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Review – Voiding Dysfunction

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Cardiovascular Safety of β_3-adrenoceptor Agonists for the Treatment of Patients with Overactive Bladder Syndrome

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Abstract

Context: Mirabegron, the first β_3-adrenoceptor agonist in clinical practice, is approved for treatment of overactive bladder (OAB) syndrome symptoms. Because β_3-adrenoceptors are expressed in cardiovascular (CV) tissues, there are concerns that OAB treatment with β_3-adrenoceptor agonists may affect the heart and vasculature.
Objective: To provide a summary of CV effects of β_3-adrenoceptor agonists in clinical studies.
Evidence acquisition: A systematic literature search from inception until November 2014 was performed on studies in PubMed and Medline.
Evidence synthesis: Twenty papers, published between 1994 and 2014, were identified: mirabegron (16), solabegron (2), AK-677 (1), and BRL35135 (1). More detailed CV data from mirabegron studies were available in online regulatory documents filed with the US Food and Drug Administration and the UK National Institute for Health and Care Excellence.
Conclusions: The CV safety of mirabegron appears to be acceptable at therapeutic doses and comparable with that of antimuscarinic agents, currently first-line therapy for OAB.
Patient summary: In this review we looked at the cardiovascular (CV) effects of β_3-adrenoceptor agonists used for the treatment of overactive bladder (OAB). The CV safety of mirabegron (the only clinically approved β_3-adrenoceptor agonist) appears to be acceptable at therapeutic doses and comparable with that of antimuscarinic agents, the current first-line therapy for OAB.

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1. Introduction

Overactive bladder (OAB) syndrome is estimated to affect >400 million people worldwide [1]. Prevalence increases with age, affecting approximately 15% aged ≥65 yr [2] and 30–40% ≥75 yr [3]. Many patients with OAB have multiple concomitant cardiovascular (CV) comorbidities, such as hypertension, diabetes, and heart failure [4–6]. In this context, the CV safety of OAB pharmacotherapy is important.

Antimuscarinic agents have been the mainstay of OAB treatment [7] and are generally considered to have good CV safety [8]. Although rare, CV adverse events (AEs) of

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antimuscarinics administered to patients with OAB are noteworthy and may be clinically important. The most common cardiac AEs associated with antimuscarinics are increases in QT interval prolongation and heart rate (HR) related to fesoterodine, propiverine, tolterodine, solifenacin, and trospium use [8]. More important, antimuscarinic efficacy is limited by poor levels of persistence, often due to undesirable AEs such as dry mouth, constipation, and blurred vision [8].

Advances in the understanding of OAB pathophysiology have identified three β-adrenoceptor subtypes—β_1, β_2, and β_3—in the bladder detrusor muscle and urothelium [9,10]. In human bladder, β_3-adrenoceptors account for 97% of total β-adrenoceptor messenger RNA [11], and they are thought to be the main subtype mediating relaxation of detrusor smooth muscle during the storage phase [12]. However, all three adrenoceptor subtypes are expressed in the CV system, leading to potential concerns about the CV effects of β-adrenoceptor agonists. Both β_1 and β_3 receptors are expressed in the heart; β_1-mediated effects increase HR and force of contraction; compounds with relatively limited β_3-adrenoceptor agonist selectivity and activity trigger positive inotropic effects in human atrial tissue and negative inotropic effects in ventricular tissue [13]. In addition, β_2-adrenoceptors are located in vascular smooth muscle, mediating vasodilation (especially in arteriolar beds in extremities) [14].

Mirabegron, the first β_3-adrenoceptor agonist to enter clinical practice, is approved at doses of 25 and 50 mg for the treatment of OAB symptoms; in vitro, it shows substantially higher (150- and 33-fold) affinity for β_3-adrenoceptors versus that for β_1- and β_2-adrenoceptors, respectively [15]. Other β_3-adrenoceptor agonists have reported clinical (solabegron [16], TAK-677 [17,18]) or preclinical (ritobegron [19,20], TRK-380 [21], BRL35135 [22]) results.

Because β_3-adrenoceptors are also expressed in CV tissues, there are concerns that OAB treatment with β_3-adrenoceptor agonists may have "off-target" effects on regulation of the heart and vasculature [23]. This article provides a summary of CV effects of β_3-adrenoceptor agonists in clinical studies.

2. Evidence acquisition

A systematic literature search was performed on the CV effects of β_3-adrenoceptor agonists in the PubMed and Medline databases from inception until November 2014. The following text word and Medical Subject Headings terms (*mirabegron* OR *solabegron* OR *ritobegron* OR *TAK677* OR *BRL35135*) AND *clinical trial*[ptyp] AND *English*[lang] were used to identify suitable randomized controlled trials. We applied screening criteria including CV end points—Antiplatelet Trialists' Collaboration/Major Adverse CV Events (APTC/MACE), thorough QT (TQT), vital signs, electrocardiogram (ECG) parameters—to 160 identified references (Supplementary Fig. 1). Supplementary Table 1 presents inclusion and exclusion criteria. Two independent reviewers screened the full text of the remaining articles and identified 20 that met inclusion criteria. Disagreements were resolved by discussion between reviewers. To ascertain the validity of eligible studies and minimize risk of bias, the reviewers determined the adequacy of study characteristics, although no validated quality assessments were performed. No trials were excluded at this point of the selection process.

Additional information was identified from publicly available regulatory documents filed with the US Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

3. Evidence synthesis

A total of 20 papers, published between 1994 and 2014, were identified; 16 focused on mirabegron, 2 on solabegron, 1 on TAK-677, and 1 on BRL35135 (Supplementary Table 2). Table 1 provides a design overview for mirabegron phase 2 and 3 studies and CV exclusion criteria. Only limited clinical information exists on solabegron, TAK-677, and BRL35135. More detailed CV data from mirabegron studies identified in the literature search was available in online regulatory documents filed with the FDA and NICE.

3.1. Statistical analysis

Categorical variables are given using frequencies and/or percentages. Continuous variables are given using mean, standard deviation, and overall range; means with standard error (SE) were used when the former was unavailable. Statistical methods used to analyze change from baseline to final visit in vital signs, treatment differences, and to estimate relative risks versus placebo are described in Supplement 1.

