hoc analysis were: change from baseline to month 12 (observed cases and last observation carried forward [LOCF]) in MSHQ total and sexual function domain scores by baseline characteristics (age, country, total MSHQ score, IPSS, PVol, PSA level and body mass index [BMI]); the cumulative distribution function for change from baseline in MSHQ total and domain scores; and association between quantitative, validated MSHQ scores and spontaneously reported SexAEs. The MSHQ domains included in this analysis were total score (ie sum of the erection, ejaculation and satisfaction domain scores, as calculated in the primary analysis[11]) and the individual scores for the ejaculation, erection, satisfaction and sexual desire domains. For the purpose of this analysis, the sexual desire items (questions 22, 23 and 25; range 3-15) of the MSHQ were used to represent changes in libido, as they were considered to more accurately reflect libido than sexual activity (questions 19 and 20; range 2-10).

## 2.4 | Statistical analysis

### 2.4.1 | Primary analysis

The sample size was based on the anticipated change in total MSHQ score. Assuming a 6-unit treatment difference with a standard deviation of 18 units, 190 patients per treatment group were required to provide a 90% power at a 0.05 significance level. Assuming a 20% withdrawal rate, 238 patients were randomised per treatment group.

The MSHQ was completed by patients themselves at baseline (Visit 1) and at all subsequent visits, except Visit 3 (week 2 when the MSHQ assessment was not performed), until visit 8 (month 12, end of treatment). The change in total MSHQ scores from baseline was analysed using a mixed-model repeated-measures (MMRM) analysis. A step-down procedure for interpreting *P*-values was adopted.

Baseline erection, ejaculation and satisfaction domain scores for the MSHQ were summarised descriptively by the treatment group. The MMRM statistical approach was used to compare the change in scores from baseline to month 12 for individual MSHQ domains between the DUT-TAM FDC therapy group and the placebo group (observed cases).

### 2.4.2 | Post hoc analysis

Baseline variable subgroups analysed were as follows: age (<65, ≥65 and <75, ≥75 years); country; total MSHQ score (<64, ≥64); IPSS (<20, ≥20); PVol (<40, ≥40 cc); PSA level (<3, ≥3 ng/mL) and BMI (<27.5, ≥27.5 kg/m$^2$). Mean changes from baseline MSHQ score at month 12 were presented by treatment group for all levels of the baseline characteristics evaluated. Associated treatment group differences and 95% confidence intervals were generated for each stratum using a generalised linear model with effects for treatment, baseline characteristic and treatment by baseline characteristic interaction. *P*-values for the test of treatment by

baseline characteristic interaction are presented for each baseline characteristic.

MSHQ scores and number of patients who reported SexAEs were analysed descriptively. The total MSHQ score (ie the sum of the erection, ejaculation and satisfaction domain scores[11]) and the individual ejaculation, erection, satisfaction and sexual desire (libido) domain score changes at month 12 (LOCF) from baseline were characterised using cumulative distribution functions and waterfall plots for each treatment group; spontaneously reported SexAEs (including ejaculation disorders, "impotence" [erectile dysfunction] and altered [decreased] libido) were also recorded. A Mantel-Haenszel test stratified by treatment was used to evaluate the association of the worsening/no worsening of the MSHQ score changes at month 12 (LOCF) with the corresponding occurrence/no occurrence of SexAEs.

## 3 | RESULTS

### 3.1 | Study population

The intent-to-treat population comprised 489 patients randomised to either DUT-TAM FDC (n = 243) or placebo (n = 246). As reported previously, patients in both treatment groups had similar demographics and baseline characteristics.[11]

### 3.2 | MSHQ response rates

At month 12, MSHQ response rates were 69% (n = 167/243) and 70% (n = 171/246) for the DUT-TAM FDC and placebo groups respectively. For missing data, MSHQ total scores were imputed, which were then used to impute data for the erection, ejaculation and satisfaction domains when ≥50% of questions in each domain were answered (non-missing).

### 3.3 | MSHQ total score change stratified by baseline characteristics

Changes from baseline to month 12 in total MSHQ score stratified by baseline characteristics are shown in Table 1. Treatment with DUT-TAM FDC led to a numerically greater reduction from baseline (worsening) in total MSHQ score than placebo within each of the subgroups (Table 1). Treatment differences were homogeneous across strata for each of the baseline characteristics evaluated regardless of whether analysis was done using observed cases or LOCF (Table 1).

### 3.4 | Cumulative distribution functions

Cumulative distribution function plots for MSHQ total and domain scores (ejaculation, erection, satisfaction and sexual desire [libido]) at month 12 are shown in Figure 1. These plots show the cumulative proportion of patients in each treatment group (*y* axis) who have a given change in MSHQ scores (*x* axis), i.e. <0 points representing worsening or >0 representing improvement in sexual function.

As previously reported,[11] changes from baseline in MSHQ total score and ejaculation domain score were larger (denoting worsening) in patients treated with DUT-TAM FDC vs placebo at month 12 (Figure 1A,B). The differences between DUT-TAM FDC and placebo groups observed for the erection, sexual desire (libido) and satisfaction domain scores were minimal (Figure 1C-E).

