

Mirabegron

**Reproductive and Urologic Drugs
Advisory Committee
April 5th, 2012**

Astellas Pharma Global Development

Agenda

Steven Ryder, MD FACP

Introduction

**Prof. Christopher Chapple MD,
FRCS (Urol)**

Medical Need

Leticia Delgado-Herrera, RPh MS

Overview and Efficacy

William Fitzsimmons, PharmD MS

Safety

Steven Ryder, MD FACP

Benefit and Managing the Risk

Attending Experts

**Christopher Chapple, BSc, MD,
FRCS (Urol), FEBU**

Consultant Urological Surgeon,
Royal Hallamshire Hospital
Honorary Senior Lecturer of Urology, University
of Sheffield

Willis Maddrey, MD

Professor, Internal Medicine
Adelyn & Edmund Hoffman Distinguished Chair,
Medical Science
University of Texas, Southwestern Medical
Center

Gary Koch, PhD

Professor of Biostatistics
School of Public Health
Director, Biometrics Consulting Lab
University of North Carolina

Michael Weber, MD

Professor of Medicine
State University of New York
Downstate College of Medicine
Chair, ASH Hypertension Specialists Program

Neil J Korman, MD PhD

Professor, Department of Dermatology
Case Western Reserve University
Medical School
University Hospitals- Case Medical Center

William B. White, MD

Professor of Medicine
Chief, Division of Hypertension and Clinical
Pharmacology
Calhoun Cardiology Center
University of Connecticut School of Medicine

Peter Kowey, MD

Chief, Division of Cardiovascular Diseases,
Lankenau Hospital and
Professor of Medicine and Clinical
Pharmacology
Jefferson Medical College
Thomas Jefferson University

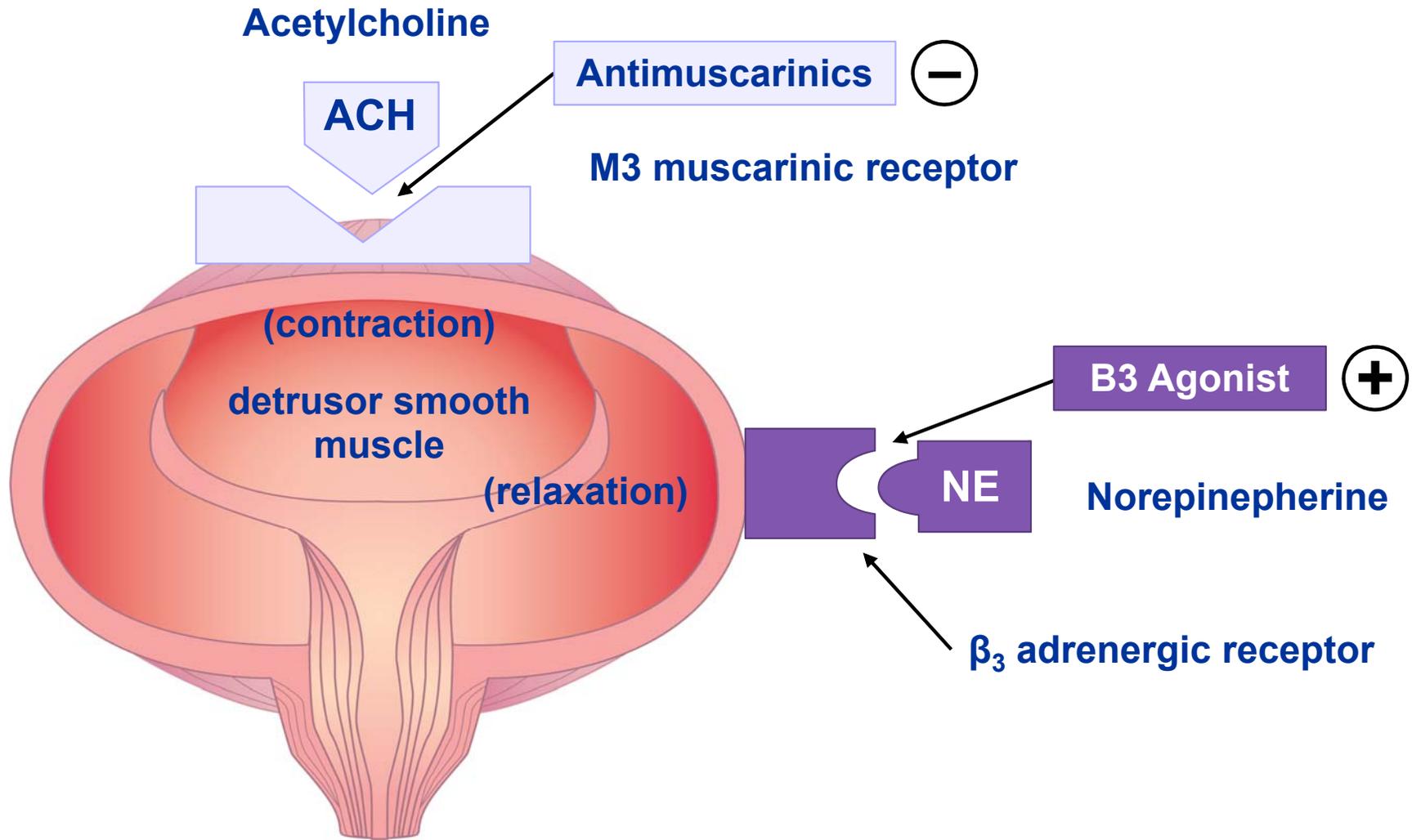
Gary Williams, MD

Professor of Pathology
Director of Environmental Pathology
and Toxicology
New York Medical College

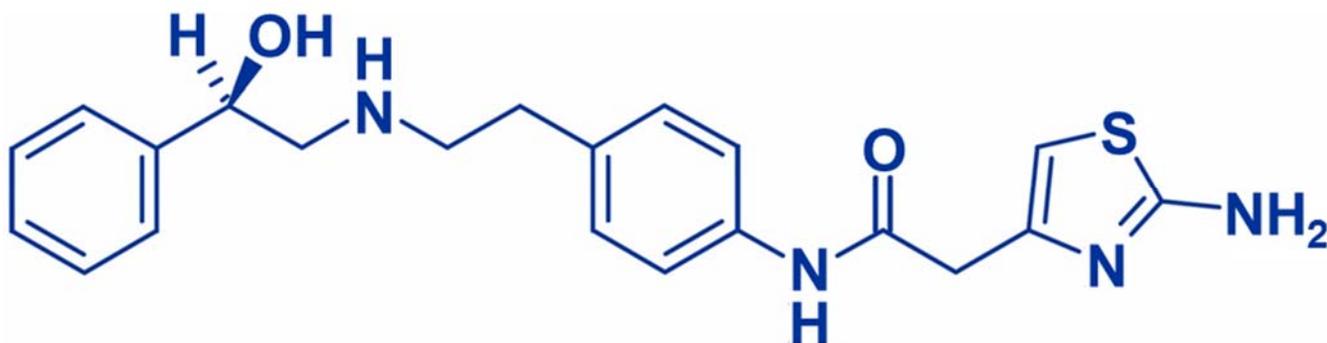
Overactive Bladder (OAB)

- **Defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia**
- **Overall estimated prevalence of 12-17% in the US and Europe, with the prevalence increasing with age**
- **Burden of disease for OAB is often noted to be underestimated due to reluctance of OAB patients to seek medical attention**
- **Significant impact on health-related quality of life – decreased work productivity, ability to socialize and fully participate in activities of life, altered sexuality, sleep disturbance and decreased emotional well-being**
- **The pharmacotherapeutic treatment options indicated for OAB are muscarinic receptor antagonists; agents that also affect the salivary gland, intestine and eye, resulting in side effects such as dry mouth, constipation and blurred vision**

Neurologic Innervation and Control of Bladder Musculature



Mirabegron

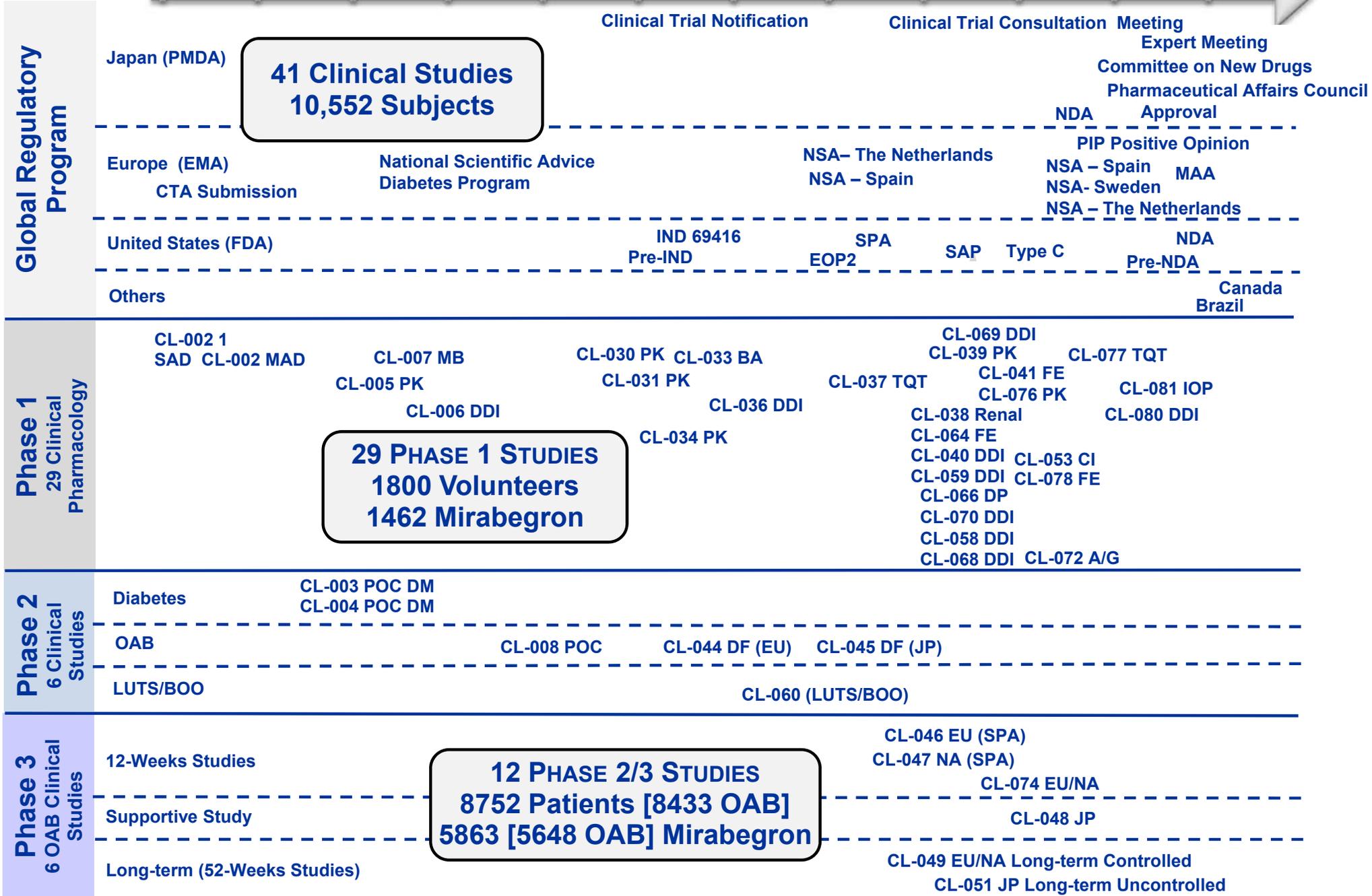


Affinity of Mirabegron for Human β -Adrenoceptor Subtypes

| K _i (nmol/L) | | |
|-------------------------|----------------|---------------|
| β_1 | β_2 | β_3 |
| 4200 \pm 900 | 1300 \pm 300 | 40 \pm 20.2 |

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

Mirabegron Development Program



Mirabegron Clinical Program

- **Nonclinical proof of principle that mirabegron enhances urine storage by stimulating β 3-adrenoceptors in the bladder**
- **Consistently improved urinary frequency and urge incontinence in OAB controlled clinical trials**
- **Safety and toleration established in a global program involving 5648 OAB patients, with 622 receiving mirabegron for at least 1 year**
- **Well tolerated with:**
 - **A frequency of typical anticholinergic side effects (e.g. dry mouth) similar to placebo**
 - **A low incidence of urinary tract infection (2.9% compared with 1.8% placebo) and tachycardia (1.2% compared with 0.6% placebo); both comparable to active control**
 - **An ~1 bpm mean increase in pulse with clinically relevant categorical changes in pulse comparable to active control**
 - **An ~0.4-0.6 mmHg mean increase in BP with clinically relevant categorical changes and reports of hypertension comparable to placebo**
- **Mirabegron, at a recommended dose of 50 mg orally once daily, is safe, effective, and well tolerated for the treatment of OAB**

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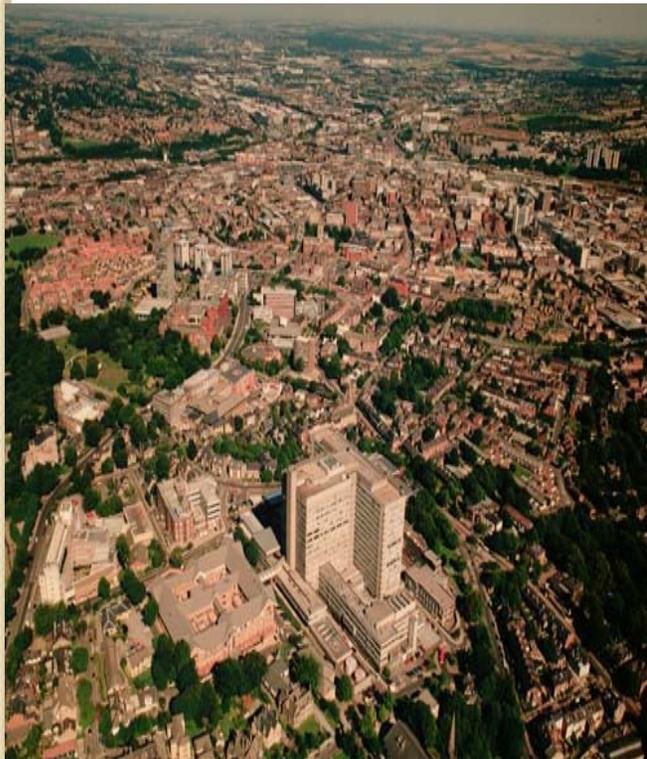
Safety

Steven Ryder, MD FACP

Benefit and Managing the Risk

Contemporary Medical Therapy for Overactive Bladder (OAB)

Christopher Chapple MD FRCS(Urol)
Consultant Urological Surgeon
Sheffield Teaching Hospitals
NHS Foundation Trust
UK



Sheffield Teaching Hospitals 
NHS Trust

 *Sheffield*
Hallam University

Disclosures

- I have acted as a consultant/or researcher to the following organizations:
 - Astellas
 - GSK
 - Pfizer
 - Novartis
 - Recordati
 - Xention
 - Tanabe
 - Ono

Synopsis

- OAB is a clinical syndrome with significant impacts due to 'burden of disease' on QOL.
- OAB is amenable to pharmacologic interventions.
- Current pharmacotherapy for OAB has significant limitations:
 - efficacy
 - tolerability
- Summary – why develop 'new therapy'?

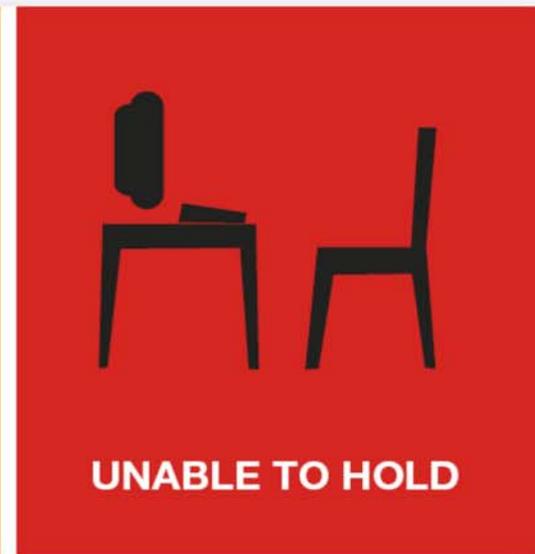
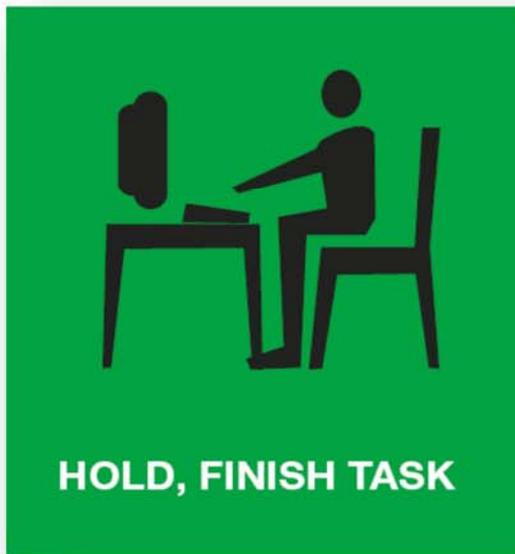
Classification of Lower Urinary Tract Symptoms (LUTS)

| Storage | Voiding | Post-micturition |
|---|--|---|
| <ul style="list-style-type: none">• Frequency• Urgency• Nocturia• Incontinence | <ul style="list-style-type: none">• Slow stream• Splitting or spraying• Intermittency• Hesitancy• Straining• Terminal dribble | <ul style="list-style-type: none">• Post-micturition dribble• Feeling of incomplete emptying |

Overactive Bladder

Urgency Definition

Urgency is an *abnormal, or inappropriate* sudden, compelling desire to pass urine, which is *very* difficult *or impossible* to defer *for fear of leakage*



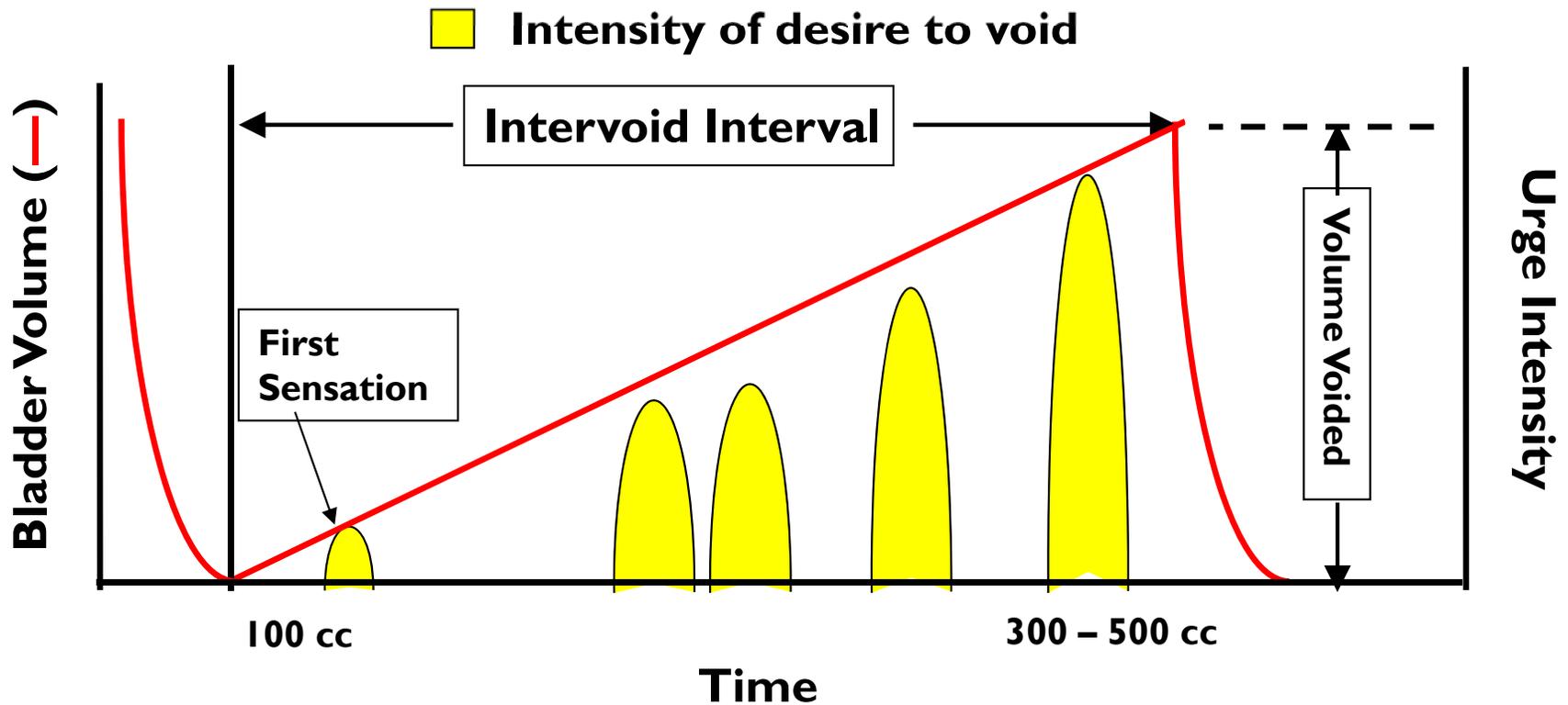
Abrams P et al. *Neurourol Urodyn*. 2006; 25: 293-294

Cardozo L et al. *BJU Int*. 2005; 95:591-596



MICTURITION CYCLE AND OAB

Desire to Void and the Normal Micturition Process

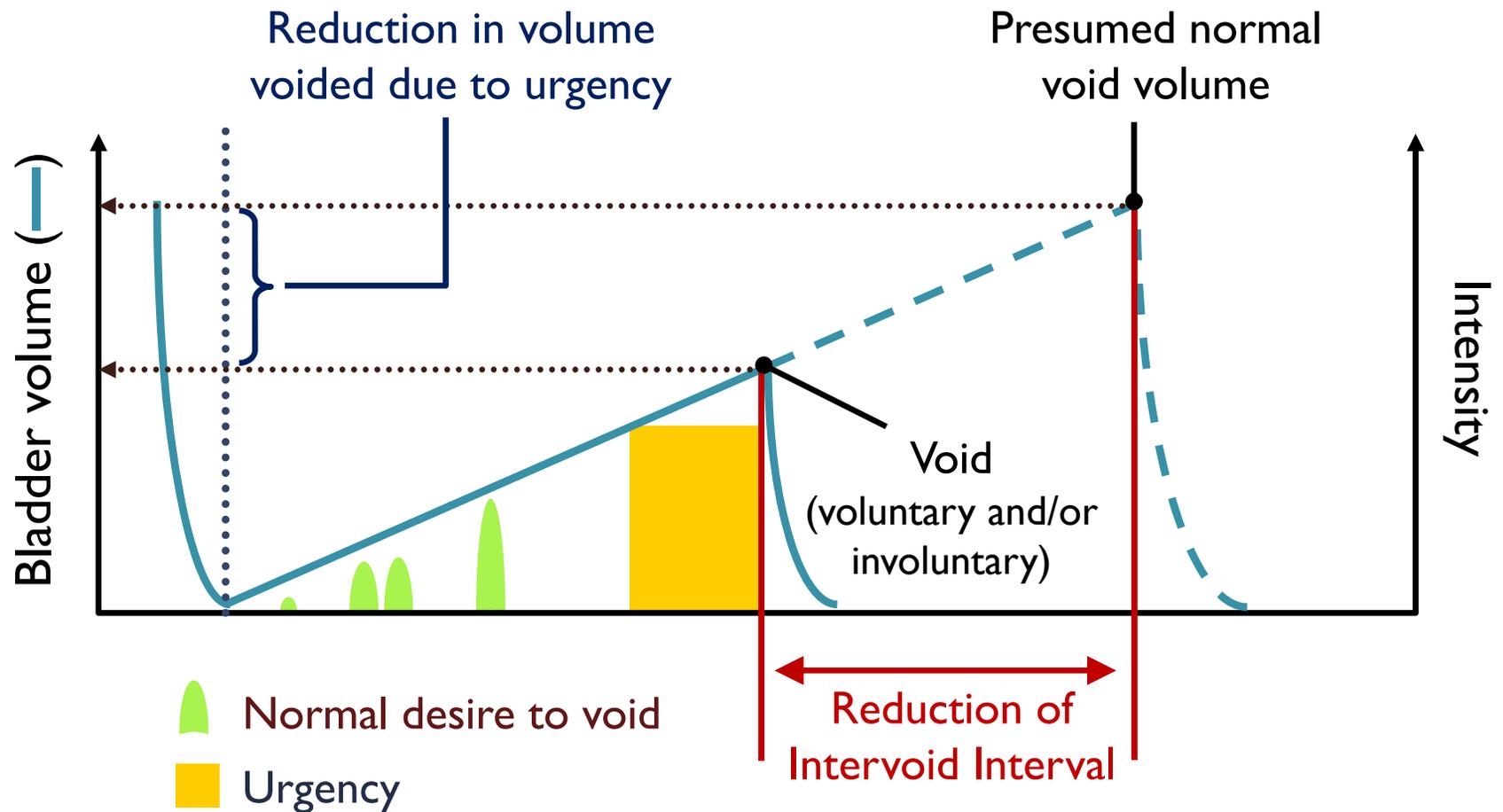


Urge: A physiological desire to void

- Gradual onset
- Increases as a function of bladder volume
- Can usually be deferred with appropriate strategies

The Micturition Cycle in OAB

Effect of Urgency





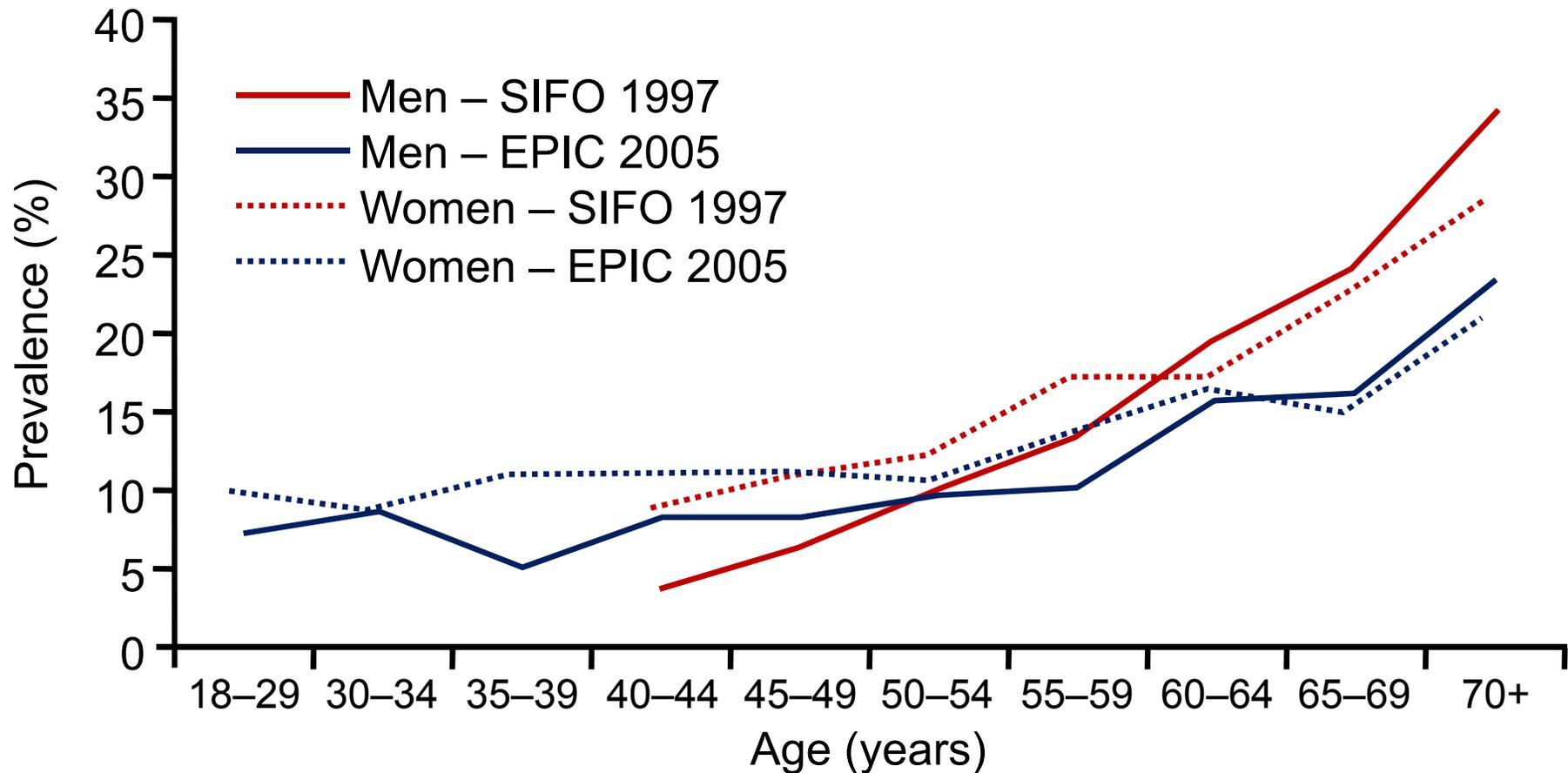




PREVALENCE OF OAB

Epidemiology of OAB

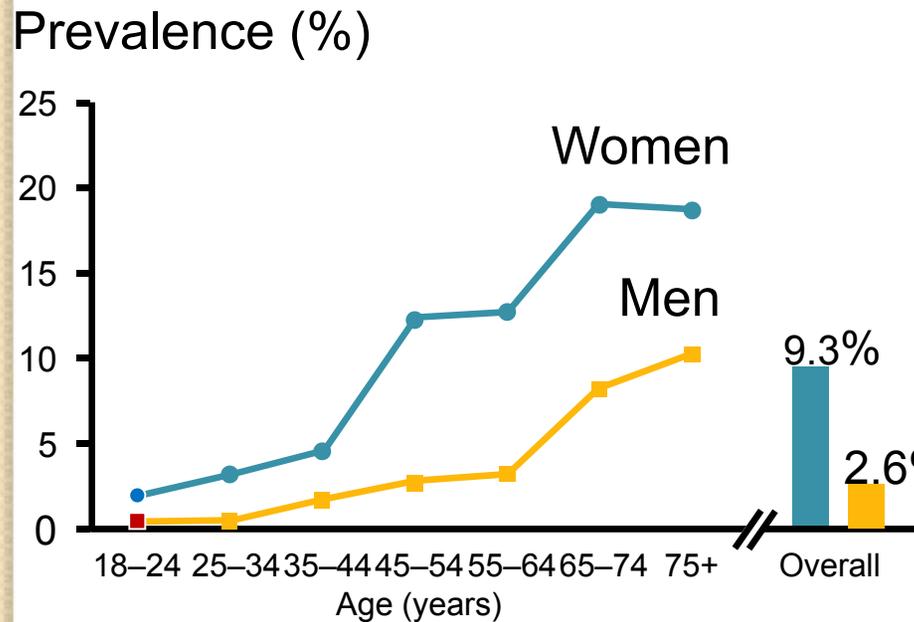
Comparison of data from the SIFO Study 1997
and the EPIC Study 2005



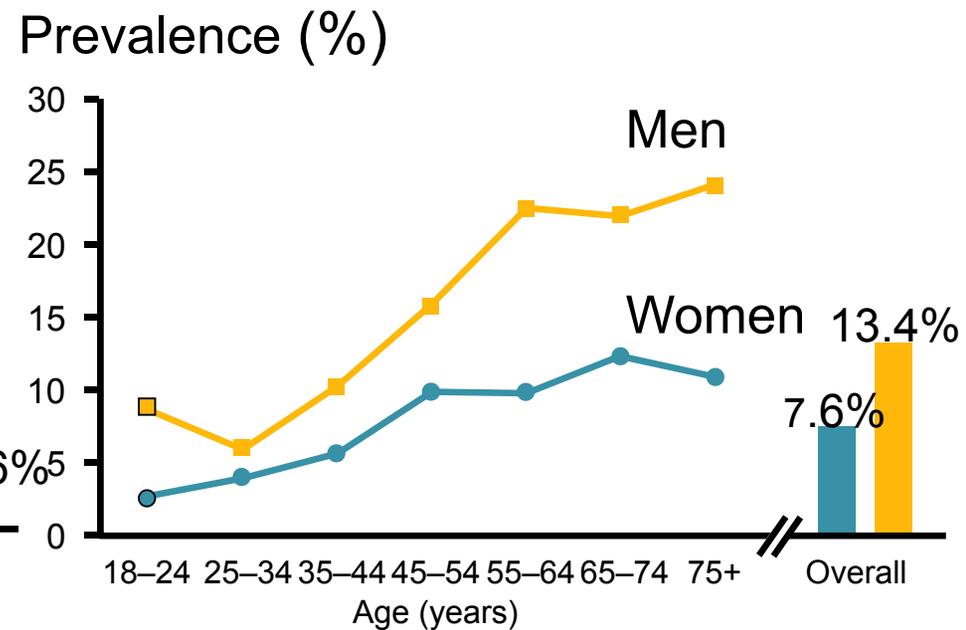
Milsom I, et al. BJU Int 2001;87:760-6
Irwin DE, et al. Eur Urol 2006;50:1306-14