3.2. Overview of cardiovascular effects: analysis of data from 12-wk and 1-yr clinical trials

As the only clinically approved agent in the class, the bulk of the available information on the CV effects of β_3-adrenoceptor agonists is derived from the mirabegron clinical trial program. Mirabegron's CV safety was analyzed in a detailed prospective analysis of the pooled populations of three 12-wk phase 3 trials (046 [NCT00689104], 047 [NCT00662909], and 074 [NCT00912964]) [24] and separately in a 1-yr phase 3 trial (049 [NCT0688688]) [25]. These studies enrolled men and women aged ≥18 yr with OAB symptoms (Table 2). Data from placebo and mirabegron 50 mg arms of studies 046, 047, and 074 were pooled, and data from the mirabegron 100 mg arms of studies 046 and 047 were pooled. Only study 074 included a mirabegron 25 mg arm. CV-related events of interest were hypertension, corrected QT (QTc) prolongation, and cardiac arrhythmia (including atrial fibrillation and tachycardia). Overall, 0.5–1.9% of patients had a history of atrial fibrillation/atrial flutter (Table 2). Supplementary Table 3 provides an overview of CV data from these studies. Of note, the pooled studies used a consistent rigorous definition for defining the AE of hypertension or tachycardia. A hypertension AE was defined as average systolic blood pressure (SBP)

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Table 1 – Summary of mirabegron phase 2 and 3 trials

Study number	Patients enrolled, *n*	Patients randomized, *n*	Mirabegron dose	Placebo control	Active comparator	Study duration, double-blind treatment period	CV exclusion criteria
008	314	262	100 or 150 mg twice daily*	Yes	Tolterodine 4 mg ER once daily	4 wk	Any clinically significant CV complication including CVA, recent MI, and uncontrolled hypertension, indicated by a sitting SBP ≥180 mm Hg and/or DBP ≥110 mm Hg
044	1108	928	25, 50, 100, or 200 mg once daily	Yes	Tolterodine 4 mg ER once daily	12 wk	Clinically significant CV or cerebrovascular diseases within 6 mo prior to placebo run-in, such as MI, uncontrolled angina, significant ventricular arrhythmias, sinus tachycardia, heart failure (NYHA class II/IV), orthostatic hypotension, stroke, and uncontrolled hypertension, indicated by a sitting SBP ≥160 mm Hg and/or DBP ≥100 mm Hg Patients with a HR <45 and >100 ECG on visit 1 showing a QTc interval >470 ms, patients with risk factors for torsades de pointes, hypokalemia, familial long QT syndrome, patients receiving comedication with QT-prolonging drugs Any other clinically significant abnormal ECG that in the opinion of the investigator makes the patient unsuitable for the study
046	2336	1987	50 or 100 mg once daily	Yes	Tolterodine 4 mg ER once daily	12 wk	Severe hypertension, defined as a sitting average SBP ≥180 mm Hg and/or average DBP ≥110 mm Hg A clinically significant abnormal ECG that in the opinion of the investigator made the patient unsuitable for the study
047	2149	1329	50 or 100 mg once daily	Yes	No	12 wk	As for study 046
074	2030	1306	25 or 50 mg once daily	Yes	No	12 wk	As for study 046
049	2801	2444	50 or 100 mg once daily	No	Tolterodine 4 mg ER once daily	12 mo	As for study 046
048	1332	1139	50 mg once daily	Yes	Tolterodine 4 mg ER once daily	12 wk	Acute cerebrovascular disease, serious CV disease (eg, MI, cardiac insufficiency, uncontrolled angina pectoris, or serious arrhythmias) or clinically significant orthostatic hypotension within 24 wk prior to initiating the run-in period Uncontrolled hypertension (sitting SBP ≥180 mm Hg or DBP ≥110 mm Hg when BP was measured prior to run-in or at baseline PR ≥110 bpm or <50 bpm when measured prior to run-in ECG abnormalities measured prior to the run-in period that caused the ECG readers to deem the patient unsuitable for the study
090	1506	1126	50 mg once daily	Yes	Tolterodine 4 mg ER once daily	12 wk	Patients who experienced acute cerebrovascular disorder, serious CV disorder (eg, MI, cardiac failure, uncontrolled angina, serious arrhythmia) or clinically significant orthostatic hypotension within 24 wk before initiation of the run-in period Patients with uncontrolled hypertension (indicated by a sitting SBP ≥180 mm Hg or DBP ≥110 mm Hg measured prior to run-in) Patients with a pulse rate ≥10 bpm or <50 bpm or any clinically significant abnormal ECG as judged by the cardiologist prior to run-in Patients with clinically significant, serious cardiac disease

CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; ECG = electrocardiogram; ER = extended release; HR = heart rate; MI = myocardial infarction; NYHA = New York Heart Association functional classification; PR = pulse rate; SBP = systolic blood pressure.
* Immediate release formulation.

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Table 2 – Patient demographics and baseline characteristics by treatment group: pooled 12-wk populations (studies 046, 047, and 074) and 1-yr population (safety analysis set)

