Differences with Age in Effects of Adrenergic and Anti-Muscarinic Drugs on Vital Signs

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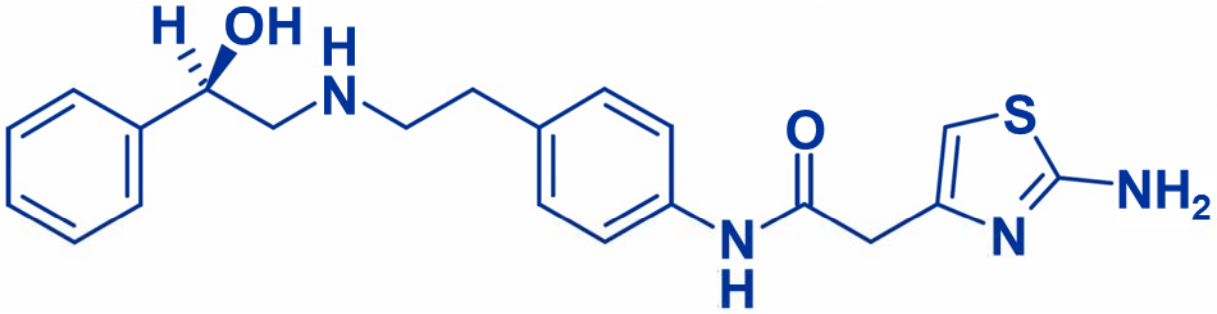
Reason for my interest in the topic: Mirabegron

Selective β-3 adrenergic agonist approved in Japan (2011) and US (2012) for treatment of Overactive Bladder (OAB)



Affinity of Mirabegron for Human β-Adrenoceptor Subtypes

Ki (nmol/L)		
β_1	B_2	B_3
4200 ± 900	1300 ± 300	40 ± 20.2

Ki values are expressed as the mean ± SE of 3 runs; receptor binding study using membrane fractions from Chinese hamster ovary (CHO) cells expressing human β-AR subtypes

Changes in response to drugs with age

- The changes in response to drugs with age are summarized in the chapter “Pharmacology across the ageing continuum” (Gronich).
- Particularly notable are changes in the cholinergic and adrenergic systems with aging. Changes in the CV system with age are summarized in the chapter “Effects of aging on cardiovascular structure and function” (Kitzman).
  - Gronich N, Abernethy DR, in Waldman SA, Terzic A, Pharmacology and Therapeutics, 2009, Sanders, Philadelphia.
  - Kitzman DW, Taffet G. in Hazzard’s Geriatric Medicine and Gerontology, 6th Ed. 2009, McGraw-Hill, New York.
- There are changes in autonomic tone with age that affect the response to drugs that act on this system.

Cholinergic system

- Decreased cholinergic responsiveness in aged rats (Ayyagari) is the basis for the use of donepezil and other cholinesterase inhibitors to treat Alzheimer's disease.
  - Ayyagari PV, Gerber M, Joseph JA, Crews FT. Uncoupling of muscarinic cholinergic phosphoinositide signals in senescent cerebral cortical and hippocampal membranes. Neurochem Int 1998; 32:107-115.
- The PI for Sanctura® trospium reports the following from the TQT study: Also in this study, the immediate-release formulation of trospium chloride was associated with an increase in heart rate that correlated with increasing plasma concentration, with a mean elevation in heart rate compared to placebo of 9 beats per minute for the 20 mg dose and of 18 beats per minute for the 100 mg dose. In the two Phase 3 SANCTURA XR® trials the mean increase in heart rate compared to placebo was approximately 3 beats per minute in both studies.

Adrenergic system

- CNS adrenergic outflow in subcortical suprabulbar regions is increased with age, and this has been associated with a state of generalized adrenergic activation (Esler; Seals). Central and peripheral beta-adrenorecepters are reduced.
  - Esler M, Hasting J, Lambert G et al. The influence of aging on the human sympathetic nervous system and brain norepinephrine turnover. Am J Physiol 2002; 282:R909-R916.
  - Seals DR, Dinenno FA. Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. Am J Physiol 2004; 287:H1895-H1905.
- In the CV system both $beta_1$- and $beta_2$-adrenergic responses are decreased with advancing age (Schutzer). The decline in $beta_1$-adrenergic responsiveness results in decreased tachycardic response to sympathetic stimulation. The decline in $beta_2$-adrenergic responsiveness leads to a relative state of peripheral vascular vasoconstriction owing to loss of $beta_2$-adrenergic vasorelaxation (Pan).
  - Schutzer WE, Mader SI. Age-related changes in vascular adrenergic signaling: clinical and mechanistic Implications. Aging Res Rev 2003; 2:169-190.
  - Pan HYM, Hoffman BB, Porsche RA, Blaschke TF. Decline in beta-adrenergic receptor-mediated vascular relaxation with aging in man. J Pharmacol Exp Ther 1986; 239: 802-807.

Adrenergic system (cont.)

- α_1-adrenergic vasoconstrictor responses are impaired in older individuals (Hogikyan). Older patients show less tachycardia than younger patients when exposed to beta$_2$-adrenergic agonists for treatment of pulmonary diseases (Vestel). An isoproterenol dose that increases heart rate by 25 bpm in healthy young men produces an increase of only 10 bpm in older subjects (Kitzman, ref. on slide #3). These different factors contribute to the well-known reduction with increasing age in maximal heart rate achievable with exercise (Tanaka).
  - Hogikyan RV, Supiano MA. Arterial alpha-adrenergic responsiveness is decreased and SNS activity is increased in older humans. Am J Physiol 1994; 266:E717-724.
  - Vestal RE, Wood AJJ, Shand DG. Reduced beta-adrenergic sensitivity in the elderly. Clin Pharmacol Ther 1979; 26: 181-186.
  - Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol 2001; 37:153-156.

Qsymia: age-related differences in vital signs

- With a 15 mg dose of phentermine in combination with topiramate (Qsymia, a sympathomimetic antiobesity drug)

Vital sign parameter	Phase 3 patients	Healthy volunteers
Mean delta HR	+1.6 bpm	+16 bpm
Mean delta SBP	-2.1 mmHg	+4 mmHg
Mean delta DBP	-1.9 mm Hg	+4 mmHg

VI-0521 (QNEXA®) Advisory Committee Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. July 15, 2010. VIVUS, Inc. NDA 022580

Milnacipran: age-related differences in vital signs

- Another example is milnacipran (serotonin-norepinephrine re-uptake inhibitor; for fibromyalgia). In a phase 1 Healthy Volunteer study (Clinical Pharmacology review. Aug. 29, 2008. NDA 22-256) conducted to examine cardiovascular safety, doses of 50, 100 and 200 mg/day (administered as 25, 50, 100 mg bid) increased heart rate (compared to placebo) 5.7, 7.0, and 10.3 bpm on Day 1 and 10.8, 11.5, and 16.2 bpm on Day 3. In Phase 3, increases with milnacipran 100-200 mg/day were 7-8 bpm.
- Similarly, in healthy volunteers milnacipran 50, 100 and 200 mg/day increased SBP (compared to placebo) 5-7, 4, and 6-9 mmHg on Days 1-3 and increased DBP 3-7, 3-8, and 5-8 mmHg on Days 1-3. In Phase 3, increases with milnacipran 100-200 mg/day were 3 mmHg SBP and 2-3 mmHg DBP (compared to placebo).