Prevalence of OAB by Age - US

With incontinence



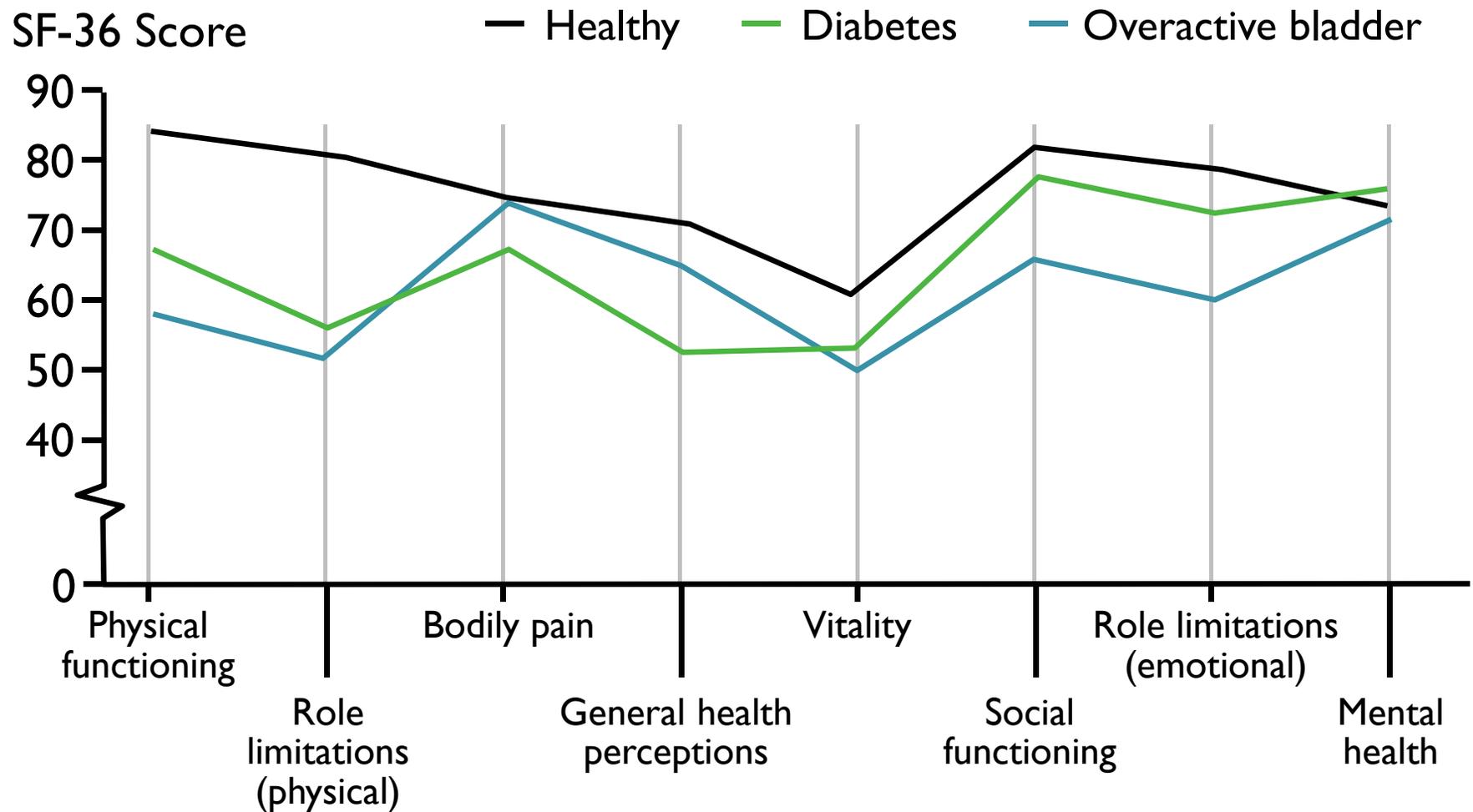
Without incontinence





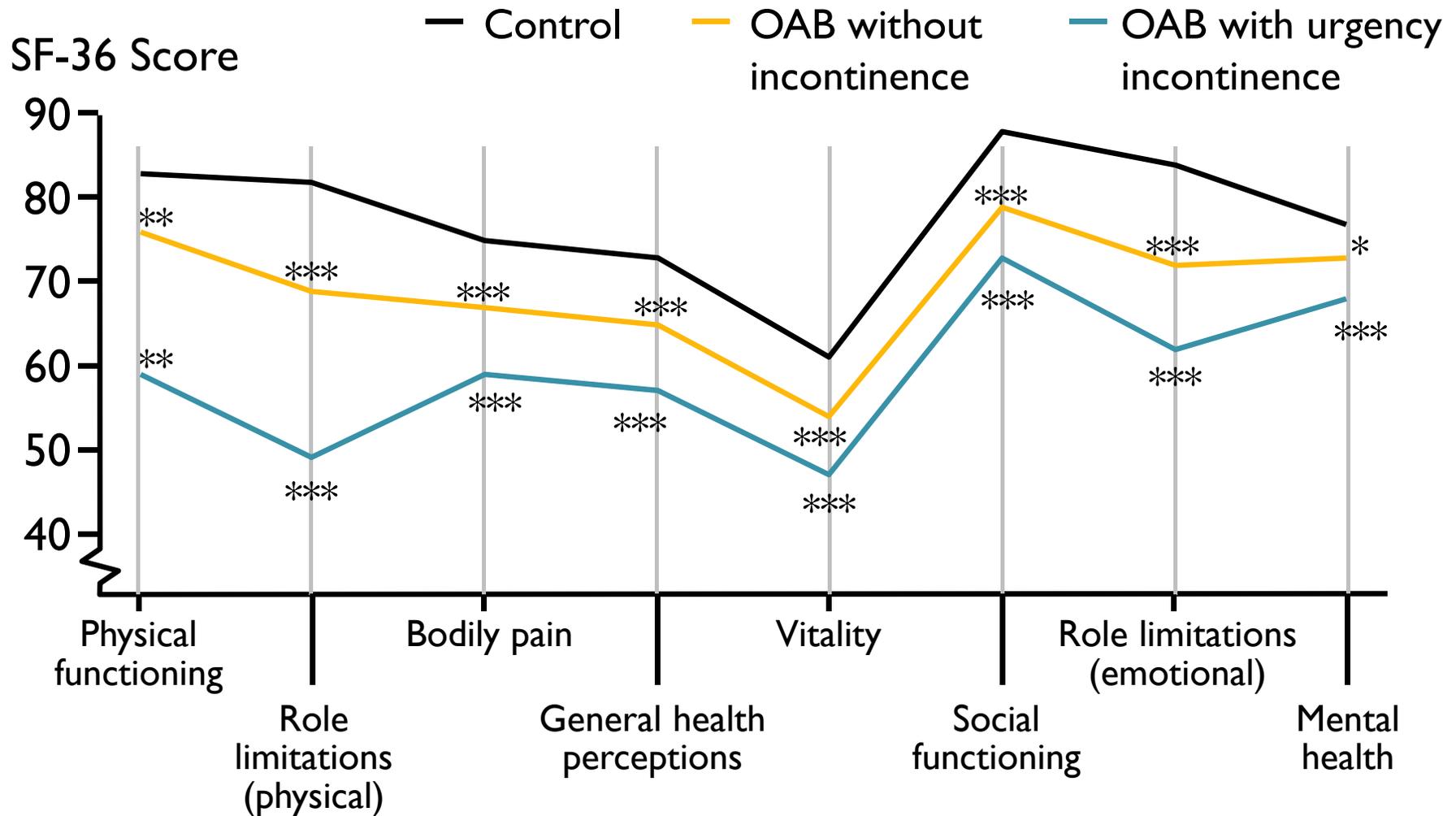
**OAB AS A SOURCE OF
MORBIDITY AND THE BURDEN
OF DISEASE IMPACT ON QOL**

Impact of OAB and Diabetes Disease Burden on QoL - SF36



Komaroff AL, et al. Am J Med 1996;101:281-90
Abrams & Wein. The Overactive Bladder 1998

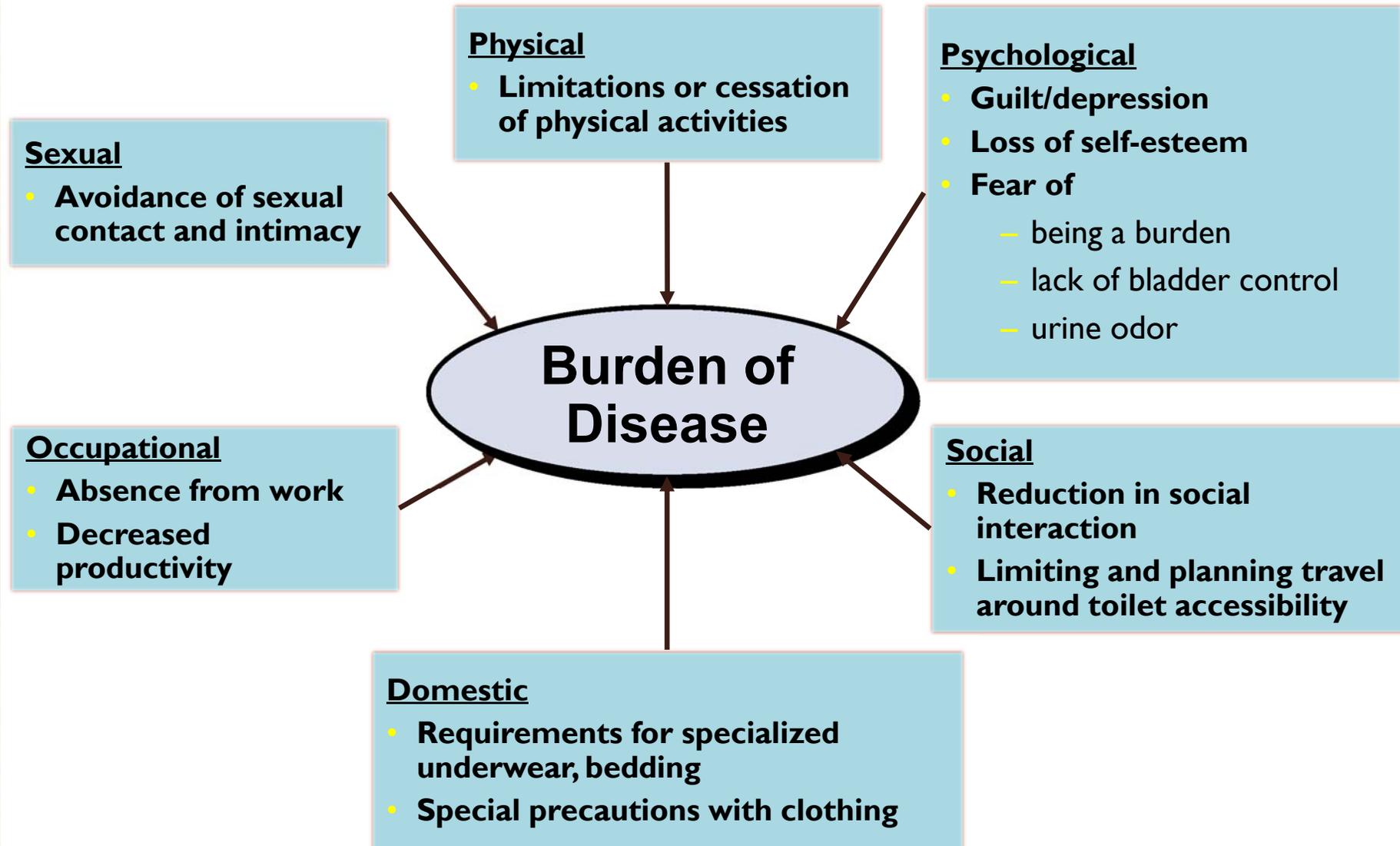
OAB wet has a greater burden of disease impact on QoL than OAB dry



*p<0.01; **p<0.001; ***p<0.0001 vs control

Stewart K, et al. J Am Pharm Assoc. 2002;42:469–78

Impact of OAB Disease Burden on Quality of Life



The patient's perspective

- **Loss of control and self-esteem**
 - incontinence leads to loss of control of personal and social life.
 - feelings of low self esteem are particularly prevalent in patients aged <70 years¹
- **Depression**
 - Subjects with OAB score significantly lower than controls on the CES-D depression scale²
- **Avoidance of activities**
 - effect of urgency incontinence is strongly correlated with frequency and nocturia¹
- **Sexual intimacy**
 - Approximately 25% of women with urinary incontinence reported impaired sexual function²
 - Incontinence can lead to feelings of being unattractive and embarrassed
 - Many women do not report this problem and may avoid sexual intimacy because of fear of possible urinary leakage during sex

1. Brown JS, et al. J Women's Health 1998;7:1263–9
2. Stewart WF, et al. World J Urol 2003;20:327–36

1. Brown JS, et al. J Women's Health 1998;7:1263–9
2. Temml C, et al. Neurourol Urodyn 2000;19:259–71

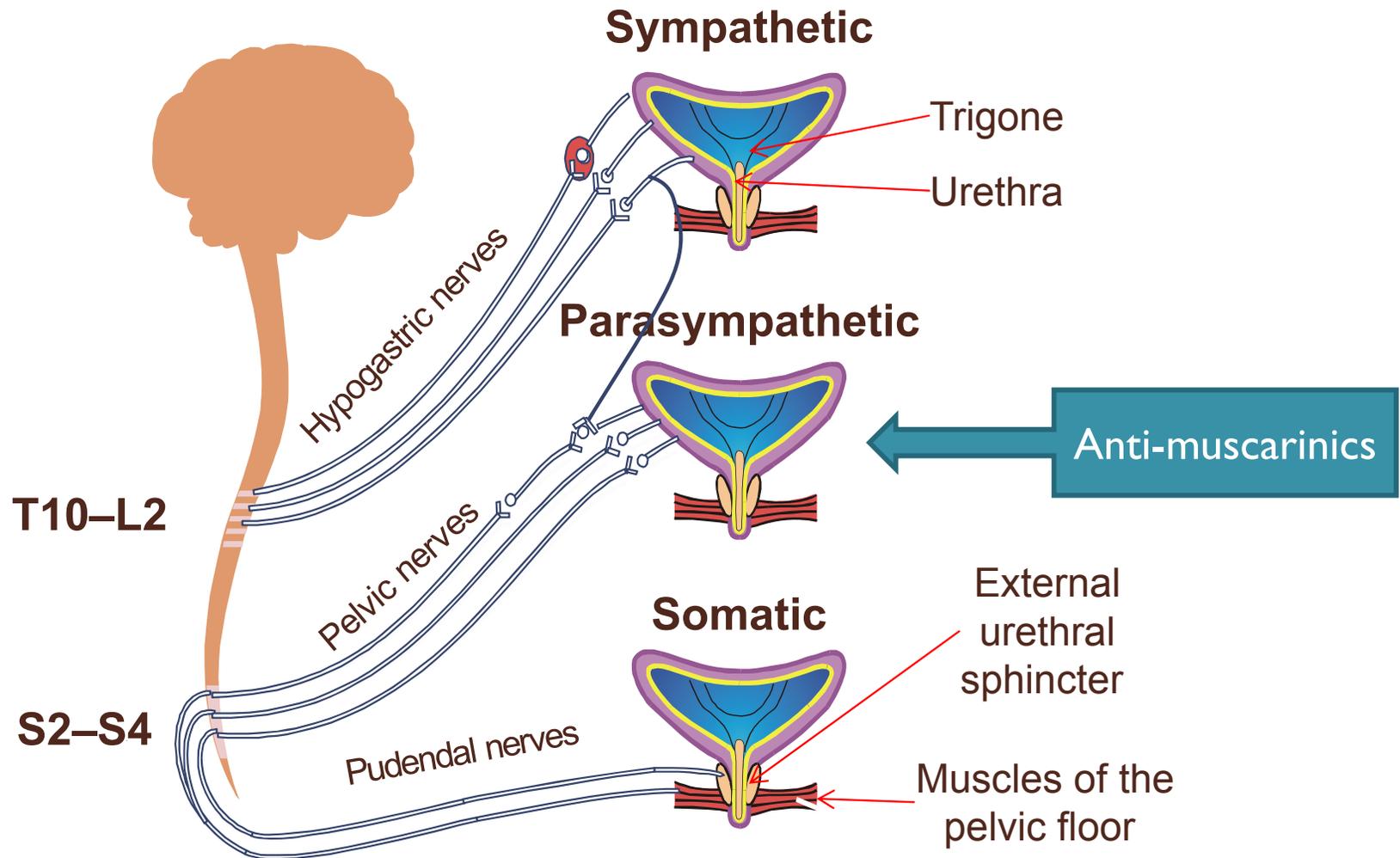


OAB THERAPY

Therapeutic Interventions for OAB

- **Behavioural therapy**
 - Bladder retraining
 - Pelvic floor training exercises
 - Others
 - Biofeedback
 - Electrostimulation
- **Containment**
 - Pads
 - Intermittent self-catheterisation
- **Pharmacotherapy**
 - Antimuscarinic agents
 - Imipramine
 - Oestrogens
- **Invasive**
 - Botox injection
 - Electrical stimulation of the sacral nerve / posterior tibial nerve
 - Surgery (augmentation cystoplasty)

Lower Urinary Tract Innervation



Activation of the parasympathetic pathway results in detrusor muscle contraction and micturition.

Activation of the sympathetic pathway inhibits detrusor contraction and contracts the bladder outlet.

Placebo effect size

Incontinence episodes per day

12 studies 1847 patients

The mean weighted change +/- standard deviation (STDEV) was -1.12 ± 0.59 (P=0.001)

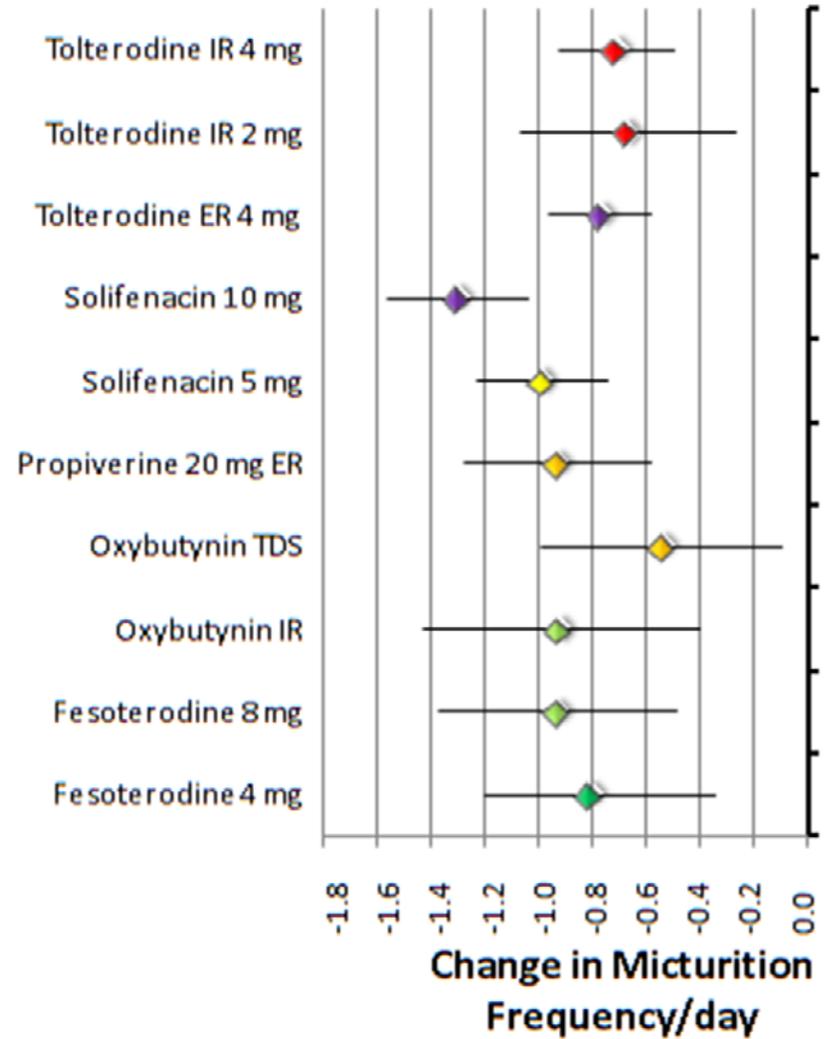
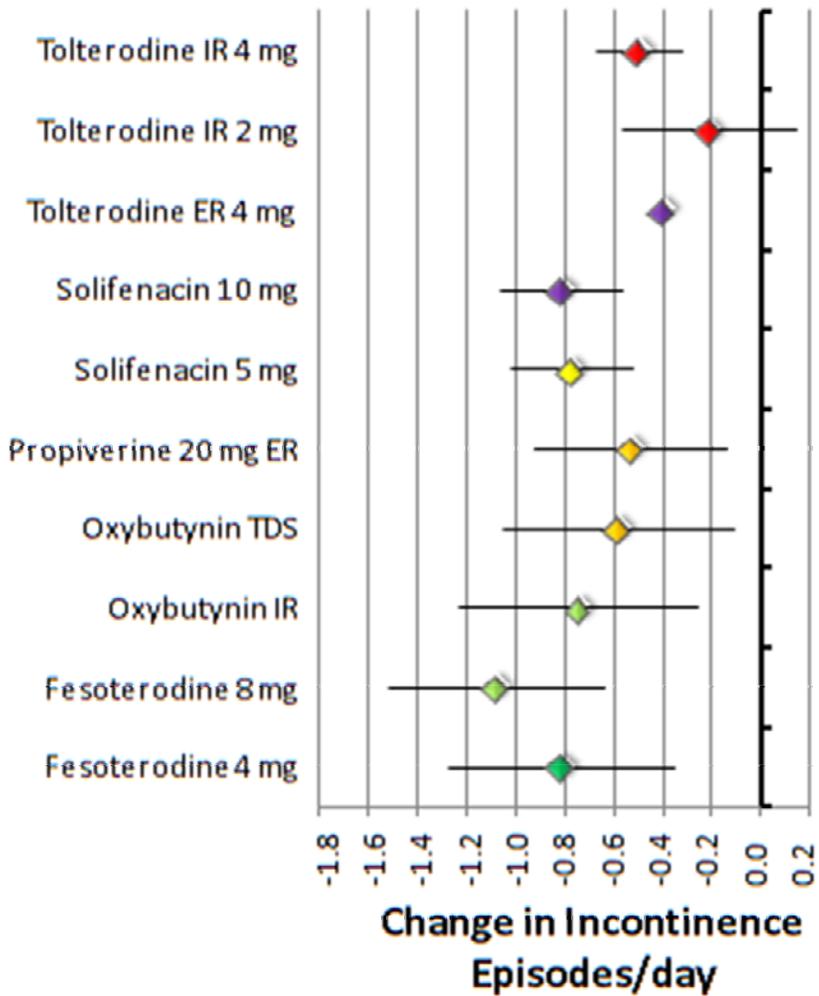
Micturition episodes per day

11 studies 1938 patients

The mean weighted change +/- standard deviation (STDEV) was -1.04 ± 0.8 (P=0.0016)

Mangera A, Chapple CR et al
Nat Rev Urol. 2011 Jul 5;8(9):495-503.

Efficacy of Antimuscarinics



Muscarinic Receptor Distribution and Potential Adverse Events with Antagonists

Tissue Distribution

Brain
 M_1 - M_5

Eye
 M_3

Salivary glands
 M_3

Heart
 M_2 - M_3

Intestine
 M_3

Bladder
 M_2 - M_3

Potential AEs

Decreased cognitive function
Short-term memory loss
Altered sleep cycle

Decreased lacrimation
Decreased accommodation

Xerostomia
(dry mouth)

Tachycardia

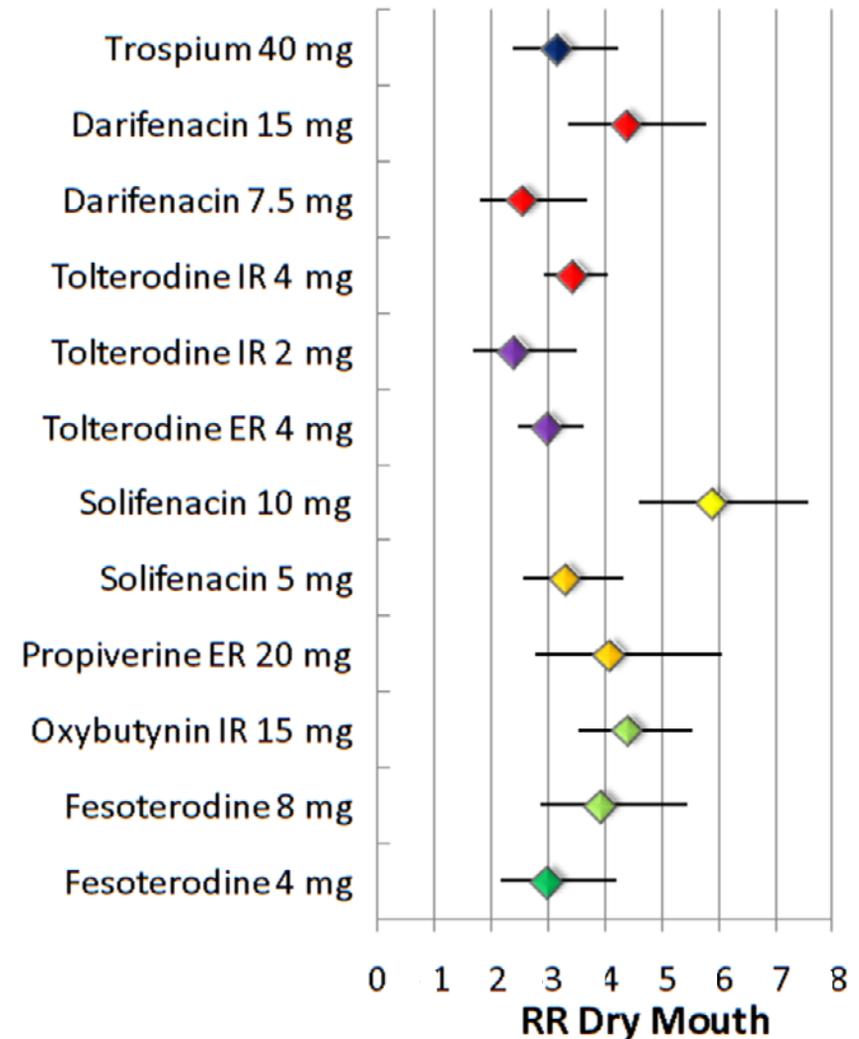
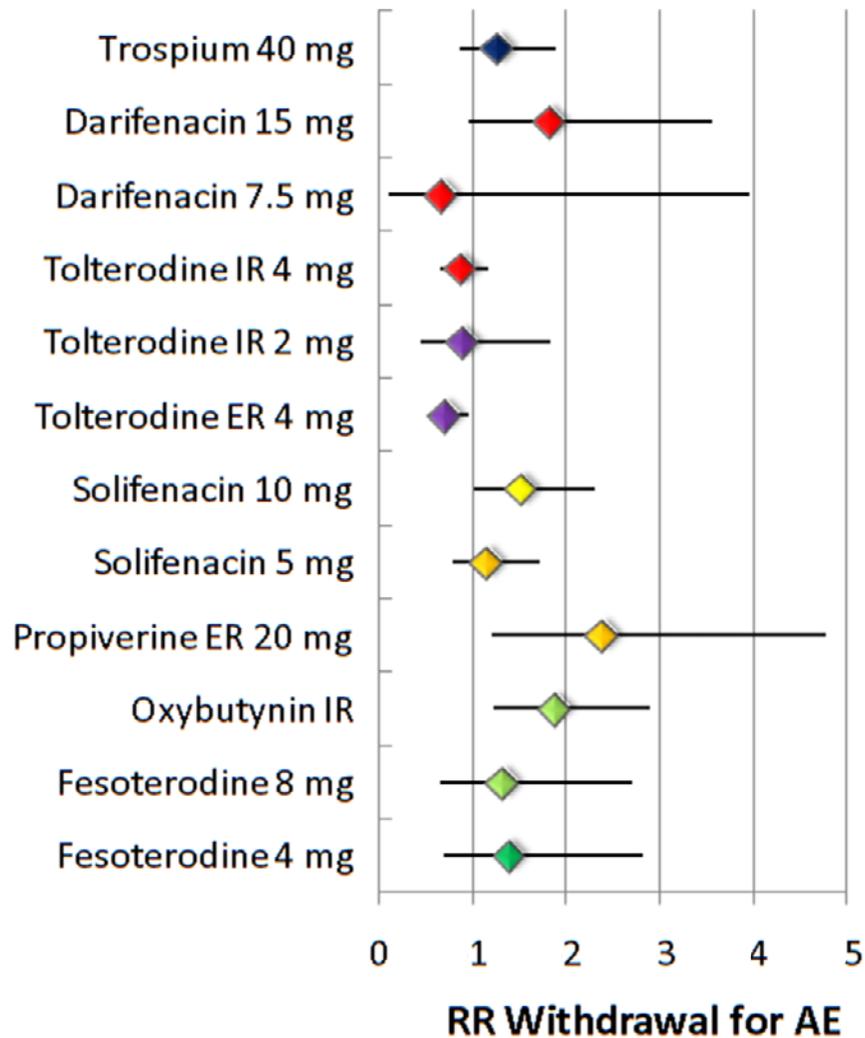
Constipation

Urinary retention

- M_2 reverses sympathetically mediated smooth muscle relaxation
- M_3 causes detrusor contraction

