1 ABSTRACT

Title

Non-Interventional Study Assessing Quality of Life, Treatment Satisfaction, Resource Utilisation, and Persistence with Treatment in Overactive Bladder (OAB) Patients Prescribed Betmiga™ - A Multicenter Non-interventional Post Authorisation Study (PAS)

Keywords

Betmiga, Mirabegron, Quality of Life, Non-interventional clinical study

Rationale and background

Antimuscarinics are currently a mainstay pharmacotherapy option available for patients with OAB (Chapple et al, 2008). However, some patients have a suboptimal response or are unwilling to continue antimuscarinic treatment due to side effects (Benner et al, 2010). Mirabegron (Betmiga), a β_3 adrenoceptor agonist, has a novel mode of action compared to antimuscarinics and is the first of a new class of oral treatment for OAB. Betmiga was launched across Europe in 2013 and provides patients and clinicians an alternative treatment option for OAB. The efficacy and safety profile of Betmiga has been established in a robust clinical trial programme. Clinical trials are conducted in a controlled and restricted environment, and aim to reflect patient management in actual clinical practice as far as possible. However, observational studies are becoming increasingly important as they can provide healthcare professionals and payers with evidence about patient outcomes in a real world clinical practice setting. This non-interventional study was designed to capture the quality of life (QoL), treatment persistence, patient satisfaction and healthcare resource utilisation data for patients who had been prescribed mirabegron in a non-interventional clinical study setting.

Research question and objectives

To understand the impact of mirabegron on patient QoL, treatment satisfaction, persistence with treatment, patterns of healthcare resource utilisation and safety in a non-interventional clinical study setting. The primary objective was to evaluate change from baseline in QoL.

Study design

A prospective non-interventional study in OAB patients prescribed mirabegron as part of routine clinical practice.

Setting

Adult patients, with OAB symptoms at enrolment and whose physician had made the decision to prescribe mirabegron as part of routine clinical practice and who were about to start treatment.

Patient and study size, including dropouts

Male or female OAB patients, 18 years or older, whose physician had made the decision to prescribe mirabegron as part of routine clinical practice and who were about to start

treatment. It was expected that up to 800 patients would be enrolled in the study, from approximately 80 centers in 8 countries across Europe. However, a total of 59 centers recruited 863 patients in this study, of which, one patient (Patient [redacted]) was removed from the database due to protocol violation. This patient completed the Baseline visit without a signed informed consent form (ICF) and the Baseline visit was done at a different site, which was not recorded in the Central Ethics Committee (CEC) approval and no Clinical Trial Agreement (CTA) was fully executed between [redacted] and the new site.

Variables and data sources

The primary variable was change from baseline in QoL based on the overactive bladder questionnaire (OAB-q) subscales.

The following were secondary variables:

- Change from baseline in patient treatment satisfaction based on Treatment Satisfaction Visual Analogue Scale (TS-VAS).
- Change from baseline in QoL based on the European Quality of Life-5 Dimensions (EQ-5D-5L) subscales and Work Productivity Activity Index (WPAI).
- Utilisation of healthcare resources related to the management of OAB.
- Treatment patterns/persistence with treatment
    - Treatment patients were switched to and reasons associated with switch.
    - Stopped treatment and reasons associated with discontinuation.
    - Number of treatment days on current treatment.
    - Time from treatment initiation to discontinuation or switching to another treatment.
    - Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.
- Invasive/surgical treatment of OAB symptoms (e.g. Botulinum toxin (BTX) type A, neural stimulation [SNS], percutaneous tibial nerve stimulation [PTNS]) during the study.
- Change from baseline in incontinence status during the study.
- Adverse events (AEs) and adverse drug reaction (ADR) reported during the study.

Study databases, AE/ADR worksheets, hospital or clinical practice medical records, all questionnaires, and healthcare resource utilisation worksheet, were considered source documents.