Mirabegron: Healthy Volunteers

Vital Sign (Pulse, BP) in Healthy Volunteers (Median age 31-32 years)

Study	Dose (mg)	Subjects (n)	VS Measurement Condition	VS Measurement Day	Multiple of Recommended Dose		Mean* (SD) ↑Pulse (bpm)	Mean* (SD) ↑BP (mmHg)	
					Dose	Exposure		SBP	DBP
PK (031)	50	12	supine	Day 13	1x	1x	5.4 (4.85)	2.5 (6.13)	3.1 (4.67)
	100	12	supine	Day 13	2x	2.1x	8.5 (4.07)	5.1 (4.31)	1.9 (3.78)
	200	12	supine	Day 13	4x	5.5x	12.4 (6.70)	9.0 (8.58)	6.2 (2.55)
	300	12	supine	Day 13	6x	10.1x	17.2 (5.24)	6.4 (6.30)	4.6 (5.04)
TQT (077)	50	83	supine	Day 9	1x	1x	6.3 (6.44)	4.5 (7.98)	0.7 (5.64)
	100	82	supine	Day 9	2x	2.6x	9.3 (7.06)	6.7 (8.12)	3.6 (6.85)
	200	84	supine	Day 9	4x	6.5x	14.4 (7.91)	9.6 (9.17)	5.5 (7.08)

* Mean Area Under the Effective Change Curve over 11.5 hrs for -031 and 24 hrs for -077

Pulse Rate Changes in Healthy Volunteers and in OAB Patients at Recommended Doses

Drug	Dose	Mean Increase in Pulse (bpm)	
		Healthy Volunteers	OAB Patients
Mirabegron	50 mg	5.4	1.0
Results from Sanctura (09/2011) Approved US label			
Trospium	60 mg	9	3 - 4

Cardiovascular Safety Assessment of Phase 3 Studies conducted in Europe & North America

- 12 week phase 3 studies and long-term (52-week) controlled study
  - Vital sign measurements
    - Patient diary
    - Office device
    - 24 hour ABPM in a subset of patients
- Analysis of BP and Pulse
  - Quantitative characterization
    - Central tendency
    - Exposure response analyses
    - Categorical analyses
  - Clinical assessment
    - Adverse event reporting using SPA definitions of hypertension and tachycardia

Scheme of Values Included in Calculation of Average Vital Sign Values for Each Visit and AM/PM (Diary Data) for 12-Week Phase 3 Studies: SPA-Recommended Procedure

Morning/ Afternoon	Sequence	Visit																			
		Baseline					Week 4					Week 8					Week 12				
		Diary Day					Diary Day					Diary Day					Diary Day				
		1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
AM	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	2	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
	3	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
PM	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	2	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
	3	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●

The 6 shaded values are averaged to calculate the visit value.

○ – **Represents an individual vital sign measurement that was not included in the calculation of a patient's average value per visit and time of day**

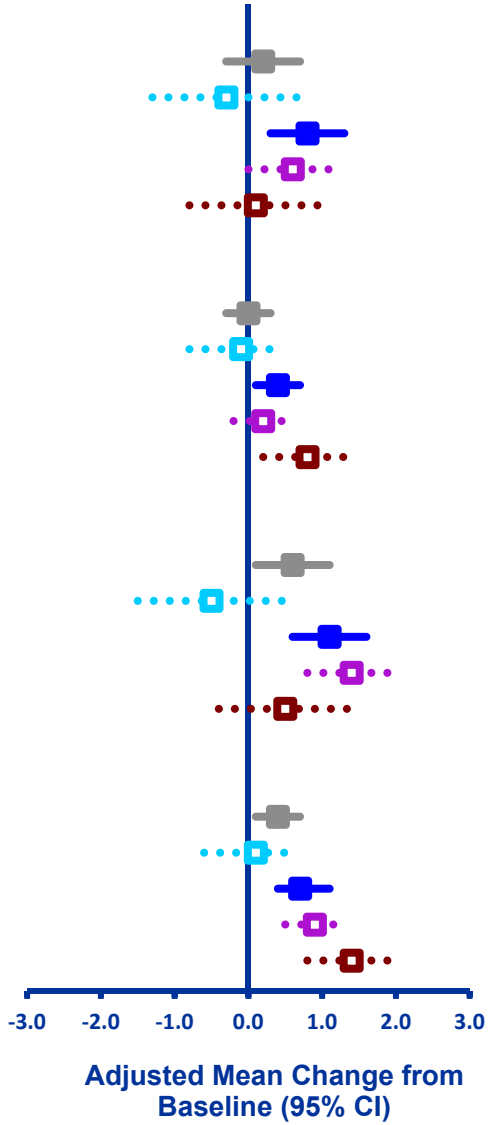
● – **Represents an individual vital sign measurement that was included in the calculation of a patient's average value per visit and time of day**

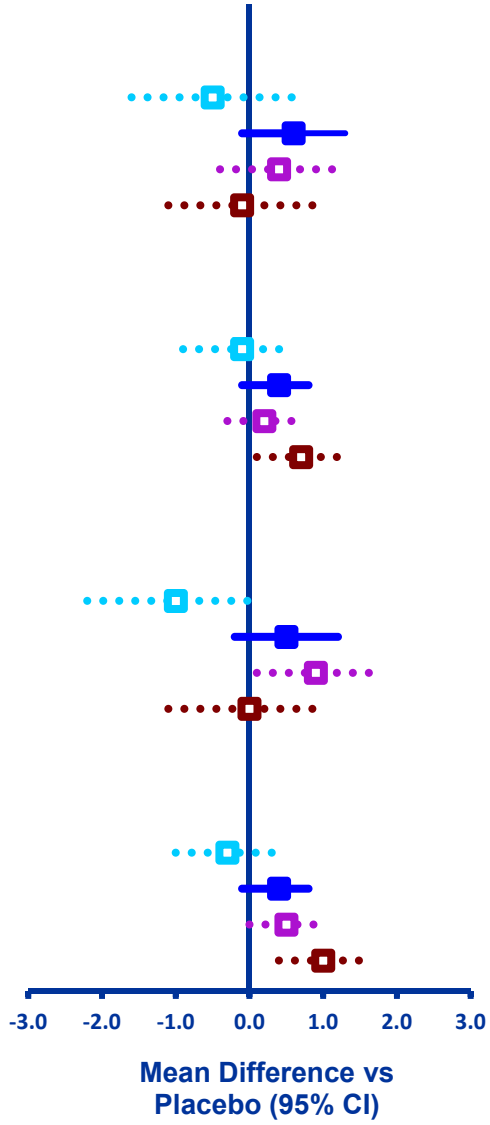
935,961 pulse; 935,950 SBP; 935,745 DBP measurements

Verberk WJ, Kroon AA, Kessels AGH, et al. The optimal scheme of self blood pressure measurement as determined from ambulatory blood pressure recordings. *J Hypertension* 2006;24:1541-1548.