Adverse Events of Antimuscarinics

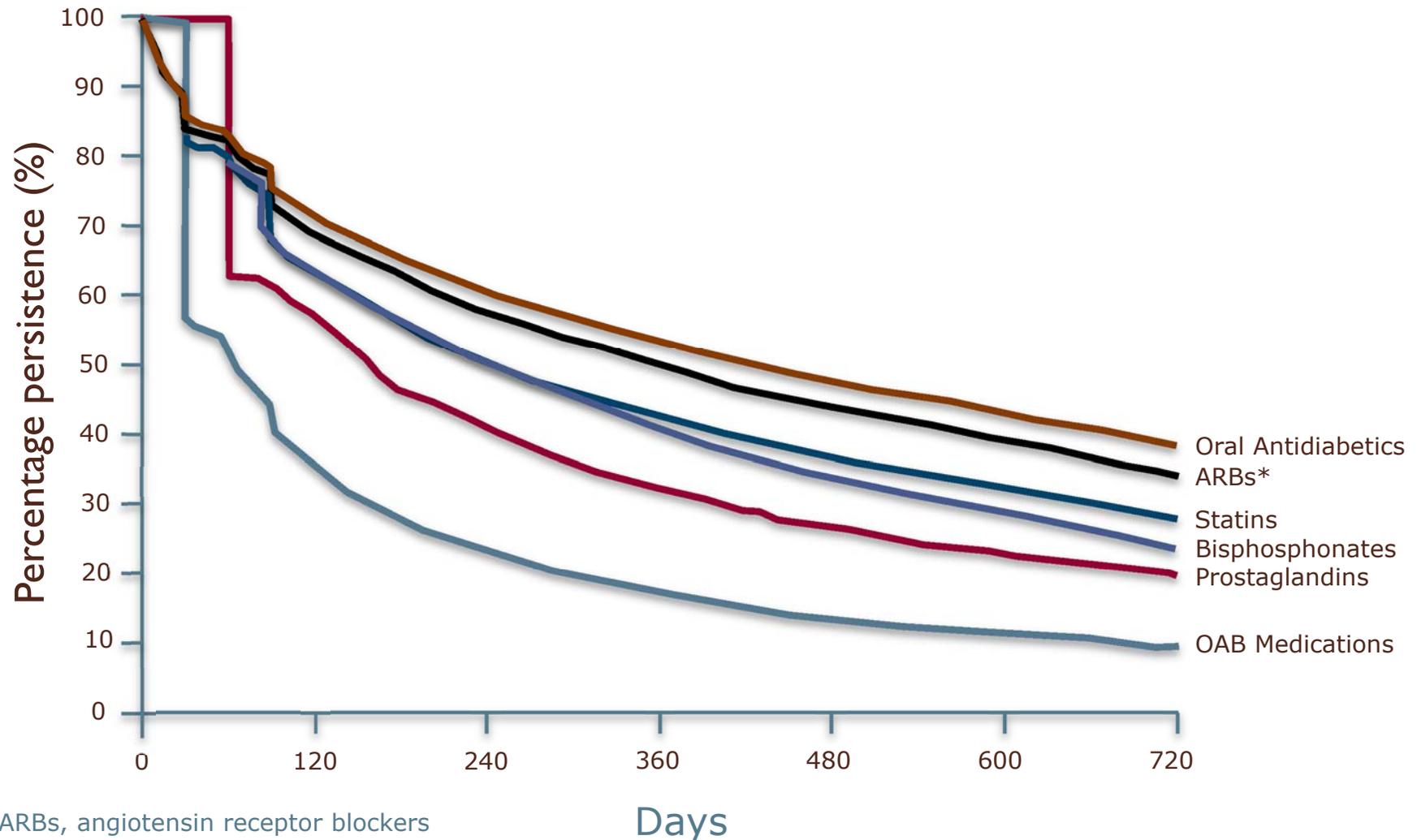
Relative Risk vs. Placebo





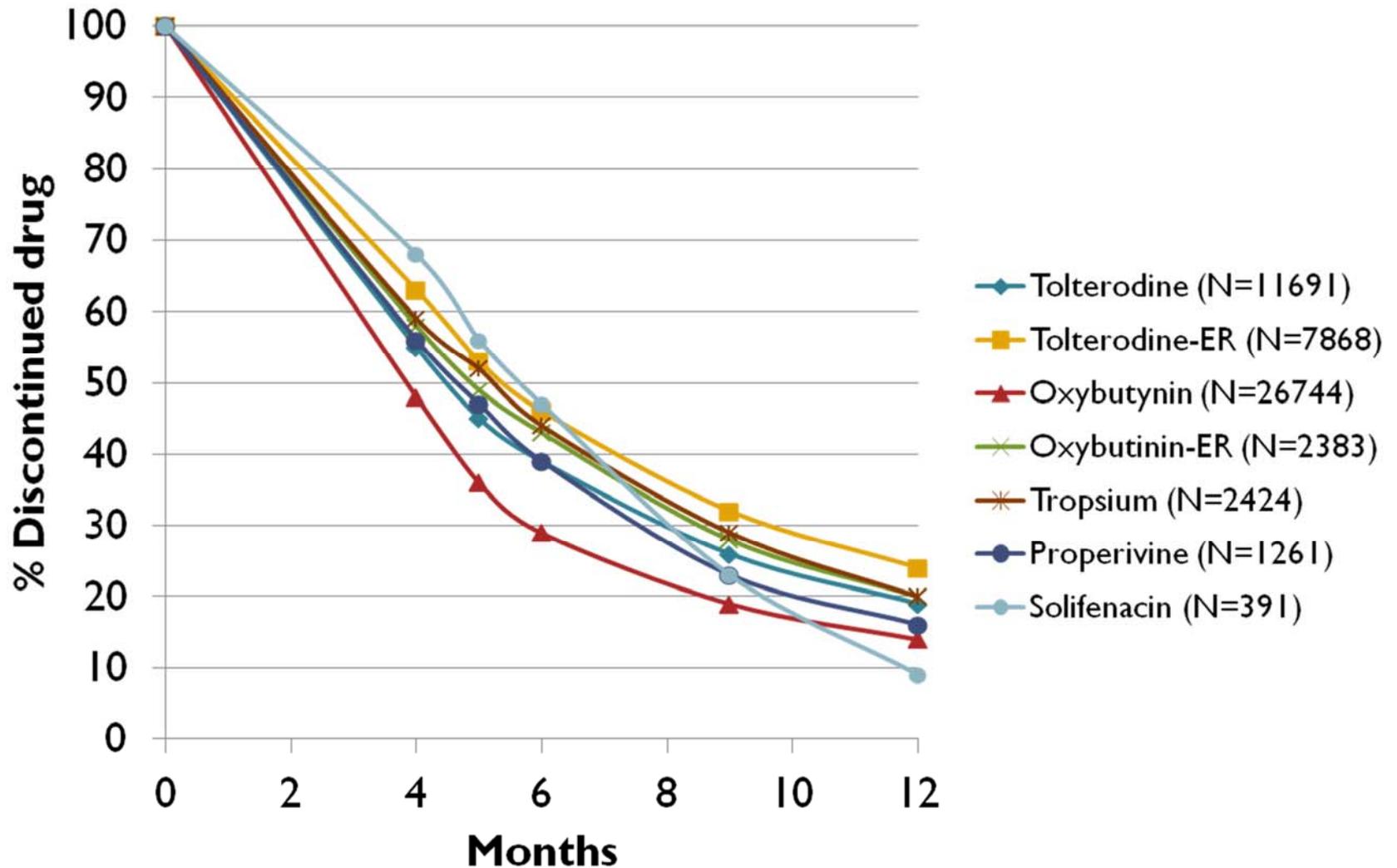
ADHERENCE TO ANTIMUSCARINIC THERAPY

Time to drug discontinuation in six chronic therapy classes

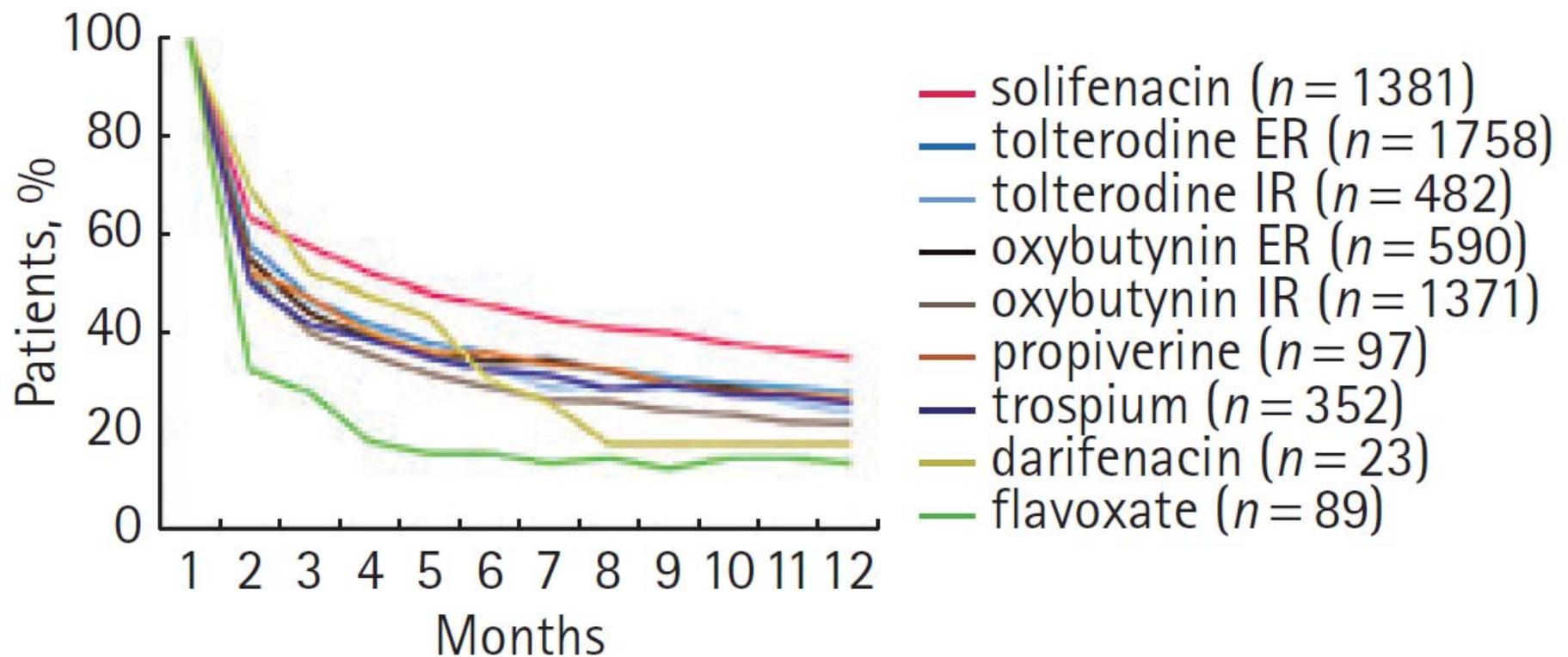


*ARBs, angiotensin receptor blockers

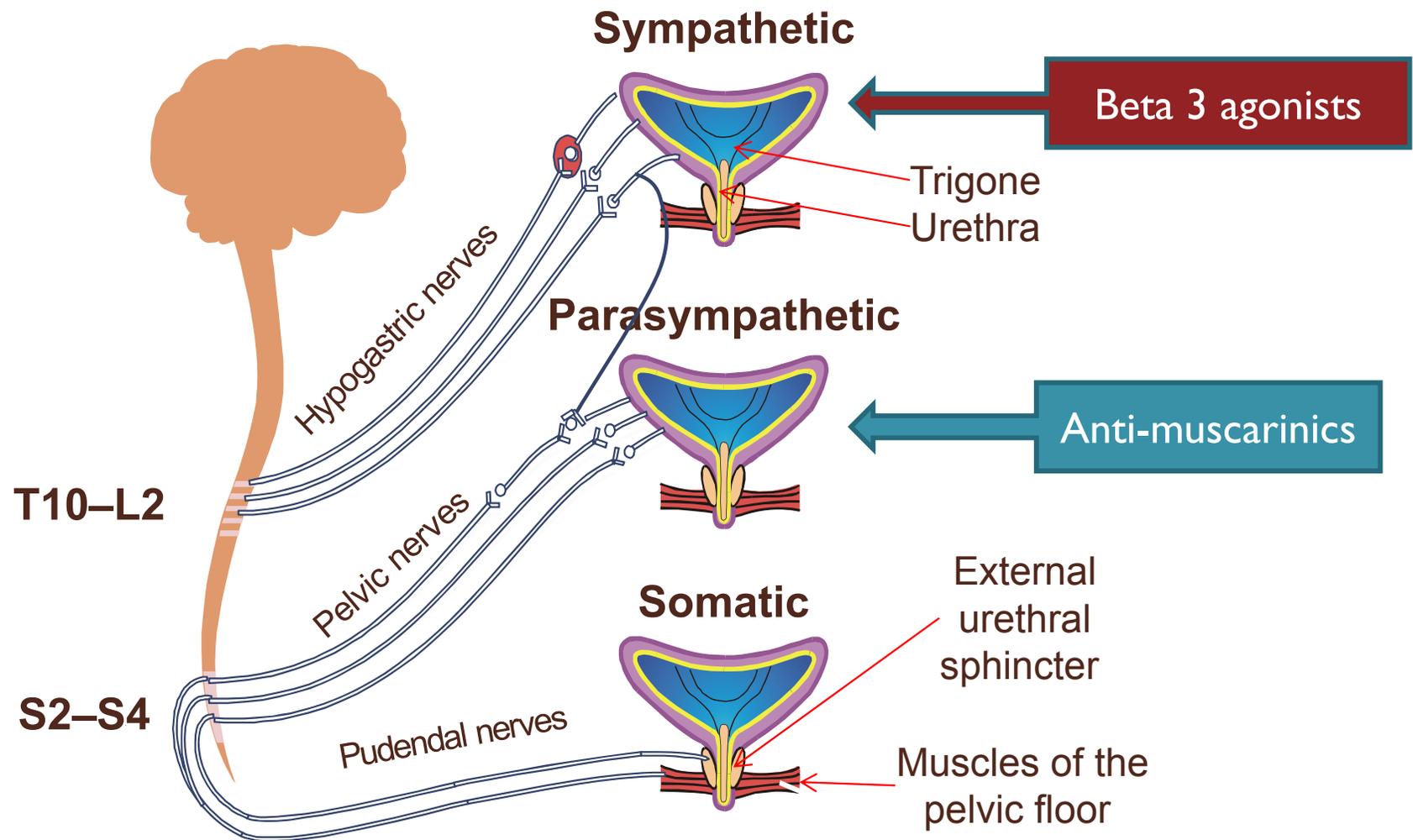
Antimuscarinic Therapy of OAB Time to Discontinuation - US



Antimuscarinic Therapy of OAB Persistence with Treatment - UK



Rationale for New Therapies

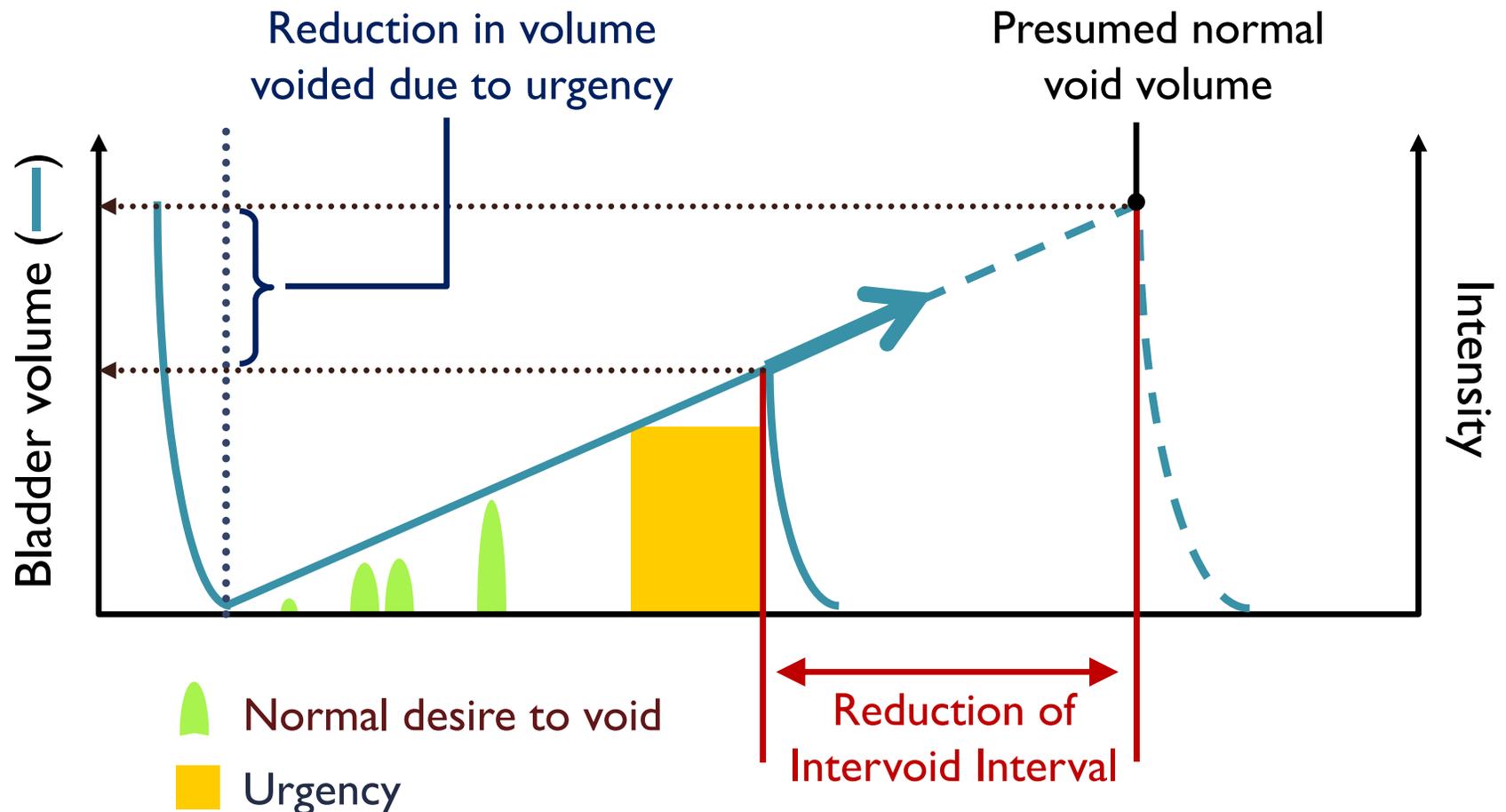


Activation of the parasympathetic pathway results in detrusor muscle contraction and micturition.

Activation of the sympathetic pathway inhibits detrusor contraction and contracts the bladder outlet.

The Micturition Cycle in OAB

Efficacy of Pharmacotherapy



Summary

- OAB is a highly prevalent clinical syndrome
 - OAB wet is more prevalent in women
 - OAB dry is more prevalent in men
 - Which increases with age
 - Where there is concern over the risk of retention in men treated with existing therapy for OAB
- OAB has severe repercussions on QoL
- Current therapy for OAB is hampered by tolerability issues and low persistence on therapy
- New agents with an **alternative mechanism of action** and **different safety profile** will be a valuable addition to the therapeutic armamentarium for the **practising clinician and to benefit patients.**

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Medical Need

Leticia Delgado-Herrera, RPh MS

Overview and Efficacy

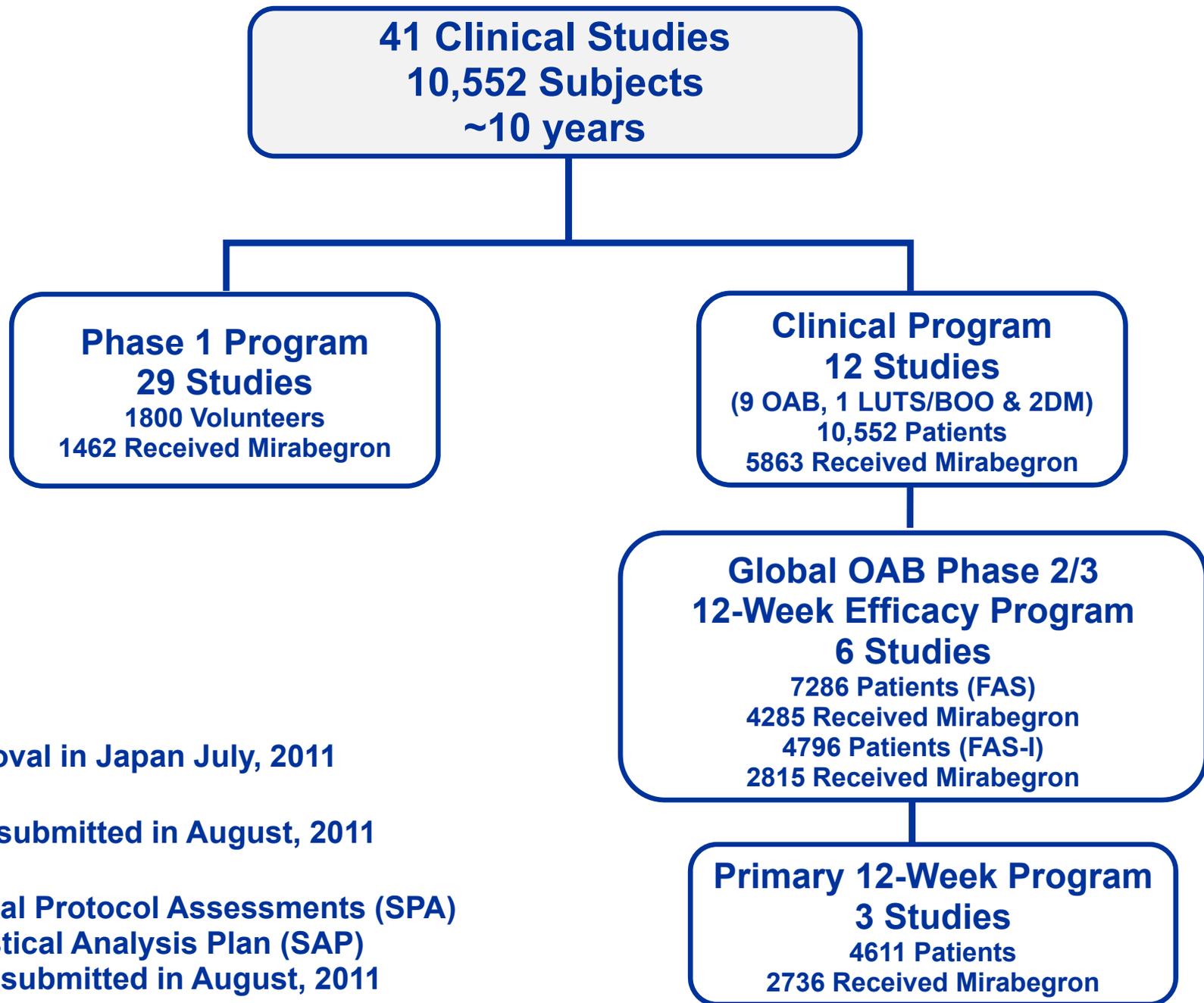
William Fitzsimmons, PharmD MS

Safety

Steven Ryder, MD FACP

Benefit and Managing the Risk

Clinical Development Overview



- **PMDA**
 - Approval in Japan July, 2011
- **EMA**
 - MAA submitted in August, 2011
- **FDA**
 - Special Protocol Assessments (SPA)
 - Statistical Analysis Plan (SAP)
 - NDA submitted in August, 2011

Clinical Pharmacology Studies

29 PHASE 1 STUDIES

1800 Volunteers

1462 Received Mirabegron

Single Ascending Dose

178-CL-001

Multiple Ascending Dose

178-CL-002

Mass Balance

178-CL-007

Dose Proportionality

178-CL-066

Bioavailability

178-CL-033

Food Effect Studies

178-CL-041

178-CL-064

178-CL-078

Pharmacokinetic Studies

178-CL-030

178-CL-031

178-CL-034

178-CL-076

Hepatic

178-CL-039

Renal

178-CL-038

Age/Gender

178-CL-072

Drug-drug Interaction Studies

178-CL-005 – metoprolol

178-CL-006 – metformin

178-CL-036 – ketoconazole

178-CL-040 – warfarin

178-CL-058 – desipramine

178-CL-059 – digoxin

178-CL-068 – combined oral contraceptive (ethinyl estradiol and levonorgestrel)

178-CL-069 – solifenacin

178-CL-070 – rifampin

178-CL-080 – tamsulosin (PK & cardiovascular interactions)

Cardiac Impedance

178-CL-053

Thorough QT Studies

178-CL-037

178-CL-077

Intraocular pressure

178-CL-081

Mirabegron Pharmacokinetics

- **General Pharmacokinetics**

- **Absorption**

- Absorbed with $T_{max} \sim 3$ to 4 hours

- **Distribution**

- Protein binding 71%; mainly albumin followed by α -1-acid glycoprotein
 - Volume of distribution of ~ 1670 L across studies

- **Elimination**

- No single predominating clearance pathway
 - Urine and fecal excretion accounted for 55% and 34% of ^{14}C respectively

- **Metabolism**

- Metabolized by multiple enzymes [e.g., UGTs , esterase, CYP3A4, CYP2D6]

- **Biopharmaceutical Studies**

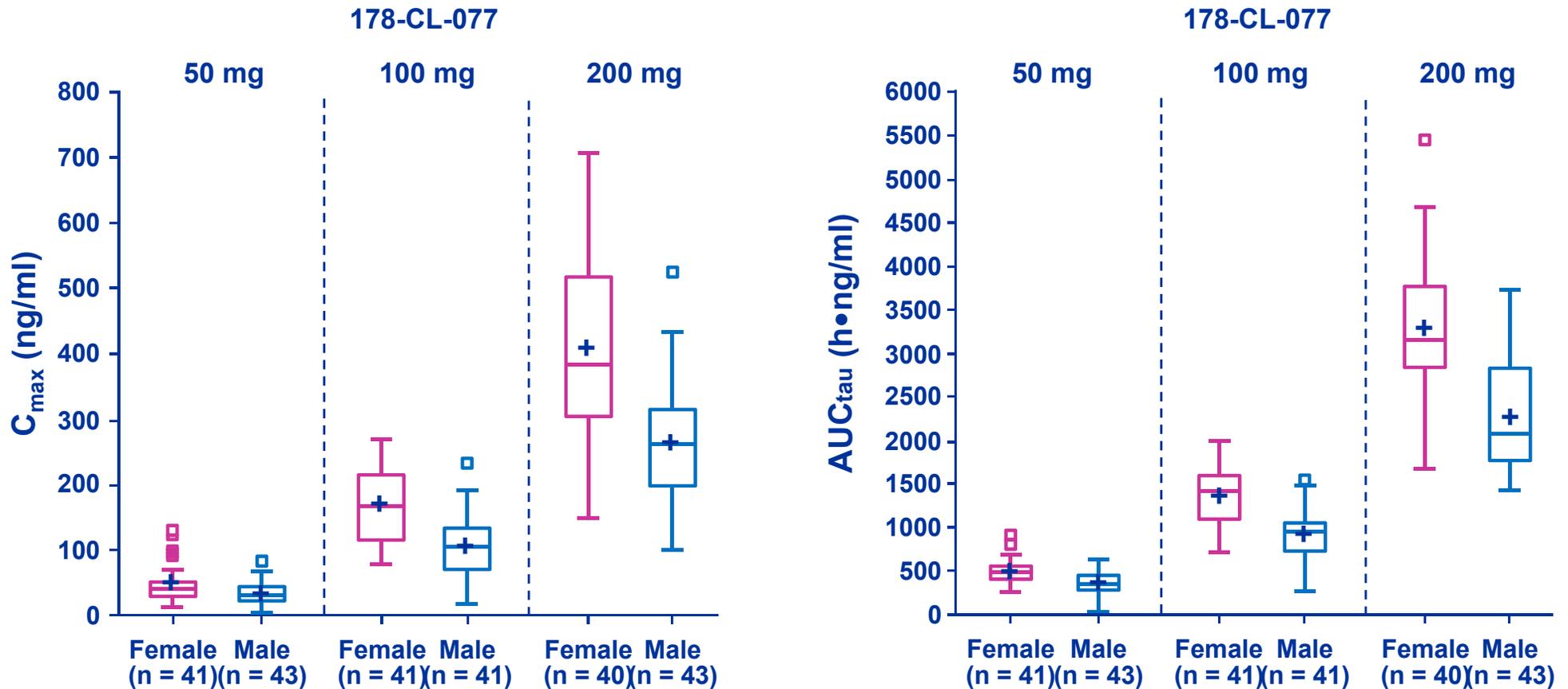
- **Food Effect**

- Food decreased mirabegron exposure (high-fat: 17% \downarrow AUC; low-fat: 51% \downarrow AUC)
 - Phase 3 program with and without food with no discernible difference in safety and efficacy

- **Absolute bioavailability increases with dose**

- 29% at 25 mg (recommended dose for severe renal impairment or moderate hepatic impairment)
 - 35% at 50 mg (general recommended dose)

Exposure (C_{max} and AUC_{tau}) After Multiple Doses of Mirabegron in Healthy Male and Female Volunteers



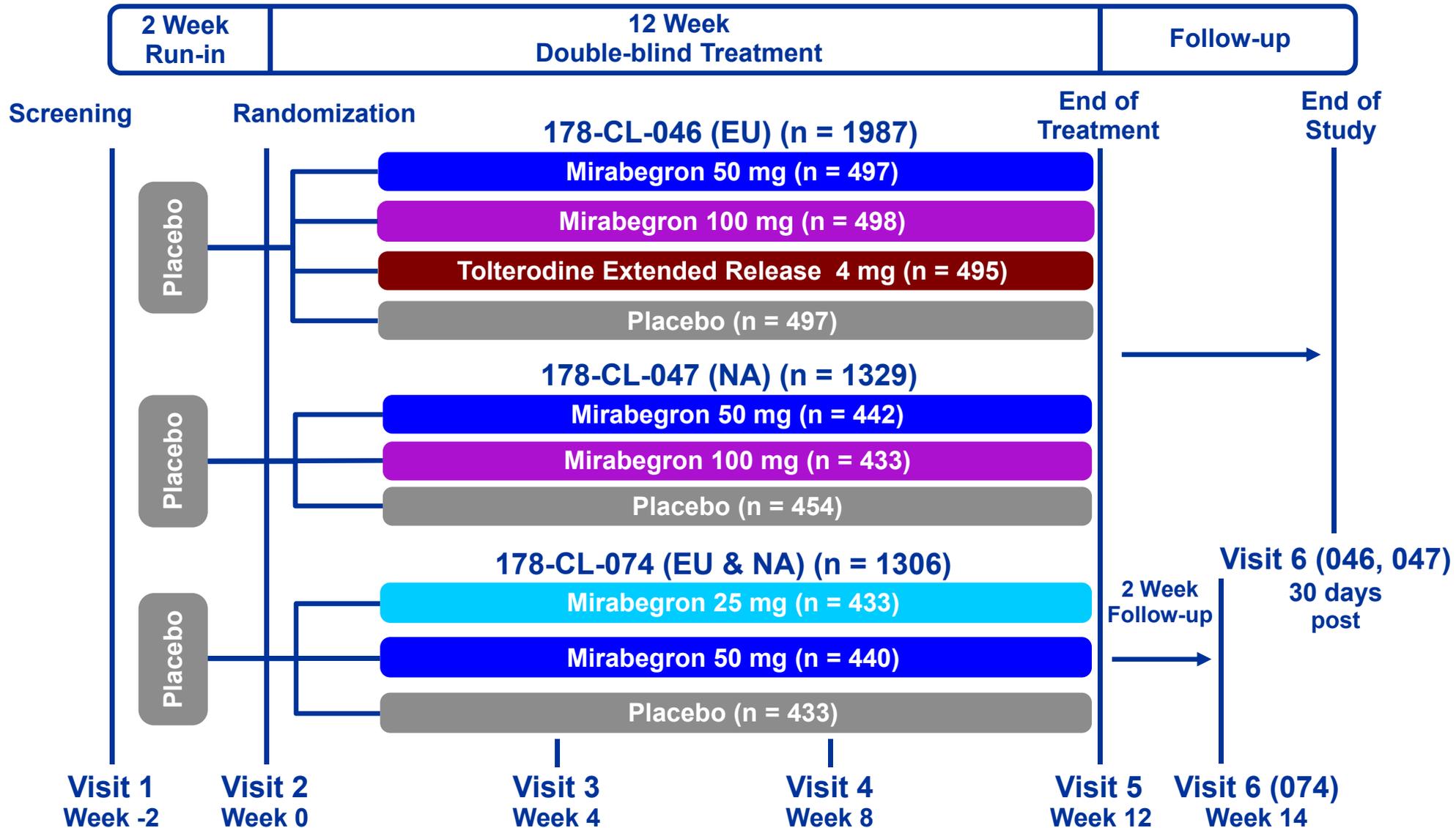
- Exposure in females ~ 30 to 60% C_{max} and ~40–50% AUC_{tau} higher than in males
- Exposure at 100 mg dose is associated with a 2.9 and 2.6-fold increase C_{max} and AUC_{tau} respectively compared with a therapeutic 50 mg dose
- Exposure at 200 mg dose is associated with an 8.4 and 6.5-fold increase C_{max} and AUC_{tau} respectively compared with a therapeutic 50 mg dose

Mirabegron Key Clinical Pharmacology Findings

- **Extensive characterization of the pharmacokinetics of mirabegron**
- **Mirabegron can be taken with or without food**
- **Multiple intrinsic factors examined**
 - **No dose adjustments necessary based on age, gender, race, genetic polymorphism for CYP2D6**
 - **Dose adjustment to 25 mg in severe renal and moderate hepatic impairment**
- **Multiple extrinsic factors examined**
 - **Limited potential for drug-drug interactions**
 - **Caution for drugs metabolized by CYP2D6 and with narrow therapeutic index**
 - **For combination of mirabegron and digoxin the lowest dose for digoxin should be prescribed initially**
- **Not studied and not recommended in end-stage renal disease, severe hepatic impairment or pediatric patients**

Efficacy

Phase 3 Study Design of the OAB Clinical Studies (12-Week)



Phase 3 Demographics & Baseline Characteristics of the OAB Clinical Studies (12-Week)

| Parameter | FAS (n = 4427) | FAS-I (n = 2871) |
|----------------------------------|-------------------|---------------------|
| Gender | | |
| Female | 71.8% | 81.9% |
| Age (years) | | |
| Mean | 59.4 | 60.3 |
| Age (years) | | |
| ≥ 65 | 37.8% | 40.4% |
| ≥ 75 | 10.8% | 12.3% |
| Race | | |
| White | 93.6% | 93.3% |
| Black or African American | 4.7% | 5.2% |
| Asian | 1.0% | 0.9% |
| Other | 0.6% | 0.7% |
| Prior OAB Medication (%) | | |
| Yes | 52.4% | 58.2% |

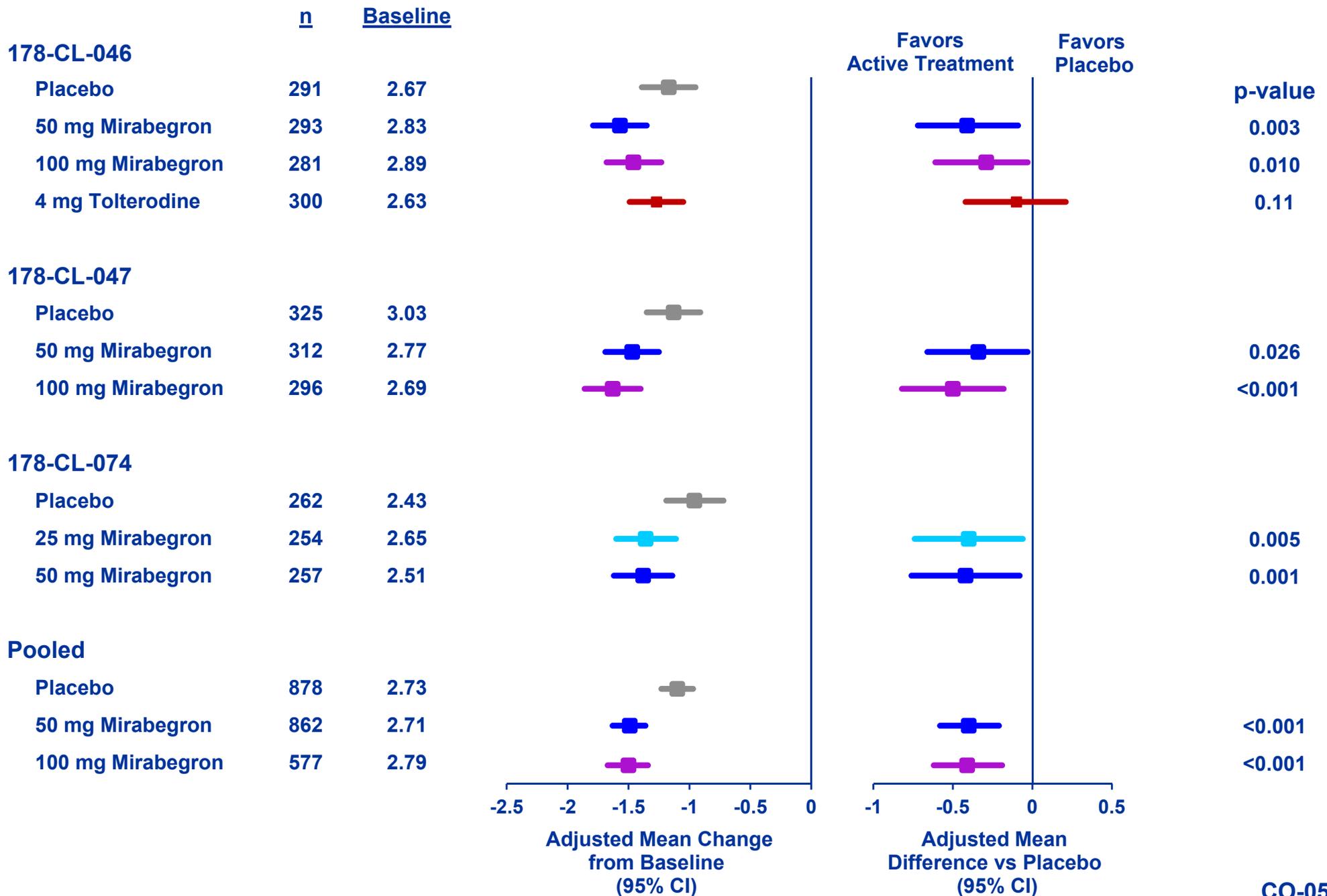
Full Analysis Set (FAS): All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one post-baseline visit diary with a micturition measurement .

Full Analysis Set – Incontinence (FAS-I): All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one post-baseline visit diary with a micturition measurement .

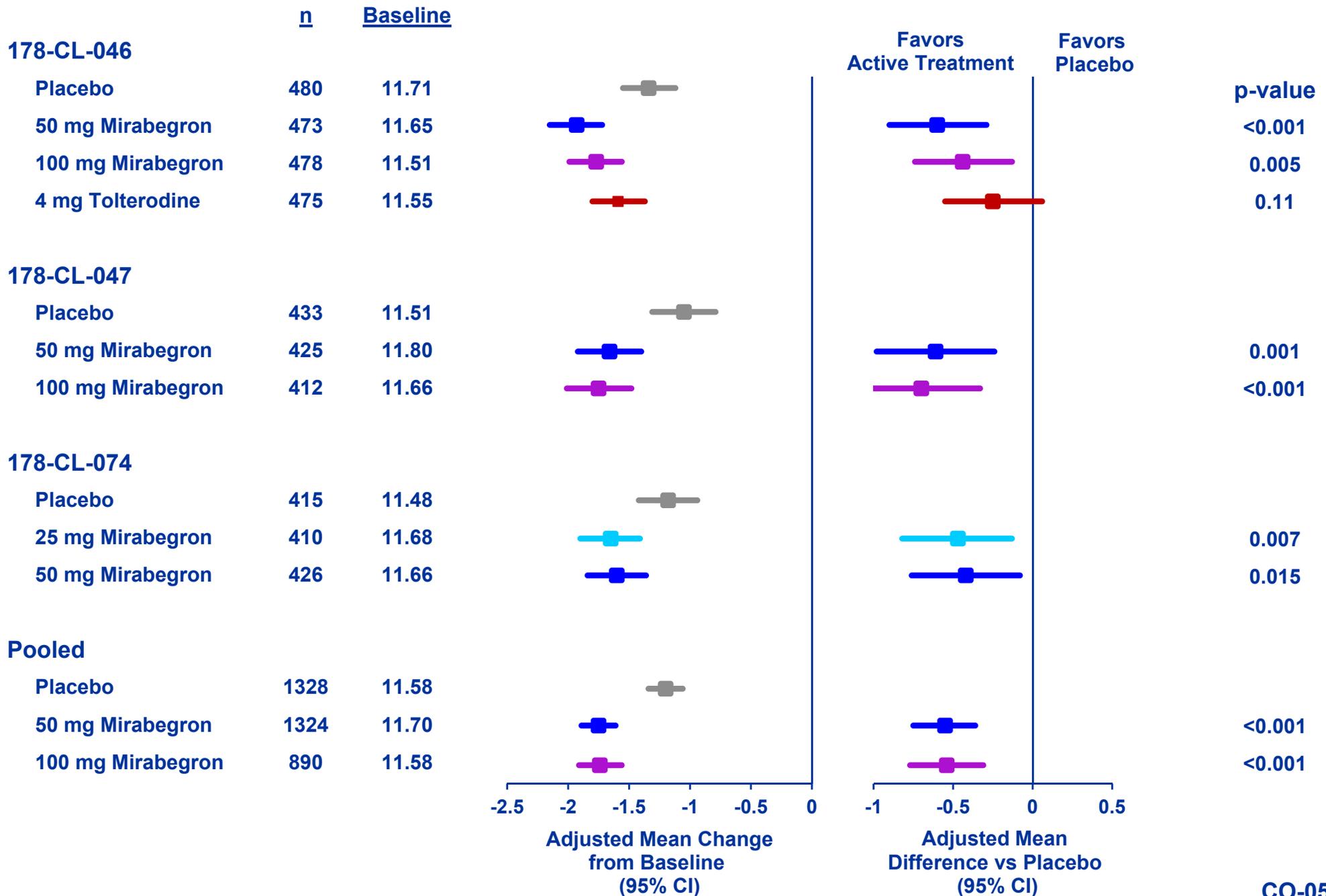
Primary 12-Week Clinical Studies Efficacy Endpoints

- **Co-Primary**
 - Mean number of incontinence episodes per 24 hours
 - Mean number of micturitions per 24 hours
- **Key Secondary**
 - Mean volume voided per micturition
- **Quality of Life Measurements**
 - Overactive Bladder Questionnaire (OAB-q)
 - Patient Perception of Bladder Condition (PPBC)
 - Treatment Satisfaction-Visual Analog Scale (TS-VAS)