	Pooled* 12-wk phase 3 studies (046, 047, and 074)					1-yr phase 3 study (049)		
	Placebo (*n* = 1380)	Mirabegron			Tolterodine ER 4 mg (*n* = 495)	Mirabegron		Tolterodine ER 4 mg (*n* = 812)
		25 mg (*n* = 432)	50 mg (*n* = 1375)	100 mg (*n* = 929)		50 mg (*n* = 812)	100 mg (*n* = 820)	
Sex, *n* (%)								
Female	1002 (73)	293 (68)	982 (71)	675 (73)	361 (73)	602 (74)	608 (74)	600 (74)
Male	378 (27)	139 (32)	393 (29)	254 (27)	134 (27)	210 (26)	212 (26)	212 (26)
Age, yr								
Mean (SD)	59.2 (13.3)	58.5 (12.9)	59.5 (12.7)	59.9 (13.0)	59.1 (12.9)	59.2 (12.6)	60.1 (11.9)	59.6 (12.5)
Range	20–95	22–85	21–91	19–90	18–83	21–87	22–86	21–87
Race, *n* (%)								
White	1274 (92)	394 (91)	1279 (93)	873 (94)	490 (99)	778 (96)	774 (94)	780 (96)
Black	84 (6.1)	32 (7.4)	66 (4.8)	38 (4.1)	3 (0.6)	22 (2.7)	30 (3.7)	20 (2.5)
Asian	13 (0.9)	5 (1.2)	19 (1.4)	10 (1.1)	2 (0.4)	8 (1.0)	8 (1.0)	5 (0.6)
Other	9 (0.7)	1 (0.2)	11 (0.8)	8 (0.9)	0	4 (0.5)	8 (1.0)	7 (0.9)
BMI, kg/m^2								
Mean (SD)	29.1 (6.3)	29.8 (6.5)	29.0 (6.1)	29.0 (6.1)	27.8 (5.0)	29.0 (6.3)	28.8 (6.0)	28.5 (5.7)
Range	16–58	18–58	16–60	16–63	18–49	16–58	19–60	16–53
Hypertension status 1 at baseline, *n* (%)**,†								
Normotensive	857 (62)	250 (58)	873 (64)	555 (60)	300 (61)	488 (60)	509 (62)	478 (59)
Hypertensive	523 (38)	182 (42)	502 (37)	374 (40)	195 (39)	324 (40)	311 (38)	334 (41)
Hypertension status 2 at baseline, *n* (%)**,‡								
Normal	455 (33)	101 (23)	432 (31)	317 (34)	133 (27)	226 (28)	236 (29) (*n* = 819)	229 (28)
Prehypertension	637 (46)	219 (51)	665 (48)	445 (48)	259 (52.3)	431 (53)	426 (52)	411 (51)
Stage 1 hypertension	255 (19)	96 (22.2)	228 (16.6)	142 (15.3)	87 (17.6)	132 (16.3)	139 (17.0)	159 (19.6)
Stage 2 hypertension	33 (2.4)	16 (3.7)	50 (3.6)	25 (2.7)	16 (3.2)	23 (2.8)	18 (2.2)	13 (1.6)
History of tachyarrhythmia, *n* (%)	28 (2.0)	7 (1.6)	34 (2.5)	15 (1.6)	8 (1.6)	17 (2.1)	20 (2.4)	20 (2.5)
History of atrial fibrillation/atrial flutter, *n* (%)	16 (1.2)	6 (1.4)	26 (1.9)	11 (1.2)	5 (1.0)	4 (0.5)	15 (1.8)	14 (1.7)
Use of systemic β-blockers at baseline, *n* (%)	214 (16)	77 (18)	191 (14)	166 (18)	91 (18)	137 (17)	128 (16)	134 (17)
Baseline QTcF, *n* (%)								
≤450 ms	1295 (96) (*n* = 1346)	419 (97)	1294 (96) (*n* = 1350)	861 (96) (*n* = 901)	459 (97) (*n* = 473)	779 (97) (*n* = 804)	787 (97) (*n* = 813)	769 (96) (*n* = 801)
>450 ms	51 (3.8)	13 (3.0)	56 (4.1)	40 (4.4)	14 (3.0)	25 (3.1)	26 (3.2)	32 (4.0)
History of hyperlipidemia, *n* (%)	332 (24)	117 (27)	335 (24)	207 (22)	75 (15)	181 (22)	158 (19)	161 (20)
History of atherosclerotic disease, *n* (%)	147 (11)	42 (10)	144 (11)	112 (12)	63 (13)	67 (8.3)	90 (11)	92 (11)
History of cardiac failure, *n* (%)	6 (0.4)	1 (0.2)	3 (0.2)	7 (0.8)	4 (0.8)	2 (0.2)	4 (0.5)	3 (0.4)

BMI = body mass index; ER = extended release; QTcF = QT interval corrected for heart rate using Fridericia formula; SD = standard deviation.

* Because the mirabegron 25 mg dose was used only in study 074 and the tolterodine (active control arm) only in study 046, these data are not pooled.

** Baseline hypertension status 1 based on medical history and medication history.

† The hypertensive population comprised all patients who had a medical history of hypertension and received concurrent antihypertensive treatment at the screening visit; the normotensive population comprised all patients who did not meet the definition of hypertensive.

‡ Baseline hypertension status 2 based on baseline diary systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were SBP <120 mm Hg and DBP <80 mm Hg = normal; SBP 120–139 mm Hg or DBP 80–89 mm Hg = prehypertension; SBP 140–159 mm Hg or DBP 90–99 mm Hg = stage 1 hypertension; SBP ≥160 mm Hg or DBP ≥100 mm Hg = stage 2 hypertension.

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≥140 mm Hg and/or average diastolic blood pressure (DBP) ≥90 mm Hg at two consecutive visits after baseline for normotensive patients; average SBP increased ≥20 mm Hg and/or average DBP increased ≥10 mm Hg from baseline at two consecutive visits in patients with hypertension at baseline or at initiation/increase in antihypertensive medication. Tachycardia was reported as an AE if the average daytime (AM) and nighttime (PM) resting pulse rate (PR) measured by the patient over 3 d was >100 beats per minute (bpm). An independent CV committee adjudicated serious potential CV-related AEs and deaths for all mirabegron studies using the categorization of APTC/MACE or non-APTC/MACE [26].

3.2.1. APTC/MACE or non-APTC/MACE

APTC/MACE events have become the standard so-called hard end point for assessing the CV effects of drugs. In the pooled 12-wk and 1-yr mirabegron studies, APTC/MACE events were not increased in the mirabegron population for any dose and were comparable with placebo [27]. In the 1-yr study, APTC/MACE events occurred in 0.7% of patients in the mirabegron 50 mg group ($n = 812$): nonfatal stroke (three patients), nonfatal myocardial infarction (two patients), and CV death (one patient) (Table 3). Such events occurred in 0.5% of patients in the tolterodine extended-release (ER) group ($n = 812$): CV death (two patients), nonfatal myocardial infarction (one patient), and nonfatal stroke (one patient).

Among all mirabegron patients in studies 044, 045, 046, 047, 048, and 074, there was no evidence of risk for the occurrence of APTC/MACE events versus placebo (relative risk [RR] for all mirabegron doses vs placebo events: 0.24; 95% confidence interval [CI], 0.02–1.69]). Similarly, there was no evidence of risk in the 1-yr study versus tolterodine (RR for mirabegron 50 mg vs tolterodine: 0.75; 95% CI, 0.18–3.60), although a large increase in risk cannot be discounted [27].