12-Week Phase 3 Studies
Change from Baseline to Final Visit SBP/DBP (Patient Diary)

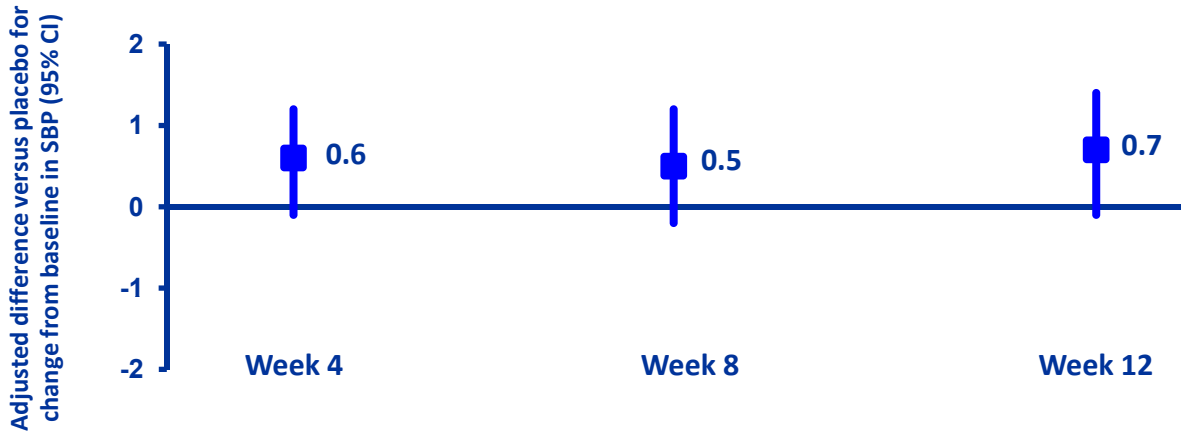
	N	Baseline
AM SBP		
Placebo	**1329**	**125.9**
25 mg mirabegron	410	129.2
50 mg mirabegron	**1327**	**126.4**
100 mg mirabegron	891	125.0
Tolterodine	476	128.2
AM DBP		
Placebo	**1329**	**77.1**
25 mg mirabegron	410	78.2
50 mg mirabegron	**1327**	**77.2**
100 mg mirabegron	890	77.4
Tolterodine	476	76.8
PM SBP		
Placebo	**1326**	**125.0**
25 mg mirabegron	410	129.0
50 mg mirabegron	**1327**	**125.6**
100 mg mirabegron	890	123.7
Tolterodine	476	127.4
PM DBP		
Placebo	**1326**	**75.3**
25 mg mirabegron	410	76.1
50 mg mirabegron	**1327**	**75.4**
100 mg mirabegron	890	75.3
Tolterodine	476	75.4





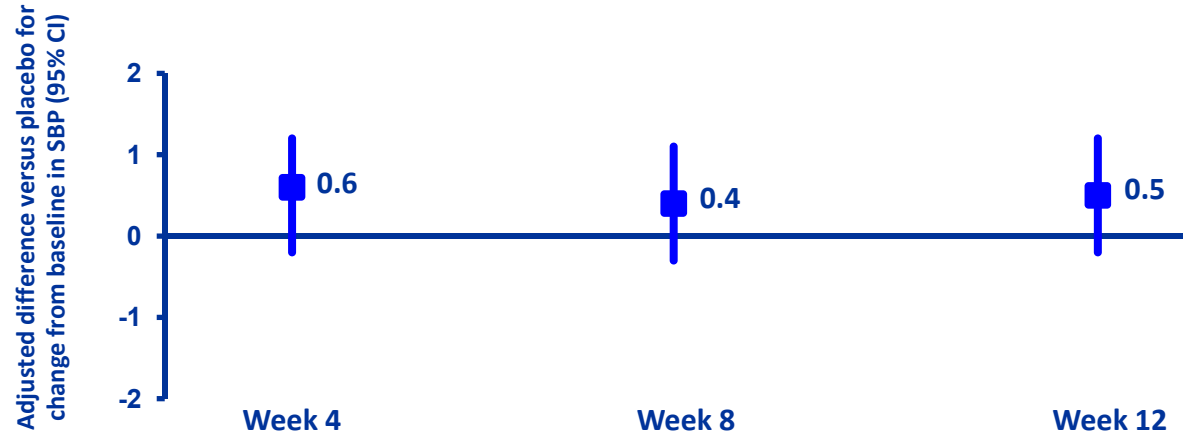
12-Week Phase 3 Studies
Adjusted Differences versus Placebo for Change from Baseline in SBP at Each Visit