### 3.5 | MSHQ scores and spontaneously reported SexAEs

In total, 30.5% (n = 74/243) and 12.2% (n = 30/246) patients in the DUT-TAM FDC and placebo groups, respectively, reported SexAEs. Of these, 21% (n = 56/243) and 3.7% (n = 9/246) patients in the DUT-TAM FDC and placebo groups, respectively, reported ejaculation-related SexAEs, 9.9% (n = 24/243) and 6.9% (n = 17/246) reported "impotence"-related SexAEs (erectile dysfunction) and 9.9% (n = 24/243) and 4.9% (n = 12/246) reported altered (decreased) libido SexAEs.

#### 3.5.1 | Total MSHQ score

There was a higher proportion of patients reporting a worsening of the MSHQ total score at month 12 in patients reporting one or more SexAEs, compared with patients not reporting a SexAE in both the DUT-TAM FDC group (86% [n = 57] vs 66% [n = 90], respectively) and the placebo group (67% [n = 16] vs 50% [n = 91], respectively; Table 2). The association between the worsening of MSHQ total score and reporting of SexAEs was statistically significant ($\chi^2_{MH}$ = 11.5; $P$ < .001) across both treatment groups (Figure 2A). At an approximate decrease from baseline of 6-10 points in total MSHQ score, patients treated with DUT-TAM FDC and placebo were more likely to report SexAEs (Figure 3A).

#### 3.5.2 | Ejaculation domain score

There was a higher proportion of patients reporting a worsening of the MSHQ ejaculation domain score at month 12 in patients reporting an ejaculation-related SexAE, compared with patients not reporting an ejaculation-related SexAE in both the DUT-TAM FDC group (90% [n = 45] vs 70% [n = 119], respectively) and the placebo group (75% [n = 6] vs 49% [n = 103], respectively; Table 2 and Figure 3B). The association between MSHQ ejaculation domain score and ejaculation-related SexAEs was statistically significant ($\chi^2_{MH}$ = 9.9; $P$ = .002) across both treatment groups (Figure 2B).

**TABLE 1** Subgroup analyses of change from baseline to month 12 in total MSHQ score, (A) observed cases and (B) LOCF; ITT population (N = 489[a])

| | Placebo (n = 162) | | DUT-TAM FDC (n = 151) | | Difference | |
|---|---|---|---|---|---|---|
| **Parameter** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **Mean (95% CI)** | ***P*-value[b]** |
| (A) | | | | | | |
| Age, y | | | | | | |
| <65 | 80 | −1.2 (7.37) | 72 | -6.8 (13.11) | -5.6 (−9.0, −2.2) | .48 |
| ≥65 | 82 | −1.0 (9.72) | 79 | −8.3 (11.42) | −7.3 (−10.6, −4.0) | |
| <75 | 153 | −1.3 (8.53) | 140 | −7.8 (12.34) | −6.6 (−9.0, −4.2) | .86 |
| ≥75 | 9 | 1.0 (10.15) | 11 | −4.7 (10.88) | −5.7 (−15.0, 3.6) | |
| Country | | | | | | |
| Australia | 10 | −1.9 (5.30) | 13 | −10.2 (12.88) | −8.3 (−17.0, 0.5) | .84 |
| France | 12 | −0.8 (5.72) | 10 | −4.5 (10.78) | −3.8 (−12.6, 5.1) | |
| Germany | 27 | −2.4 (7.89) | 28 | −11.3 (11.33) | −8.8 (−14.4, −3.2) | |
| Greece | 25 | −2.2 (7.38) | 25 | −8.2 (11.50) | −6.0 (−11.8, −0.1) | |
| Hungary | 22 | −1.7 (10.82) | 24 | −4.5 (13.78) | −2.8 (−8.9, 3.4) | |
| The Netherlands | 27 | 0.5 (7.91) | 18 | −5.7 (11.28) | −6.1 (−12.5, 0.2) | |
| Spain | 39 | −0.3 (10.42) | 33 | −7.4 (12.97) | −7.2 (−12.1, −2.3) | |
| Baseline total MSHQ score | | | | | | |
| <64 | 72 | 2.1 (9.32) | 79 | −6.5 (13.89) | −8.6 (−11.9, −5.3) | .14 |
| ≥64 | 90 | −3.7 (7.06) | 72 | −8.8 (10.08) | −5.1 (−8.3, −1.9) | |
| Baseline IPSS | | | | | | |
| <20 | 135 | −1.5 (8.37) | 134 | −7.5 (11.89) | −6.0 (−8.5, −3.5) | .34 |
| ≥20 | 27 | 0.6 (9.73) | 17 | −8.8 (15.06) | −9.4 (−15.8, −2.9) | |
| Baseline PVol, cc | | | | | | |
| <40 | 37 | −1.2 (8.47) | 35 | −10.0 (10.90) | −8.8 (−13.7, −3.9) | .28 |
| ≥40 | 125 | −1.1 (8.69) | 116 | −6.9 (12.57) | −5.8 (−8.5, −3.1) | |
| Baseline total PSA, ng/mL | | | | | | |
| <3 | 63 | −0.2 (9.37) | 67 | −7.2 (13.71) | −7.0 (−10.6, −3.3) | .76 |
| ≥3 | 99 | −1.7 (8.09) | 84 | −7.9 (10.99) | −6.2 (−9.3, −3.2) | |
| Baseline BMI, kg/m$^2$ | | | | | | |
| <27.5 | 92 | −2.5 (9.05) | 77 | −8.3 (11.37) | −5.7 (−8.9, −2.5) | .43 |
| ≥27.5 | 69 | 0.7 (7.74) | 73 | −6.9 (13.21) | −7.6 (−11.1, −4.2) | |
| | **Placebo (n = 207)** | | **DUT-TAM FDC (n = 203)** | | **Difference** | |
| **Parameter** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **Mean (95% CI)** | ***P*-value[b]** |
| (B) | | | | | | |
| Age, y | | | | | | |
| <65 | 99 | −0.9 (7.31) | 88 | −7.7 (13.23) | −6.8 (−10.1, −3.4) | .31 |
| ≥65 | 108 | −0.7 (11.27) | 115 | −9.8 (13.32) | −9.1 (−12.2, −6.1) | |
| <75 | 191 | −0.7 (9.24) | 187 | −9.0 (13.14) | −8.3 (−10.6, −5.9) | .58 |
| ≥75 | 16 | −1.8 (13.13) | 16 | −7.8 (15.34) | −5.9 (−14.0, 2.1) | |
| Country | | | | | | |
| Australia | 14 | −1.5 (6.21) | 17 | −9.3 (12.61) | −7.8 (−16.1, 0.5) | .92 |
| France | 21 | 0.4 (7.15) | 17 | −9.9 (17.09) | −10.3 (−17.8, −2.8) | |
| Germany | 31 | −2.5 (7.64) | 30 | −11.5 (10.99) | −9.0 (−14.9, −3.1) | |