3.2.2. Blood pressure

Hypertension was the most commonly reported treatment-emergent adverse event (TEAE) across the OAB phase 3 population, occurring in approximately 8.7% of patients receiving mirabegron 50 mg versus 8.5% on placebo in the pooled 12-wk studies (Table 3); however, the mean increase in SBP/DBP associated with mirabegron 50 mg was ≤1 mm Hg in OAB patients and was reversible upon treatment discontinuation. Specifically, for pooled 12-wk studies, adjusted mean difference versus placebo for change from baseline to week 12/final visit in SBP was 0.6 (SE: 0.35) and 0.5 (SE: 0.36) for AM and PM measurements, respectively; and for DBP was 0.4 (SE: 0.22) and 0.4 (SE: 0.23) for AM and PM measurements, respectively. Hypertension incidence decreased as mirabegron dose increased from 25 to 100 mg (Table 3) and was similar between mirabegron 50 mg and placebo in pooled 12-wk studies and between mirabegron and tolterodine in the 1-yr study. More detailed accounts of changes in vital signs are available in regulatory documents (Supplementary Fig. 2 and 3) [27]. Increases from baseline in SBP/DBP were generally similar across placebo, mirabegron, and tolterodine groups (Tables 4 and 5). Changes from baseline in blood pressure (BP) and PR when analyzed in patients with stage 1 and 2 hypertension were consistent with those in the total patient population (Supplementary Fig. 4a and 4b). Subgroup analyses by age group showed very similar mean changes for SBP/DBP across age groups, with larger PR changes in younger patients in some analyses (Supplementary Fig. 4c and 4d). Changes in vital signs for studies 046, 047, and 074 individually are shown in Supplementary Table 4–6.

In a study in a mixed non-Japanese Asian OAB population, hypertension TEAEs occurred with an incidence of 0.5% and 0.8% in the mirabegron 50 mg and tolterodine ER 4 mg groups, respectively [28]. Adjusted mean differences from placebo in SBP and DBP upon awakening were similar in the mirabegron 50 mg and tolterodine groups (0.22 [95% CI, −1.38 to 1.82] and 0.28 [95% CI, −1.33 to 1.88], respectively) [28]. There were also no clinically relevant effects on SBP/DBP or ECG findings in OAB patients in the proof-of-concept, dose-finding, or Japanese phase 3 studies [29–31].

In a QT/QTc study in healthy volunteers, maximum mean increases in SBP/DBP with mirabegron 50 mg were approximately 4.0/1.6 mm Hg greater than placebo [32,33]. Modest BP increases were observed in a multiple-dose pharmacokinetic study that was not clearly correlated with increasing mirabegron dose (50–300 mg). No participant showed a positive orthostatic stress test [34]. In a study in healthy Japanese participants, there were dose-dependent increases in SBP at 3–6 h after dose, but these were possibly due to circadian rhythm because of the timing of the initial dose (9 AM). There were no changes in mean DBP for any mirabegron dose (50–400 mg) [35].

Because α_1-adrenoceptor antagonists such as tamsulosin are associated with CV AEs and may be used concomitantly with mirabegron in men with lower urinary tract symptoms characteristic of benign prostatic hyperplasia, potential pharmacokinetic and CV interactions upon add-on of mirabegron 100 mg or tamsulosin 0.4 mg to existing tamsulosin or mirabegron monotherapy were evaluated [36]. In 48 healthy men aged 44–72 yr, tamsulosin and mirabegron cotherapy did not cause clinically relevant changes in assessed CV parameters up to 12 h after dose [36].

3.2.2.1. Solabegron. Other than mirabegron, solabegron is the only β_3-adrenoceptor agonist tested in phase 2 clinical trials for OAB treatment [37]. In a randomized double-blind proof-of-concept study in women with OAB, hypertension was reported by 2 of 88 participants (2.3%) receiving 8 wk of twice daily solabegron 50 mg and 3 of 85 participants (3.5%) receiving twice daily 125 mg solabegron. However, comparisons with other agents are difficult because exact criteria for classification of hypertension were not reported. In 24-h ambulatory BP monitoring, solabegron did not induce significant changes from baseline to week 8 in SBP (adjusted mean difference from placebo: –1.9, 1.3 mm Hg), DBP (–2.1; –0.1 mm Hg), or HR (0.8; 1.1 bpm) for the 50 mg and 125 mg groups, respectively. A similar lack of effect on vital signs was noted during office visits, and there were no noteworthy changes in ECG parameters or morphology [37].

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Table 3 – Summary of cardiovascular and electrocardiogram safety analysis set (SAF): pooled 12-wk populations (studies 046, 047, and 074) and 1-yr population (SAF)

	Pooled* 12-wk phase 3 studies (046, 047, and 074)					1-yr phase 3 study (049)		
	Placebo (*n* = 1380)	Mirabegron			Tolterodine ER 4 mg (*n* = 495)	Mirabegron		Tolterodine ER 4 mg (*n* = 812)
		25 mg (*n* = 432)	50 mg (*n* = 1375)	100 mg (*n* = 929)		50 mg (*n* = 812)	100 mg (*n* = 820)	
CV events								
Incidence, *n* (%), of APTC/MACE	4 (0.3)	0	0	0	1 (0.2)	6 (0.7)	0	4 (0.5)
Relative risk** of APTC/MACE (95% CI)	–	NE	NE	NE	–	1.50 (0.35–7.3)	NE	–
Incidence, *n* (%), of:								
Hypertension TEAEs	117 (8.5)	52 (12)	120 (8.7)	58 (6.2)	48 (9.7)	89 (11)	83 (10)	86 (11)
Hypertension SAEs	0	0	1 (0.1)	0	1 (0.2)	1 (0.1)	1 (0.1)	0
Discontinuations due to hypertension TEAEs	3 (0.2)	2 (0.5)	5 (0.4)	4 (0.4)	1 (0.2)	4 (0.5)	2 (0.2)	4 (0.5)
Relative risk** of hypertension TEAE (95% CI)	–	1.3 (0.86–1.8)	1.0 (0.79–1.3)	0.78 (0.56–1.1)	–	1.0 (0.77–1.4)	0.94 (0.70–1.3)	–
Incidence, *n* (%), of:								
Tachycardia overall†	43 (3.1)	21 (4.9)	52 (3.8)	43 (4.6)	16 (3.2)	25 (3.1)	49 (6.0)	53 (6.5)
Tachycardia TEAEs	9 (0.7)	10 (2.3)	18 (1.3)	7 (0.8)	3 (0.6)	10 (1.2)	19 (2.3)	26 (3.2)
Tachycardia SAEs	0	0	0	1 (0.1)	0	0	0	0
Discontinuations due to tachycardia TEAEs	0	1 (0.2)	2 (0.1)	2 (0.2)	1 (0.2)	0	0	0
ECG QT prolongation events	0	0	0	0	2 (0.4)	3 (0.4)	2 (0.2)	3 (0.4)
ECG data								
QTcF interval								
Patients, *n* (%), meeting threshold criteria, maximum value of:								
>450 ms	44 (3.5)	14 (3.4)	32 (2.6)	27 (3.2)	18 (4.1)	36 (4.9)	29 (3.9)	32 (4.4)
>480 ms	3 (0.2)	0	3 (0.2)	5 (0.6)	3 (0.7)	5 (0.7)	2 (0.3)	6 (0.8)
>500 ms	1 (0.1)	0	0	1 (0.1)	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)
Patients, *n* (%), with increase from baseline of:								
≥30 ms	44 (3.6)	9 (2.2)	53 (4.3)	24 (2.9)	25 (5.9)	76 (10)	67 (9.0)	77 (11)
≥60 ms	2 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.5)	3 (0.4)	3 (0.4)	3 (0.4)