SBP AM



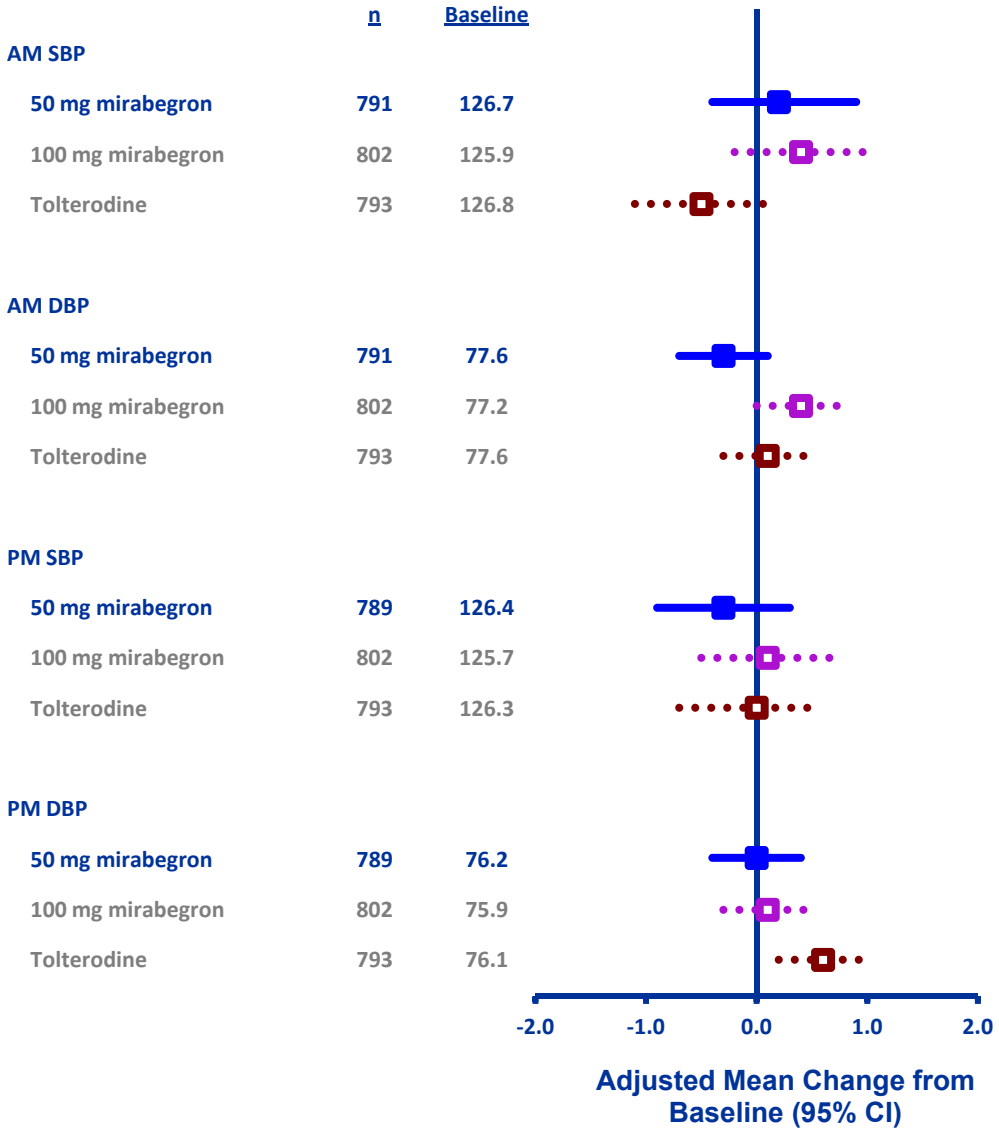
Mirabegron 50 mg

SBP PM



Source: CVRR 9.3.1.1

Long-Term (52-Week) Controlled Study
Change from Baseline to Final Visit SBP/DBP (Patient Diary)