(Continues)

**TABLE 1** (Continued)

| | Placebo (n = 207) | | DUT-TAM FDC (n = 203) | | Difference | |
|---|---|---|---|---|---|---|
| **Parameter** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **Mean (95% CI)** | ***P*-value[b]** |
| Greece | 30 | −1.4 (11.41) | 29 | −9.5 (12.48) | −8.2 (−14.1, −2.2) | |
| Hungary | 31 | −2.4 (12.32) | 34 | −7.1 (15.66) | −4.7 (−10.4, 1.0) | |
| The Netherlands | 34 | 0.1 (8.25) | 34 | −8.0 (11.64) | −8.1 (−13.6, −2.5) | |
| Spain | 46 | 0.6 (10.17) | 42 | −8.4 (13.66) | −9.0 (−13.9, −4.1) | |
| Baseline total MSHQ score | | | | | | |
| <64 | 105 | 2.1 (10.73) | 103 | −7.6 (14.23) | −9.7 (−12.8, −6.7) | .14 |
| ≥64 | 102 | −3.9 (7.04) | 100 | −10.3 (12.17) | −6.4 (−9.5, −3.2) | |
| Baseline IPSS | | | | | | |
| <20 | 171 | −1.3 (9.41) | 179 | −8.7 (12.99) | −7.4 (−9.8, −5.0) | .17 |
| ≥20 | 36 | 1.2 (10.16) | 24 | −10.8 (15.53) | −11.9 (−17.9, −6.0) | |
| Baseline PVol, cc | | | | | | |
| <40 | 45 | −0.9 (7.98) | 52 | −10.7 (13.48) | −9.8 (−14.5, −5.2) | .39 |
| ≥40 | 162 | −0.8 (9.98) | 151 | −8.3 (13.21) | −7.5 (−10.1, −4.9) | |
| Baseline total PSA, ng/mL | | | | | | |
| <3 | 78 | 0.2 (10.50) | 92 | −8.4 (14.22) | −8.6 (−12.1, −5.1) | .75 |
| ≥3 | 129 | −1.5 (8.93) | 111 | −9.4 (12.52) | −7.9 (−10.8, −4.9) | |
| Baseline BMI, kg/m$^2$ | | | | | | |
| <27.5 | 115 | −2.2 (10.59) | 105 | -10.2 (13.47) | −8.0 (−11.0, −4.9) | .89 |
| ≥27.5 | 89 | 0.7 (7.88) | 97 | −7.6 (13.10) | −8.3 (−11.6, −5.0) | |

BMI, body mass index; CI, confidence interval; DUT-TAM FDC, fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg; LOCF, last observation carried forward; IPSS, International Prostate Symptom Score; ITT, intent-to-treat; MSHQ, Male Sexual Health Questionnaire, PSA, prostate-specific antigen; PVol, prostate volume; SD, standard deviation.