APTC/MACE = Antiplatelet Trialists' Collaboration/Major Adverse CV Event; CI = confidence interval; ECG = electrocardiogram; ER = extended release; NE = not evaluated due to insufficient data; QTcF = QT interval corrected for heart rate using Fridericia formula; SAE = serious adverse event; SAF = safety analysis set: all randomized patients who took one dose or more of double-blind study drug; TEAE = treatment-emergent adverse event.

* Because the mirabegron 25 mg dose was used only in study 074 and the tolterodine (active control arm) only in study 046, these data are not pooled.

** Relative risk (RR) is versus placebo in pooled analysis and versus tolterodine in study 049; RR of hypertension estimated using hazard ratios and 95% CIs from a proportional hazards model (stratified by study in the pooled analysis); RR of APTC/MACE estimated using odds ratios and exact 95% CIs.

† Based on TEAE and/or observations of pulse rate ≥100 bpm captured by patient diary.

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Table 4 – Summary of changes from baseline to final visit in vital signs measured by patient's diary: pooled 12-wk populations (studies 046, 047, and 074) [24]

	Placebo (n = 1380)		Mirabegron 25 mg (n = 432)		Mirabegron 50 mg (n = 1375)		Mirabegron 100 mg (n = 929)		Tolterodine ER 4 mg (n = 495)	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
BP, mm Hg										
SBP										
n	1329	1326	410	410	1327	1327	891	890	476	476
Baseline, mean (SE)	125.9 (0.47)	125.0 (0.41)	129.2 (0.81)	129.0 (0.71)	126.4 (0.47)	125.6 (0.43)	125.0 (0.55)	123.7 (0.49)	128.2 (0.75)	127.4 (0.64)
Final visit, mean (SE)	126.2 (0.45)	125.7 (0.41)	128.8 (0.75)	128.3 (0.67)	127.2 (0.46)	126.6 (0.41)	125.6 (0.51)	125.2 (0.46)	128.4 (0.70)	127.9 (0.63)
Adjusted change from baseline, mean (SE) (95% CI)*	0.2 (0.25) (−0.3 to 0.7)	0.6 (0.25) (0.1–1.1)	−0.3 (0.52) (−1.3 to 0.7)	−0.5 (0.53) (−1.5 to 0.6)	0.8 (0.25) (0.3–1.3)	1.1 (0.25) (0.6–1.6)	0.6 (0.32) (−0.0 to 1.2)	1.4 (0.33) (0.8–2.1)	0.1 (0.45) (−0.8 to 1.0)	0.5 (0.46) (−0.4 to 1.4)
Difference vs placebo, mean (SE) (95% CI)**	–	–	−0.5 (0.57) (−1.6 to 0.6)	−1.0 (0.58) (−2.2 to 0.1)	0.6 (0.35) (−0.1 to 1.3)	0.5 (0.36) (−0.2 to 1.2)	0.4 (0.41) (−0.4 to 1.2)	0.9 (0.42) (0.1–1.7)	−0.1 (0.52) (−1.1 to 1.0)	−0.0 (0.53) (−1.1 to 1.0)
DBP										
n	1329	1326	410	410	1327	1327	890	890	476	476
Baseline, mean (SE)	77.1 (0.26)	75.3 (0.23)	78.2 (0.48)	76.1 (0.46)	77.2 (0.25)	75.4 (0.24)	77.4 (0.30)	75.3 (0.28)	76.8 (0.40)	75.4 (0.38)
Final visit, mean (SE)	77.2 (0.25)	75.7 (0.24)	77.6 (0.43)	75.7 (0.42)	77.6 (0.24)	76.2 (0.24)	77.7 (0.28)	76.3 (0.28)	77.7 (0.39)	76.6 (0.36)
Adjusted change from baseline, mean (SE) (95% CI)*	0.0 (0.16) (−0.3 to 0.3)	0.4 (0.16) (0.1–0.7)	−0.1 (0.33) (−0.8 to 0.5)	0.1 (0.34) (−0.6 to 0.7)	0.4 (0.16) (0.1–0.7)	0.7 (0.16) (0.4–1.1)	0.2 (0.21) (−0.2 to 0.6)	0.9 (0.21) (0.5–1.3)	0.8 (0.29) (0.2–1.3)	1.4 (0.30) (0.8–2.0)
Difference vs placebo, mean (SE) (95% CI)**	–	–	−0.1 (0.37) (−0.9 to 0.6)	−0.3 (0.37) (−1.0 to 0.4)	0.4 (0.22) (−0.1 to 0.8)	0.4 (0.23) (−0.1 to 0.8)	0.2 (0.26) (−0.3 to 0.7)	0.5 (0.27) (−0.0 to 1.0)	0.7 (0.33) (0.1–1.4)	1.0 (0.34) (0.4–1.7)
PR, bpm										
n	1329	1326	410	410	1327	1327	891	890	476	476
Baseline, mean (SE)	70.5 (0.28)	75.3 (0.29)	71.0 (0.50)	75.5 (0.51)	70.4 (0.28)	74.9 (0.28)	70.4 (0.34)	74.4 (0.34)	69.8 (0.44)	73.9 (0.45)
Final visit, mean (SE)	70.9 (0.29)	74.7 (0.29)	71.7 (0.52)	75.3 (0.53)	71.8 (0.29)	75.5 (0.28)	72.9 (0.34)	76.5 (0.34)	71.4 (0.44)	76.0 (0.45)
Adjusted change from baseline, mean (SE) (95% CI)*	0.4 (0.17) (0.1–0.8)	−0.4 (0.18) (−0.8 to 0.1)	1.3 (0.36) (0.6–2.0)	0.2 (0.37) (−0.6 to 0.9)	1.4 (0.17) (1.1–1.8)	0.6 (0.18) (0.2–0.9)	2.3 (0.22) (1.9–2.8)	1.9 (0.23) (1.4–2.3)	1.4 (0.31) (0.8–2.0)	1.7 (0.32) (1.1–2.3)
Difference vs placebo, mean (SE) (95% CI)**	–	–	0.9 (0.40) (0.1–1.6)	0.6 (0.41) (−0.2 to 1.4)	1.0 (0.24) (0.5–1.5)	1.0 (0.25) (0.5–1.5)	1.9 (0.28) (1.3–2.5)	2.3 (0.29) (1.7–2.9)	1.0 (0.36) (0.3–1.7)	2.1 (0.37) (1.4–2.8)