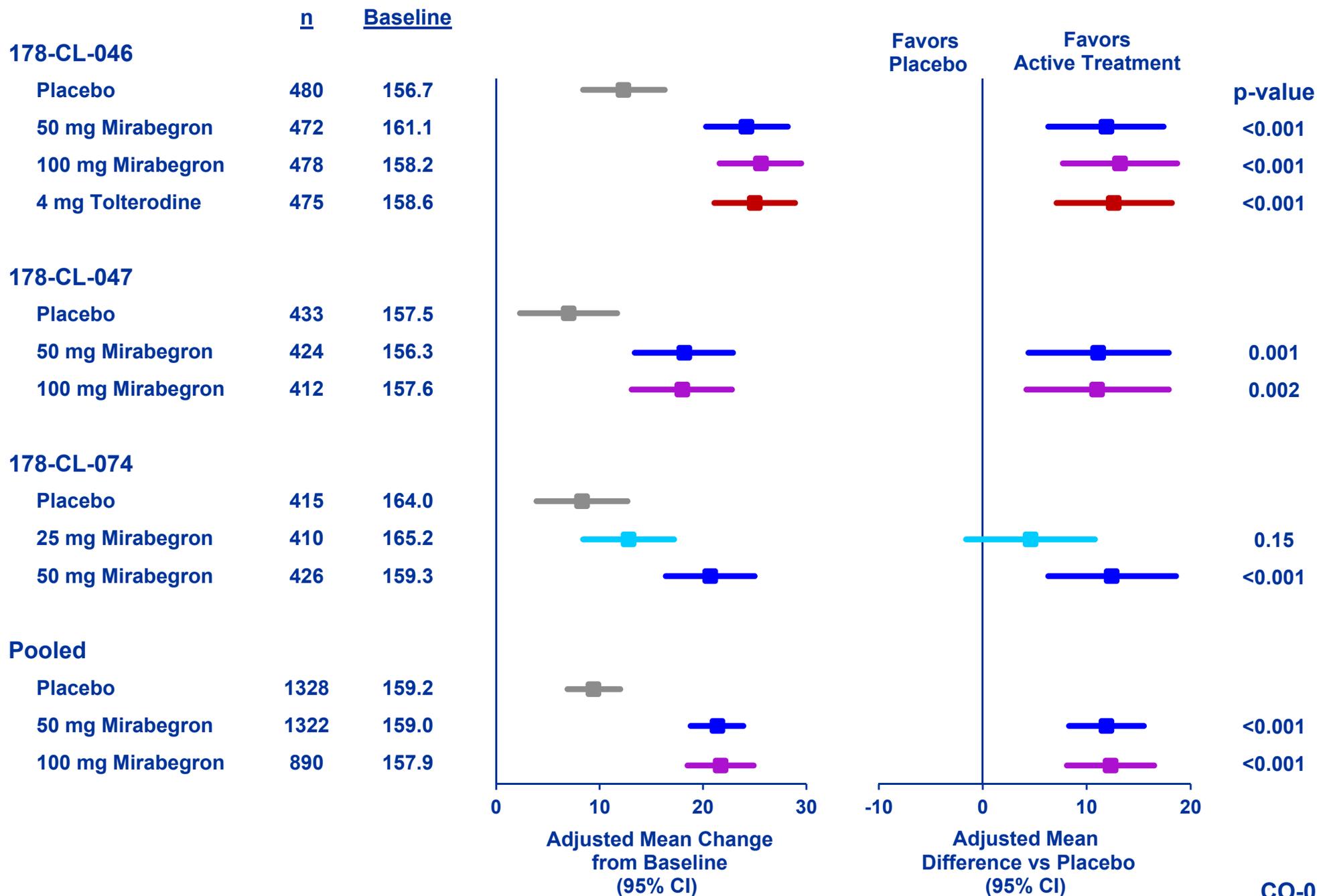
Co-Primary Endpoint Incontinence Episodes per 24 Hours Individual and Pooled Primary 12-Week Studies



Co-Primary Endpoint Micturitions per 24 Hours Individual and Pooled Primary 12-Week Studies

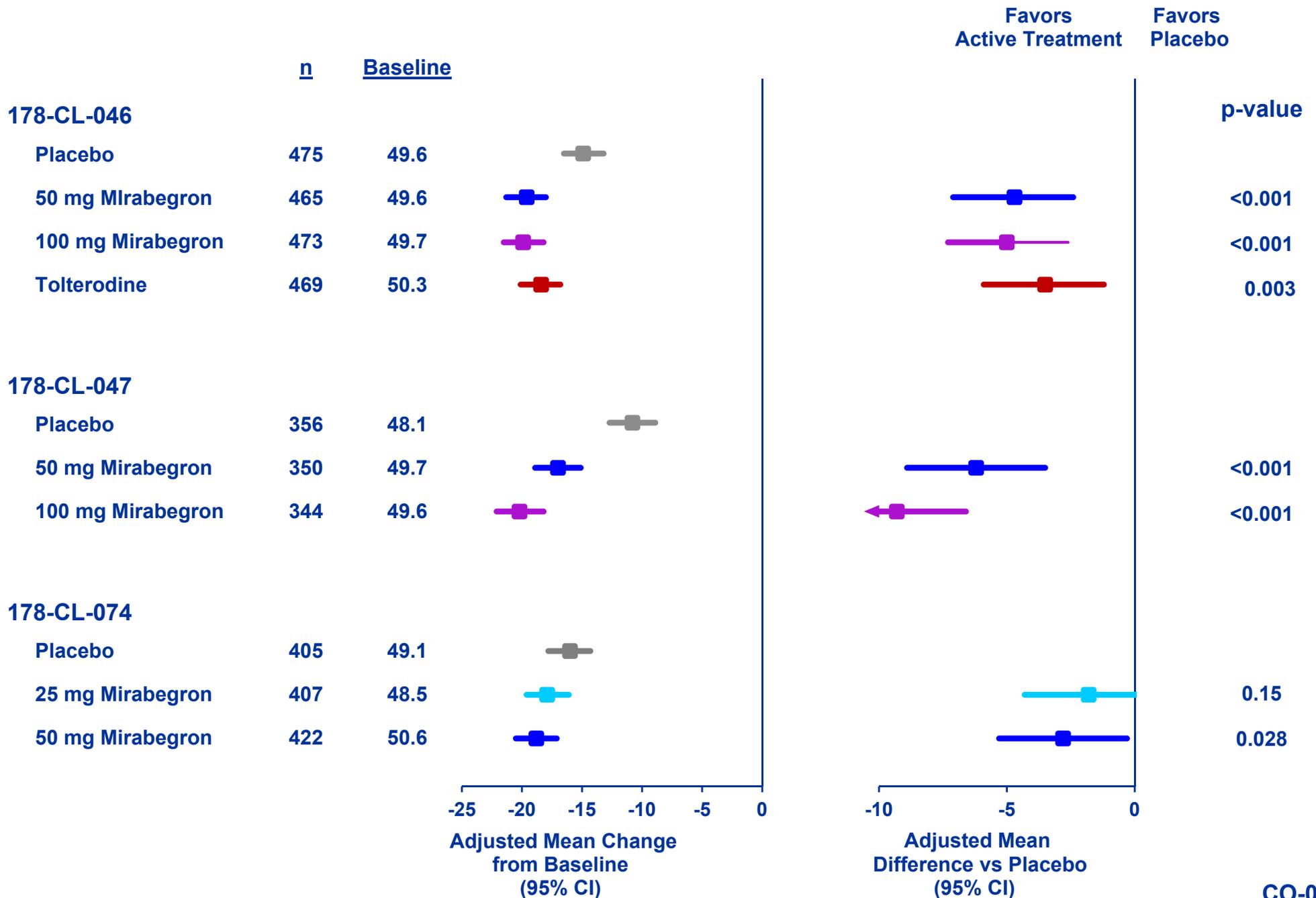


Key Secondary Endpoint Mean Volume Voided (mL) per Micturition Individual Primary and Pooled 12-Week Studies



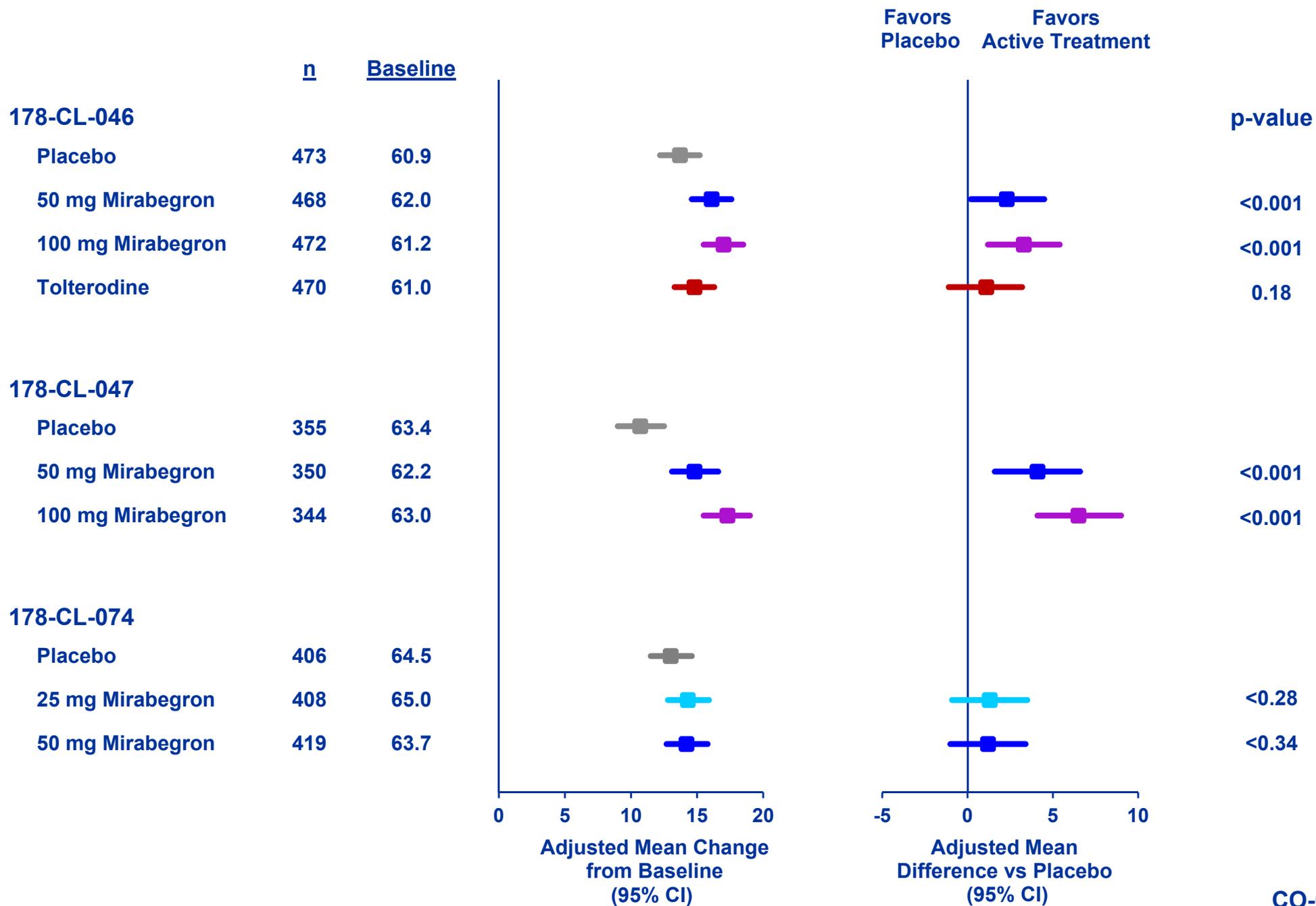
Overactive Bladder Questionnaire (OAB-q) Symptom Bother Scale

Primary 12-Week Studies



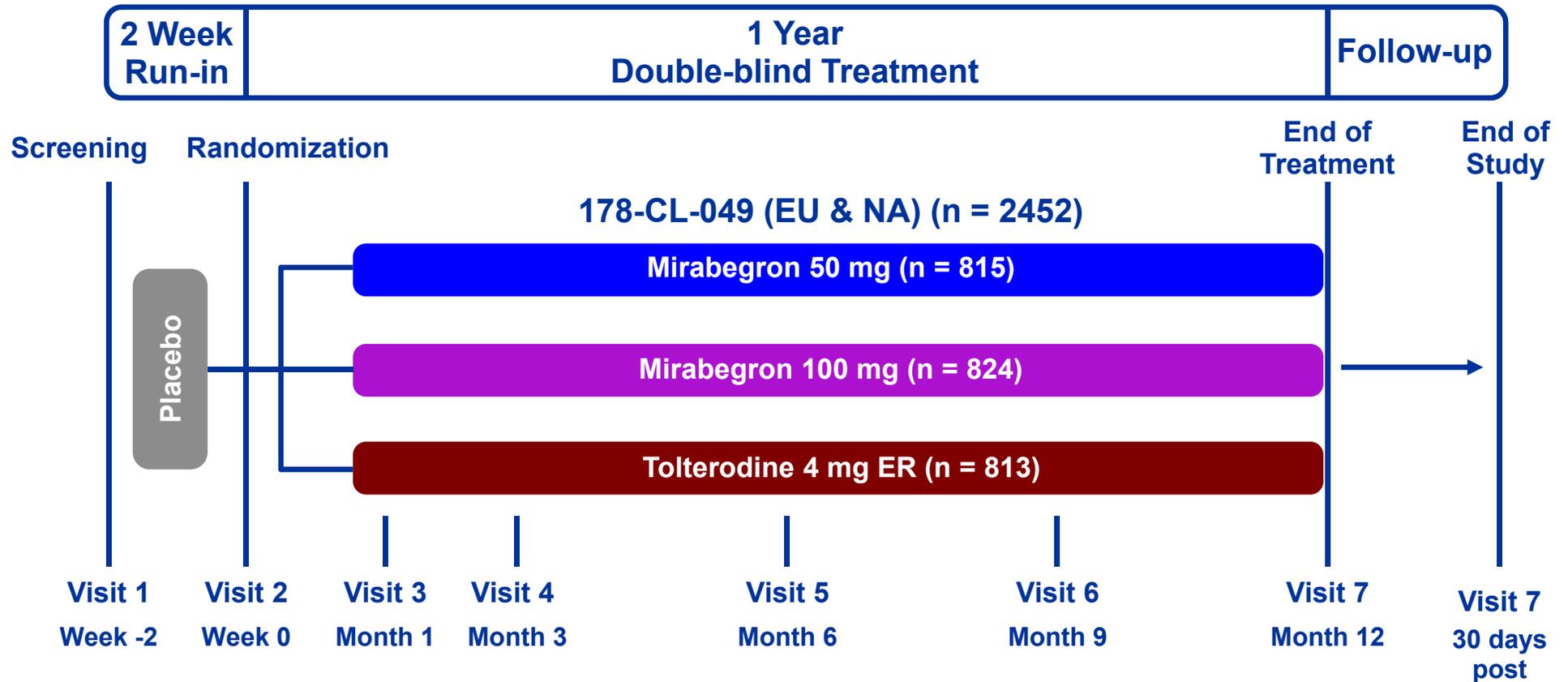
OAB-q Health-Related QOL Total Score

Primary 12-Week Studies



Phase 3 Supportive Study Design

52-Week Long-Term Controlled Study (178-CL-049)



- 81.3% of patients were previously treated in 046 and 047

| | | | |
|------------------|-------|-------------------|-------|
| Placebo | 22.3% | Mirabegron 100 mg | 23.7% |
| Mirabegron 50 mg | 21.3% | Tolterodine | 14.1% |

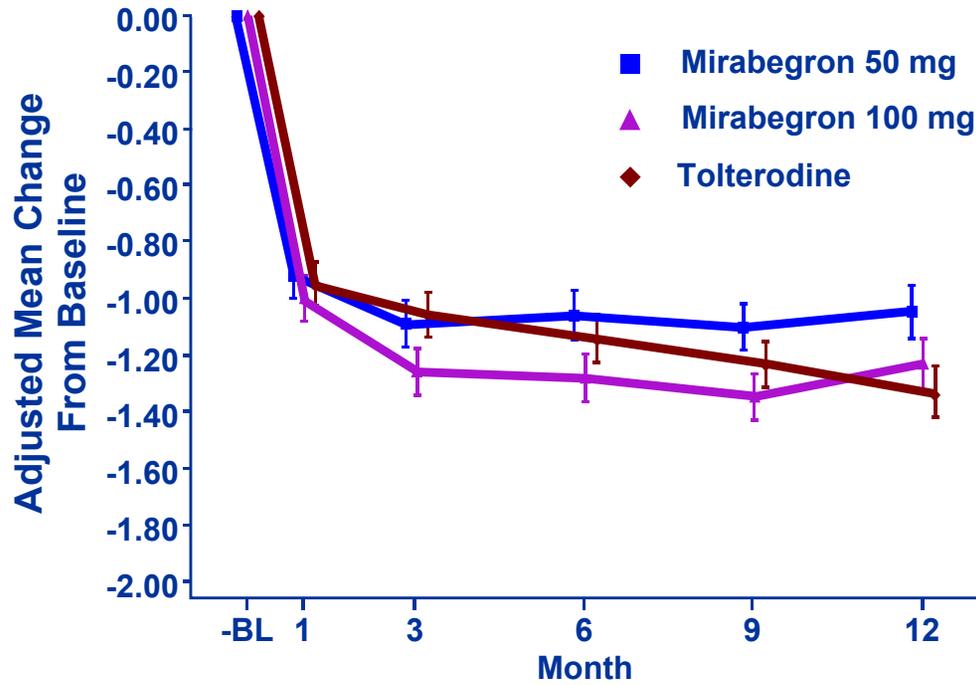
- 18.7% of patients were new to program

Phase 3 Supportive Demographics & Baseline Characteristics 52-Week Long-Term Controlled Study (178-CL-049)

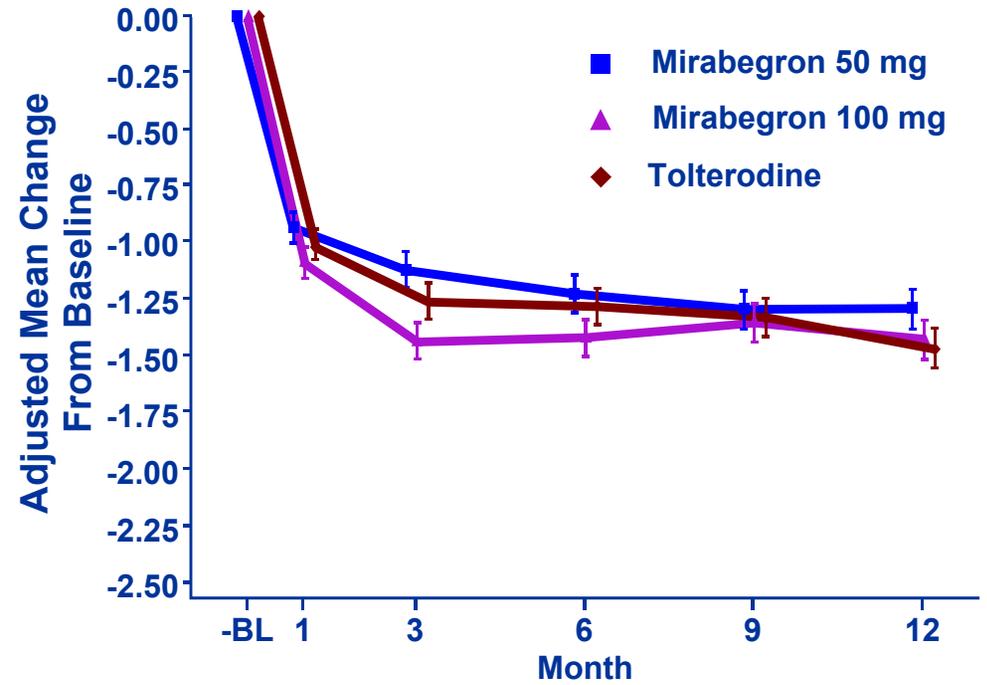
| Parameter | Mirabegron | | Tolterodine |
|---------------------------|--------------------|---------------------|----------------------|
| | 50 mg (n = 812) | 100 mg (n = 820) | ER 4 mg (n = 812) |
| Gender | | | |
| Female | 74.1% | 74.1% | 73.9% |
| Age (years) | | | |
| Mean | 59.2 | 60.1 | 59.6 |
| Age (years) | | | |
| ≥ 65 | 35.6% | 38.5% | 37.3% |
| ≥ 75 | 9.2% | 9.9% | 10.2% |
| Race | | | |
| White | 95.8% | 94.4% | 96.1% |
| Black or African American | 2.7% | 3.7% | 2.5% |
| Asian | 1.0% | 1.0% | 0.6% |
| Other | 0.5% | 1.0% | 0.9% |

Phase 3 Supportive Efficacy Outcomes 52-Week Long-Term Controlled Study (178-CL-049)

Incontinence †



Micturitions †



| N | -BL | 1 | 3 | 6 | 9 | 12 |
|-------------|-----|-----|-----|-----|-----|-----|
| Mira 50 mg | 478 | 478 | 447 | 409 | 387 | 370 |
| Mira 100 mg | 479 | 479 | 443 | 428 | 402 | 387 |
| Tolterodine | 485 | 485 | 452 | 418 | 387 | 379 |

| N | -BL | 1 | 3 | 6 | 9 | 12 |
|-------------|-----|-----|-----|-----|-----|-----|
| Mira 50 mg | 789 | 786 | 742 | 684 | 656 | 627 |
| Mira 100 mg | 802 | 797 | 741 | 705 | 667 | 642 |
| Tolterodine | 791 | 786 | 735 | 684 | 645 | 623 |

† Mean ± SE

Overall Efficacy Conclusions

- **The efficacy of mirabegron 50 mg has been demonstrated by improvement in:**
 - Incontinence
 - Micturition
 - Quality of life measurements
- **Efficacy established:**
 - In a population representative of OAB
 - Across multiple studies and subpopulations
 - Treatment naïve-patients and those who received prior antimuscarinic therapy
- **Efficacy established within one month and maintained over 52 weeks**

Agenda

Steven Ryder, MD FACP

Introduction

Prof. Christopher Chapple MD,
FRCS (Urol)

Medical Need

Leticia Delgado-Herrera, RPh MS

Overview and Efficacy

William Fitzsimmons, PharmD MS

Safety

Steven Ryder, MD FACP

Benefit and Managing the Risk

Global Phase 2/3 Safety Population

Demographics, Baseline Characteristics and Study Drug Exposure

| | Mirabegron |
|--|-----------------------|
| Gender, n | 5863 |
| Female | 4399 (75.0%) |
| Age (years), n | 5863 |
| Mean | 59 |
| Age (years), n | 5863 |
| ≥ 65 | 2095 (35.7%) |
| ≥ 75 | 574 (9.8%) |
| Race, n | 5858 |
| White | 4387 (74.9%) |
| Asian | 1259 (21.5%) |
| Black | 179 (3.1%) |
| Duration of Exposure (days) | 152.0 (125.78) |
| Mean (SD) | 4191 (71.5%) |
| ≥ 84 | 622 (10.6%) |
| ≥ 365 | |
| Total patient-years of exposure | 2439.44 |

Cardiovascular Baseline Characteristics

| | 12-Week Phase 3 Studies n = 4611 | Long-Term (52-Week) Controlled Study n = 2444 | HIRD OAB n = 6607 |
|-----------------------|-------------------------------------|--|----------------------|
| Hypertension | 1776 (38.5%) | 969 (39.6%) | 1790 (27.1%) |
| Diabetes | 377 (8.2%) | 187 (7.7%) | 538 (8.1%) |
| Lipid Lowering Agents | 1317 (28.6%) | 631 (25.8%) | Not reported |
| Antithrombotics | 963 (20.9%) | 501 (20.5%) | Not reported |

HIRD study from Andersson et al. Cardiovascular morbidity, heart rates and use of antimuscarinics in patients with overactive bladder. *BJUI*. 2010;106:268-274

Mirabegron Safety

- **Deaths**
- **Serious Adverse Events**
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- **Common Adverse Events**
- **Cardiovascular**
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mortality (11 Deaths) in Mirabegron Clinical Program

| | Study | Subject No | Prior Treat | Treat | Dose | Age | Gender | MedDRA | Day of Death | Onset/Stop (Last Dose) | Relationship | Adjud Term |
|-----------------------------|------------|------------|-------------|-------|--------|-----|--------|--|--------------|------------------------|--------------|------------|
| 12-week Program | 178-CL-046 | 1598 | | Tolt | 4 mg | 74 | M | Ruptured Cerebral Aneurysm | 70 | 68/70 (60) | Possible | CV Death |
| | 178-CL-047 | 6697 | | Pbo | - | 76 | F | Cardiac Arrest | 142 | 142/142 (86) | Not Related | CV Death |
| | 178-CL-047 | 6141 | | Mira | 100 mg | 66 | F | Bladder cancer & colon cancer metastatic | 99 | 38/99 (49) | Not Related | Non CV |
| Long-term (52-week) Program | 178-CL-049 | 6486 | 50 mg | Tolt | 4 mg | 57 | F | Coronary Artery Disease | 208 | 208/208 (208) | Not Related | CV Death |
| | 178-CL-049 | 6983 | 100 mg | Tolt | 4 mg | 68 | M | Cerebrovascular Accident & Pneumonia Aspiration | 72 | 62/72 (62) | Not Related | CV Death |
| | 178-CL-049 | 2380 | | Mira | 50 mg | 72 | F | Cardiac Failure | 190 | 190/190 (190) | Not Related | CV Death |
| | 178-CL-049 | 3438 | | Mira | 50 mg | 27 | F | Completed Suicide | 359 | 359/359 (267 E) | Possible | Non CV |
| | 178-CL-049 | 6120 | | Mira | 50 mg | 64 | F | Pneumonia | 108 | 104/108 (86 E) | Possible | Non CV |
| | | | | | | | | Acute Respiratory Failure Multi-organ Failure Renal Vein Thrombosis Staphylococcal Sepsis | | 107/108 | Not Related | |
| | 178-CL-051 | 1503 | 50 mg | Mira | 100 mg | 59 | F | Aortic Dissection | 237 | 237/237 (224) | Not Related | CV Death |
| Ongoing Studies | 178-CL-090 | 90701 | | Pbo | | 57 | M | Sudden Death | 45 | 45/45 (44) | Not Related | CV Death |
| | 178-CL-090 | 90724 | | Pbo | - | 55 | F | Chemical Poisoning | 10 | 8/10 (2) | Not Related | Non CV |

Mortality by Treatment Group

| Treatment Group | Total Number of Patients | Total Number of Deaths | Patient-years of Exposure | Mortality per 1000 Patient Years |
|------------------------|---------------------------------|-------------------------------|----------------------------------|---|
| Placebo | 2208 | 1 | 469.4 | 2.1 |
| Mirabegron | 5648 | 5 | 2555.6 | 2.0 |
| Tolterodine | 1726 | 3 | 902.5 | 3.3 |

Mirabegron Safety

- **Deaths**

- The observed number and causes of death are not unexpected in the OAB population

- **Serious Adverse Events**

- Neoplasms
- Hepatotoxicity
- Hypersensitivity

- **Common Adverse Events**

- **Cardiovascular**

- QT
- Phase 1 healthy volunteer vital signs
- Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
- Framingham Risk Estimates

Mirabegron Safety

- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Serious Adverse Events Occurring in >1 Patient per Mirabegron Group

Global OAB 12-Week Phase 2/3 Studies

| | Placebo (n = 2142) | Mirabegron | | | | | Tolterodine (n = 958) |
|---------------------|-----------------------|--------------------|---------------------|----------------------|---------------------|---------------------|--------------------------|
| | | 25 mg (n = 811) | 50 mg (n = 2131) | 100 mg (n = 1305) | 200 mg (n = 167) | Total (n = 4414) | |
| Overall | 38 (1.8) | 11 (1.4) | 34 (1.6) | 29 (2.2) | 3 (1.8) | 77 (1.7) | 16 (1.7) |
| Atrial fibrillation | 1 (<0.1) | 0 | 3 (0.1) | 2 (0.2) | 0 | 5 (0.1) | 0 |
| Chest pain | 2 (0.1) | 1 (0.1) | 0 | 3 (0.2) | 0 | 4 (0.1) | 0 |
| Pneumonia | 1 (<0.1) | 0 | 2 (0.1) | 0 | 2 (1.2) | 4 (0.1) | 0 |
| Prostate cancer | 0 | 0 | 2 (0.1) | 0 | 0 | 2 (<0.1) | 0 |
| Bunion operation | 0 | 0 | 0 | 2 (0.2) | 0 | 2 (<0.1) | 0 |

Long-Term (52-Week) Controlled Study

| | Mirabegron | | | Tolterodine (n = 812) |
|------------------------------|--------------------|---------------------|---------------------|--------------------------|
| | 50 mg (n = 812) | 100 mg (n = 820) | Total (n = 1632) | |
| Overall | 42 (5.2) | 51 (6.2) | 93 (5.7) | 44 (5.4) |
| Cerebrovascular accident | 3 (0.4) | 0 | 3 (0.2) | 1 (0.1) |
| Osteoarthritis | 2 (0.2) | 1 (0.1) | 3 (0.2) | 1 (0.1) |
| Atrial fibrillation | 2 (0.2) | 0 | 2 (0.1) | 3 (0.4) |
| Liver function test abnormal | 0 | 2 (0.2) | 2 (0.1) | 0 |
| Breast cancer | 0 | 2 (0.2) | 2 (0.1) | 2 (0.2) |
| Lung neoplasm malignant | 0 | 2 (0.2) | 2 (0.1) | 0 |
| Prostate cancer | 0 | 2 (0.2) | 2 (0.1) | 0 |

Mirabegron Safety

- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- Cardiovascular
 - QT
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Summary of Nonclinical Genotoxicity and Carcinogenicity Studies

| Assay/Test | Concentration/Dose | Results |
|-----------------------------------|---|---|
| Bacterial Reverse Mutation Assay | 1.6 - 5000 mcg/plate with and without S9 microsomal fraction | Negative |
| Chromosome Aberration Assay | 655 - 1280 mcg/mL with S9 110 - 215 mcg/mL without S9 | Negative |
| Rat Micronucleus Test | 100 - 400 mg/kg, oral gavage | Negative |
| Mouse 104-week Carcinogenicity | 25, 50, and 100 mg/kg, oral gavage (21-38 x MRHD*) | No increase in the incidence of tumors or hyperplastic findings |
| Rat 104-week Carcinogenicity | Males: 12.5, 25 and 50 mg/kg oral gavage (38 x MRHD*) Females: 25, 50 and 100 mg/kg oral gavage (45 x MRHD*) | No increase in the incidence of tumors or hyperplastic findings |
| Monkey 52-week Chronic Toxicology | 0, 3, 10 and 30 mg/kg oral gavage (8-13 x MRHD*) | No neoplastic, pre-neoplastic or hyperplastic findings |

*maximum recommended human dose

Total Number of Patients with a New Malignant AE

| Study | Placebo N = 2142 | | Mirabegron N = 6046 | | Tolterodine N = 1770 | |
|------------|---------------------|------------|------------------------|------------|-------------------------|------------|
| | n | New AE (%) | n | New AE (%) | n | New AE (%) |
| 178-CL-044 | 169 | 0 | 673 | 0 | 85 | 0 |
| 178-CL-045 | 213 | 0 | 626 | 0 | | |
| 178-CL-046 | 494 | 1 (0.20%) | 989 | 0 | 495 | 0 |
| 178-CL-047 | 453 | 0 | 875 | 6 (0.69%) | | |
| 178-CL-048 | 380 | 0 | 379 | 0 | 378 | 0 |
| 178-CL-074 | 433 | 1 (0.23%) | 872 | 1 (0.11%) | | |
| 178-CL-049 | | | 1632 | 12 (0.74%) | 812 | 4 (0.49%) |

Global OAB
12-Week Phase 2/3
Studies

Long-Term
(52-Week)
Controlled Study

New Malignant AE by Tumor Type and Dose

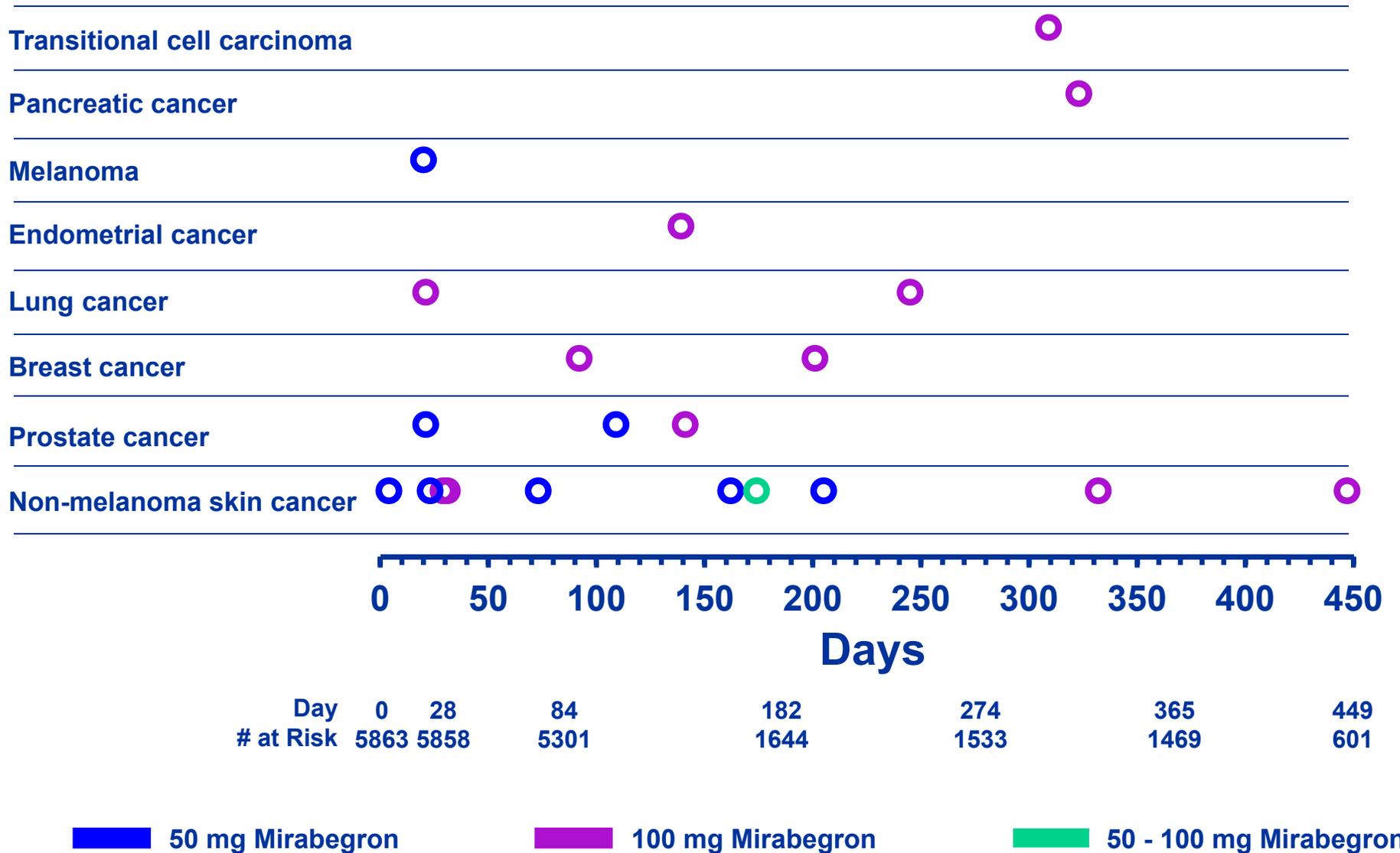
| Global OAB 12-Week Phase 2/3 Studies | | | | | | Long-Term (52-Week) Controlled Study | | | |
|--------------------------------------|---------------------|------------------|-------------------|--------------------|-------------------|--------------------------------------|--------------------|---------------------|--------------------------|
| | Placebo (n=2142) | Mirabegron | | | | Tolterodine (n = 958) | Mirabegron | | Tolterodine (n = 812) |
| | | 25 mg (n=811) | 50 mg (n=2131) | 100 mg (n=1305) | 200 mg (n=167) | | 50 mg (n = 812) | 100 mg (n = 820) | |
| Overall | 2 (0.09%) | 0 | 5 (0.23%) | 2 (0.15%) | 0 | 0 | 3 (0.37%) | 9 (1.10%) | 4 (0.49%) |
| Skin (Non-melanoma) | 2 (0.09%) | 0 | 2 (0.09%) | 1 (0.08%) | 0 | 0 | 3 (0.37%) | 2 (0.24%) | 1 (0.12%) |
| Prostate | 0 | 0 | 2 (0.40%) | 0 | 0 | 0 | 0 | 1 (0.47%) | 0 |
| Melanoma | 0 | 0 | 1 (0.05%) | 0 | 0 | 0 | | | |
| Lung | 0 | 0 | 0 | 1 (0.08%) | 0 | 0 | 0 | 1 (0.12%) | 0 |
| Breast | | | | | | | 0 | 2 (0.33%) | 2 (0.33%) |
| Uterus | | | | | | | 0 | 1 (0.16%) | 1 (0.17%) |
| Bladder | | | | | | | 0 | 1 (0.12%) | 0 |
| Pancreas | | | | | | | 0 | 1 (0.12%) | 0 |

Neoplasm Epidemiologic Data: Observed versus Expected Malignancies

| | Observed in Mirabegron | Expected † | Standardized Morbidity Rate (95% CI) |
|-----------------|------------------------|-------------|---|
| Breast | 2 | 4.51 | 0.433 (0.054, 1.601) |
| Prostate | 3 | 2.69 | 1.113 (0.230, 3.253) |
| Lung | 2 | 3.66 | 0.547 (0.066, 1.976) |