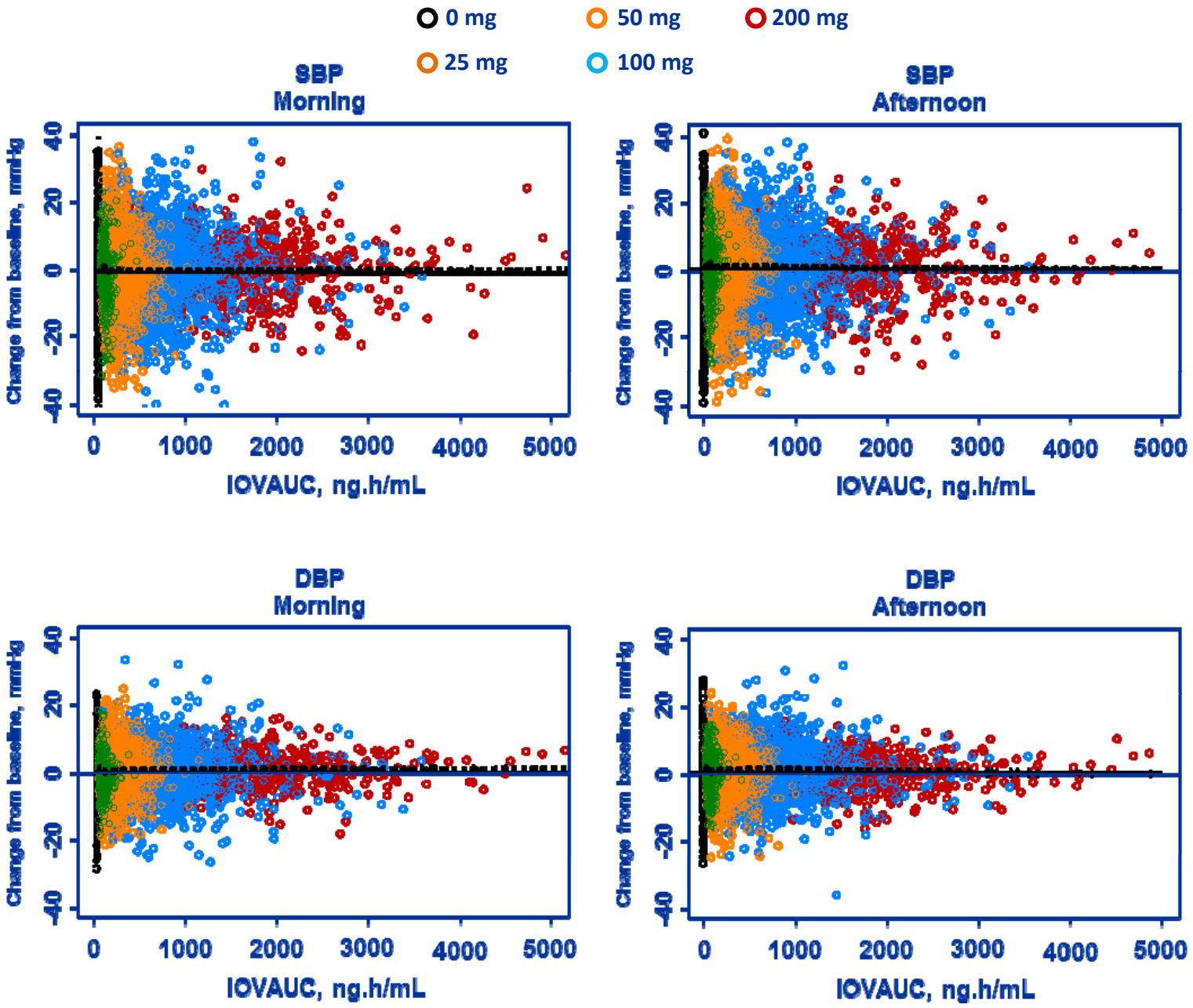


Categorical Analysis of Blood Pressure

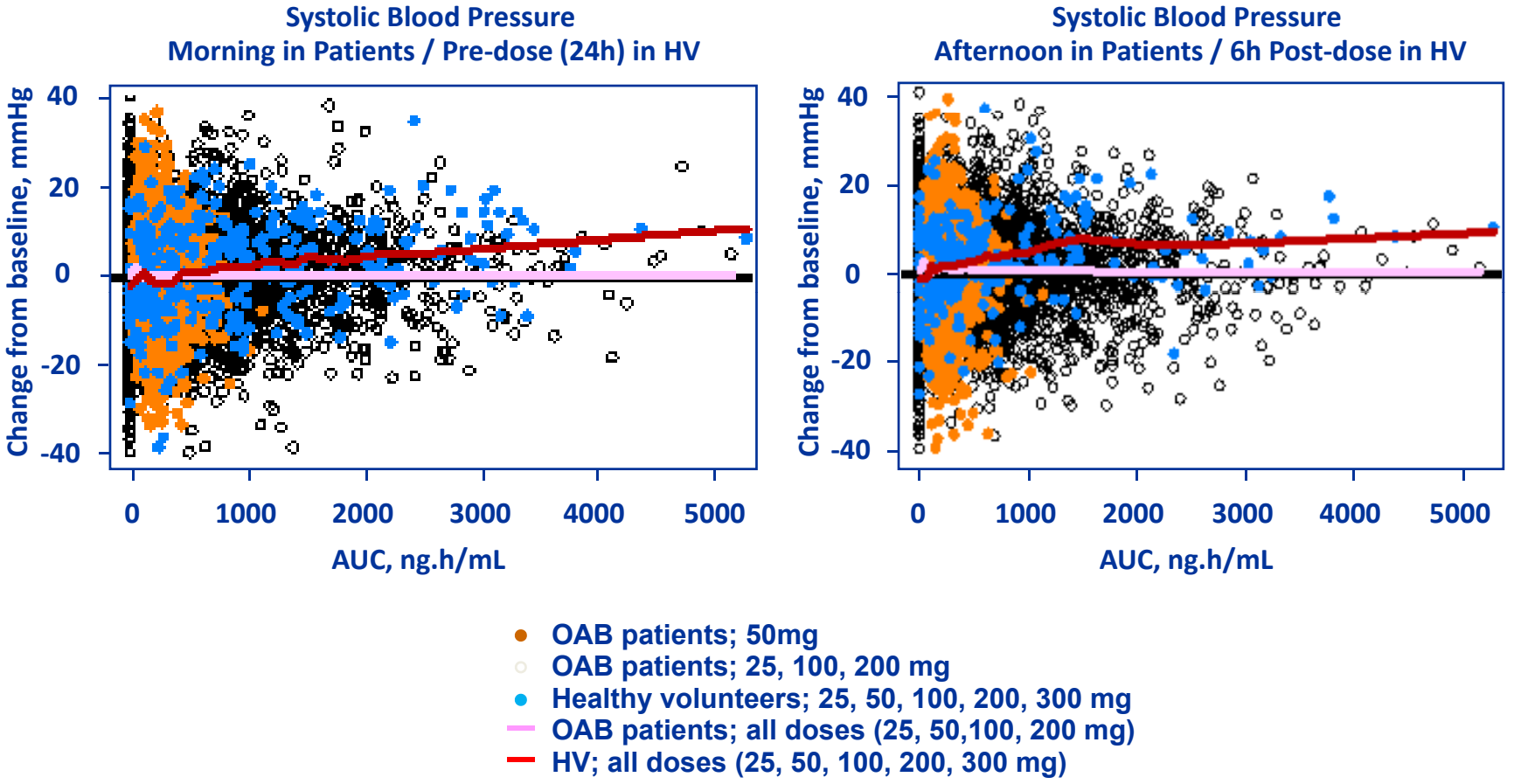
EU/NA 12-Week Phase 3 Studies

n (%) of Patients	Placebo N = 1380	Mirabegron 50 mg N = 1375
SBP AM	(n = 1196)	(n = 1202)
3 Consecutive Post-Baseline Visits		
Change from baseline ≥ 2 mm Hg	252 (21.1%)	255 (21.2%)
Change from baseline ≥ 5 mm Hg	136 (11.4%)	140 (11.6%)
Change from baseline ≥ 10 mm Hg	28 (2.3%)	35 (2.9%)
Change from baseline ≥ 15 mm Hg	8 (0.7%)	8 (0.7%)
Change from baseline ≥ 20 mm Hg	6 (0.5%)	5 (0.4%)
DBP AM	(n = 1196)	(n = 1202)
3 Consecutive Post-Baseline Visits		
Change from baseline ≥ 2 mm Hg	170 (14.2%)	219 (18.2%)
Change from baseline ≥ 5 mm Hg	62 (5.2%)	80 (6.7%)
Change from baseline ≥ 10 mm Hg	11 (0.9%)	10 (0.8%)
Change from baseline ≥ 15 mm Hg	0	1 (0.1%)

Regression Analysis of Exposure Response for Blood Pressure



Baseline Corrected SBP Versus AUC in Healthy Subjects & OAB Patients



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Hypertension Adverse Events Based on SPA Criteria: Prospectively Applied in Phase 3 Protocols

	12-Week Phase 3 Studies		Long-Term (52-Week) Controlled Study		
			Mirabegron		
	Placebo (n = 1380)	Mirabegron 50 mg (n = 1375)	50 mg (n = 812)	100 mg (n = 820)	Tolterodine (n = 812)
Patients with any hypertension AE	117 (8.5%)	120 (8.7%)	89 (11.0%)	83 (10.1%)	86 (10.6%)

1. Average SBP >140 mm Hg and/or average DBP >90 mm Hg at 2 consecutive post-baseline visits for patients normotensive at baseline
2. Average increase in SBP >20 mm Hg and/or average increase in DBP >10 mm Hg at 2 consecutive post-baseline visits for patients hypertensive at baseline
3. Initiation of treatment for hypertension or an increase in dose of anti-hypertensive medication

Conclusions

- Effects of adrenergic and anti-muscarinic drugs on vital signs are larger in young adults typically used in phase 1 and clinical pharmacology studies than in older patients.
- To characterize the effects of such drugs in patients it is better to make the measurements in patients rather than in younger healthy subjects, or if healthy subjects are used age-match them to the patients.