Results

Analysis Populations: This study had 3 analyses populations including 1) Safety Analysis Set (SAF) consisted of all patients who received at least one dose of mirabegron during the study; 2) Full Analysis Set (FAS) included all enrolled patients who signed the informed consent and completed OAB-q at baseline and at least at one follow up visit; and 3) Per Protocol Set (PPS) included all patients on mirabegron at 10-12 months who completed OAB-q at baseline and at 10-12 months.

Baseline Characteristics

A total of 862 patients were enrolled in this study, of which 848 (98.4%) patients were included in SAF, 796 (92.3%) patients were included in FAS, and 452 (52.4%) patients were included in PPS. A total of 700 (81.2%) patients completed the study and 162 (18.8%) patients were discontinued from the study. The most common reasons for discontinuation were lost to follow-up (SAF = 79 [9.3%]; FAS = 54 [6.8%]) and withdrawal by patient (SAF = 39 [4.6%]; FAS = 20 [2.5%]) in the SAF and FAS population sets. In the PPS, 2 (0.4%) patients were discontinued, of which 1 was lost to follow-up and another was due to "other" reason. A total of 7 (0.8%) patients died during the study.

In the FAS population, a total of 107 (13.4%) patients were reported with at least 1 minor protocol deviation during the study. Patients reported with minor protocol deviations of 2 categories including 'ICF issue' and 'questionnaire issue as identified by the clinical research associates (CRAs)'.

The mean patients' age was 61.2 years in the FAS and SAF populations and 61.5 years in the PPS population and patients who were < 65 years of age were 50.4% in the PPS population, 52.0% in the SAF population, and 52.3% in the FAS population; and rest of the patients were of age ≥65 years. The majority of patients in all the populations were female (71.9% in the PPS population and 74.2% in the SAF population) and white (96.1% in the SAF population and 98.7% in the PPS population). Overall, 693 (81.7%) patients in the SAF population and 653 (82.0%) patients in the FAS population were reported with at least 1 medical history at study entry. Overall, the most commonly reported medical conditions by preferred term (PT) were hypertension, hypercholesterolaemia, hypothyroidism, depression, diabetes mellitus, and benign prostatic hyperplasia.

Overall, 506 (59.7%) patients in the SAF population received prior OAB medications. The most commonly used prior OAB medications by PT were solifenacin (157 [18.5%] patients), solifenacin succinate (147 [17.3%] patients), trospium chloride (86 [10.1%] patients), oxybutynin (50 [5.9%] patients), tolterodine (48 [5.7%] patients), and fesoterodine fumarate (47 [5.5%] patients). Overall, 664 (78.3%) patients in the SAF population received prior non-OAB medications.

The most commonly used concomitant OAB medications other than mirabegron by PT were solifenacin (122 [14.4%], solifenacin succinate (95 [11.2%] patients), trospium chloride (47 [5.5%] patients], oxybutynin (36 [4.2%], fesoterodine fumarate (34 [4.0%] patients), fesoterodine (33 [3.9%] patients), and tolterodine (24 [2.8%] patients).

Overall, 679 (80.1%) patients in the SAF population received concomitant non-OAB medications. The most commonly used concomitant non-OAB medications by PT were omeprazole (95 [11.2%] patients), levothyroxine sodium (79 [9.3%] patients), acetylsalicylic acid (77 [9.1%] patients), simvastatin (70 [8.3%] patients), atorvastatin calcium (58 [6.8%] patients), paracetamol (49 [5.8%] patients), and atorvastatin (40 [4.7%] patients.