[a]N = 489 in the ITT population (n = 246 in placebo and n = 243 in DUT-TAM FDC). The number of subjects with non-missing change from baseline values in the observed case and LOCF analyses is n = 313 (n = 162 in placebo and n = 151 for DUT-TAM FDC) and n = 410 (n = 207 in placebo and n = 203 in DUT-TAM FDC), respectively.

[b]*P*-values for a test of treatment by baseline characteristic interaction from a generalised linear model including effects for treatment, baseline characteristic and treatment by baseline characteristic interaction.

### 3.5.3 | Erection domain score

The proportion of patients reporting a worsening of the MSHQ erection domain score at month 12 in patients reporting an erection-related SexAE was higher when compared with patients not reporting an erection-related SexAE in both the DUT-TAM FDC group (73% [n = 16] vs 51% [n = 103], respectively) and the placebo group (87% [n = 13] vs 44% [n = 92], respectively; Table 2 and Figure 3C). This association between MSHQ erection domain score and erection-related SexAEs was statistically significant ($\chi^2_{MH}$ = 12.3; $P$ < .001) across both treatment groups (Figure 2C).

### 3.5.4 | Sexual desire (libido) domain score

The proportion of patients reporting a worsening of the MSHQ sexual desire (libido) domain score in patients reporting a libido-related SexAE was slightly higher compared with patients not reporting a libido-related SexAE in both the DUT-TAM FDC group (64% [n = 14] vs 52% [n = 102], respectively) and the placebo group (55% [n = 6] vs 43% [n = 90], respectively; Table 2). Importantly, there was no statistically significant association between MSHQ libido domain worsening and the occurrence of a libido-related SexAE ($\chi^2_{MH}$ = 1.6; $P$ = .203) across both treatment groups (Figure 2D). Overall, altered (decreased) libido SexAEs appeared to be equally distributed among patients stratified by the MSHQ sexual desire (libido) domain score in both the DUT-TAM FDC therapy and placebo groups (Figure 3D).

## 4 | DISCUSSION

Results from the primary FDC116115 Phase 4, double-blind study, the first domain-specific quantitative evaluation of the impact of DUT-TAM FDC therapy on sexual function in men with LUTS secondary to BPH, have recently been published.[11] The study showed a greater reduction in MSHQ total and ejaculation domain scores in patients treated with DUT-TAM FDC therapy vs placebo.[11] This post