† International Agency for Research on Cancer – age and gender weighted analysis for nine geographic regions (Canada, Japan, USA Northeast, USA Midwest, USA South, USA West, Europe West, Europe East, and Southern Hemisphere) *Curado et al, 2007*

Time to Onset of New Malignant Events for Mirabegron-Treated Patients Global Phase 2/3 Studies



Neoplasm Summary

- **Genotoxicity studies negative**
- **No evidence of carcinogenicity or hyperproliferation in lifetime rodent carcinogenicity studies**
 - Mouse
 - Rat
- **No evidence of pre-neoplasia in a 52-week monkey study**
- **No consistent dose response across the 12-week phase 3 studies and long-term (52-week) controlled study**
- **No consistency across the 12-week phase 3 studies**
- **Frequency of neoplasm events did not increase with longer term exposure**
- **No predominant tumor type and the incidence of prostate, breast and lung cancer is similar to epidemiologic data for a relevant population**
- **Time of onset of neoplasms biologically implausible for exposure to a carcinogen**

Mirabegron Safety

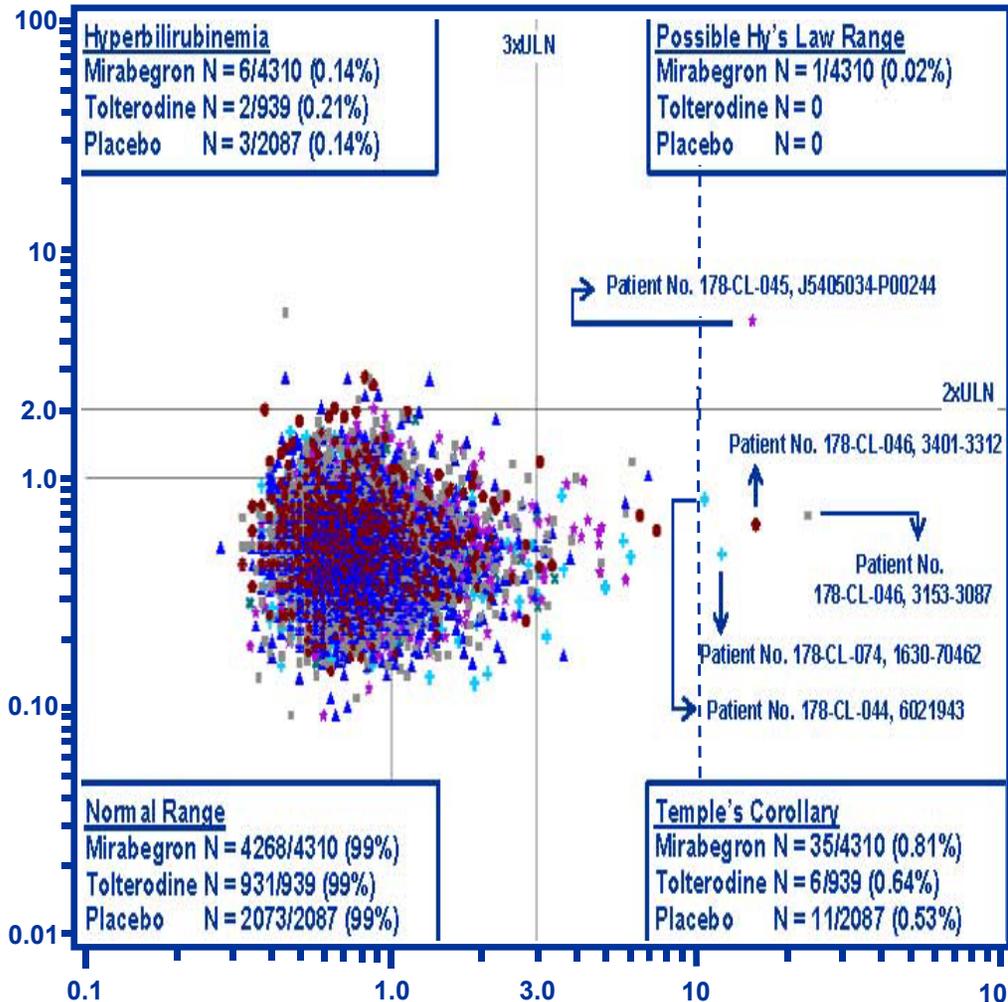
- Deaths
- Serious Adverse Events
 - Neoplasms
 - Data do not support a risk for neoplasm with mirabegron
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mirabegron Safety

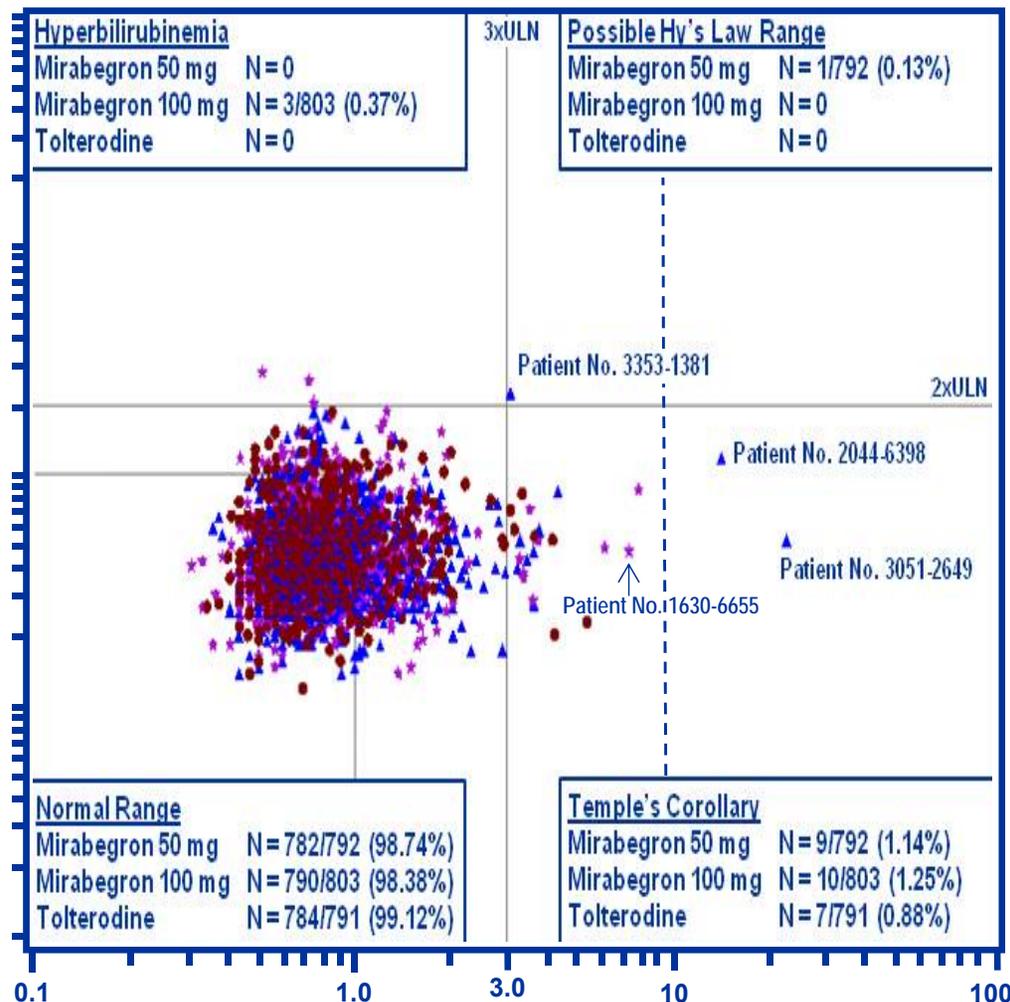
- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - **Hepatotoxicity**
 - Hypersensitivity
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Scatterplot of Peak Total Bilirubin Values vs. Peak AST/ALT Global OAB Phase 2/3 Studies

12-Week Phase 2/3 Studies



Long-Term (52-Week) Controlled Study



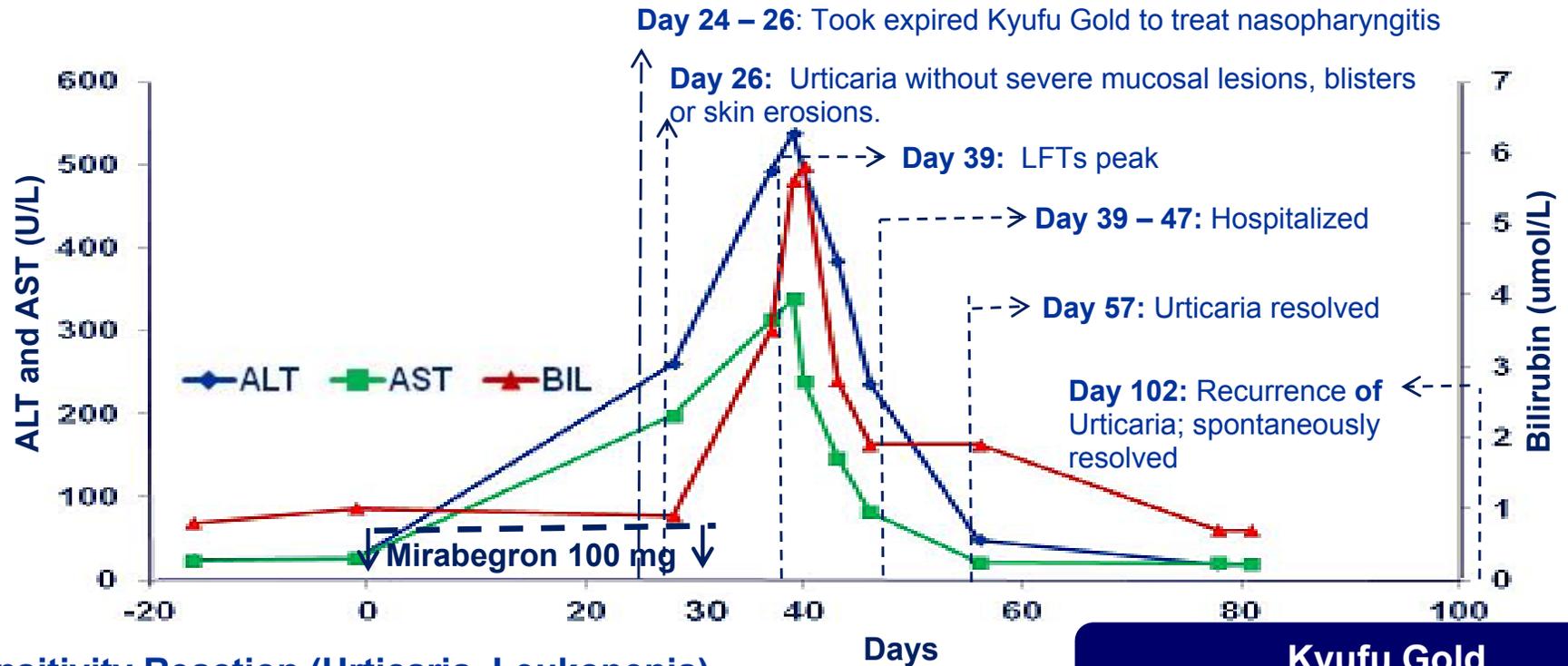
Peak ALT or AST (xULN)

- Placebo (N=2087)
- + Mirabegron 25 mg (N=792)
- ▲ Mirabegron 50 mg (N=2079)
- ★ Mirabegron 100 mg (N=1273)
- ✱ Mirabegron 200 mg (N=166)
- Tolterodine ER 4 mg (N=939)

Peak ALT or AST (xULN)

- ▲ Mirabegron 50 mg (N=792)
- ★ Mirabegron 100 mg (N=803)
- Tolterodine ER 4 mg (N=791)

Review of First Case Fulfilling Hy's Law Laboratory Criteria Patient J5405034-P00244



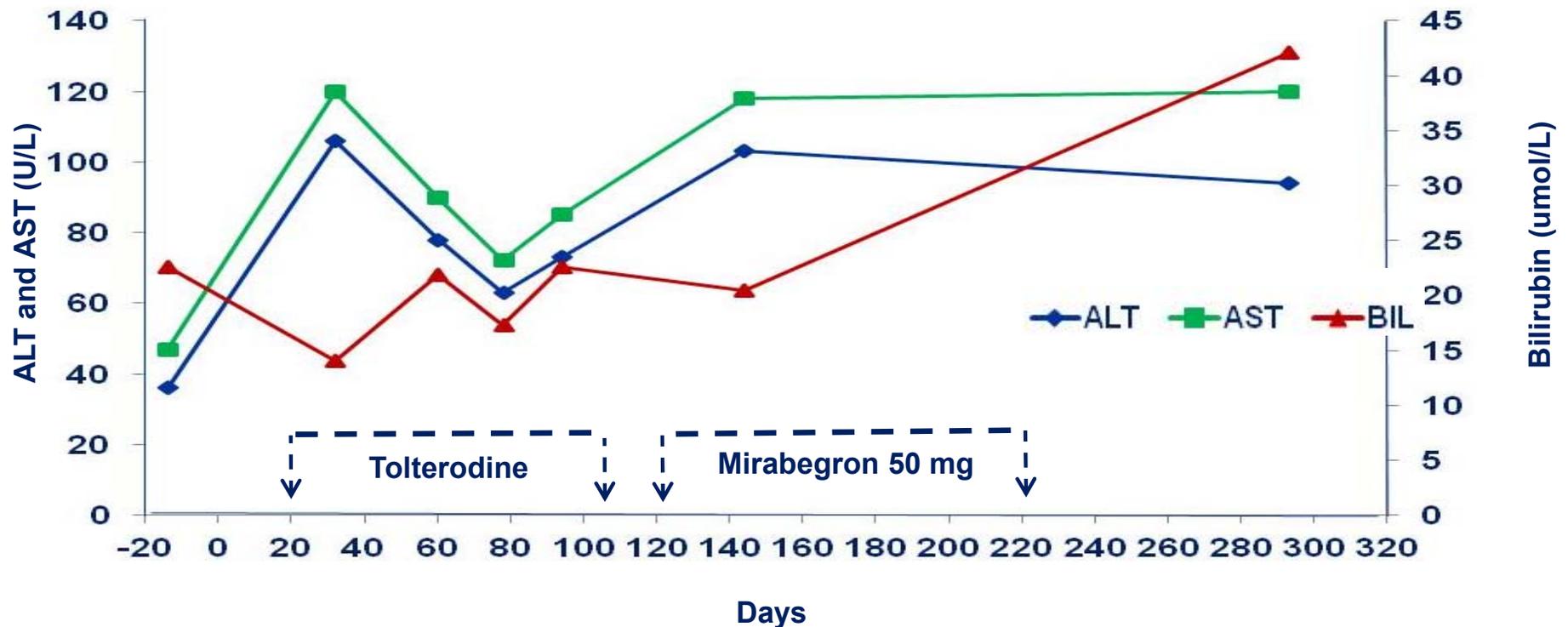
Hypersensitivity Reaction (Urticaria, Leukopenia)

- 74 year old female in Japanese Phase 2 OAB 12-week study
- Investigator: Initially drug-induced urticaria changed to SJS as reported to the investigator by the hospital
- Patient did not consent to allow Investigator access to the hospital medical records
- Independent Adjudication Committee:
 - Urticaria and leukopenia possibly related to mirabegron, with the alternative explanation of hypersensitivity reaction to expired Kyufu Gold
 - Did not meet criteria of SJS based on available information
- Japan-issued mirabegron label lists the adverse reactions of white blood cell count decreased, rash, urticaria and does not list SJS
- Japan-issued Kyufu Gold label states “On rare occasions, the serious symptoms listed may occur: Oculomucocutaneous Syndrome (SJS), Toxic Epidermal Necrolysis (Lyell’s Syndrome); Liver Failure”

| Kyufu Gold | |
|----------------------------------|--|
| Ingredients | In a daily dose (6 capsules) |
| Dilong (Earthworm) Dried Extract | 129 mg (Based on the original formulation conversion of 993.3 mg) |
| Acetaminophen | 600 mg |
| Anhydrous Caffeine | 75 mg |
| Chlorpheniramine Maleate | 7.5 mg |
| Dihydrocodeine Phosphate | 24 mg |
| di-Methylephedrine Hydrochloride | 60 mg |
| Magnesium oxide | 140 mg |

Also contains potato starch, calcium carbonate, calcium carbonate, calcium stearate, gelatin, etc., as additives.

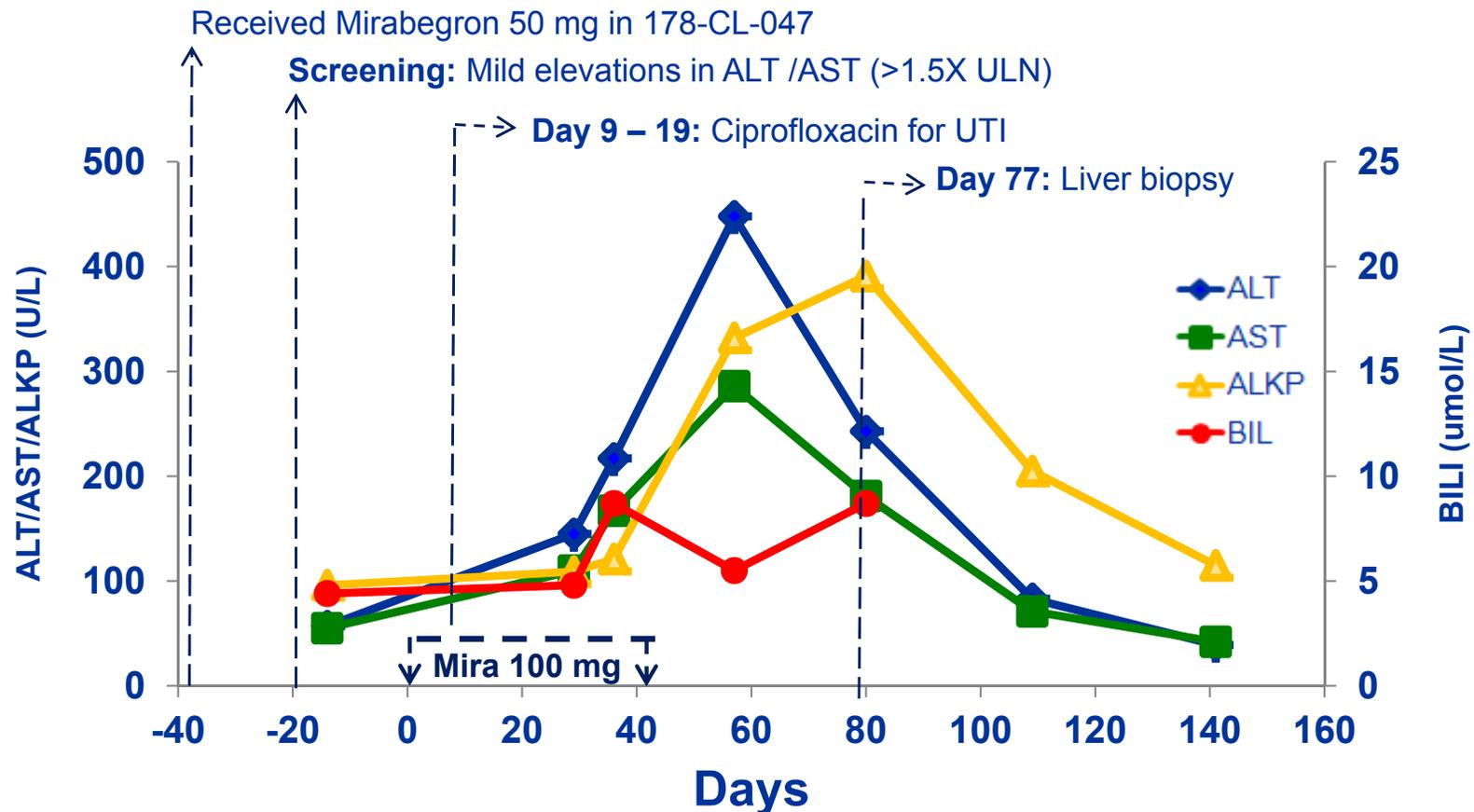
Review of Second Case Fulfilling Hy's Law Laboratory Criteria Patient 3353-1381



Viral Hepatitis; Alcohol Abuse

- 67 year old male in long-term (52-week) controlled study, preceded by the 12-week phase 3 study
- Chronic hepatitis B and a history of alcohol abuse
- Elevated LFTs throughout the long-term (mirabegron 50 mg) and prior 12-week study (tolterodine)

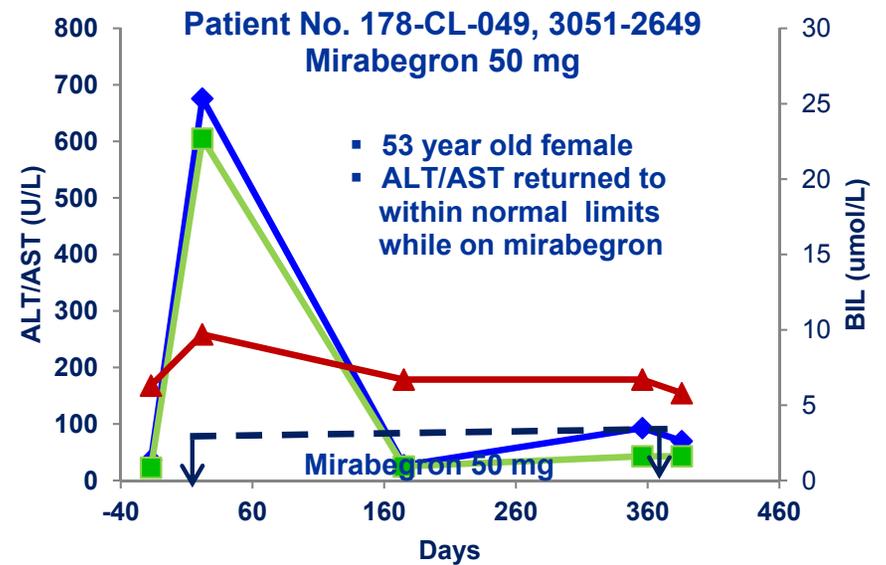
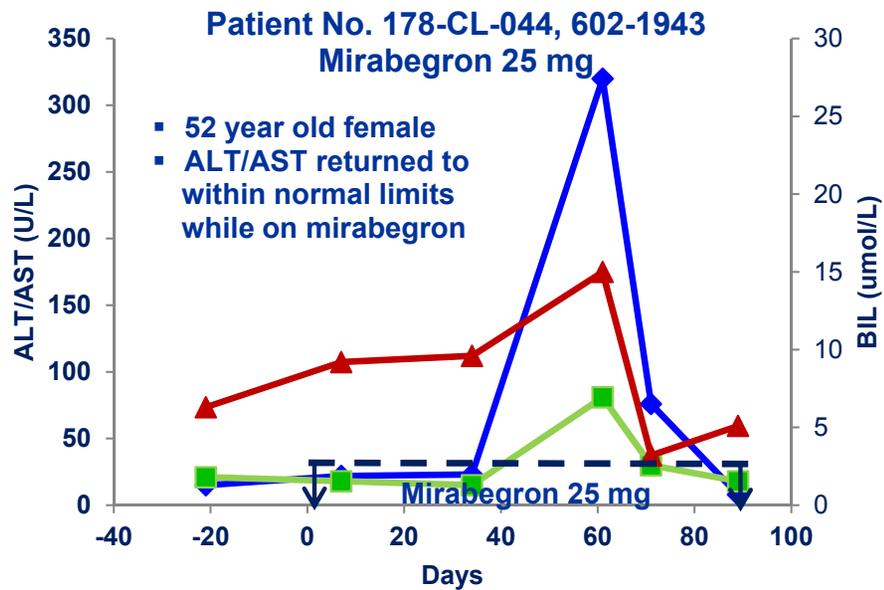
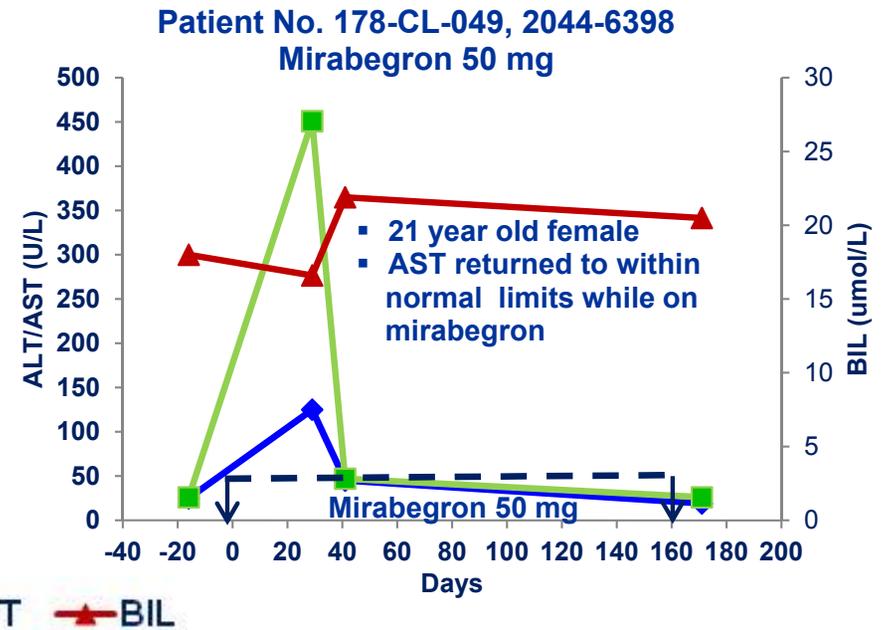
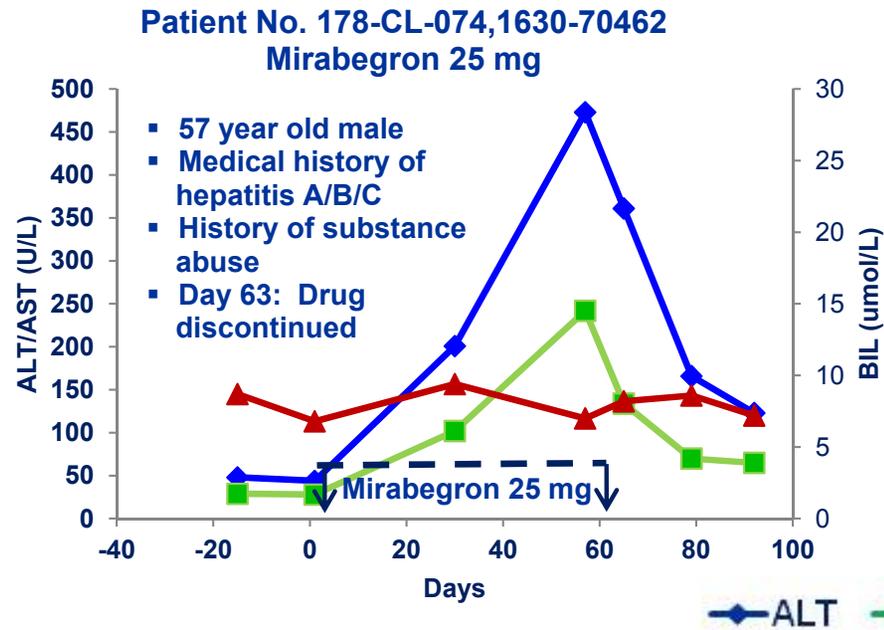
Review of Patient 178-CL-049-1630-6655



History of Hashimoto's thyroiditis

- 58 year old female in long-term (52-week) controlled study, preceded by the 12-week phase 3 study
- Liver biopsy performed on day 77 revealed dense lymphocytic infiltrate and granulomas in the portal tracts with focal destruction of bile ducts, abundant plasma cells and rare mixed eosinophils. Granulomas were also present in the lobules with marked piecemeal necrosis and lobular inflammation; acidophil bodies were noted. No steatosis was seen and focal portal fibrosis was identified on trichrome stain
- Subject had negative viral serology and negative serum antibodies

Review of 4 Cases with Laboratory Criteria of ALT/AST > 10X ULN



In the three cases with no underlying pre-existing liver disease, ALT/AST returned within normal limits on continued mirabegron treatment

Mirabegron Safety

- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - **Hepatotoxicity**
 - **Low frequency (~1%) of transaminase elevations > 3X ULN; No DILI cases without an alternative explanation**
 - Hypersensitivity
- Common Adverse Events
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mirabegron Safety

- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - Hepatotoxicity
 - **Hypersensitivity**
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Plausible Hypersensitivity Reactions: Categorization and Dose Response

Global 12-Week Phase 2/3 Studies

| Hypersensitivity Reaction | Placebo (n =2292) | Mirabegron | | | | Total (n=4759) | Tolterodine (n=1022) |
|---|----------------------|---------------------------|-----------------------------|------------------------------------|-----------------------|-------------------|-------------------------|
| | | ≥ 25 < 50 mg (n = 811) | ≥ 50 < 100 mg (n = 2201) | ≥ 100 mg < 200 mg (n = 1370) | ≥ 200 mg (n = 297) | | |
| Plausible hypersensitivity cases | 3 (0.1%) | 3 (0.4%) | 6 (0.3%) | 10 (0.7%) | 4 (1.3%) | 23 (0.5%) | 5 (0.5%) |
| Immediate | 1 (<0.1%) | 0 | 0 | 1 (0.1%) | 0 | 1 (<0.1%) | 0 |
| Nonimmediate – primarily cutaneous | 1 (<0.1%) | 3 (0.4%) | 6 (0.3%) | 6 (0.4%) | 3 (1.0%) | 18 (0.4%) | 3 (0.3%) |
| Nonimmediate – primarily noncutaneous | 0 | 0 | 0 | 3 (0.2%) | 0 | 3 (0.1%) | 2 (0.2%) |
| Undetermined type | 1 (<0.1%) | 0 | 0 | 1 (0.1%) | 1 (0.3%) | 2 (<0.1%) | 0 |

Long-Term (52-Week) Controlled Study

| Hypersensitivity Reaction | Mirabegron | | | Tolterodine (n=812) |
|---|------------------|-------------------|-------------------|------------------------|
| | 50 mg (N=812) | 100 mg (N=820) | Total (n=1632) | |
| Plausible hypersensitivity cases | 2 (0.2%) | 9 (1.1%) | 11 (0.7%) | 1 (0.1%) |
| Immediate | 0 | 0 | 0 | 0 |
| Nonimmediate – primarily cutaneous | 2 (0.2%) | 7 (0.9%) | 9 (0.6%) | 0 |
| Nonimmediate – primarily noncutaneous | 0 | 1 (0.1%) | 1 (0.1%) | 0 |
| Undetermined type | 0 | 1 (0.1%) | 1 (0.1%) | 1 (0.1%) |

Mirabegron Safety

- Deaths
- **Serious Adverse Events**
 - Neoplasms
 - Hepatotoxicity
 - **Hypersensitivity**
 - **Low frequency of non-immediate, mostly cutaneous hypersensitivity: generally mild-moderate, reversible and more often at doses \geq 100 mg**
- Common Adverse Events
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- **Common Adverse Events**
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
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 - Framingham Risk Estimates

Treatment Emergent Adverse Events

| | 12-Week Phase 3 Studies | | | Long-Term (52-Week) Controlled Study | |
|-------------------------|-------------------------|-----------------------------------|--------------------------|--------------------------------------|--------------------------|
| Patients, n (%) | Placebo (n = 1380) | Mirabegron 50 mg (n = 1375) | Tolterodine (n = 495) | Mirabegron 50 mg (n = 812) | Tolterodine (n = 812) |
| Overall | 658 (47.7) | 647 (47.1) | 231 (46.7) | 485 (59.7) | 508 (62.6) |
| Hypertension | 105 (7.6) | 103 (7.5) | 40 (8.1) | 75 (9.2) | 78 (9.6) |
| Nasopharyngitis | 35 (2.5) | 54 (3.9) | 14 (2.8) | 32 (3.9) | 25 (3.1) |
| Urinary tract infection | 25 (1.8) | 40 (2.9) | 10 (2.0) | 48 (5.9) | 52 (6.4) |
| Headache | 42 (3.0) | 44 (3.2) | 18 (3.6) | 33 (4.1) | 20 (2.5) |
| Dry mouth | 29 (2.1) | 23 (1.7) | 50 (10.1) | 23 (2.8) | 70 (8.6) |
| Tachycardia | 8 (0.6) | 17 (1.2) | 0 | 8 (1.0) | 25 (3.1) |

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- **Common Adverse Events**
 - **UTI and tachycardia related to mirabegron and > placebo; dry mouth similar to placebo**
- Cardiovascular
 - QT
 - Phase 1 healthy volunteer vital signs
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- **Cardiovascular**
 - QT
 - Phase 1 healthy volunteer vital signs
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QT

- **Nonclinical in vitro data showed that neither mirabegron nor the 5 most abundant human metabolites significantly altered the I_{kr} (hERG) or other ion channels**
- **Mirabegron and its metabolites did not significantly alter the action potential duration in guinea pig papillary muscle**
- **In the dog ventricular wedge model, mirabegron did not prolong the QT interval**
- **In the TQT study, at the proposed therapeutic dose of 50 mg and at 100 mg (2.6 fold increase in exposure relative to 50 mg), the upper bound of the 1 sided 95% confidence interval for the QT_c did not exceed 10 msec at any point in time**
- **In the TQT study at the suprathereapeutic dose of 200 mg (6.5 fold increase exposure relative to 50 mg), the QT_c upper bound exceeded 10 msec in females but not males**
- **No QT_c increase at the highest potential exposure in OAB patients at the therapeutically recommended mirabegron dose of 50 mg**

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- **Cardiovascular**
 - QT
 - **Phase 1 healthy volunteer vital signs**
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Phase 1 (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 |
| | 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) |

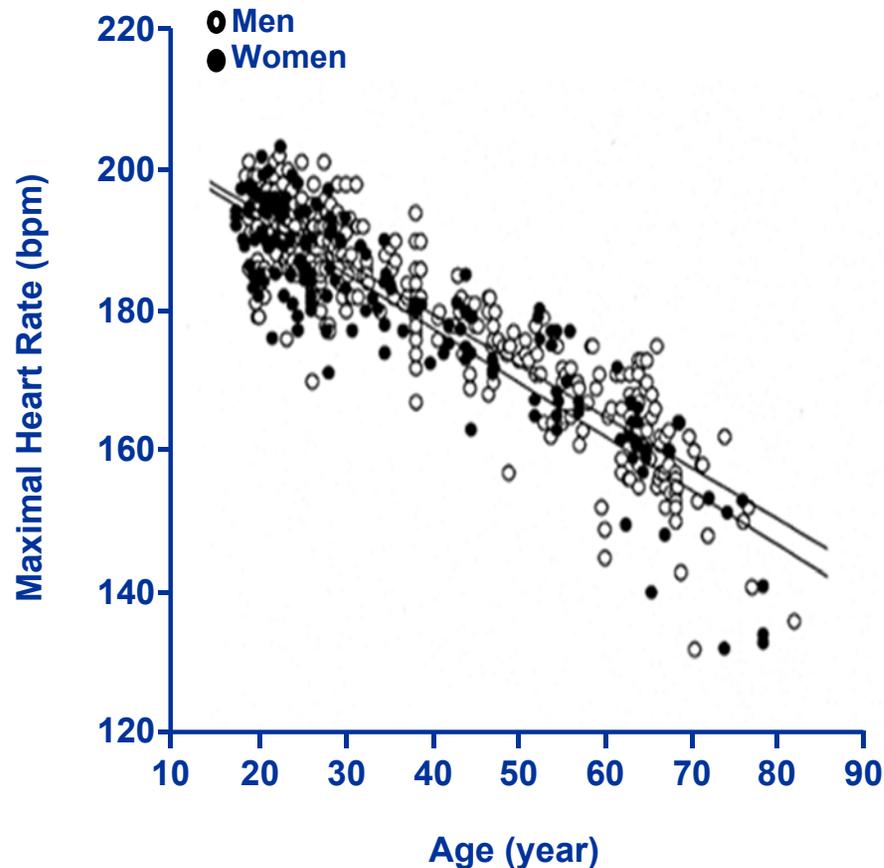
* Mean Area Under the Effective Change Curve over 11.5 hrs for -031 and 24 hrs for -077