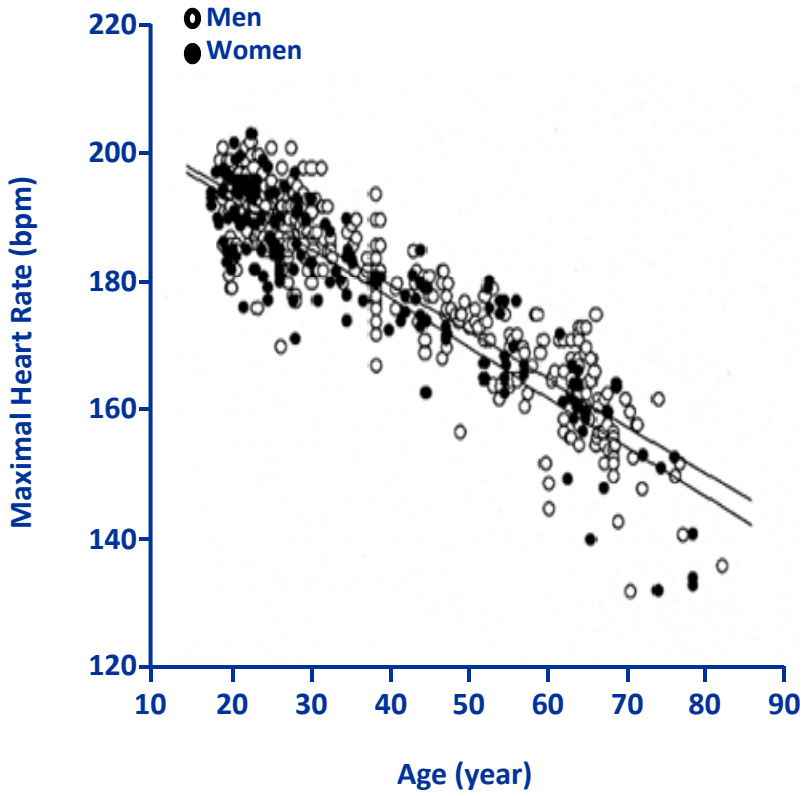
Acknowledgements

- Astellas colleagues: Mike Allen, Mary Beth Blauwet, Paul de Koning, Leticia Delgado-Herrera, William Fitzsimmons, Marcel van Gelderen, Virginie Kerbusch-Herben, Salim Mujais, Steve Ryder
- Reviewers at PMDA, FDA and EMA with whom we interacted during review of the NDA for mirabegron.

Back-up

Phase 1 (Healthy Volunteers) Not Representative of Phase 2/3 (OAB Patients) Vital Sign Measurements

1A. Maximum heart rate decreases with age



1B. Adrenergic responsiveness to Beta-agonist decreases with age

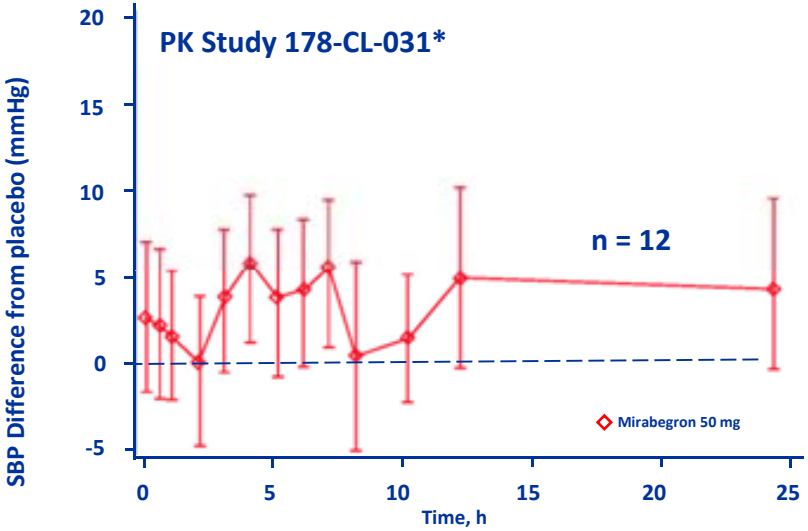
- Cardiovascular responses to isoproterenol were reduced in healthy older men compared to younger men: heart rate, systolic and diastolic blood pressures

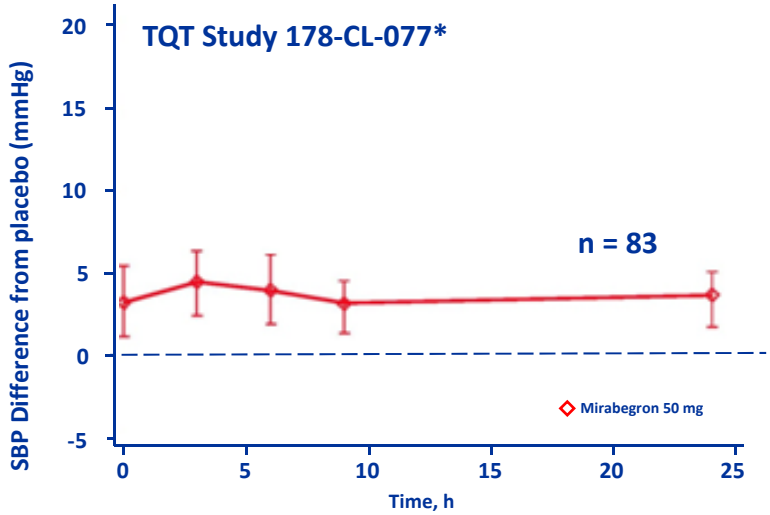
Tanaka, et al, 2001; Stratton et al. 1992; Kitzman and Taffet 2009

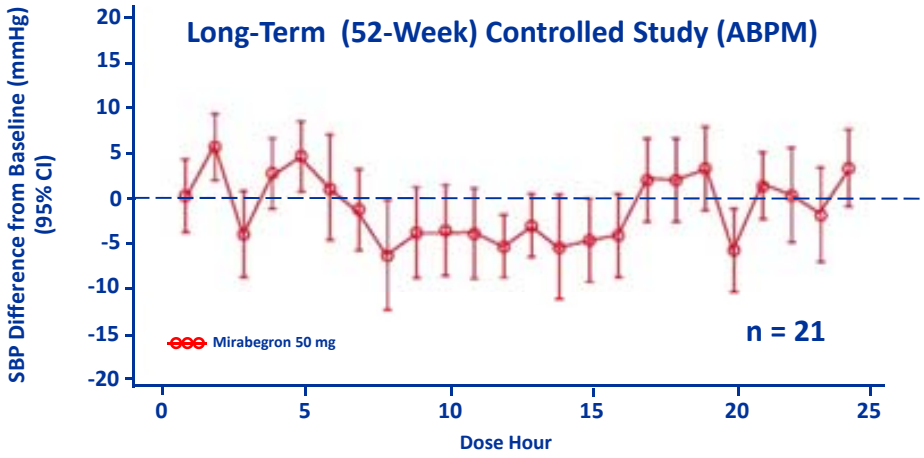
Phase 1 (Healthy Volunteers) Not Representative of Phase 2/3 (OAB Patients) Vital Sign Measurements