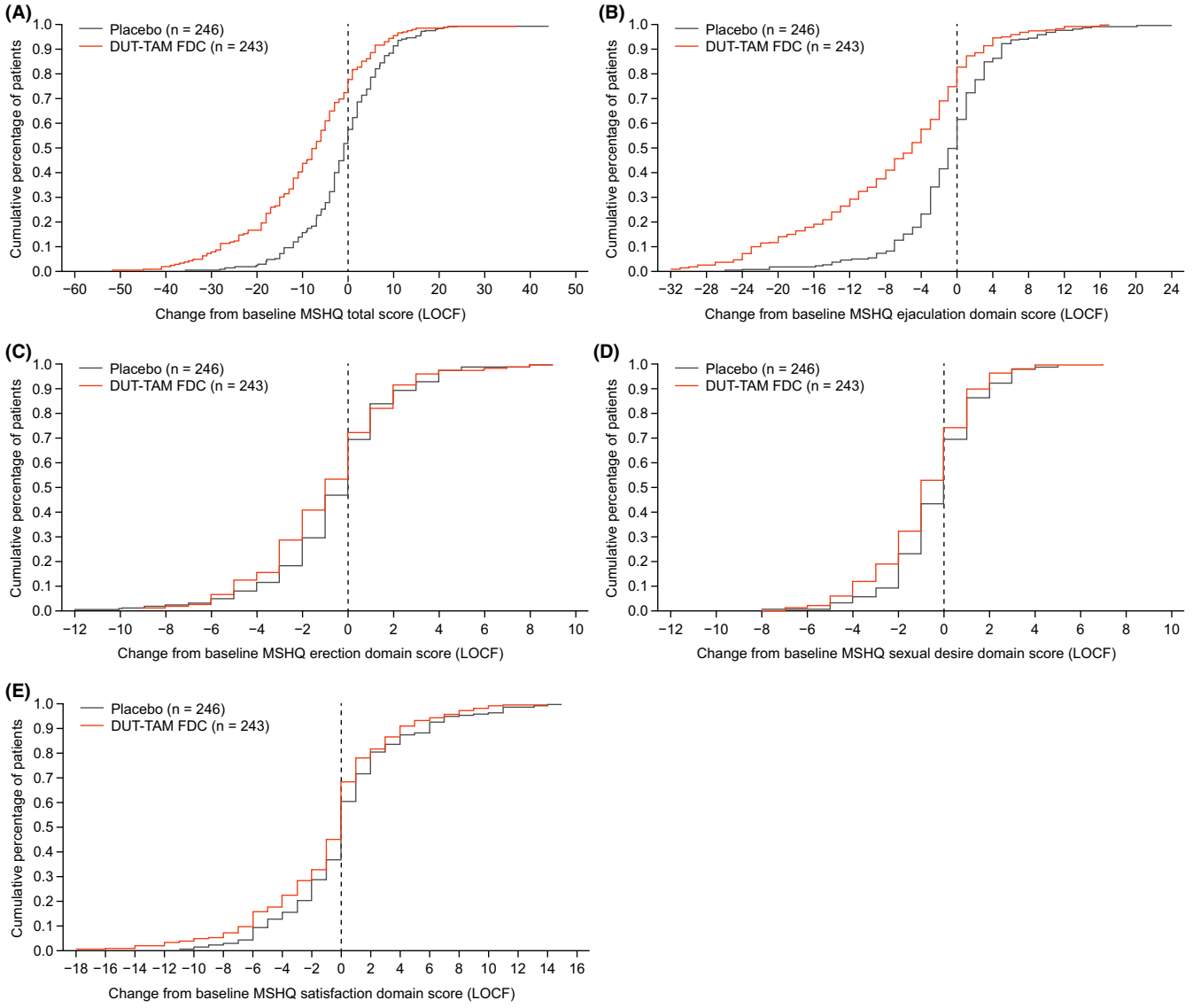


**FIGURE 1** Cumulative distribution function plot for change from baseline in MSHQ, illustrating the cumulative proportion of patients in each treatment group (*y* axis) who have a given change in MSHQ scores (*x* axis) at month 12 (LOCF). (A) total MSHQ, (B) ejaculation domain, (C) erection domain, (D) sexual desire (libido) domain and (E) satisfaction domain scores at month 12 (LOCF). DUT-TAM FDC, fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg; LOCF, last observation carried forward; MSHQ, Male Sexual Health Questionnaire

hoc analysis probed the clinical relevance of MSHQ score changes in more depth, and sought to examine the association between these quantitative, validated MSHQ changes and the spontaneous reporting of SexAEs in these patients.

Stratification of the change from baseline in total MSHQ score by baseline characteristics highlighted that DUT-TAM FDC therapy was associated with a negative impact on sexual function, irrespective of baseline characteristics.

We observed that spontaneous reporting of sexual, ejaculation and impotence SexAEs was positively associated with a worsening of MSHQ total, ejaculation and erection domain scores, respectively, at month 12 in both the DUT-TAM FDC and placebo groups. This observation is supporting the clinical utility of the MSHQ tool in assessing the impact of DUT-TAM on sexual function, though, such an association was not observed for libido. A threshold effect for incident SexAEs was seen in patients whose MSHQ scores changed in the range of 6-10 points. Whether this constitutes a clinically relevant threshold needs further investigation.

Regarding ejaculation-related SexAEs, most patients across both treatment groups reporting these SexAEs had worsening MSHQ ejaculation domain scores at month 12. The ejaculation domain subscale of the MSHQ has shown treatment sensitivity to pharmacological and other treatments of BPH,[13,14] although a minimum clinically meaningful change in ejaculation has yet to be determined.

A previous study evaluating changes in sexual function in 22 males treated with dutasteride therapy or placebo for 12 months showed no significant difference between the treatment groups

**TABLE 2** Association between MSHQ total and domain scores worsening at month 12 (LOCF) and spontaneously reported SexAEs

| | Experienced MSHQ total score worsening (baseline to month 12) | | Experienced MSHQ ejaculation domain worsening (baseline to month 12) | | Experienced MSHQ erection domain worsening (baseline to month 12) | | Experienced MSHQ sexual desire domain worsening (baseline to month 12) | |
|---|---|---|---|---|---|---|---|---|
| | DUT-TAM FDC (n = 74)[a] | Placebo (n = 30)[a] | DUT-TAM FDC (n = 56)[a] | Placebo (n = 9)[a] | DUT-TAM FDC (n = 24)[a] | Placebo (n = 17)[a] | DUT-TAM FDC (n = 24)[a] | Placebo (n = 12)[a] |
| Reported SexAEs, n/N (%) | 57/66 (86) | 16/24 (67) | 45/50 (90) | 6/8 (75) | 16/22 (73) | 13/15 (87) | 14/22 (64) | 6/11 (55) |
| | DUT-TAM FDC (n = 169)[a] | Placebo (n = 216)[a] | DUT-TAM FDC (n = 187)[a] | Placebo (n = 237)[a] | DUT-TAM FDC (n = 219)[a] | Placebo (n = 229)[a] | DUT-TAM FDC (n = 219)[a] | Placebo (n = 234)[a] |
| No SexAEs, n/N (%) | 90/137 (66) | 91/183 (50) | 119/169 (70) | 103/211 (49) | 103/201 (51) | 92/208 (44) | 102/196 (52) | 90/209 (43) |

The fractions presented in the table are showing the proportions of patients within each treatment group who have either spontaneously reported a SexAE or had no SexAEs among those who have shown worsening of their MSHQ scores. The denominator value within each fraction represents the number of patients for whom data on spontaneously reported SexAEs and changes in MSHQ from baseline to month 12 were available.