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 |

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

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

2. Condition-Dependent Augmentation of Phase 1 Vital Sign Changes:

- Protocol-specified in-unit confinement with limited activity
- Protocol-specified supine vital sign measurements

- 178- CL-077 (TQT) median age = 31 years; measurement timed 3 hrs post-dose
- 178-CL-081 (IOP) median age = 34 years; measurement timed 2 – 4 hrs post-dose

| Parameter | Pulse Rate (bpm) | | SBP (mm Hg) | | DBP (mm Hg) | |
|---------------------------------|--|--|--|--|--|--|
| | Study 178-CL-077 Mirabegron 100 mg | Study 178-CL-081 Mirabegron 100 mg | Study 178-CL-077 Mirabegron 100 mg | Study 178-CL-081 Mirabegron 100 mg | Study 178-CL-077 Mirabegron 100 mg | Study 178-CL-081 Mirabegron 100 mg |
| Day 10 | | | | | | |
| n | 82 | 158 | 82 | 158 | 82 | 158 |
| Baseline mean (SE) | 63.0 (1.00) | 70.2 (0.88) | 109.5 (1.13) | 123.1 (0.94) | 67.1 (0.77) | 76.0 (0.65) |
| Mean difference vs placebo (SE) | 9.3 (0.88) | 4.4 (0.84) | 7.7 (1.03) | 1.1 (1.14) | 4.1 (0.99) | 1.1 (0.82) |
| 95% 2-sided CI | (7.51, 11.02) | (2.7, 6.0) | (5.64, 9.75) | (-1.1, 3.4) | (2.11, 6.07) | (-0.5, 2.7) |

Study 178-CL-077

- In-unit
- Supine

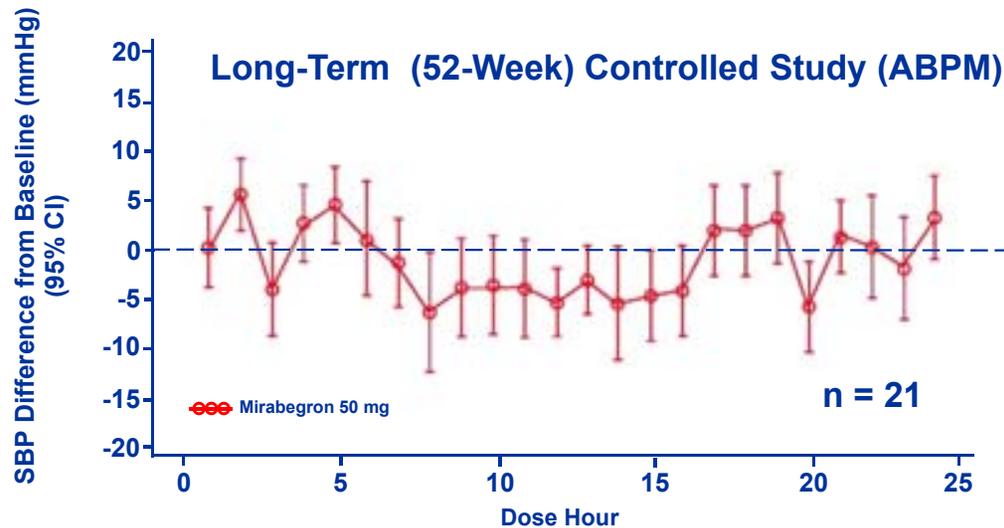
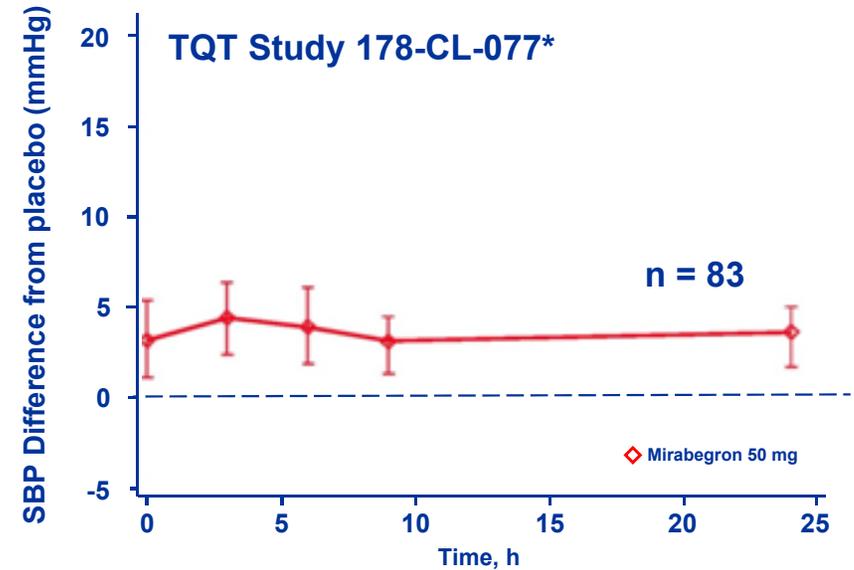
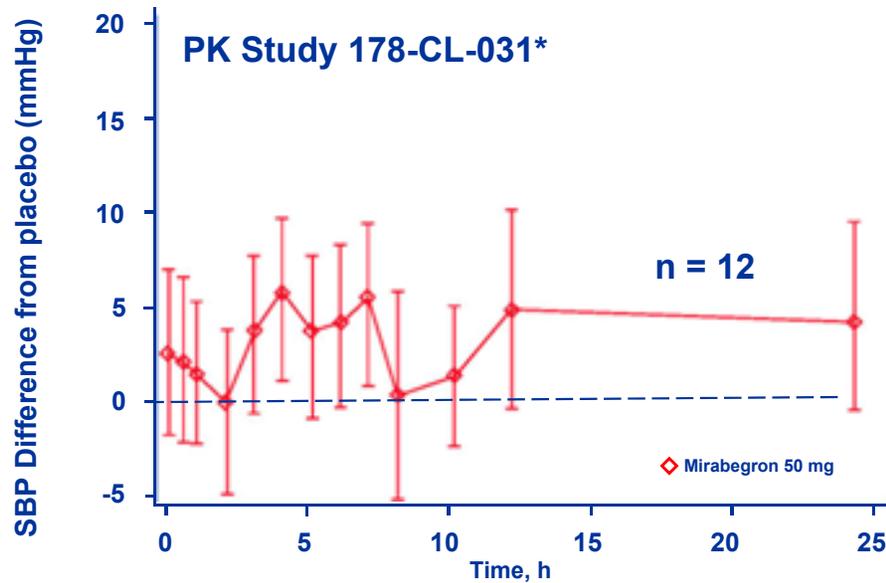
Study 178-CL-081

- Outpatient
- Sitting quietly

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

3. 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

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- **Cardiovascular**
 - QT
 - **Phase 1 healthy volunteer vital signs**
 - **Difference in age and measurement conditions account for the differences in vital sign changes between healthy volunteers and OAB patients**
 - Phase 2/3 OAB Patients
 - Vital Signs
 - Adverse Events
 - Framingham Risk Estimates

Mirabegron Safety

- Deaths
- Serious Adverse Events
 - Neoplasms
 - Hepatotoxicity
 - Hypersensitivity
- Common Adverse Events
- **Cardiovascular**
 - QT
 - Phase 1 healthy volunteer vital signs
 - **Phase 2/3 OAB Patients**
 - **Vital Signs**
 - **Adverse Events**
 - **Framingham Risk Estimates**

Cardiovascular Safety Assessment of EU/NA Phase 3 Studies

- **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
 - ECG Measurements
 - Adverse Events and SAE
 - Cardiovascular Adjudication Committee
- **Analysis of Pulse and BP**
 - 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.

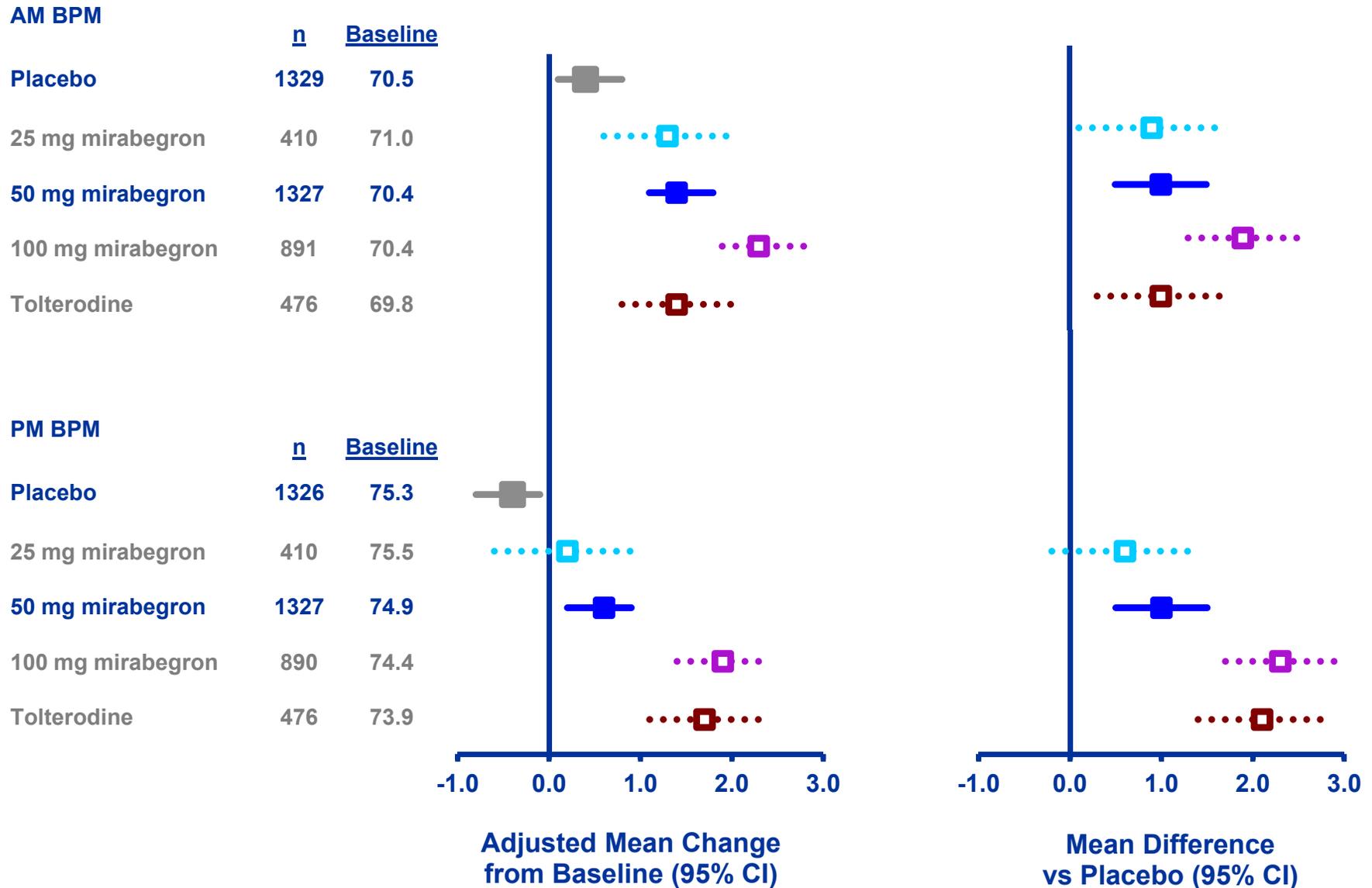
- – Represents an individual vital sign measurement that was not included in the calculation of a patient’s average value per visit and time of day
- – Represents an individual vital sign measurement that was included in the calculation of a patient’s average value per visit and time of day

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

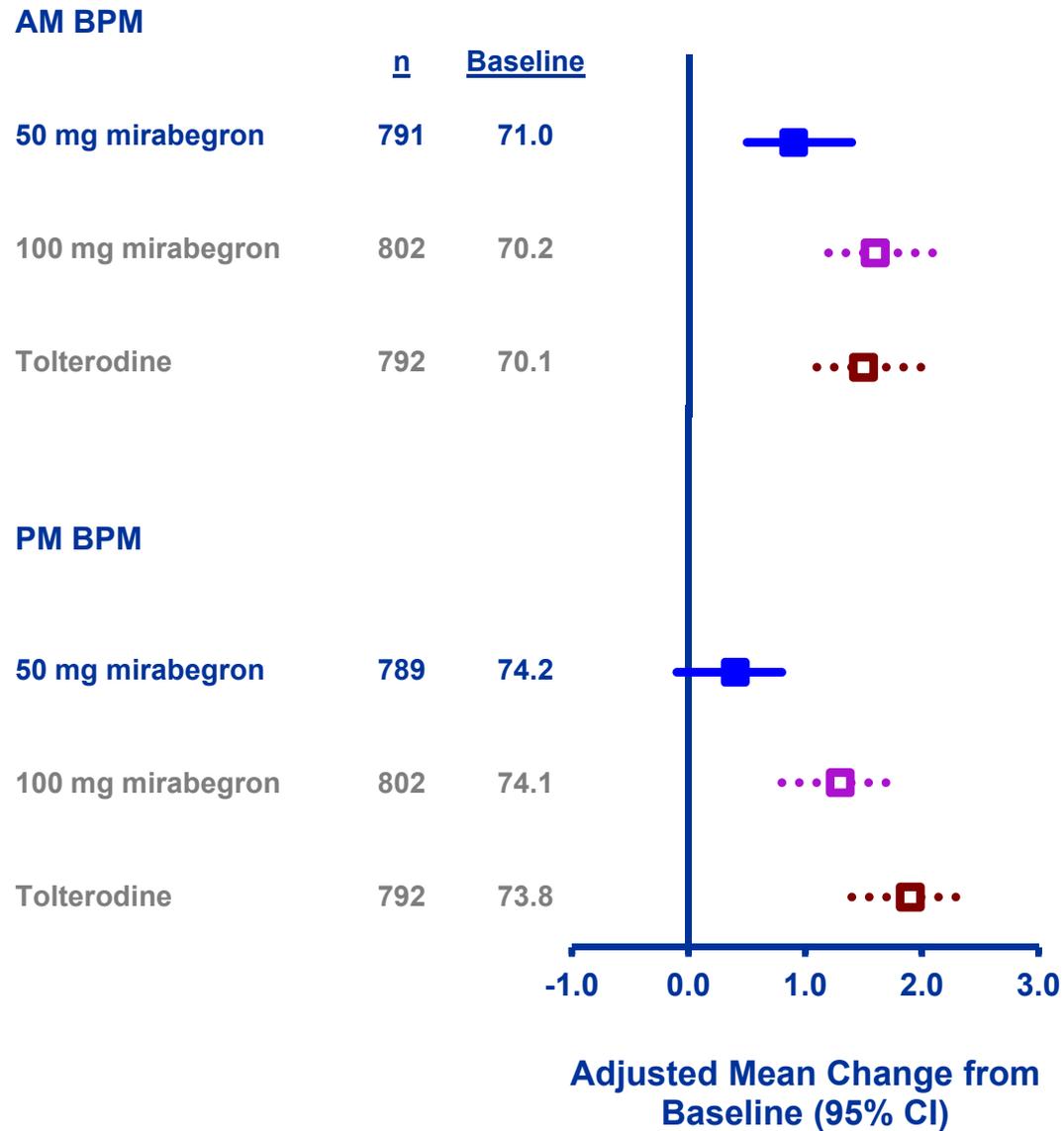
Verberk WJ, Kroon AA, Kessels AGH, et al. The optimal scheme of self blood pressure measurement as determined from ambulatory blood pressure recordings. *J Hypertension* 2006;24:1541-1548.

EU/NA 12-Week Phase 3 Studies

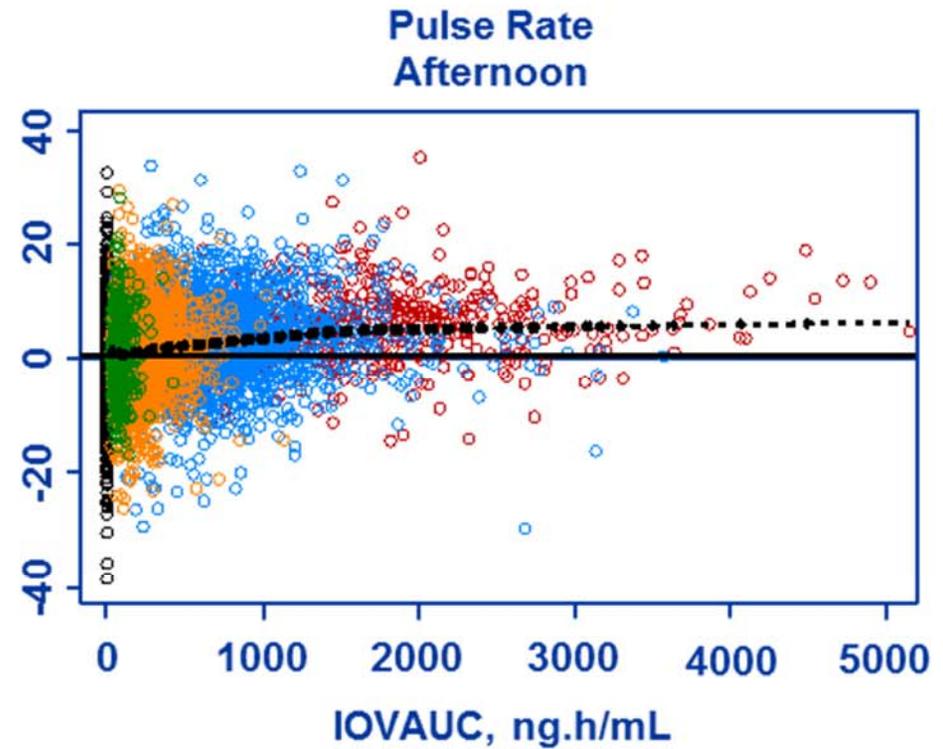
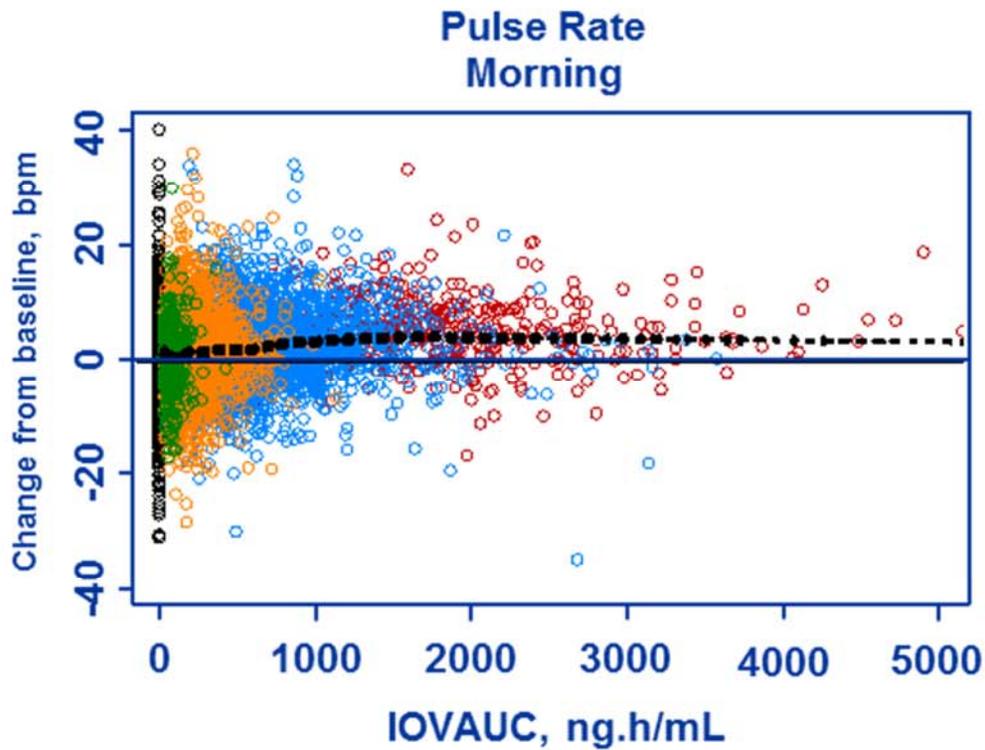
Change from Baseline to Final Visit Pulse (Patient Diary)



EU/NA 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

EU/NA 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 \geq 2 BPM | 171 (14.3%) | 247 (20.5%) |
| Change from baseline \geq 5 BPM | 77 (6.4%) | 87 (7.2%) |
| Change from baseline \geq 10 BPM | 13 (1.1%) | 13 (1.1%) |
| Change from baseline \geq 15 BPM | 4 (0.3%) | 2 (0.2%) |

Long-term (52-Week) Controlled Study

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

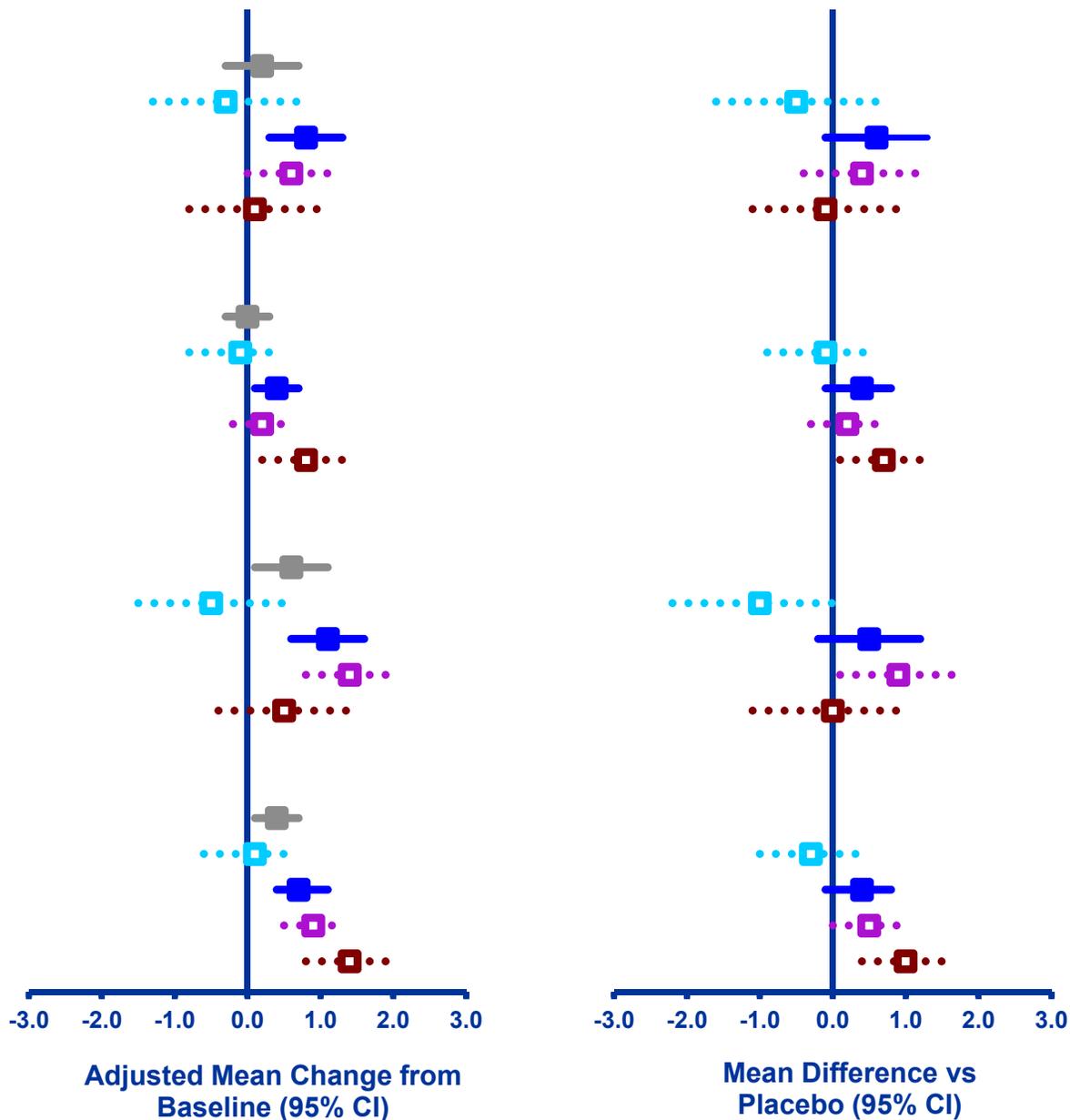
Tachycardia (AE and Pulse)

| | 12-Week Phase 3 Studies | | Long-term (52-Week) Controlled Study | | |
|--|-------------------------|---------------------|--------------------------------------|---------------------|--------------------------|
| n (%) of Patients | Placebo (n = 1380) | Mirabegron | Mirabegron | | Tolterodine (n = 812) |
| | | 50 mg (n = 1375) | 50 mg (n = 812) | 100 mg (n = 820) | |
| 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 \geq 100 bpm | 36 (2.6%) | 39 (2.8%) | 19 (2.3%) | 35 (4.3%) | 32 (3.9%) |
| Tachycardia as AE and pulse \geq 100 bpm | 2 (0.1%) | 5 (0.4%) | 4 (0.5%) | 5 (0.6%) | 5 (0.6%) |

EU/NA 12-Week Phase 3 Studies

Change from Baseline to Final Visit SBP/DBP (Patient Diary)

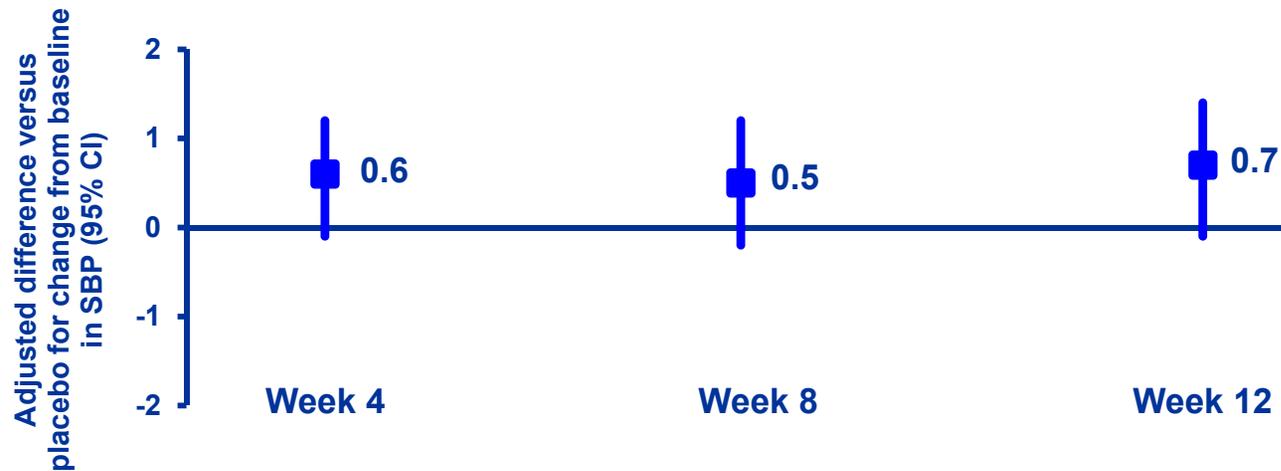
| | <u>N</u> | <u>Baseline</u> |
|-------------------|----------|-----------------|
| AM SBP | | |
| Placebo | 1329 | 125.9 |
| 25 mg mirabegron | 410 | 129.2 |
| 50 mg mirabegron | 1327 | 126.4 |
| 100 mg mirabegron | 891 | 125.0 |
| Tolterodine | 476 | 128.2 |
| AM DBP | | |
| Placebo | 1329 | 77.1 |
| 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 |



EU/NA 12-Week Phase 3 Studies

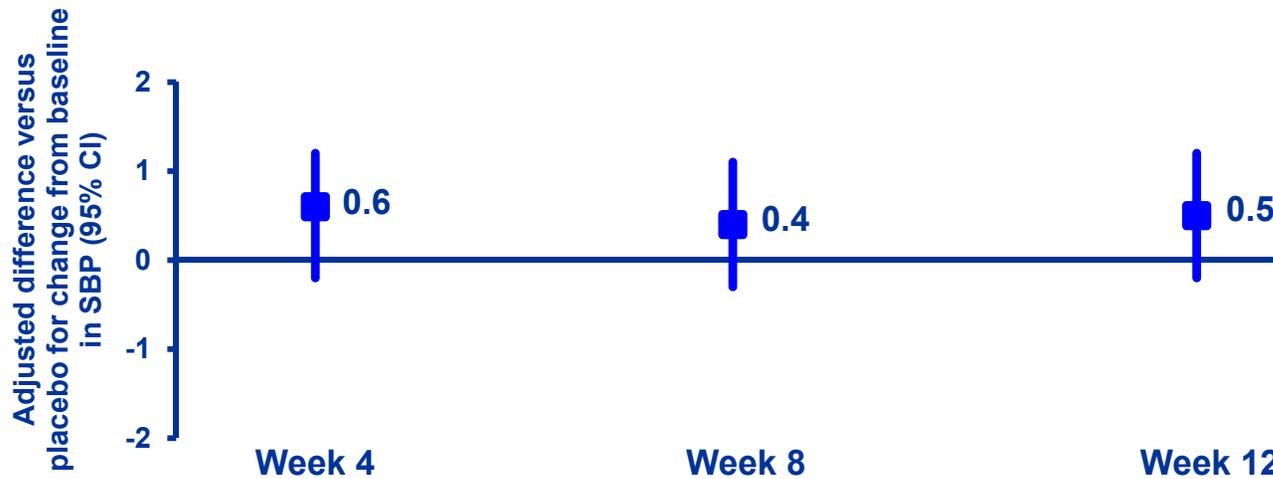
Adjusted Differences versus Placebo for Change from Baseline in SBP at Each Visit

SBP AM



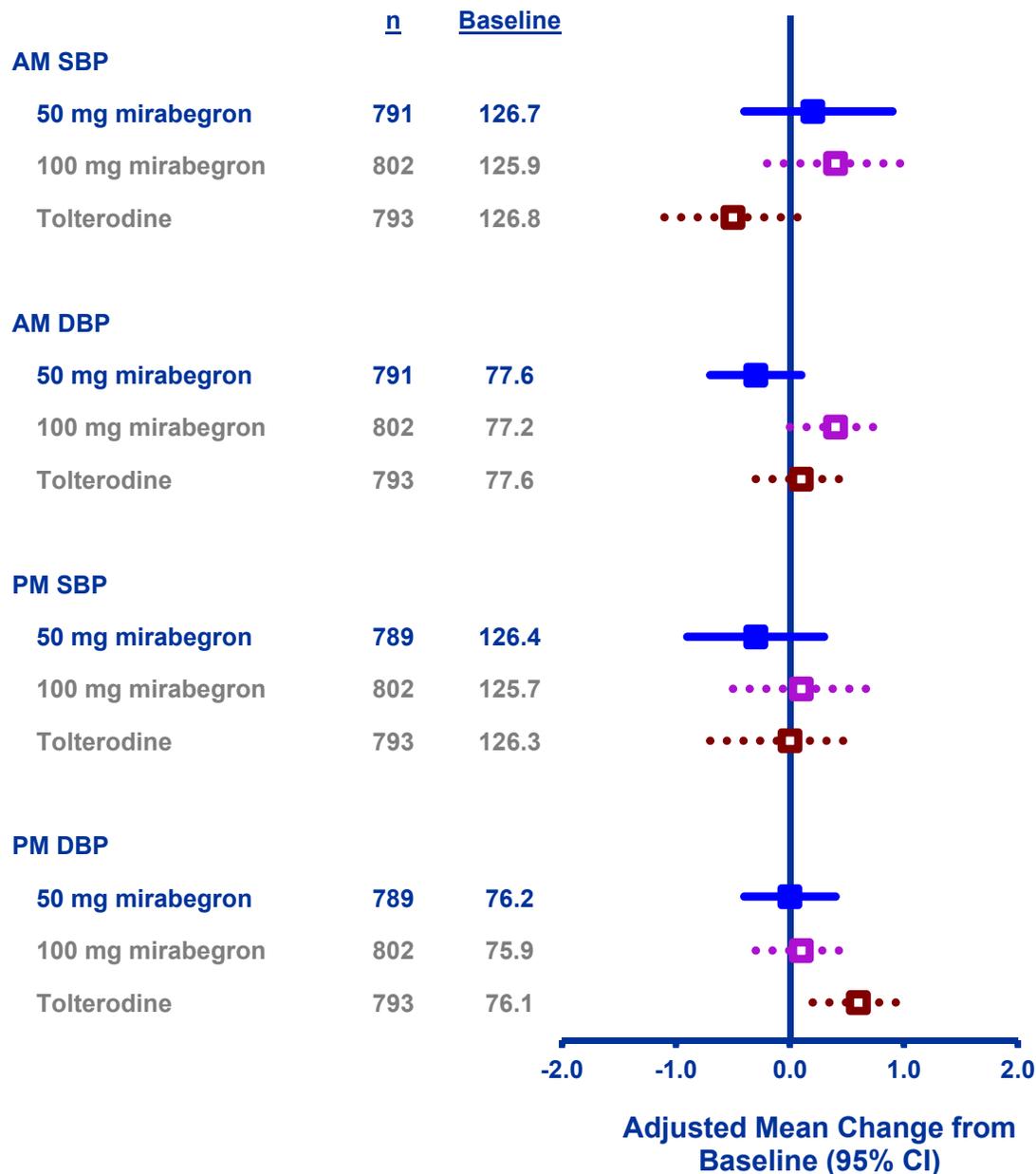
Mirabegron 50 mg

SBP PM



Long-Term (52-Week) Controlled Study

Change from Baseline to Final Visit SBP/DBP (Patient Diary)