Steady Diurnal Pharmacodynamic Effect of Mirabegron at Steady State

- Little diurnal fluctuation in vital sign pharmacodynamic effect of mirabegron

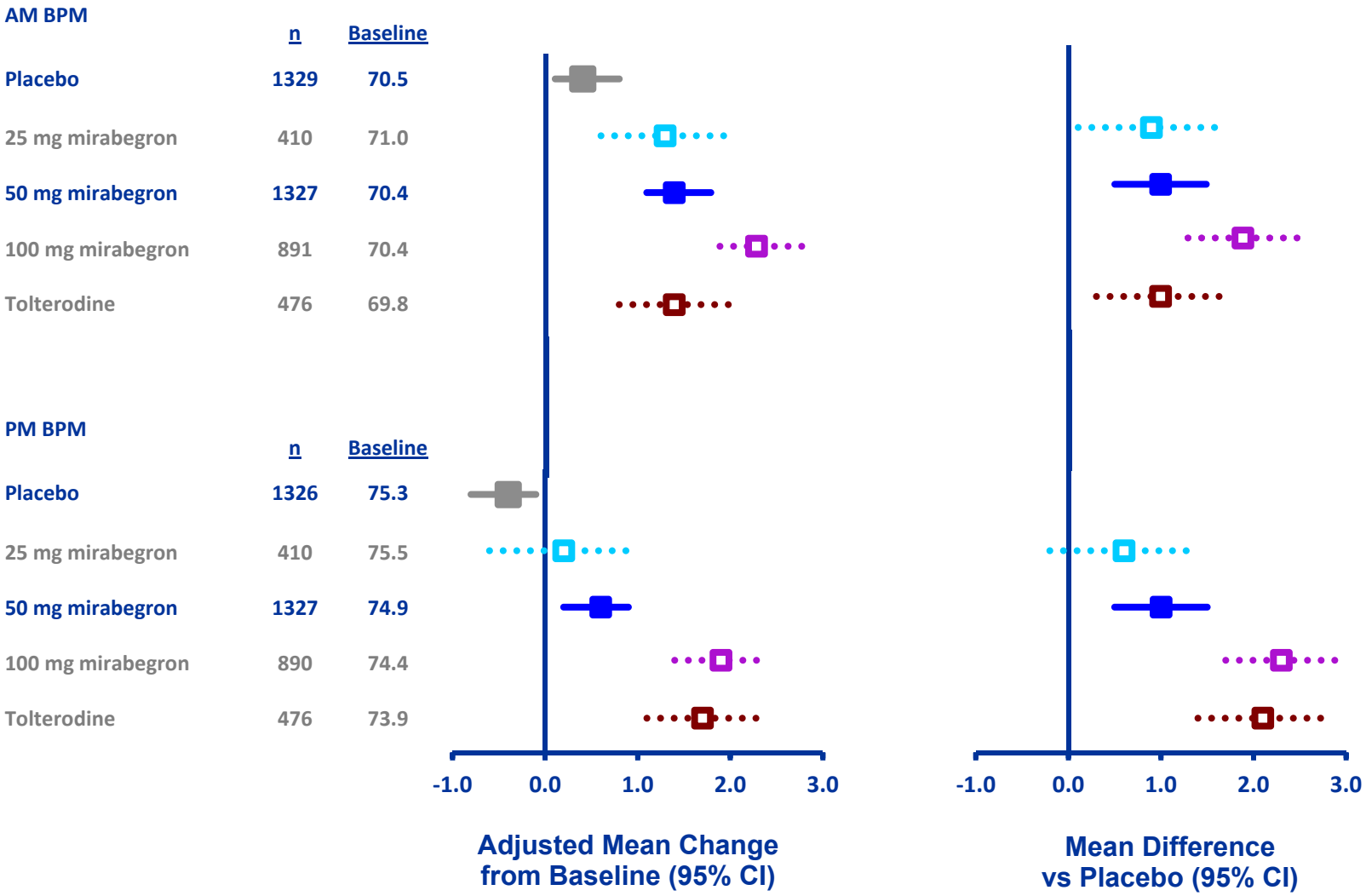




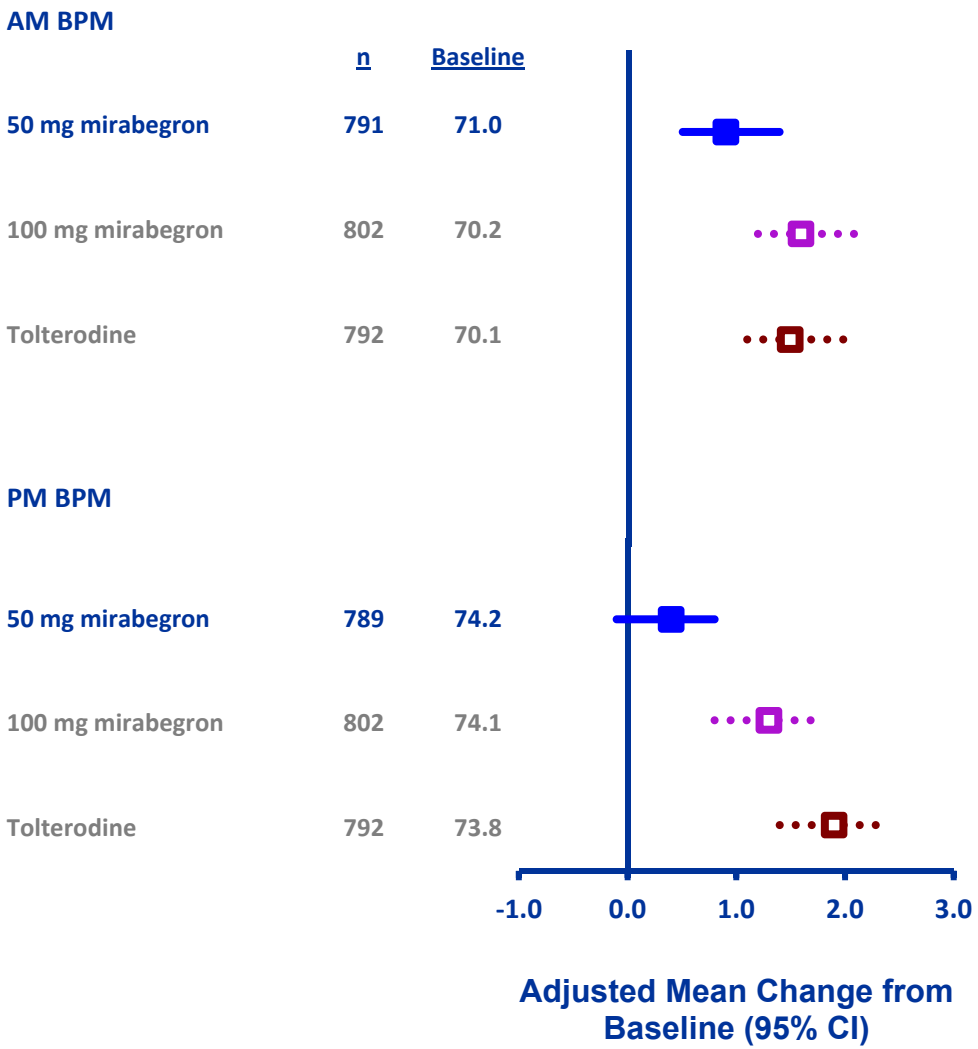


* Adapted from the FDA Background Document Dated 16 March 2012

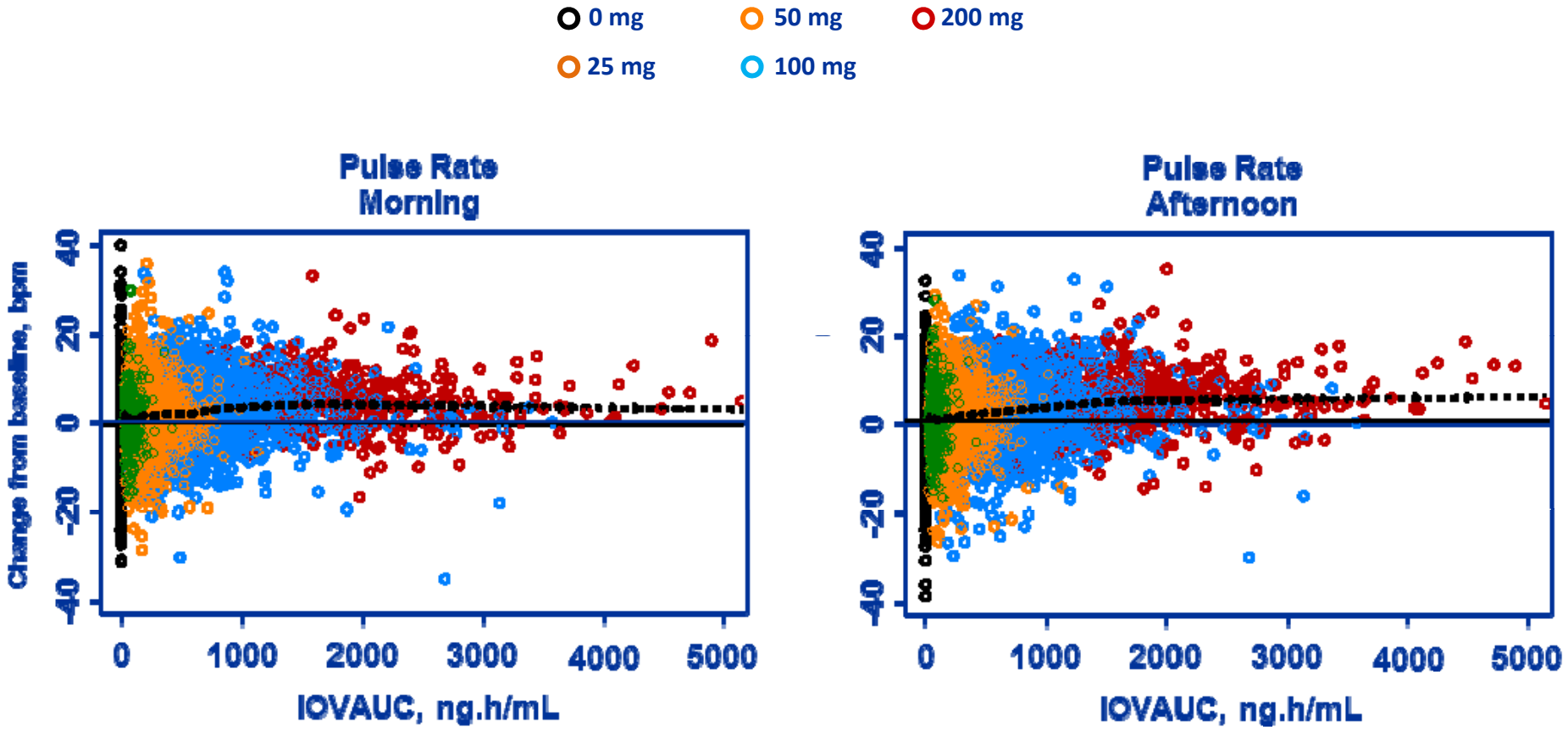
12-Week Phase 3 Studies
Change from Baseline to Final Visit Pulse (Patient Diary)



Long-Term (52-Week) Controlled Study
Change from Baseline to Final Visit Pulse (Patient Diary)



Regression Analysis of Exposure Response for Pulse



Categorical Analysis of Pulse

12-Week Phase 3 Studies

n (%) of Patients	Placebo N = 1380	Mirabegron 50 mg N = 1375
Pulse AM	(n =1196)	(n = 1202)
3 Consecutive Post-Baseline Visits		
Change from baseline ≥ 2 BPM	171 (14.3%)	247 (20.5%)
Change from baseline ≥ 5 BPM	77 (6.4%)	87 (7.2%)
Change from baseline ≥ 10 BPM	13 (1.1%)	13 (1.1%)
Change from baseline ≥ 15 BPM	4 (0.3%)	2 (0.2%)