Efficacy Results

Primary Endpoint:

- For the FAS population, the mean (SE) at baseline and mean (SE) change from baseline at 10-12 months for Symptom Bother Score were 52.3 (0.74) and -20.7 (0.93), respectively, for Coping were 51.5 (1.00) and 20.1 (1.13), respectively, for Concern were 55.5 (0.95) and 19.4 (1.04), respectively, for Sleep were 53.8 (0.95) and 17.5 (1.10), respectively, for Social Interaction were 74.4 (0.87) and 9.9 (0.87), respectively. Overall, the mean (SE) at baseline and mean (SE) change from baseline at 10-12 months for HRQoL Total Score were 57.7 (0.83) and 17.4 (0.93), respectively.
- For the PPS population, the mean (SE) at baseline and mean (SE) change from baseline at 10-12 months Symptom Bother Score were 49.7 (0.92) and -22.7 (1.10), respectively, for Coping were 52.3 (1.29) and 22.7 (1.34), respectively, for Concern were 57.8 (1.19) and 21.9 (1.19), respectively, for Sleep were 54.3 (1.19) and 20.8 (1.29), respectively, and for Social Interaction were 75.8 (1.07) and 11.5 (1.00), respectively. Overall, the mean (SE) at baseline and mean (SE) change from baseline at 10-12 months for HRQoL Total Score were 58.9 (1.05) and 19.9 (1.09), respectively.
- Overall (for both the FAS and PPS populations), there was a clinically meaningful improvement in QoL as measured by the OAB-q subscales.
- Overall (for both the FAS and PPS populations), a reduction of the Symptom Bother score from baseline to 2-4 months, 10-12 months, 10-15 months, and EOT (for the FAS only) was observed, which indicates an improvement.
- The Health Related Quality of Life (HRQoL) subscales (Coping, Concern, Sleep, Social, and HRQoL Total Score) increased from baseline to 2-4 months, 10-12 Months, 10-15 months, and EOT (for the FAS only), indicating an improvement over these observed time points for both the populations.
- Overall, the percentage of patients achieving at least a 10-point improvement in the OAB-q subscales (except Social Interaction) was >50% in both the FAS (EOT with LOCF) and PPS (10-12 months and 10-15 months) populations. A greater proportion of patients on mirabegron achieved an at least 10-point improvement in the PPS population.

Secondary Endpoints:

- For the FAS population, the mean (SE) of TS-VAS at baseline (n = 694 patients) was 3.8 (0.14). The mean (SE) change from baseline of TS-VAS was 3.3 (0.19; n = 461 patients) at 2-4 months, 3.8 (0.17; n = 534 patients) at 10-12 months, 3.8 (0.17; n = 586 patients) at 10-15 months, and 3.5 (0.16; n = 688 patients) at EOT. For the PPS population, the mean (SE) of TS-VAS at baseline (n = 403 patients) was 3.8 (0.18). The mean (SE) change from baseline of TS-VAS was 3.9 (0.23; n = 288) at

2-4 months and 4.2 (0.20; n = 401 patients) at 10-12 months and at 10-15 months. Overall, TS-VAS scores showed improvement in treatment satisfaction at all the post baseline visit windows for both the FAS and PPS populations.