DUT-TAM FDC, fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg; LOCF, last observation carried forward; MSHQ, Male Sexual Health Questionnaire; SexAE, sexual adverse event.

[a]These n values represent the proportion of patients from each treatment (DUT-TAM FDC, n = 243; placebo, n = 246) who were reported to experience a SexAE.

in terms of International Index of Erectile Function and total MSHQ scores.[15] Conversely, this study showed a relationship between worsening of the MSHQ erection domain score and spontaneously reported erection-related SexAEs in patients treated with DUT-TAM FDC therapy. The cumulative distribution curves for the DUT-TAM FDC and placebo groups, showing the change in MSHQ erection domain score, were almost overlapping. In addition, among patients spontaneously reporting erection-related SexAEs, there was minimal difference between the proportion of patients with an improvement/worsening of MSHQ erection domain scores. These findings furthermore question the impact of treatment with dutasteride or DUT-TAM FDC on erectile function.

Akin to the observations with the MSHQ erection domain, it is also noteworthy that the differences in MSHQ sexual desire (libido) domain follow a similar pattern with minimally observed difference in a cumulative proportion of patients with an improvement or worsening of MSHQ libido domain scores, In addition, the incidence of libido-related SexAEs that were spontaneously reported were comparable in those patients showing an improvement in the MSHQ libido domain score across both treatment groups. Generally, the incidence of libido-related SexAEs in patients on 5ARIs is low. In fact, in a previous study, the risk of libido alteration was comparable for both patients treated with 5ARI monotherapy and those treated with combination therapy.[16] Therefore, in this study, the MSHQ tool did not correlate well with libido-related SexAEs.

Our observation of a clear discrepancy between the directionality of MSHQ sexual desire (libido) domain scores and the likelihood of patients reporting libido-related SexAE is thought-provoking. While we do not challenge the validation of the MSHQ score, [8,9] the discrepancy does raise a question as to whether all patients completely understand the MSHQ at all times, and whether the MSHQ truly reflects individual patient perceptions of their libido. Additional study data are required to support these findings.

Of note, more patients across both the DUT-TAM FDC therapy group and the placebo group reported "impotence"-related, ejaculatory and libido SexAEs, irrespective of their MSHQ domain scores, compared with patients who reported no SexAEs but did report a worsening in the MSHQ domain scores. This suggests that patients may have been anticipating negative effects on erections and/or sexual function, thus facilitating a nocebo effect.[17] "Impotence" is a term that is often mentioned by patients to refer to a wide variety of sexual and relationship disorders (and not only erectile dysfunction). As such, clinicians need to be prepared to investigate further and clarify patients' symptoms or concerns about "impotence". A nocebo effect also seemed to be present for the reporting of SexAEs, irrespective of treatment group or changes over time in total MSHQ or individual MSHQ domain scores. This effect has been reported previously. For example, in a blinded study of men receiving finasteride or placebo for BPH (N = 107), a significant nocebo effect with finasteride was noted