AM = daytime; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; ER = extended release; PM = nighttime; PR = pulse rate; SE = standard error; SBP = systolic blood pressure.
* Adjusted changes from baseline are generated from the analysis of covariance model with treatment group, gender, and study as fixed factors and baseline as a covariate.
** Differences of the adjusted means are calculated by subtracting the adjusted mean of placebo from the adjusted mean of the treatment group.

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Table 5 – Summary of changes from baseline to final visit in vital signs measured by patient's diary; 1-yr study

	Mirabegron 50 mg (n = 812)		Mirabegron 100 mg (n = 820)		Tolterodine ER 4 mg (n = 812)	
	AM	PM	AM	PM	AM	PM
BP, mm Hg						
SBP						
n	791	789	802	802	793	793
Baseline, mean (SE)	126.7 (0.58)	126.4 (0.50)	125.9 (0.56)	125.7 (0.50)	126.8 (0.55)	126.3 (0.49)
Final visit, mean (SE)	126.9 (0.56)	126.0 (0.49)	126.4 (0.53)	126.0 (0.49)	126.3 (0.54)	126.3 (0.50)
Adjusted change from baseline, mean (SE) (95% CI)*	0.2 (0.33) (−0.4 to 0.9)	−0.3 (0.33) (−0.9 to 0.3)	0.4 (0.33) (−0.2 to 1.1)	0.1 (0.32) (−0.5 to 0.8)	−0.5 (0.33) (−1.1 to 0.2)	−0.0 (0.33) (−0.7 to 0.6)
DBP						
n	791	789	802	802	793	793
Baseline, mean (SE)	77.6 (0.31)	76.2 (0.30)	77.2 (0.29)	75.9 (0.29)	77.6 (0.30)	76.1 (0.29)
Final visit, mean (SE)	77.3 (0.30)	76.2 (0.30)	77.6 (0.29)	76.1 (0.30)	77.6 (0.31)	76.7 (0.31)
Adjusted change from baseline, mean (SE) (95% CI)*	−0.3 (0.21) (−0.7 to 0.1)	−0.0 (0.21) (−0.4 to 0.4)	0.4 (0.20) (−0.0 to 0.8)	0.1 (0.21) (−0.3 to 0.5)	0.1 (0.21) (−0.3 to 0.5)	0.6 (0.21) (0.2–1.0)
PR, bpm						
n	791	789	802	802	792	792
Baseline, mean (SE)	71.0 (0.36)	74.2 (0.36)	70.2 (0.37)	74.1 (0.37)	70.1 (0.35)	73.8 (0.36)
Final visit, mean (SE)	71.8 (0.34)	74.5 (0.35)	71.9 (0.35)	75.4 (0.36)	71.8 (0.37)	75.8 (0.36)
Adjusted change from baseline, mean (SE) (95% CI)*	0.9 (0.23) (0.5–1.4)	0.4 (0.24) (−0.1 to 0.8)	1.6 (0.22) (1.2–2.1)	1.3 (0.24) (0.8–1.7)	1.5 (0.22) (1.1–2.0)	1.9 (0.24) (1.4–2.4)

AM = daytime; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; ER = extended release; PM = nighttime; PR = pulse rate; SBP = systolic blood pressure; SE = standard error.

* Adjusted changes from baseline are generated from the analysis of covariance model with previous study history, treatment group, gender, and geographic region as fixed factors and baseline as a covariate.

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3.3. Electrophysiology data from clinical studies

The potential for mirabegron to prolong QTc was investigated in a TQT study, powered for each gender according to International Conference on Harmonisation E14 guidance (threshold of regulatory concern for proarrhythmia: an upper bound of the one-sided 95% CI of 10 ms [38]). In a randomized placebo- and active (moxifloxacin)-controlled, parallel, crossover, heart-rate–corrected QT interval (QT/QTc) study in 176 healthy men and 176 healthy women, mirabegron 50 or 100 mg did not cause QTc prolongation [32]. However, at a supratherapeutic dose (200 mg), the QTc interval was prolonged in female participants (95% CI of QTc of 13.44 ms, occurring at 5 h).

In the pooled 12-wk population, frequency of QTc prolongation AEs was low (≤0.4%) and similar across placebo, mirabegron, and tolterodine groups [24]. In the 1-yr study, no consistent trends in ECG changes were identified [25]. Categorical outliers in QT interval corrected for HR using the Fridericia formula (QTcF) were low across treatment groups (Table 3). As expected, due to longer QTc intervals generally present in women, female OAB patients had a higher frequency of maximum QTcF values >450 ms versus men in the pooled populations; this was not the case in the 1-yr study [25,27]. The frequency of QTcF change from baseline of ≥30 ms and <60 ms was similar in both genders in the pooled populations, but it was higher in women versus men in the 1-yr study. No trends between genders were observed in other categorical QTcF analyses [27]. In the non-Japanese Asian OAB study, TEAEs of potential QTc prolongation occurred with an incidence of 0.8%, 0.5%, and 1.1% in the placebo, mirabegron 50 mg, and tolterodine ER 4-mg groups, respectively. No patients on mirabegron 50 mg had absolute QTcF interval values >480 ms or an increase in QTcF intervals >60 ms [28].