- For the FAS population, the mean (SE) change from baseline of Health State as measured by the EQ-5D VAS was 4.1 (0.87) at 2-4 months, 5.5 (0.83) at 10-12 months, 5.4 (0.79) at 10-15 months, and 4.7 (0.75) at EOT. For the PPS population, the mean (SE) change from baseline of Health State as measured by the EQ-5D VAS was 4.9 (1.05) at 2-4 months, 6.8 (0.89) at 10-12 months, and 6.8 (0.89) at 10-15 months. Overall, shift tables show some improvements in all domains, which was complemented by the EQ-VAS.
- For FAS population, the mean (SE) of WPAI: SHP scores of percent time missed due to bladder condition, percent impairment while working due to bladder condition, percent overall work impairment due to bladder condition, and percent activity impairment due to bladder condition at baseline were 2.9 (0.82), 33.4 (1.78), 34.3 (1.78), and 43.4 (1.00), respectively. At 10-12 months, the mean (SE) change from baseline scores of percent time missed due to bladder condition, percent impairment while working due to bladder condition, percent overall work impairment due to bladder condition, and percent activity impairment due to bladder condition were -0.4 (0.99), -12.9 (2.29), -13.3 (2.39), and -14.5 (1.21), respectively. For PPS population, the mean (SE) scores of percent time missed due to bladder condition, percent impairment while working due to bladder condition, percent overall work impairment due to bladder condition, and percent activity impairment due to bladder condition at baseline were 3.2 (1.00), 32.7 (2.28), 34.0 (2.29), and 42.8 (1.28), respectively. At 10-12 months, the mean (SE) change from baseline scores of percent time missed due to bladder condition, percent impairment while working due to bladder condition, percent overall work impairment due to bladder condition, and percent activity impairment due to bladder condition were -1.6 (1.04), -16.2 (2.72), -16.8 (2.86), and -17.7 (1.35), respectively. Overall (for both the FAS and PPS populations), a reduction of WPAI: SHP item scores from baseline to 2-4 months, 10-12 months, 10-15 months, and EOT (for the FAS only) was observed, which indicates an improvement at work place and daily activities throughout the treatment period.
- The most common visits to a health care practitioner (HCP) as a result of OAB were to general practice consultation, urologist, and urogynaecologist. Overall resource use was low across all categories. Only 1-2% of patients had urodynamic testing and there was a negligible increase in overall resource utilisation over time. Percentage of patients progressing to surgical/interventional treatment of OAB was low (<4%).
- For the FAS population, at 12 months approximately 60% of patients remained on mirabegron according to prescription status. The Kaplan-Meier estimate for median (95% CI) time from baseline to first reported post-baseline mirabegron treatment discontinuation according to prescription status was 13.1 (12.4, 16.1) months.

According to the OAB medication log, approximately 65% of patients remained on mirabegron at 12 months. The Kaplan-Meier estimate for median (95% CI) time from baseline to first recorded post-baseline mirabegron treatment discontinuation according to the OAB medication log was 17.3 (17.3, 21.2) months.

- For the FAS population, the majority of patients who had switched treatments at baseline (discontinued other OAB treatment and switched to mirabegron) were taking mirabegron as a single agent (i.e., 184 [36.1%] out of 509 patients with available prescription status data at baseline and at 2-4 months, 165 [28.4%] out of 580 patients with available prescription status data at baseline and at 10-12 months, 176 [27.9%] out of 631 patients with available prescription status data at baseline and at 10-15 months, and 211 [27.4%] out of 770 patients with available prescription status data at baseline and at EOT). In addition, patients who were treatment naive or had no treatment for OAB ≥2 years, tended to stay on mirabegron as a single treatment (i.e., 173 [34.0%] out of 509 patients at 2-4 months, 162 [27.9%] out of 580 patients at 10-12 months, 173 [27.4%] out of 631 patients at 10-15 months, and 199 [25.8%] out of 770 patients at EOT). At all the assessment windows, the majority of patients used mirabegron as single agent.
- The majority of patients were using mirabegron as single agent within all assessment windows, followed by combination treatment.
- For the FAS population, the mean (SE) change from baseline in the number of incontinence pads used in the last 7 days was -2.9 (0.47) at 2-4 months, -2.0 (0.49) at 10-12 months, -2.1 (0.47) at 10-15 months, and -2.2 (0.45) at EOT. For the PPS population, the mean (SE) change from baseline in the number of incontinence pads used in the last 7 days was -2.7 (0.56) at 2-4 months and -2.0 (0.50) at 10-12 months and at 10-15 months. Overall, a decrease in the (mean) number of incontinence pads used in the last 7 days was observed during the treatment period for both the populations.
- For the FAS population, the percentage of patients who had an OAB dry episode was 34.9% at baseline, with an increase to 36.4% at 2-4 months and a further increase to 43.7% at 10-12 months, 46.7% at 10-15 months, and 54.9% at EOT. The mean (SE) change from baseline for the number of incontinence pads used in the last 7 days was -2.9 (0.47) at 2-4 months, -2.0 (0.49) at 10-12 months, -2.1 (0.47) at 10-15 months, and -2.2 (0.45) at EOT.
- For the PPS population, the percentage of patients who had an OAB dry episode was 38.5% at baseline, with an increase to 43.4% at 2-4 months and a further increase to 59.1% at 10-12 months and 10-15 months. The mean (SE) change from baseline for the number of incontinence pads used in the last 7 days was -2.7 (0.56) at 2-4 months, and -2.0 (0.50) at 10-12 months and 10-15 months. These results indicate an improvement of dry rate over time and a reduction of pad use over the assessment windows.