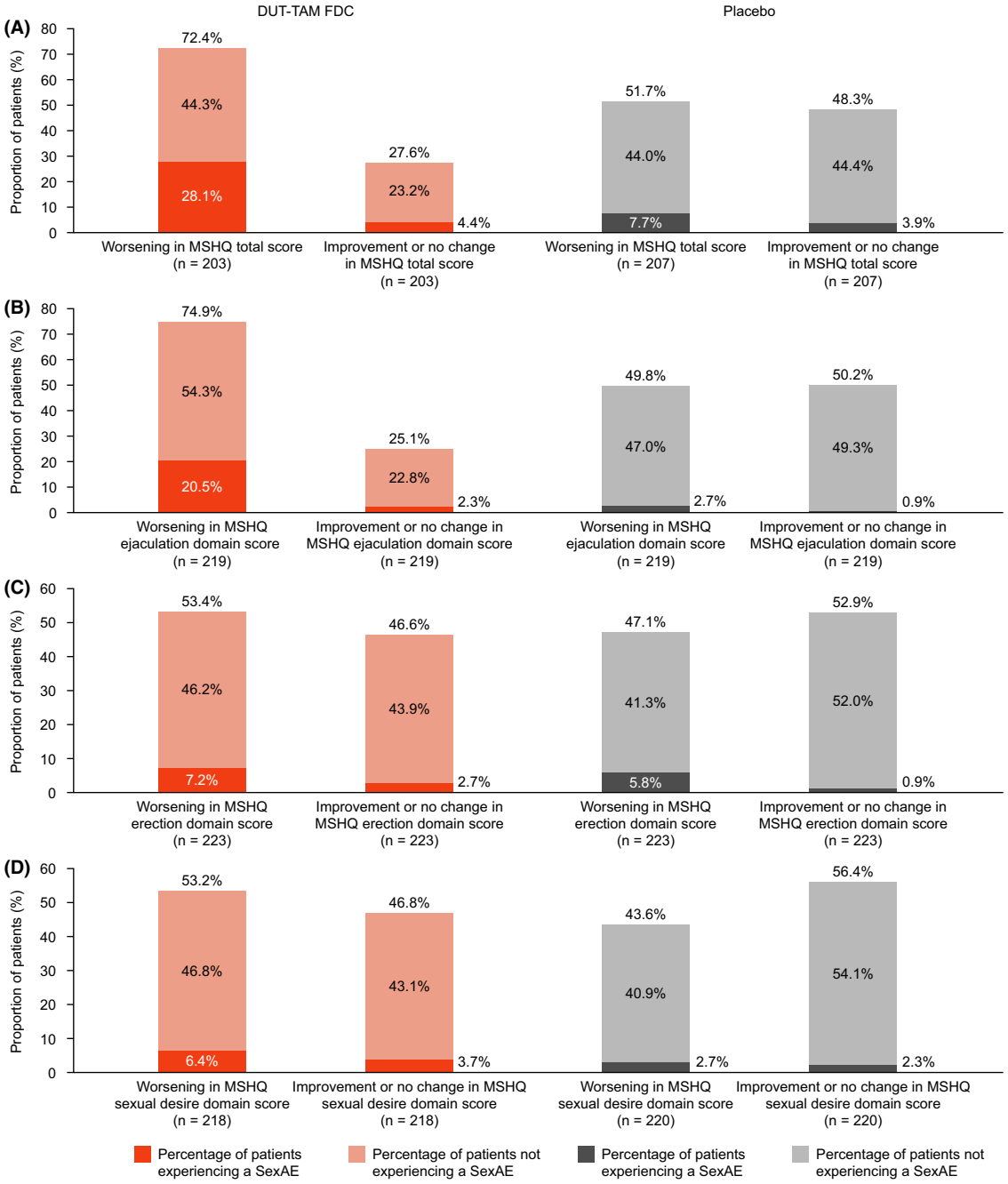


**FIGURE 2** (A) MSHQ total, (B) ejaculation domain, (C) erection domain and (D) sexual desire domain score changes from baseline to month 12 (LOCF) and spontaneously reported SexAEs. DUT-TAM FDC, fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg; LOCF, last observation carried forward; MSHQ, Male Sexual Health Questionnaire; SexAE, sexual adverse event

among patients who had been informed of possible sexual side effects, either through counselling or access to the drug information leaflet, compared with those who did not have access to this information ($P$ = .03).[17] The results of this study should therefore be interpreted with a possible nocebo effect in mind. The current findings also highlight the potential unreliability and insensitivity of spontaneous reports of SexAEs, as opposed to a quantitative, validated score of sexual dysfunction, in relation to particular therapies.

Most of the current knowledge of the clinical effects of 5ARIs and α-blockers on sexual function comes from the spontaneous reporting of SexAEs in clinical trials and postmarketing studies. However, spontaneous AE reporting in clinical trials is subject to great variability between trials and between investigator sites. For example, in some sites the study coordinator may prompt the participant to volunteer AEs, whereas in other sites the participant may be asked to select AEs from a predefined list, resulting in over/underestimation of the AEs