3.3.1. Heart rate and palpitations

Because both β_1- and β_3-adrenoceptors may affect the rate and/or force of contraction of the heart [39], direct effects on these parameters were assessed in clinical trials of β_3-adrenoceptor agonists. In mirabegron-treated OAB patients in the pooled 12-wk population, there were small dose-dependent increases from baseline in adjusted mean difference versus placebo for both AM and PM PR measurements, reversible on treatment discontinuation [33] (Table 4). However, the PR increase associated with mirabegron 50 mg versus placebo was approximately 1 bpm and was comparable with tolterodine for AM measures; mirabegron 50 mg was less than tolterodine ER 4 mg for PM measures. In the 1-yr study, adjusted mean change from baseline PR showed a small increase in each group; but again this was similar in the mirabegron 100 mg and tolterodine groups and less in the mirabegron 50-mg group (Table 5) [25]. More detailed accounts of changes in vital signs are available in regulatory documents (Supplementary Fig. 2 and 3) [27].

In the proof-of-concept study, mirabegron immediate release (IR) 150 mg twice daily caused a 5-bpm mean increase from baseline in PR, but this was not associated with a clinically significant increase in CV events such as palpitations. The effects of mirabegron IR 100 mg twice daily and tolterodine ER 4 mg once daily on PR (observed increases of −0.7 to 1.4 bpm) were not clinically relevant [31].

Although there was a small but significant ($p < 0.05$) increase from baseline PR in the mirabegron 100 and 200 mg groups in study 044 (AM 2.2 and 4.7 bpm vs 0.5 bpm for placebo; PM 2.7 and 4.6 bpm vs −0.04 bpm for placebo), this did not appear to be associated with an increased incidence of atrial fibrillation or palpitations, which was comparable with that seen with tolterodine [29]. The AM and PM PR increases from baseline for the mirabegron 25 mg group (0.34 and 0.44 bpm, respectively) and 50 mg group (1.64 and 1.12 bpm, respectively) were not statistically significant versus placebo. Adjusted mean changes from baseline in AM and PM PR seen with tolterodine were 1.50 and 2.50, respectively.

In the Japanese phase 3 study, PR increased by approximately 2 bpm after 4-wk treatment with mirabegron 50 mg versus placebo and returned to baseline 2 wk after treatment [30]. In the non-Japanese Asian OAB study, for both the mirabegron 50 mg and tolterodine ER 4 mg groups, the adjusted mean difference from placebo in PR was larger 6 h after dose (1.57 and 2.72, respectively) than on awakening (1.12 and 0.75, respectively). Also, at 6 h after dose, the adjusted mean difference from placebo in PR appeared smaller in the mirabegron 50 mg group (1.57 bpm) versus the tolterodine ER 4 mg group (2.72 bpm) [28].

In the pooled 12-wk population, the overall occurrence of tachycardia events, either based on TEAE and/or observations of PR ≥100 bpm captured by patient diary, was <5% in each treatment group and comparable with placebo and tolterodine (Table 3) [24]. In the 1-yr population, 1.2% of patients on mirabegron 50 mg versus 3.2% of patients on tolterodine ER 4 mg reported tachycardia TEAEs (Table 3), with one patient on mirabegron 50 mg experiencing a third-degree atrioventricular block.

PR changes were more apparent for young healthy volunteers than for OAB patients. In the QT/QTc healthy volunteer study, mirabegron increased HR on ECG in a dose-dependent manner 5–6 h after dose (maximum mean increases from baseline vs placebo: 6.7, 11, and 17 bpm for the 50-, 100-, and 200-mg dose groups, respectively) [40]. In healthy Japanese subjects, increases in PR or palpitations were only significant for the 400-mg group, in which PR exceeding 100 bpm 4–6 h after dosing occurred in three of six participants, one of whom developed palpitations 3 h after dosing. PR tended to increase in a dose-dependent manner 6 h after dose in the 200-mg and higher dose groups versus placebo [35].

3.3.1.1. BRL35135. In a study in eight healthy men, BRL35135 produced significant increases in HR and SBP, and significant decreases in DBP versus placebo. Most of these cardiac effects were due to β_2-adrenoceptor stimulation. It is possible that a small but significant chronotropic effect was β_3 mediated [22].

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3.3.2. Arrhythmia

In study 046, the incidence of cardiac arrhythmias was higher in tolterodine- treated than in mirabegron- and placebo-treated patients (Supplementary Table 7). Atrial fibrillation of medical importance was reported for 1 of 494 (0.2%), 2 of 493 (0.4%), 2 of 496 (0.4%), and 5 of 495 (1.0%) patients in the placebo, 50 mg mirabegron, 100 mg mirabegron, and tolterodine ER 4 mg groups, respectively [35]. In seven cases, atrial fibrillation was not present at baseline. Arrhythmia was reported for 5 of 494 (1.0%), 11 of 493 (2.2%), 9 of 496 (1.8%), and 16 of 495 (3.2%), respectively [41]. In the 1-yr study, arrhythmia was reported for 3.9%, 4.1%, and 6.0% in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg groups, respectively [25].

In study 047, arrhythmia TEAEs were reported for 4 of 453 (0.9%), 9 of 442 (2.0%), and 10 of 433 (2.3%) patients in the placebo, 50 mg, and 100 mg mirabegron groups, respectively. These events included tachycardia in 2 of 453 (0.4%), 6 of 442 (1.4%), and 3 of 433 (0.7%) patients in the placebo, 50 mg, and 100 mg mirabegron groups, and atrial fibrillation in 0, 1, (0.2%), and 2 (0.5%) patients, respectively [42] (Supplementary Table 7). In the non-Japanese Asian study, potential cardiac arrhythmia occurred with an incidence of 5.5%, 3.0%, and 2.2% in the placebo, mirabegron 50 mg, and tolterodine ER 4 mg groups, respectively [28] (Supplementary Table 7). There was no incidence of ventricular arrhythmia in any group.

3.4. Concomitant β-blocker use in clinical trials

There has been some concern that because mirabegron is a β_3-adrenoceptor agonist, its efficacy might be diminished in those taking concomitant β-blockers. In total, 17% of the mirabegron pooled 12-wk and 19% of the 1-yr population reported concomitant β-blockers (Table 6); of these approximately 11–18% were nonselective (β_1 and β_2) β-blockers. Mirabegron 50 and 100 mg were effective in reducing the mean number of incontinence episodes and micturitions per 24 h from baseline to final visit regardless of concomitant β-blocker treatment (Supplementary Table 8). In OAB patients with and without concomitant β-blockers, mirabegron was well tolerated, with a similar tolerability profile across treatment groups.