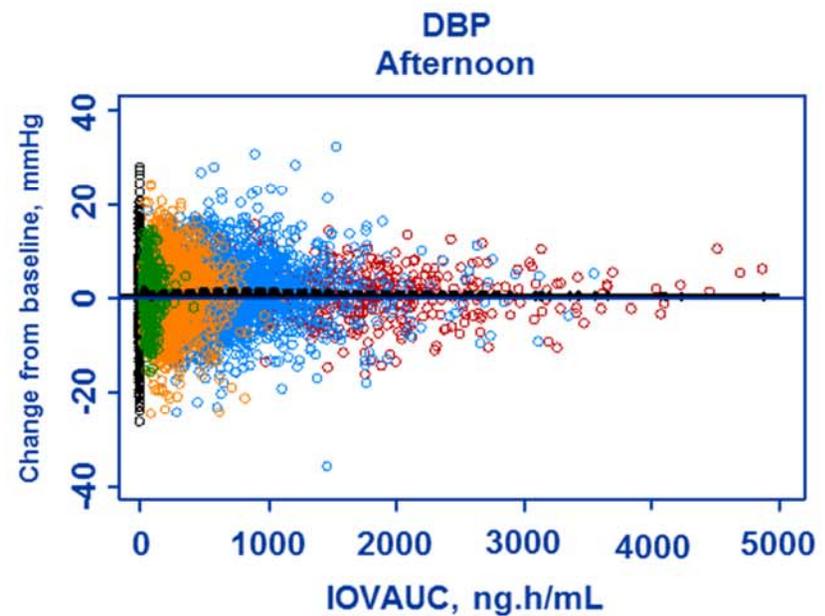
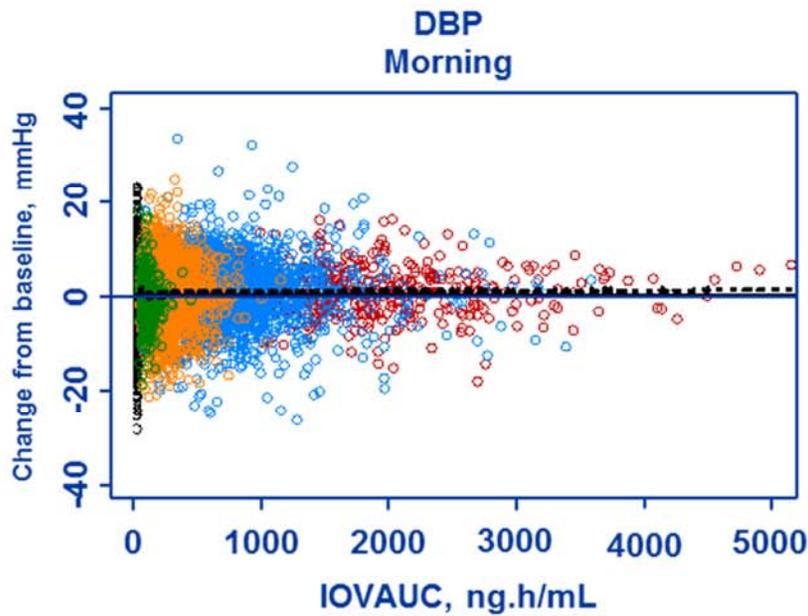
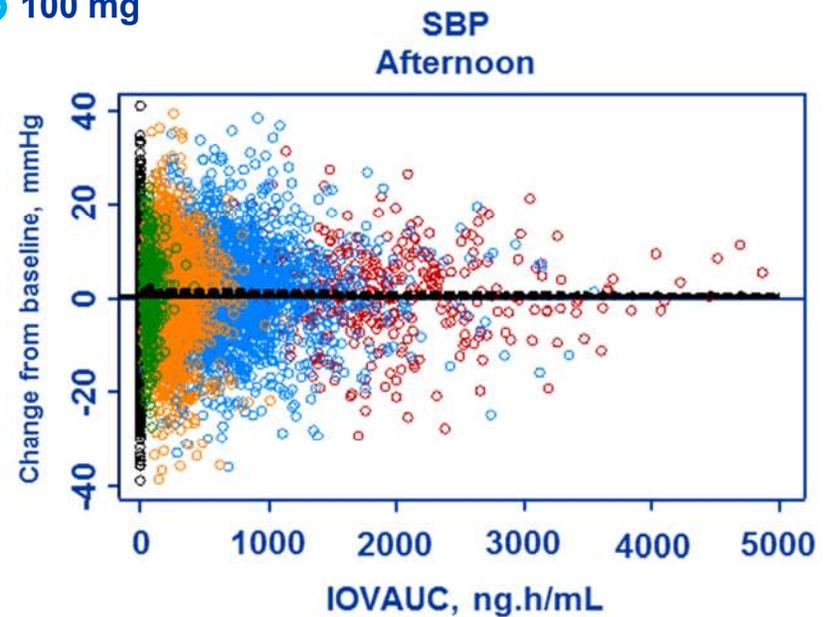
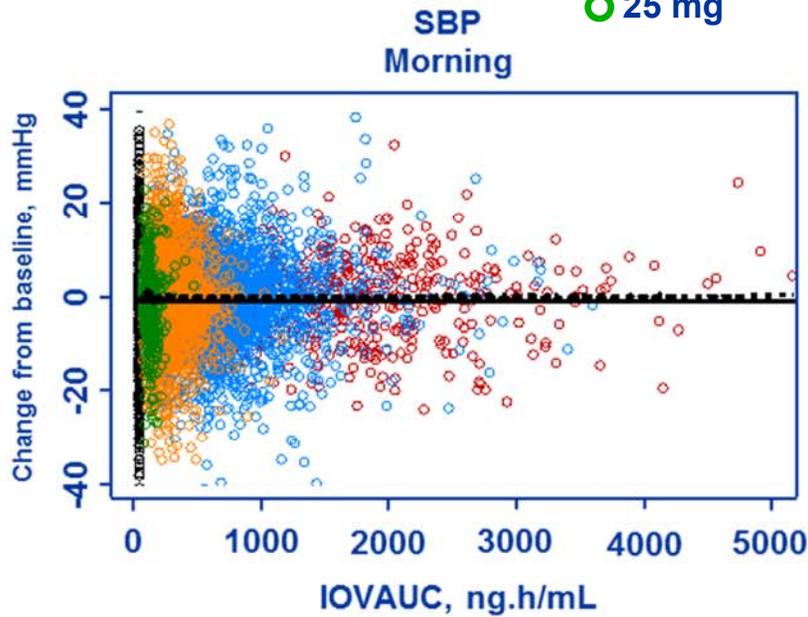


Categorical Analysis of Blood Pressure

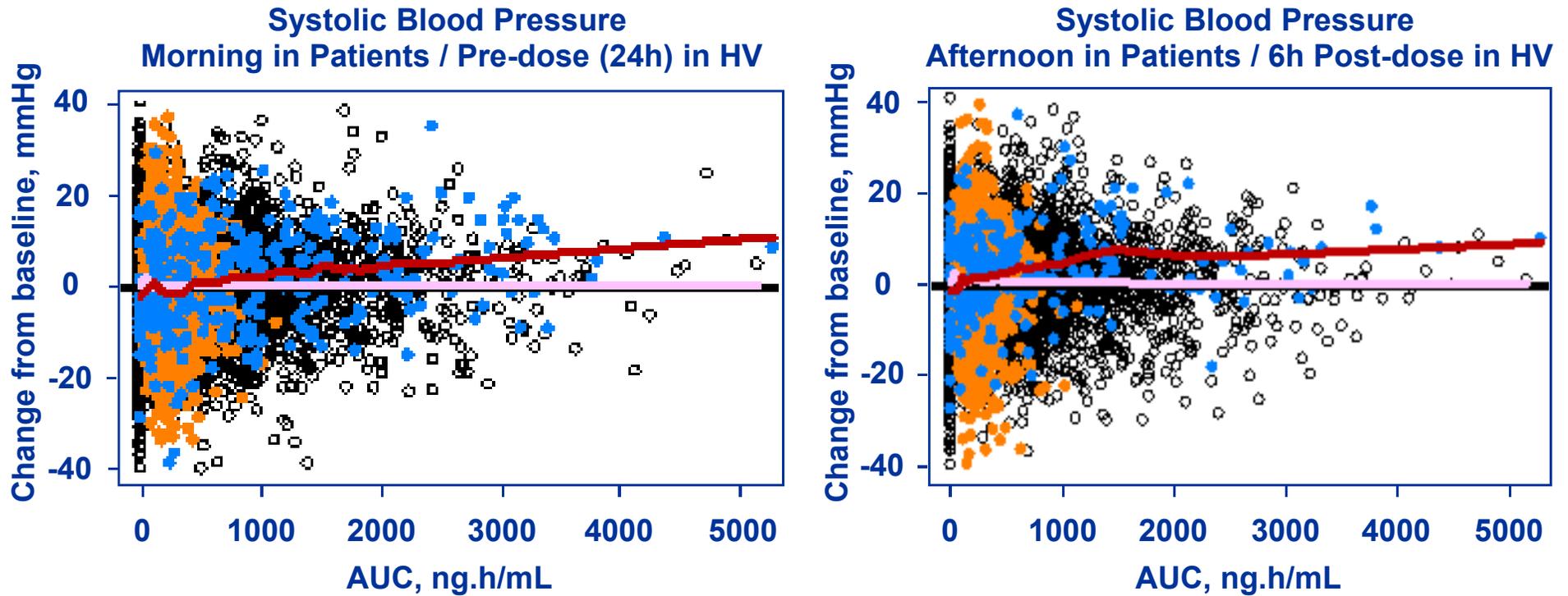
EU/NA 12-Week Phase 3 Studies

| 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 \geq 2 mm Hg | 252 (21.1%) | 255 (21.2%) |
| Change from baseline \geq 5 mm Hg | 136 (11.4%) | 140 (11.6%) |
| Change from baseline \geq 10 mm Hg | 28 (2.3%) | 35 (2.9%) |
| Change from baseline \geq 15 mm Hg | 8 (0.7%) | 8 (0.7%) |
| Change from baseline \geq 20 mm Hg | 6 (0.5%) | 5 (0.4%) |
| DBP AM | (n = 1196) | (n = 1202) |
| 3 Consecutive Post-Baseline Visits | | |
| Change from baseline \geq 2 mm Hg | 170 (14.2%) | 219 (18.2%) |
| Change from baseline \geq 5 mm Hg | 62 (5.2%) | 80 (6.7%) |
| Change from baseline \geq 10 mm Hg | 11 (0.9%) | 10 (0.8%) |
| Change from baseline \geq 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



- OAB patients; 50mg
- OAB patients; 25, 100, 200 mg
- Healthy volunteers; 25, 50, 100, 200, 300 mg
- OAB patients; all doses (25, 50, 100, 200 mg)
- HV; all doses (25, 50, 100, 200, 300 mg)

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

| | 12-Week Phase 3 Studies | | Long-Term (52-Week) Controlled Study | | |
|--|-------------------------|-----------------------------------|--------------------------------------|---------------------|--------------------------|
| | Placebo (n = 1380) | Mirabegron 50 mg (n = 1375) | Mirabegron | | Tolterodine (n = 812) |
| | | | 50 mg (n = 812) | 100 mg (n = 820) | |
| 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**

Cardiovascular Adjudicated Events

Global 12-Week Phase 2/3 Studies

| CV Event | Placebo (n = 2142) | Mirabegron | |
|-----------------------------------|-----------------------|---------------------|--------------------------|
| | | 50 mg (n = 2131) | Total (n = 4414) |
| MACE | 4 (0.2%) | 0 | 2 (<0.1%) |
| RR versus placebo (95% CI) | | | 0.24 (0.02, 1.69) |
| Nonfatal MI | 0 | 0 | 0 |
| Nonfatal stroke | 3 (0.1%) | 0 | 2 (<0.1%) |
| CV Death | 1 (<0.1%) | 0 | 0 |

Long-Term (52-Week) Controlled Study

| CV Event | Mirabegron | | | Tolterodine (n = 812) |
|---------------------------------------|--------------------------|---------------------|--------------------------|--------------------------|
| | 50 mg (n = 812) | 100 mg (n = 820) | Total (n = 1632) | |
| MACE | 6 (0.7%) | 0 | 6 (0.4%) | 4 (0.5%) |
| RR versus tolterodine (95% CI) | 1.50 (0.35, 7.27) | | 0.75 (0.18, 3.60) | |
| Nonfatal MI | 2 (0.2%) | 0 | 2 (0.1%) | 1 (0.1%) |
| Nonfatal stroke | 3 (0.4%) | 0 | 3 (0.2%) | 1 (0.1%) |
| CV Death | 1 (0.1%) | 0 | 1 (0.1%) | 2 (0.2%) |

Framingham Risk Estimates

- **Post-hoc analysis prepared at the request of FDA using the Cox proportional hazard model described by D'Agostino et al. 2008. Risk estimates:**
 - Range from 1 – 30%
 - Represent the predicted risk of a CVD event (CHD, stroke, PAD, HF) within 10 years
- **Risk factors include:**
 - Sex
 - Age
 - Total Cholesterol and HDL
 - Smoking
 - Diabetes
 - Treated Hypertension
 - SBP
- **Prepared using SBP values:**
 - Mean: AM/PM, AM alone, PM alone
 - Maximum: AM/PM, AM alone, PM alone
- **Analyzed for:**
 - EU/NA 12-week phase 3 studies (individual studies and pooled)
 - Long-term (52-week) controlled study

Framingham Risk Score (FRS) Analysis

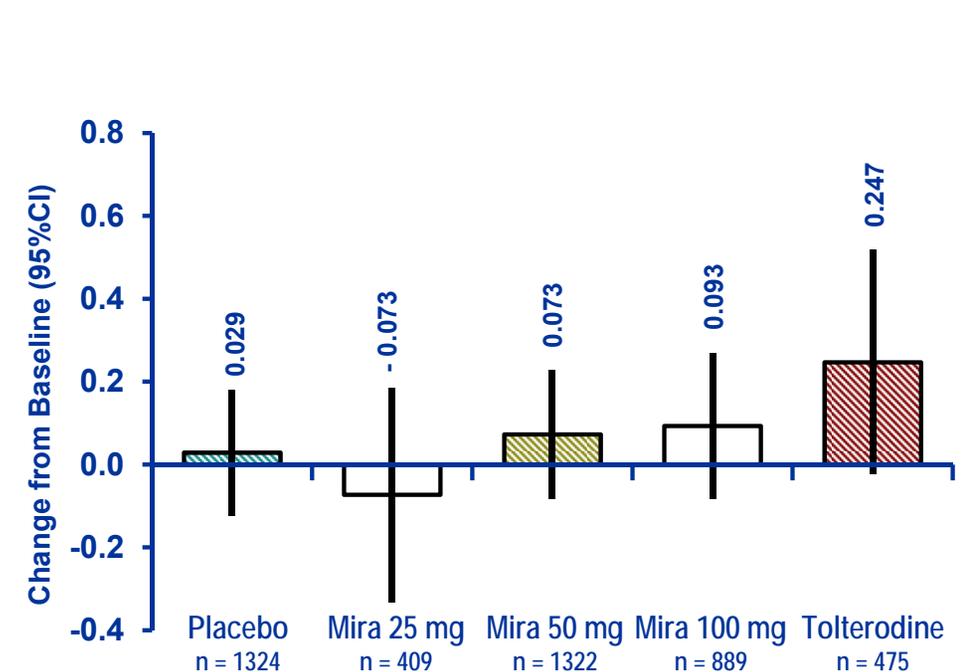
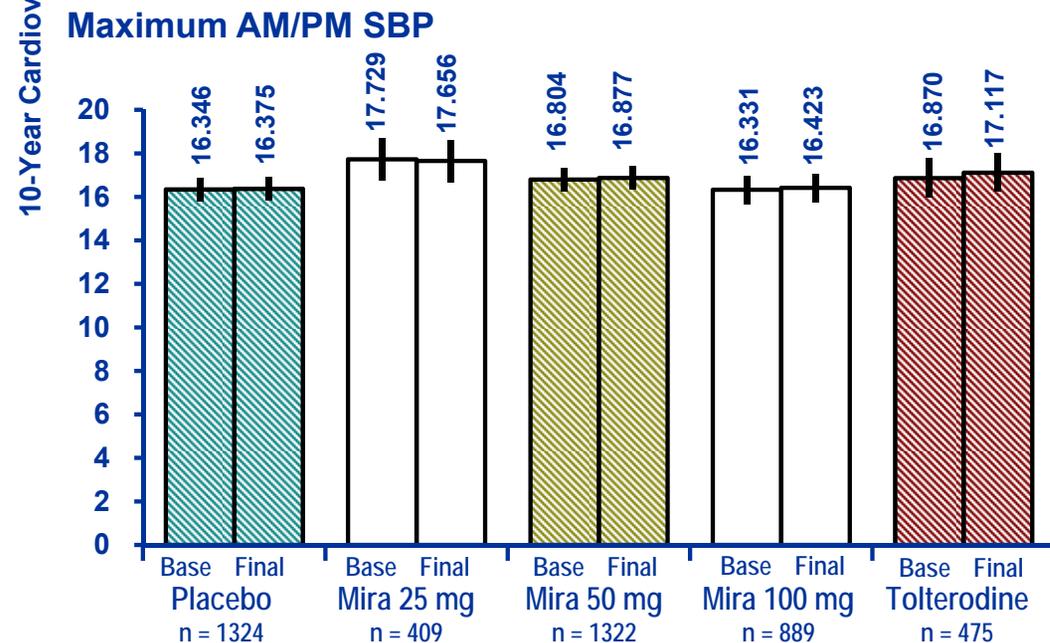
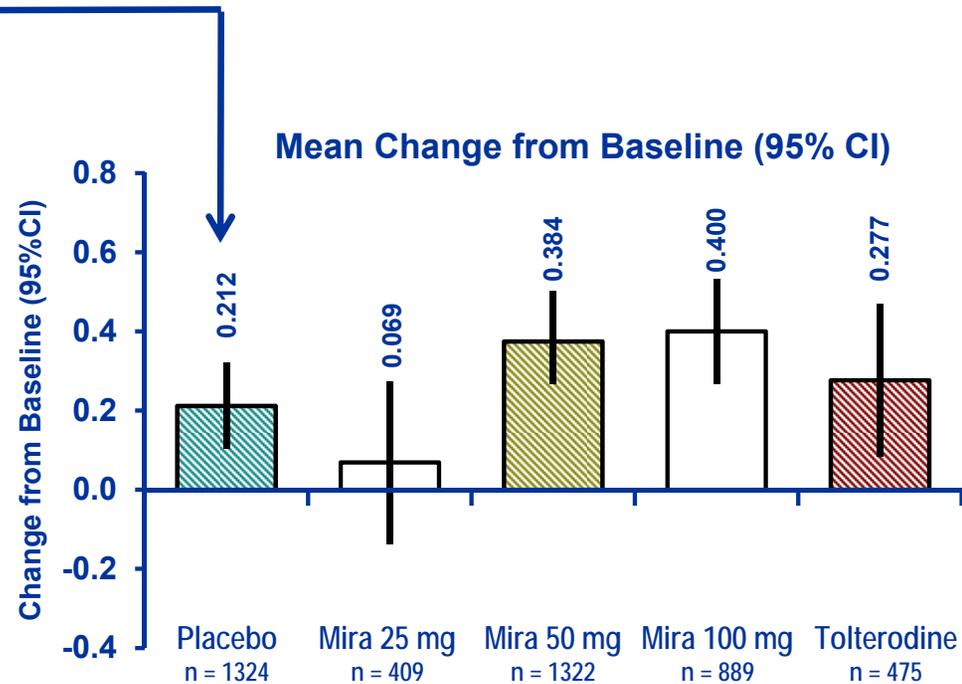
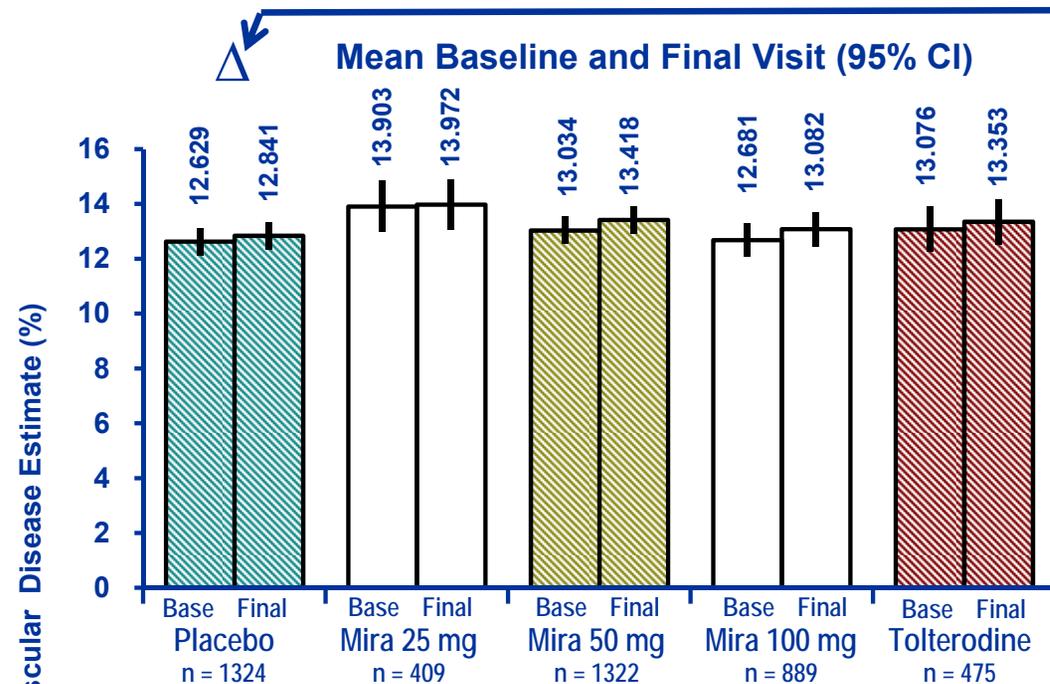
Risk factors for women include:

| Points | Age (years) | HDL (mg/dL) | Total Cholesterol (mg/dL) | SBP Not Treated (mm Hg) | SBP Treated (mm Hg) | Smoker | Diabetic |
|--------|-------------|-------------|---------------------------|-------------------------|---------------------|--------|----------|
| -3 | | | | <120 | | | |
| -2 | | 60+ | | | | | |
| -1 | | 50-59 | | | <120 | | |
| 0 | 30-34 | 45-59 | <160 | 120-129 | | No | No |
| 1 | | 35-44 | 160-199 | 130-139 | | | |
| 2 | 35-39 | <35 | | 140-149 | 120-129 | | |
| 3 | | | 200-239 | | 130-139 | Yes | |
| 4 | 40-44 | | 240-279 | 150-159 | | | Yes |
| 5 | 45-49 | | 280+ | 160+ | 140-149 | | |
| 6 | | | | | 150-159 | | |
| 7 | 50-54 | | | | 160+ | | |
| 8 | 55-59 | | | | | | |
| 9 | 60-64 | | | | | | |
| 10 | 65-69 | | | | | | |
| 11 | 70-74 | | | | | | |
| 12 | 75+ | | | | | | |

D'Agostino et al. 2008

EU/NA 12-Week Phase 3 Studies (Pooled) Framingham Risk Estimates

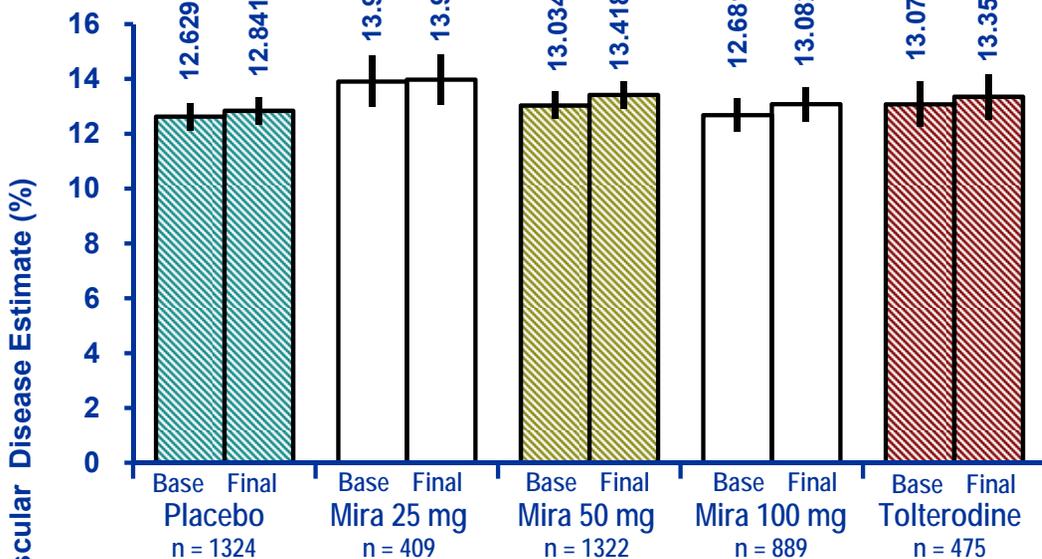
Mean AM/PM SBP



EU/NA 12-Week Phase 3 Studies (Pooled) Framingham Risk Estimates

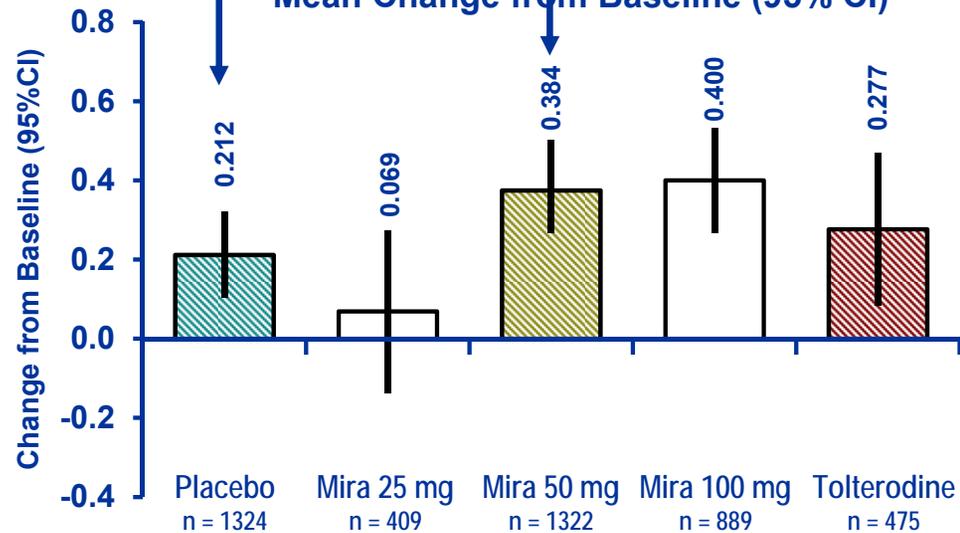
Mean AM/PM SBP

Mean Baseline and Final Visit (95% CI)

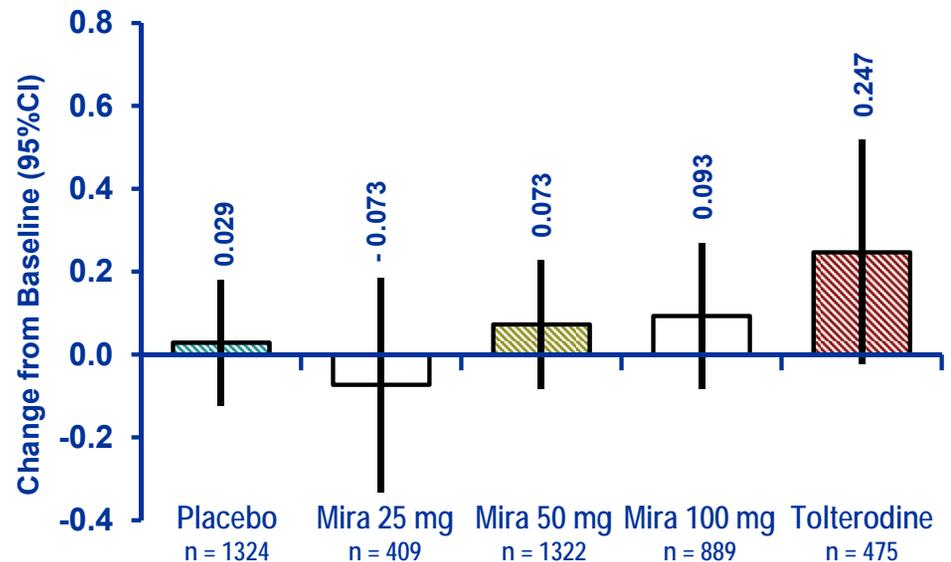
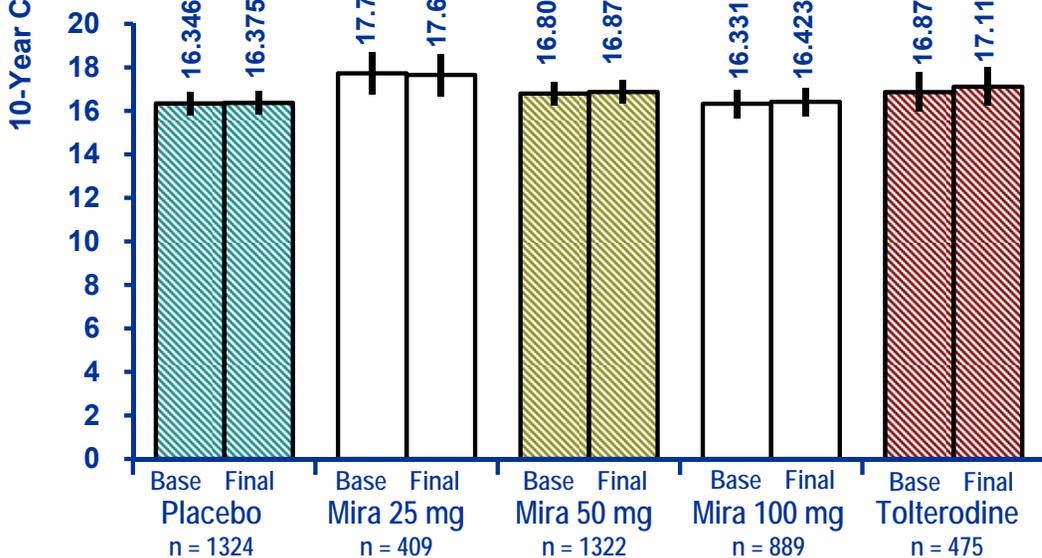


$\Delta = 0.172$

Mean Change from Baseline (95% CI)



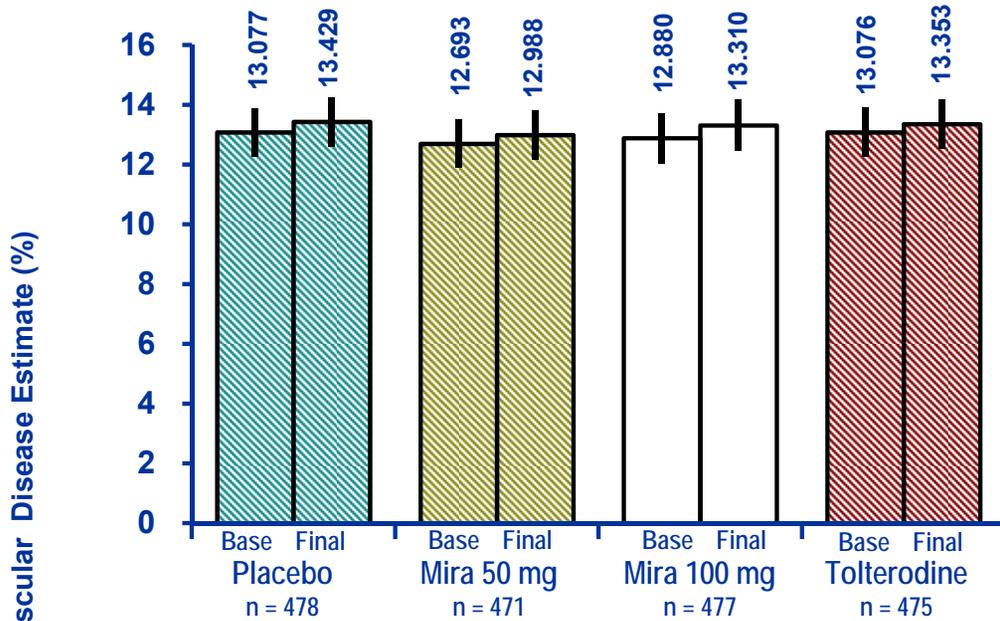
Maximum AM/PM SBP



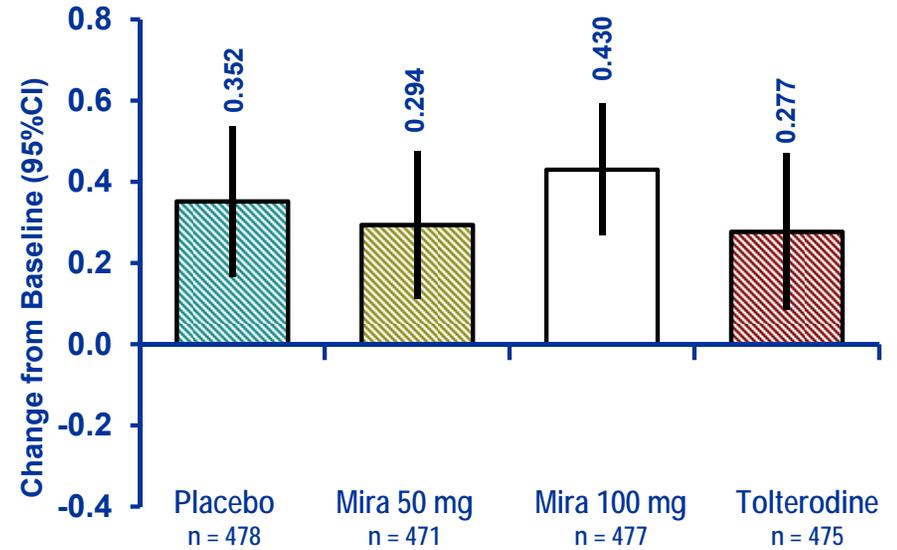
12-Week Phase 3 Study (178-CL-046) Framingham Risk Estimates

Mean AM/PM SBP

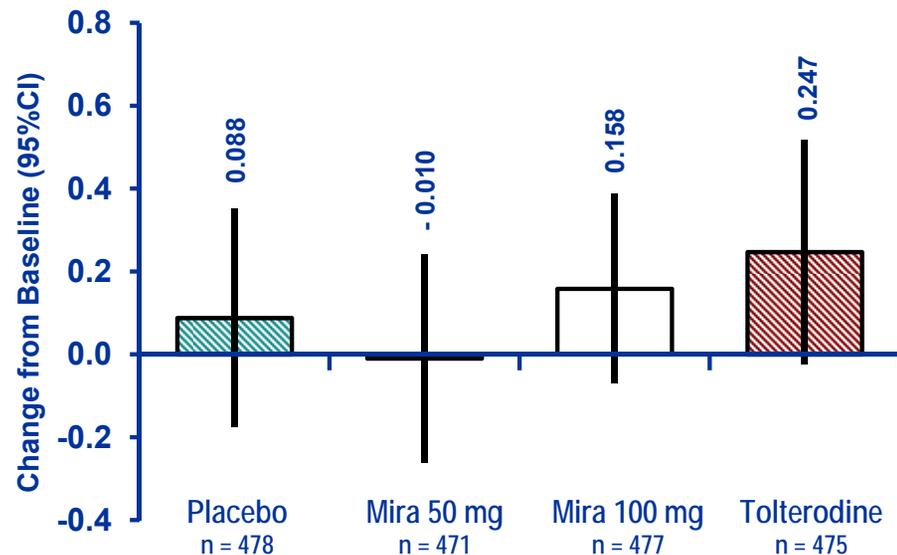
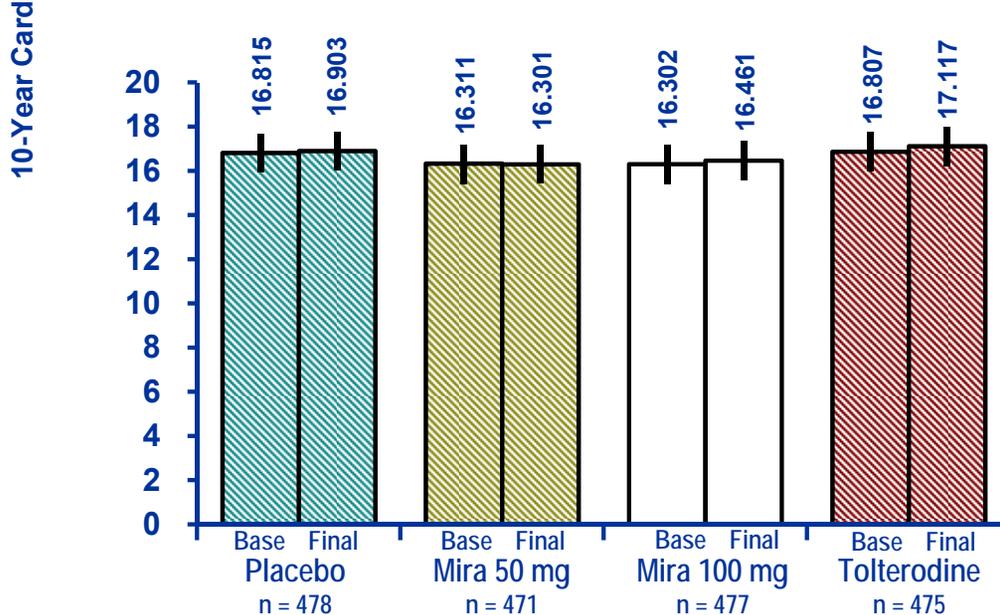
Mean Baseline and Final Visit (95% CI)