Long-term (52-Week) Controlled Study

n (%) of Patients	Mirabegron 50 mg N = 812	Mirabegron 100 mg N = 820	Tolterodine N = 812
Pulse AM	(n = 686)	(n = 704)	(n = 683)
3 Consecutive Post-Baseline Visits			
Change from baseline ≥ 2 BPM	179 (26.1%)	268 (38.1%)	217 (31.8%)
Change from baseline ≥ 5 BPM	69 (10.1%)	112 (15.9%)	87 (12.7%)
Change from baseline ≥ 10 BPM	14 (2.0%)	20 (2.8%)	19 (2.8%)
Change from baseline ≥ 15 BPM	6 (0.9%)	1 (0.1%)	2 (0.3%)

Tachycardia (AE and Pulse)

	12-Week Phase 3 Studies		Long-term (52-Week) Controlled Study		
		Mirabegron	Mirabegron		
n (%) of Patients	Placebo (n = 1380)	50 mg (n = 1375)	50 mg (n = 812)	100 mg (n = 820)	Tolterodine (n = 812)
Any occurrence of tachycardia	43 (3.1%)	52 (3.8%)	25 (3.1%)	49 (6.0%)	53 (6.5%)
Tachycardia as AE	9 (0.7%)	18 (1.3%)	10 (1.2%)	19 (2.3%)	26 (3.2%)
Tachycardia as pulse ≥ 100 bpm	36 (2.6%)	39 (2.8%)	19 (2.3%)	35 (4.3%)	32 (3.9%)
Tachycardia as AE and pulse ≥ 100 bpm	2 (0.1%)	5 (0.4%)	4 (0.5%)	5 (0.6%)	5 (0.6%)