Mirabegron is metabolized by cytochrome P450 (CYP) 3A4 [43] and to a minor extent by CYP2D6 in humans. The CYP2D6 inhibitory potential of mirabegron was investigated by evaluating the effect of concomitant mirabegron on metoprolol, a selective β_1-adrenoceptor antagonist. Mirabegron did not affect CV responses to metoprolol [44]. There are no data on rates of CV effects associated with other concomitant β-blocker and mirabegron use on PR and BP versus those not taking concomitant β-blockers.

3.5. Discussion

Mirabegron, the only clinically approved β_3-adrenoceptor agonist, provided the bulk of data identified in the systematic literature search. Across the 12-wk phase 2 and 3 population, 8.4% of patients had a history of atherosclerotic disease, 1.4% had a history of tachyarrhythmia, 0.9% had atrial fibrillation/atrial flutter, and 0.3% had cardiac failure, with CV-related intrinsic and extrinsic factors generally comparable across treatment groups (unpublished data). The mirabegron OAB trial population is representative of the general OAB population with regard to CV risk factors and concomitant therapy.

Table 6 – Concomitant cardiovascular medications during the double-blind period in mirabegron phase 3 studies

	Pooled 12-wk population (studies 046, 047, and 074) $n = 4611$	1-yr population (study 049) $n = 2444$
ACE/ARB (%)	1311 (28)	714 (29)
β-Blockers (%)*	778 (17)	451 (19)
Calcium channel blockers (%)	552 (12)	317 (13)
Diuretics (%)	477 (10)	289 (12)
Lipid-lowering agents (%)	1317 (29)	631 (26)
Antithrombotics (%)	963 (21)	501 (21)
Antidiabetics (%)	409 (9)	217 (9)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
* Of these, approximately 11–18% were nonselective (β_1 and β_2) β-blockers.

Articles have described CV comorbidities in OAB patients who were gender and age matched to non-OAB populations from the HealthCore Integrated Research Database (HIRD) and the EPIC study. Hypertension and diabetes were the two most common CV comorbidities in the OAB population, with prevalence rates significantly higher than in non-OAB gender- and age-matched groups [4,6,27]. Supplementary Table 9 shows baseline demographics and comorbidities of OAB patients from these populations and from pooled 12-wk and 1-yr populations. The percentage of patients with hypertension at baseline was higher in mirabegron OAB studies (39% for pooled 12-wk population, 40% for 1-yr population, 27% for HIRD, 29% for EPIC) [4,6,27]. The percentage of patients with diabetes at baseline in the mirabegron studies (8.2% for pooled population, 7.7% for 1-yr population) was similar to that reported in OAB populations from HIRD (8.1%) and EPIC (8.9%). Mean patient age was higher in the mirabegron pooled population (59.4 yr) and 1-yr population (59.6 yr) versus OAB populations from HIRD (50.8 yr) and EPIC (53.8 yr) [27]. In addition, patients in pooled mirabegron studies received many of the common concomitant medications used to manage these CV comorbidities (Table 6). Therefore, the safety of mirabegron was assessed in a study population representative of the general OAB population and that includes similar or greater prevalence of the two most common CV comorbidities.

Across the OAB patient population in the pooled 12-wk phase 3 population, mirabegron 50 mg was associated with small increases in BP and PR versus placebo, of approximately $\leq$1 mm Hg and 1 bpm, respectively, which were reversible upon treatment discontinuation. There was no increase in rates of hypertension (as defined by study criteria) associated with mirabegron treatment versus either placebo or tolterodine [27], and a low proportion

(<5%) of patients experienced tachycardia AEs. Similar results were observed with mirabegron 25 mg [27]. Of note, the pooled 12-wk studies used a consistent, rigorous definition for defining hypertension and tachycardia AEs [27]. The protocol-prespecified definition for hypertension AE was average SBP ≥140 mm Hg and/or average DBP ≥90 mm Hg at two consecutive visits after baseline for normotensive patients; average SBP increased ≥20 mm Hg and/or average DBP increased ≥10 mm Hg at two consecutive visits in patients with hypertension at baseline or initiation/increase in antihypertensive medication. Therefore a proportion of the population was controlled hypertensive patients. Data for patients in this pooled population represent >935 000 individual measurements of PR, SBP, and DBP; no other drug for OAB has been so extensively investigated for CV safety.

Discrepancies between CV data from clinical trials in OAB patients and the larger increases in HR observed in healthy volunteer studies, who are generally younger, may be due to a relatively higher sensitivity of the cardiac response to β-adrenoceptor agonists in young healthy volunteers [14]. Results of nonclinical and clinical pharmacology studies also support the explanation that modest activation of β_1-adrenoceptors could occur at high mirabegron exposures, with potential for causing increases in PR [27]. The change from baseline PR in clinical OAB populations is similar or less than the change from baseline PR following treatment with established antimuscarinics for OAB, such as fesoterodine 4 or 8 mg (3–5 bpm increase) [45], trospium 60 mg (3 bpm increase) [46], or tolterodine ER 4 mg (1.0–2.1 bpm increase [27]). Small changes in vital signs, predominantly PR, are not unprecedented for OAB therapies and did not result in more CV AEs or APTC/MACE events in mirabegron groups versus tolterodine.

4. Conclusions

The CV safety of mirabegron, the only clinically available β_3-adrenoceptor agonist, appears to be good and comparable with that of antimuscarinic agents, the current first-line therapy for OAB. However, data on patients with poorly controlled hypertension, arrhythmia, or cardiac heart failure are currently missing because those patients were excluded from previous studies. Further long-term data are desirable, and a European longer term observational study of mirabegron use is ongoing; this study may also allow identification of risk factors for developing CV AEs. Until research is performed specifically to study patients with other significant CV risk factors, such as coronary heart disease and cardiomyopathy, and those aged >80 yr, periodic BP and HR determinations are recommended.

Author contributions: Christopher R. Chapple had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rosa, Ferrero, Nitti, Wagg, Chapple.
Acquisition of data: Wagg.
Analysis and interpretation of data: Rosa, Ferrero, Nitti, Wagg, Saleem, Chapple.
Drafting of the manuscript: Rosa, Rosa, Ferrero, Nitti, Wagg, Saleem, Chapple.
Critical revision of the manuscript for important intellectual content: Rosa, Ferrero, Nitti, Wagg, Saleem, Chapple.
Statistical analysis: Ferrero.
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Appendix A. Supplementary data

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