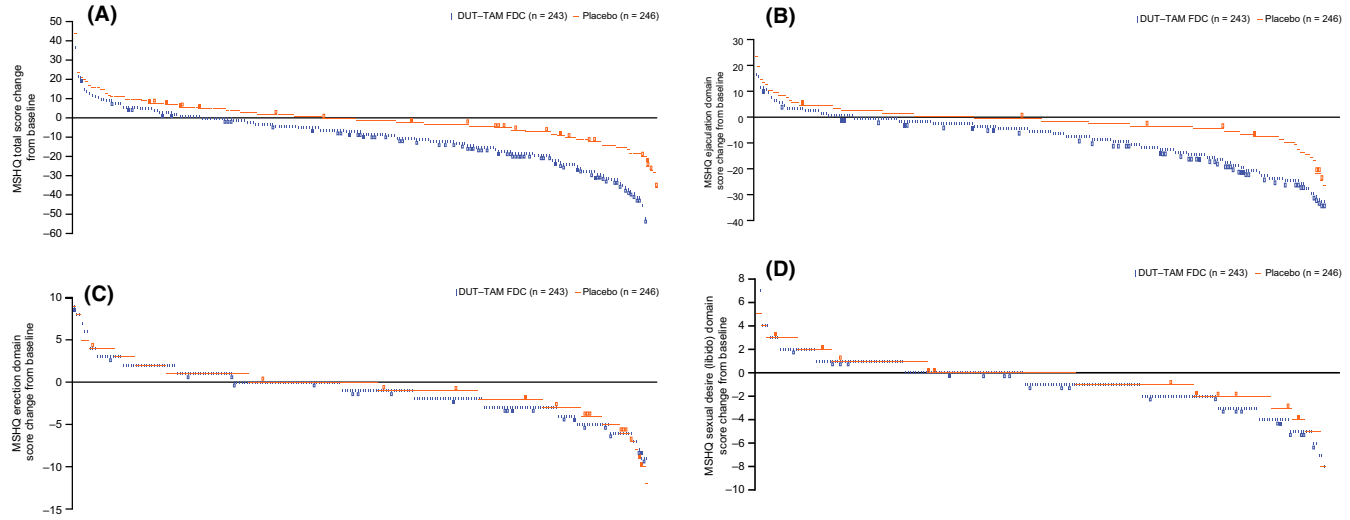


**FIGURE 3** Change from baseline at month 12 (LOCF) for (A) total MSHQ score (patients with ≥1 SexAE); (B) MSHQ ejaculation domain score (patients with ≥1 ejaculation-related SexAE); (C) MSHQ erection domain score (patients with ≥1 impotence-related SexAE); (D) MSHQ sexual desire (libido) domain score (patients with ≥1 altered [decreased] libido SexAE). Each data point represents one patient who was randomised to DUT-TAM FDC or placebo. The solid rectangle and the outline rectangle denote those patients who had (A) a sexual AE; (B) an ejaculation-related AE; (C) an impotence-related AE; or (D) an altered (decreased) libido AE with onset after the first dose of randomised study drug or with missing onset date. The solid rectangle denotes those patients for whom every AE was resolved by month 12. AE, adverse event; DUT-TAM FDC, fixed-dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg; LOCF, last observation carried forward; MSHQ, Male Sexual Health Questionnaire; SexAE, sexual adverse event

that are occurring. Additionally, AEs that are volunteered by a patient are documented by the study coordinator and often interpreted to align with terms from the Medical Dictional of Regulatory Activities and this interpretation may differ between sites and study staff. We suggest that previous trials using spontaneous AE reporting may also be subject to these limitations and recommend that future trials assess spontaneously reported AEs alongside validated patient-reported outcomes to determine whether the observed AEs are reflected by patients' experience and perception of the impact of treatment. In this study, some patients in both treatment groups (DUT-TAM FDC and placebo) who displayed positive changes in the MSHQ domain scores (ie an increase in scores), also reported a SexAE. This perhaps suggests that there is a disconnection between how patients interpret the items of the MSHQ and how they interpret the information provided by their clinician regarding possible AEs associated with pharmacological therapies. In addition, the MSHQ is unlikely to convey the full spectrum of AEs associated with such therapies. We must therefore encourage future research to assess MSHQ score changes with spontaneous reporting of AEs in all disease states and also to evaluate as many AEs as possible in order to improve our understanding of the clinical relevance of SexAEs. It would also be interesting to observe how the findings from this current study (ie the comparison of the two methods used for reporting AEs) may compare with other disease areas.

One limitation of this analysis is related to the lack of in-depth recording of sexual history, which was beyond the scope of the study. Additionally, we did not include a broad assessment of quality of life (QoL; eg using a dedicated QoL questionnaire, such as the World Health Organization Quality of Life or 36-Item Short Form Survey). The 12-month study duration did not allow for the evaluation of the long-term effects of DUT-TAM FDC therapy on sexual function. In addition, the study design did not include tamsulosin- or dutasteride-only treatment arms, which could be valuable for establishing the impact of monotherapies on sexual function via the MSHQ. A further limitation comes from the risk of bias as this was a post hoc analysis.

## 5 | CONCLUSIONS

This post hoc analysis provides valuable insights into changes in the MSHQ score and their association with the spontaneous reporting of SexAEs in sexually active patients with BPH-related LUTS. A threshold effect for incident SexAE was seen in patients whose total MSHQ scores changed by approximately 6-10 points. Whether that constitutes a clinically relevant threshold needs further investigation. Spontaneous reporting of sexual, ejaculation and impotence SexAEs was associated with a worsening of MSHQ total, ejaculation and erection domain scores in patients receiving DUT-TAM FDC and those receiving placebo. The positive association and the minimal difference between the proportion of patients with an improvement/worsening of MSHQ erection domain scores suggests that treatment with DUT-TAM FDC does not inevitably lead to erection-related AEs and further supports the findings of the primary study, which showed that the impact of DUT-TAM FDC on sexual function is primarily driven through

impact on ejaculatory function and not through erectile dysfunction or libido. The observed discrepancy between the directionality of MSHQ sexual desire scores and the likelihood of patients reporting a libido-related SexAE, may be related to limitations in the collection of spontaneously reported SexAEs or the application of the MSHQ. Further investigation into this association should be considered for future work.

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## DISCLOSURE

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## AUTHOR CONTRIBUTIONS

CGR, MJM, THW and ZL were involved in the conception or design of the study and the data analysis and interpretation. JMP-M was involved in the data analysis and interpretation. RCR and FG were also involved in the selection of study measures, data analysis and interpretation. All authors were involved in the drafting, critical revision and approval of the article.

## DATA AVAILABILITY STATEMENT

GSK makes available anonymised individual participant data and associated documents from interventional clinical studies, which evaluate medicines upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access original data for studies that have been re-analysed, other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

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