Safety Results

- Overall, 363 (42.8%) patients experienced a total of 615 AEs. Adverse events with the highest incidence by PT included drug ineffective (62 [7.3%] patients), urinary tract infection (27 [3.2%] patients), and escherichia urinary tract infection, hypertension, and headache (18 [2.1%] patients each).
- A total of 178 (21.0%) patients experienced 235 mirabegron related AEs, of which, 124 AEs were considered possibly related and 88 AEs were considered probably related to mirabegron by the Investigator. The relationship of 23 AEs could not be assessed. The most common mirabegron related AE was drug ineffective (58 [6.8%] patients).
- Overall, most patients had AEs that were assessed as mild (27.5%) or moderate (11.7%) in severity. Twenty-eight (3.3%) patients experienced 37 severe AEs, of which, 2 AEs (intra-abdominal haemorrhage and intracranial aneurysm) were considered as serious and life-threatening; both were considered not related to mirabegron by the Investigator.
- There were 7 deaths reported in this study, and none were considered to be related to mirabegron by the Investigator and Sponsor.
- Overall, 64 (7.5%) patients experienced 90 SAEs. Serious AEs with highest incidence included vertigo (4 (0.5%) patients); and acute myocardial infarction and hypertension (3 (0.4%) patients each).
- A total of 15 (1.8%) patients experienced mirabegron related SAEs. Each reported mirabegron related SAE was experienced by no more than 2 patients.
- A total of 138 (16.3%) patients experienced 186 AEs that led to mirabegron discontinuation. The most frequently reported AEs leading to discontinuation of mirabegron were drug ineffective (50 [5.9%] patients); drug effect incomplete and hypertension (10 [1.2%] patients each); headache and hypertonic bladder (6 [0.7%] patients each); palpitations and dyspepsia (5 [0.6%] patients each); and vertigo (4 [0.5%] patients).
- Overall, 119 (14.0%) patients experienced 152 mirabegron related AEs, which led to permanent discontinuation of mirabegron. Of the 152 drug related AEs leading to permanent discontinuation, 79 AEs (reported in 58 patients) were possibly related to mirabegron; 68 AEs (reported in 56 patients) were probably related to mirabegron; and 5 AEs (reported in 5 patients) were unassessable.
- Overall, AEs reported in this study were consistent with the known safety profile of mirabegron; no unexpected safety issues were observed in this study. Mirabegron was safe and well tolerated. Tolerability of mirabegron was demonstrated by high study completion rates and a low incidence of treatment related events during the study.

Discussion

The safety and efficacy data from this non-interventional study provides supporting evidence that the use of mirabegron by OAB patients in the real world setting leads to improvement in overall quality of life and health status. Mirabegron offers an effective treatment option for OAB patients. Overall, no unexpected safety issues were observed in this study. Adverse events were consistent with the known safety profile of mirabegron, were managed with concomitant medications, and the majority of them resolved without residual sequelae.

A notable improvement in dry rate from 38.5% at baseline to 59.1% at 10-12 months was reported in this study, alongside a reduction in pad use from a mean of 8.1 (N=451) pads in the last 7 days prior to the visit at baseline to 5.7 (N=421) pads at 10-12 months for the PPS population. Along with the overall improvement in quality of life (including a greater proportion of patients on mirabegron achieving a 10-point improvement in the PPS population) and low incidence of AEs, this may have contributed to the high persistence rate observed in this study, with 53.8% (428 patients of 796 patients in the FAS population) of patients remaining on mirabegron after approximately 12 months for the FAS population.

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