Mean Change from Baseline (95% CI)



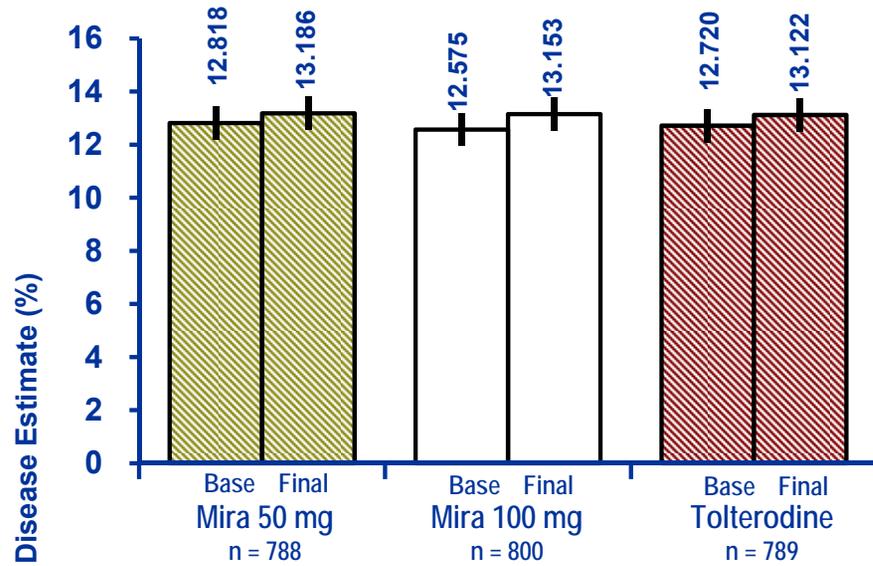
Maximum AM/PM SBP



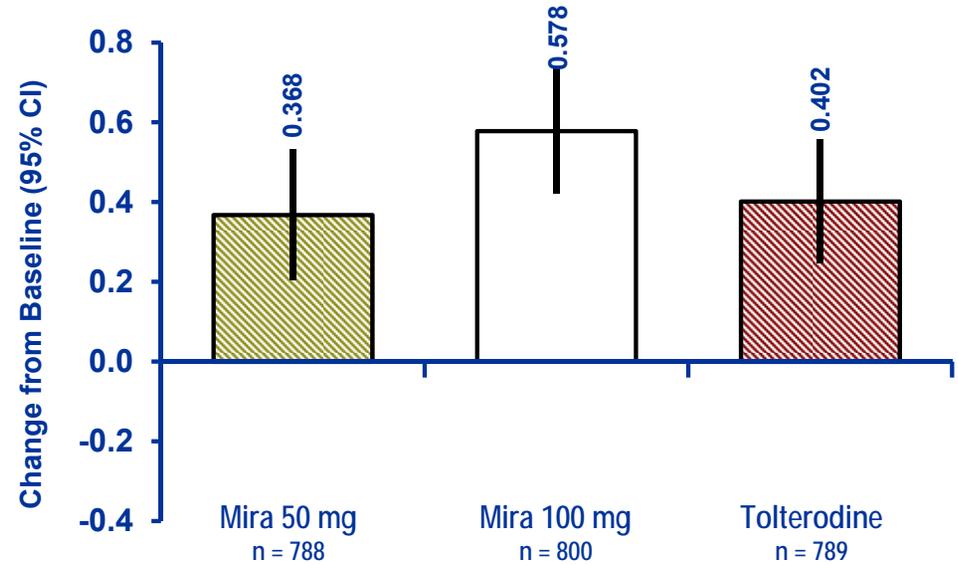
Long-Term (52-Week) Controlled Study Framingham Risk Estimates

Mean AM/PM SBP

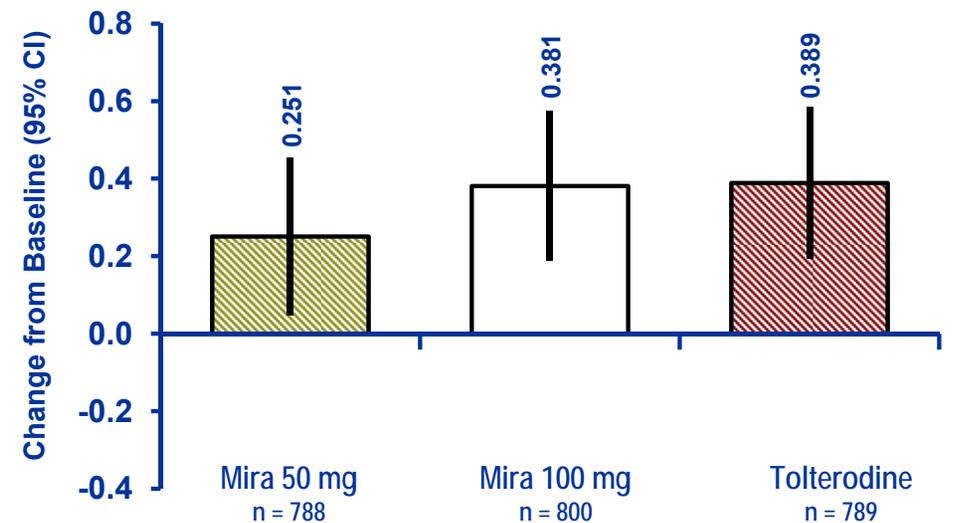
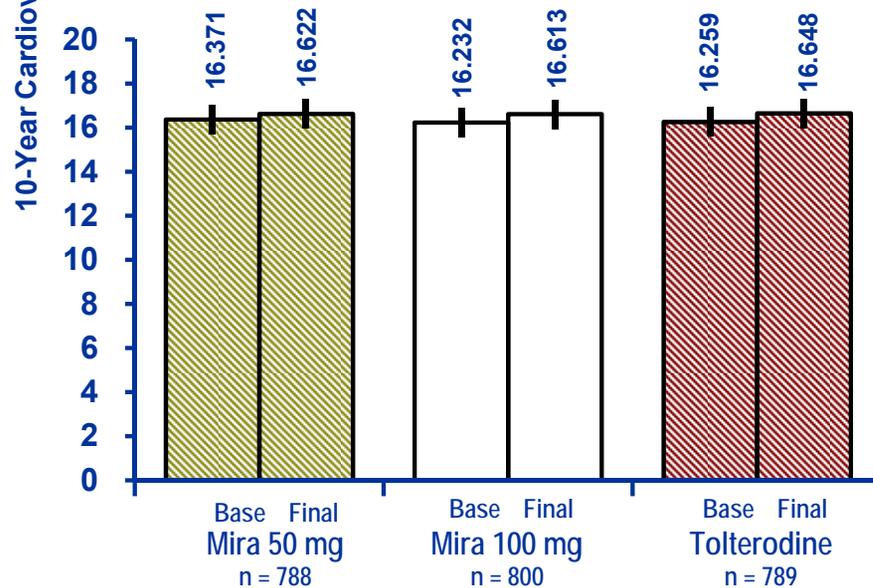
Mean Baseline and Final Visit (95% CI)



Mean Change from Baseline (95% CI)



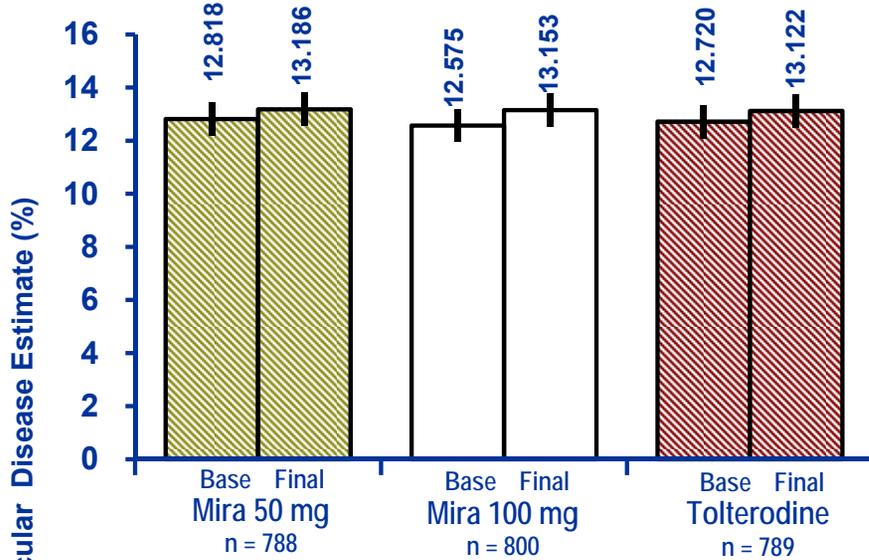
Maximum AM/PM SBP



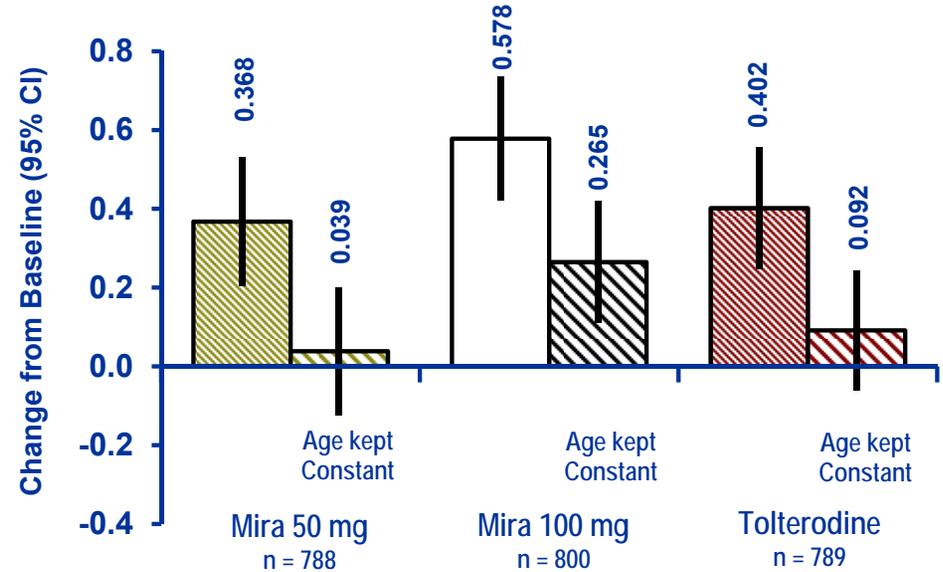
Long-Term (52-Week) Controlled Study Framingham Risk Estimates with Age Kept Constant

Mean AM/PM SBP

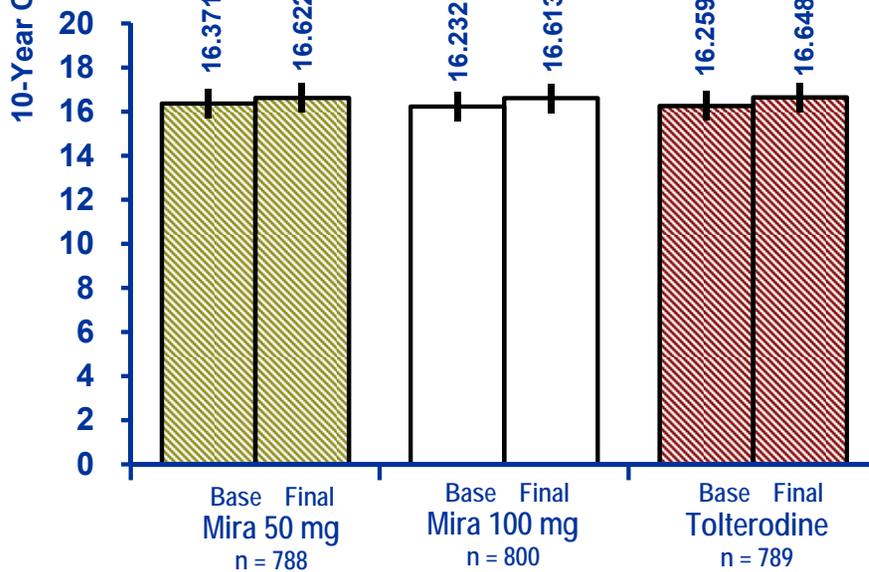
Mean Baseline and Final Visit (95% CI)



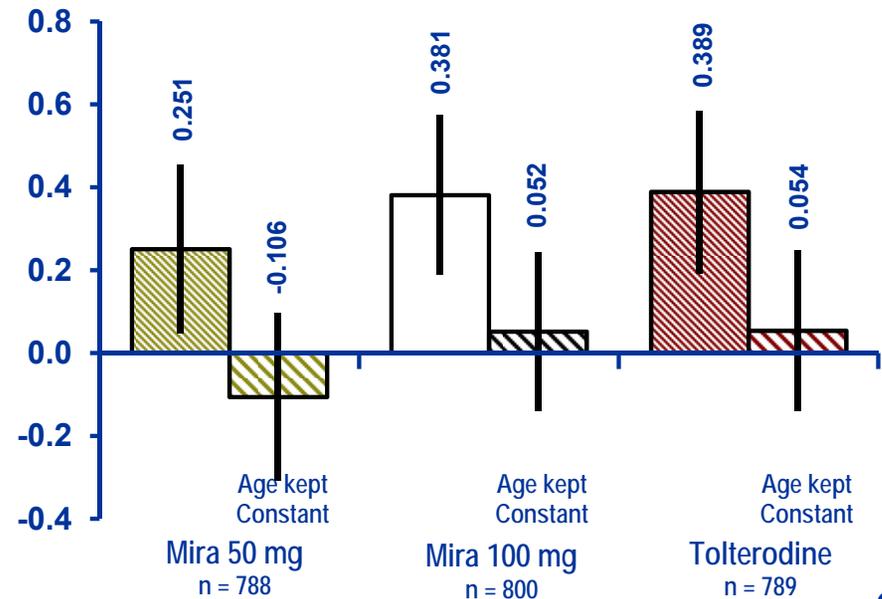
Mean Change from Baseline (95% CI)



Maximum AM/PM SBP

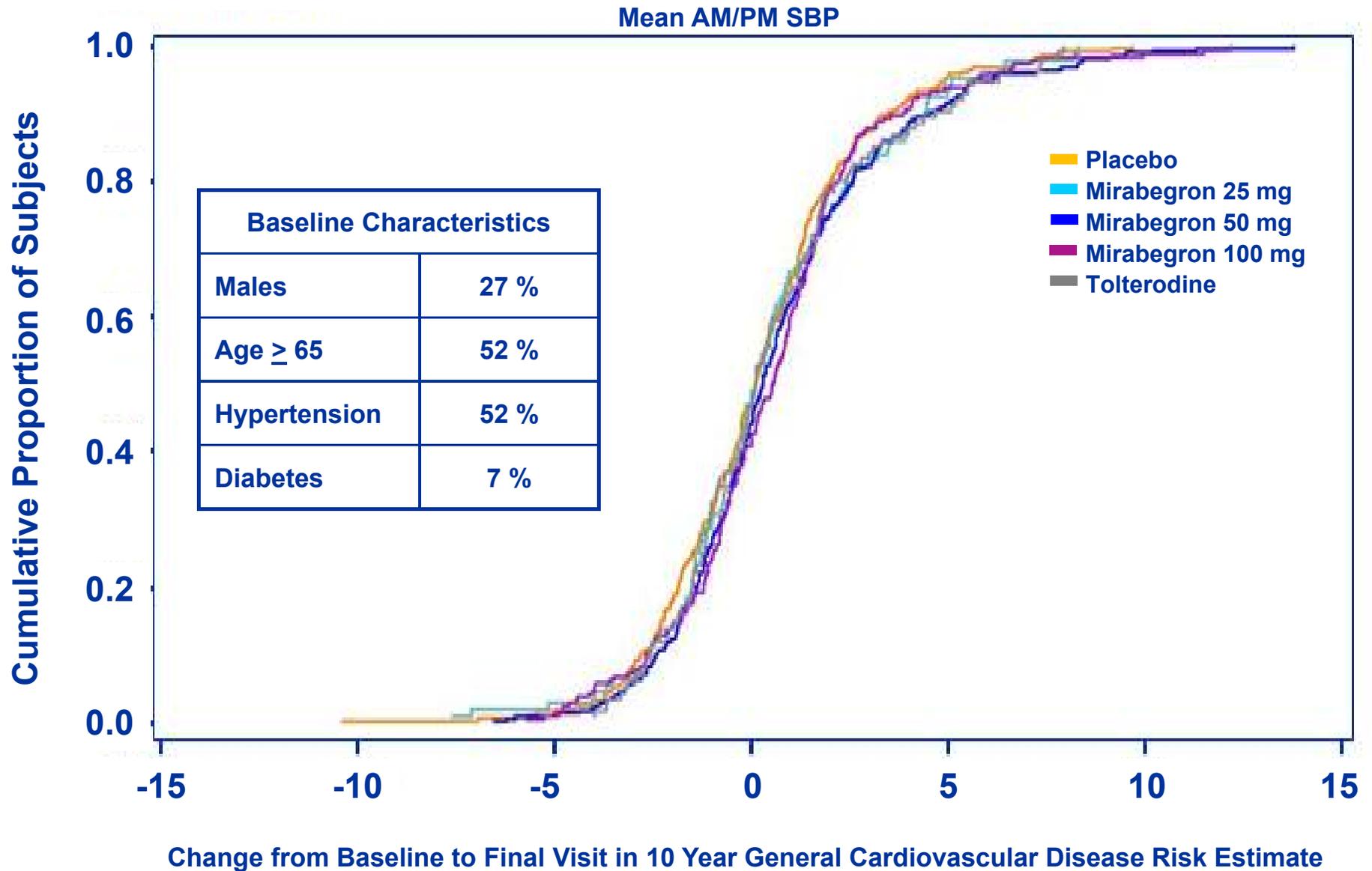


Change from Baseline (95% CI)



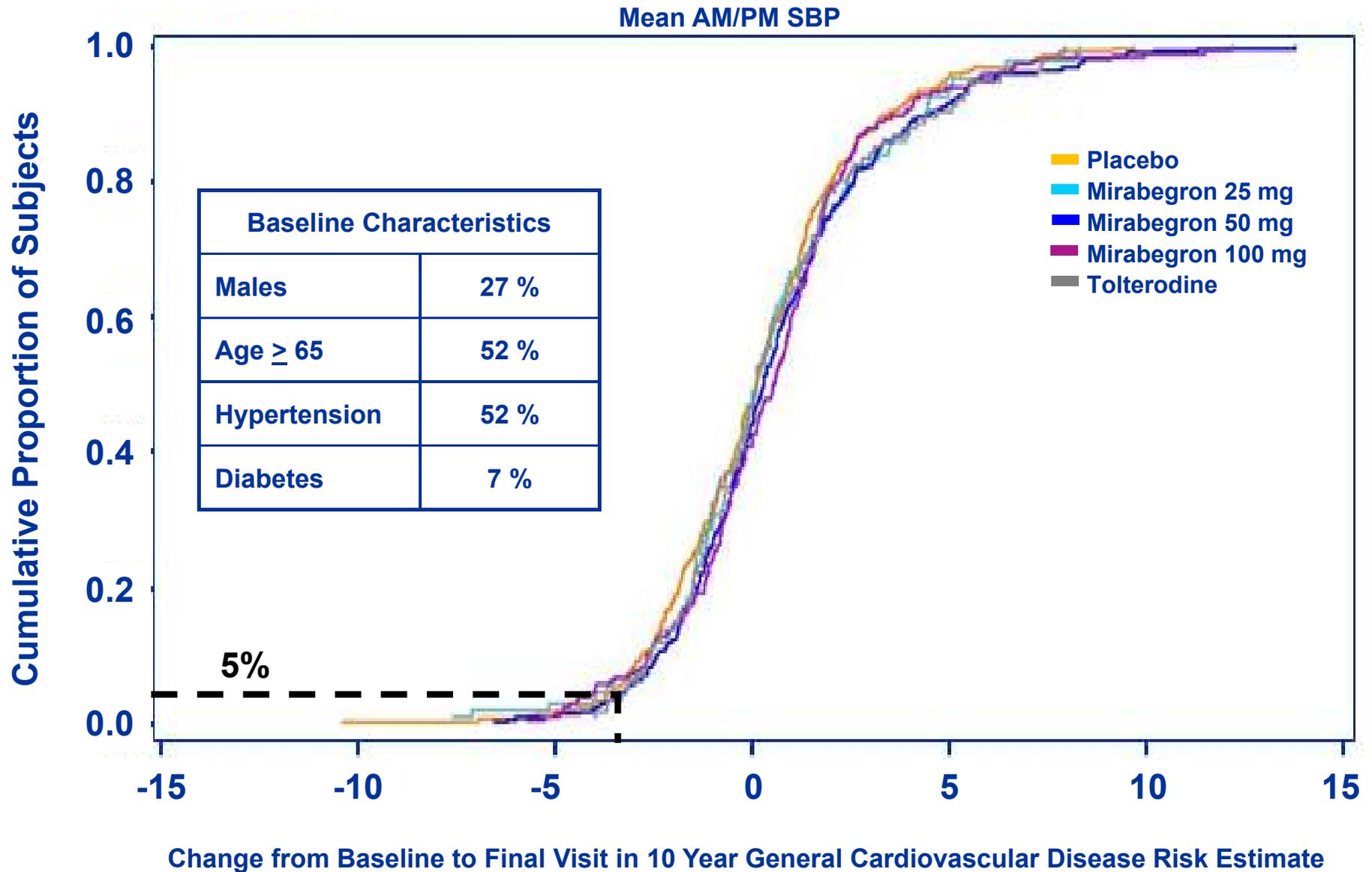
EU/NA 12-Week Phase 3 Studies (Pooled)

Framingham Risk Estimates – 3rd Quartile of Baseline Risk

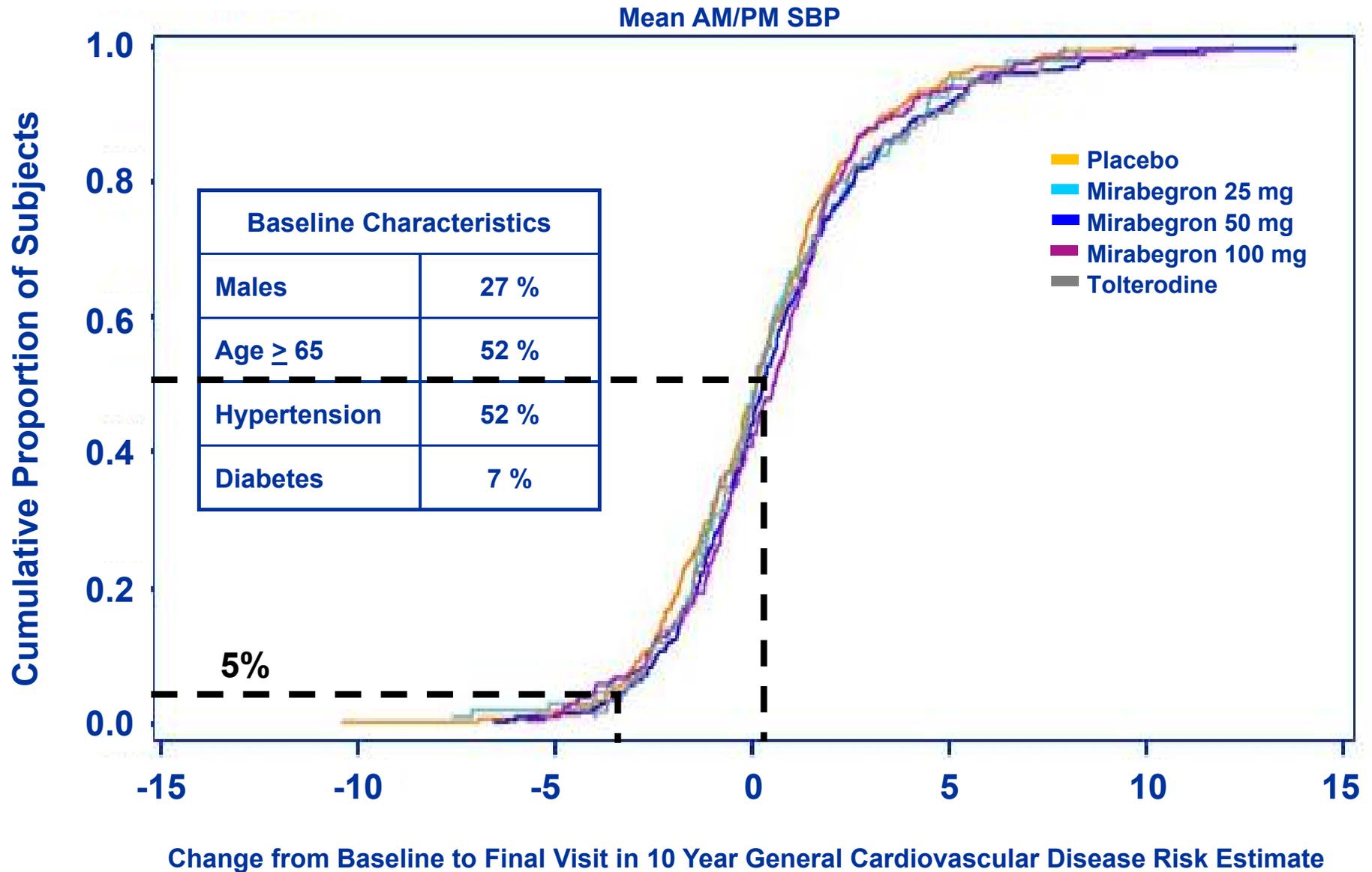


EU/NA 12-Week Phase 3 Studies (Pooled)

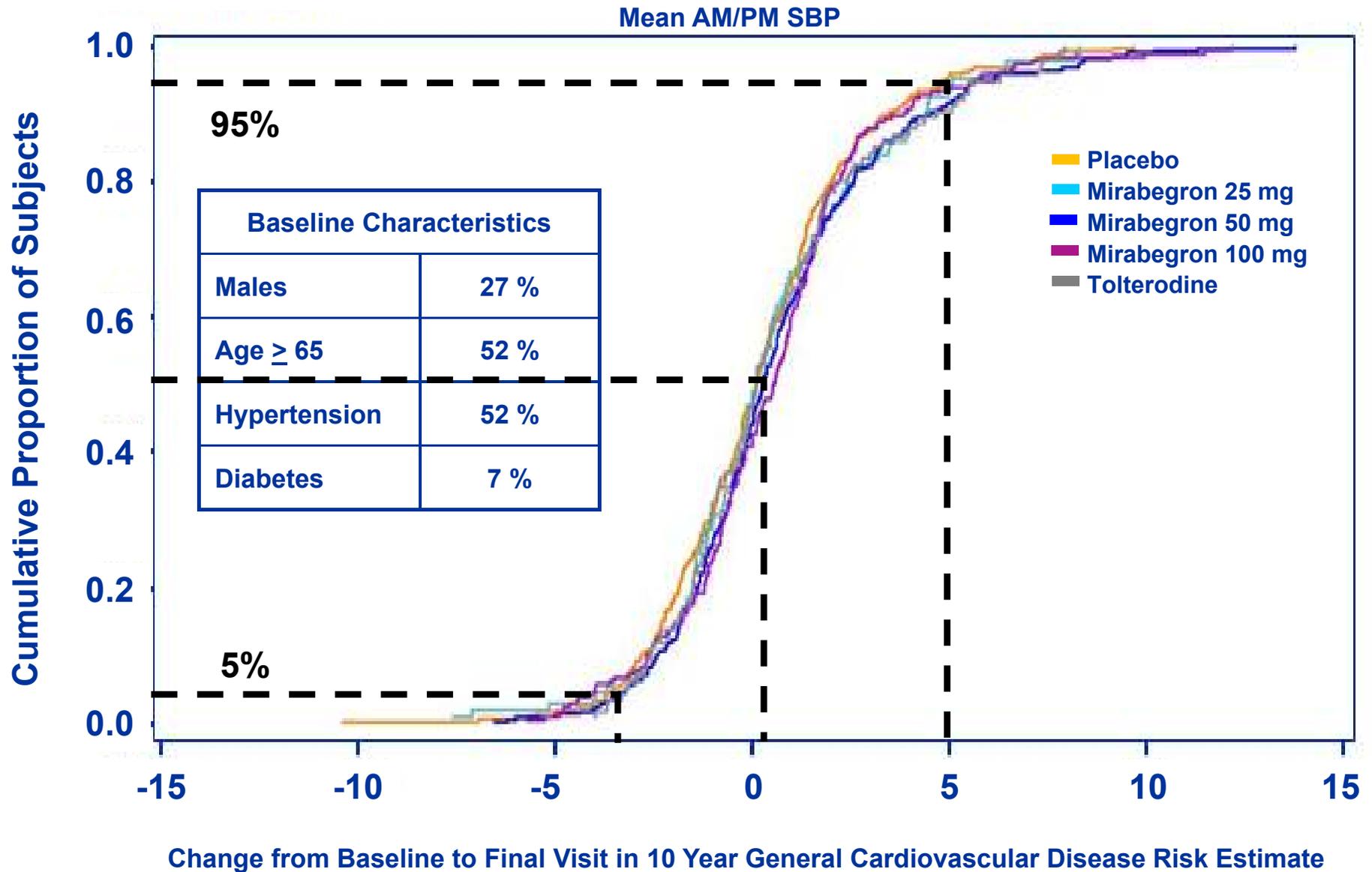
Framingham Risk Estimates – 3rd Quartile of Baseline Risk



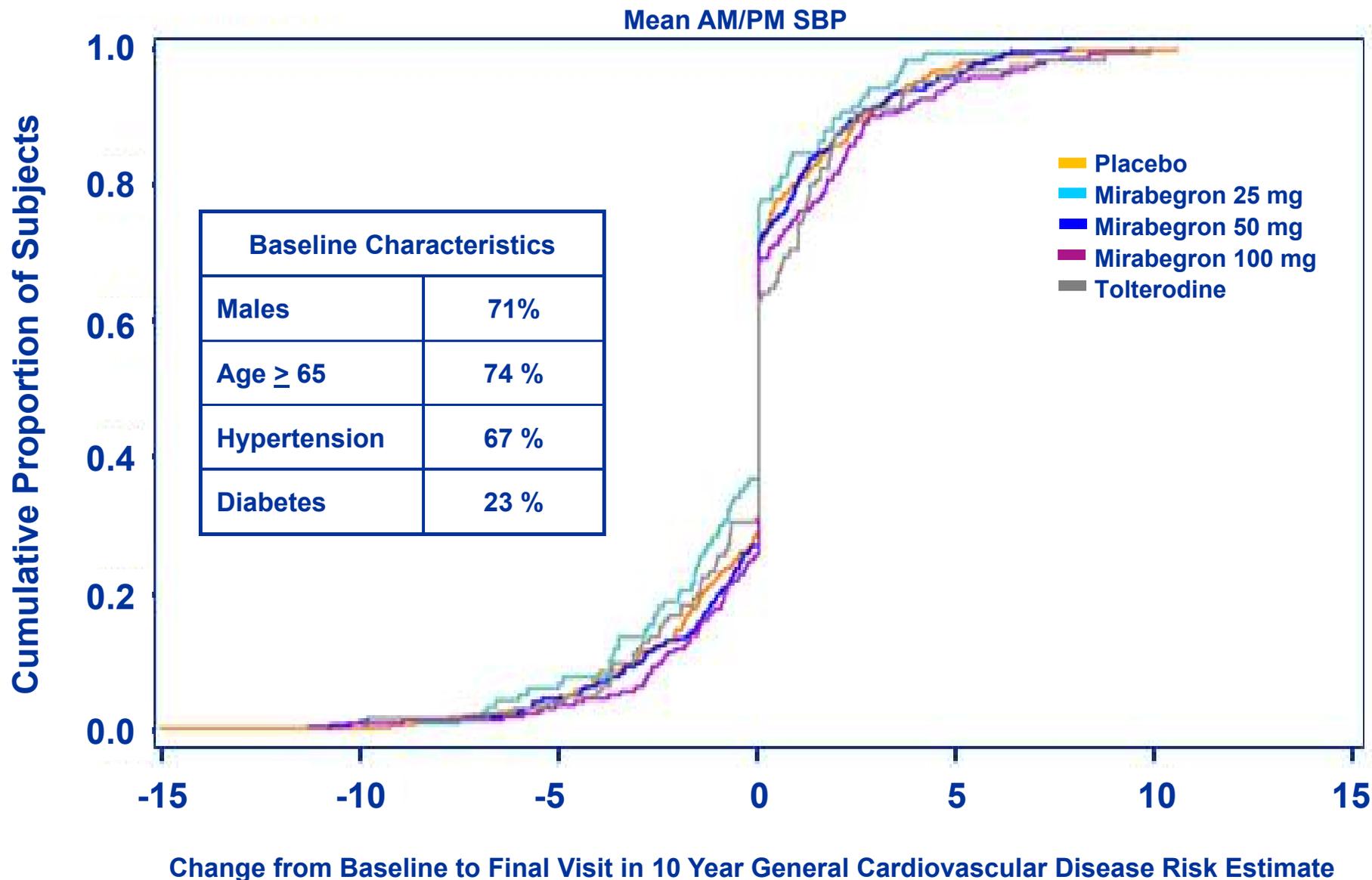
EU/NA 12-Week Phase 3 Studies (Pooled) Framingham Risk Estimates– 3rd Quartile of Baseline Risk



EU/NA 12-Week Phase 3 Studies (Pooled) Framingham Risk Estimates– 3rd Quartile of Baseline Risk



EU/NA 12-Week Phase 3 Studies (Pooled) Framingham Risk Estimates– 4th Quartile of Baseline Risk



Cardiovascular Summary

- Vital sign changes in Phase 1 healthy volunteers are not representative of the OAB population
- In the OAB population, mirabegron 50 mg is associated with
 - Pulse
 - Mean change of ~1 bpm
 - Clinically relevant categorical changes in pulse > placebo; similar to tolterodine
 - Blood pressure
 - Mean change of ~0.4-0.6 mm Hg in SBP/DBP
 - Clinically relevant categorical changes in SBP/DBP similar to placebo
 - Hypertension AE using a pre-specified criteria similar to placebo
- MACE rates are low and similar for placebo, mirabegron and tolterodine
- Framingham Risk Estimates
 - Small changes from baseline in all groups with CI limits that generally overlap
 - In the long-term controlled study, changes are substantially attributable to age increasing by 1-year
 - Similar patterns of change in all groups in the upper quartiles of baseline risk

Postmarketing Surveillance in Japan

- **Approved July 1, 2011; Market entry September 16, 2011**
- **Estimated exposure 12,257 patient-years (33,681 patients; 71% women)**
- **Using the solicited Early Post-marketing Phase Vigilance reporting system in Japan**
 - **2 Deaths (as of April 5, 2012)**
 - **Pneumonia (77 year old female, onset day 37)**
 - **Myocardial Infarction (77 year old male, multiple co-morbidities (diabetes), event 21 days post-last dose mirabegron)**
 - **Events reported as of February 19, 2012**
 - **Cardiovascular**
 - **1 Ventricular Tachycardia**
 - **1 Cardiac Failure**
 - **2 Arrhythmia**
 - **5 Increased BP/Hypertension**
 - **Hypersensitivity**
 - **1 Erythema Multiforme (as reported)**
 - **8 Skin Rash/Pruritus**
 - **Urological**
 - **27 Urinary Retention (19 male; 0.53/100 pt-years consistent with 0.6 lit value)**
- **No DILI, SJS/TEN, or Neoplasm cases reported**

Overall Safety Summary

- Safety well characterized in 5863 Phase 2/3 (5648 OAB) patients representative of the OAB population
- Nonclinical and clinical data do not support a risk for neoplasm with mirabegron
- Low frequency (~1%) of transaminase elevations > 3X ULN; no DILI cases without an alternative explanation
- Low frequency of non-immediate, mostly cutaneous hypersensitivity: generally mild-moderate, reversible and more often at doses ≥ 100 mg
- Common treatment emergent adverse events:

| EU/NA 12-Week Phase 3 studies | | |
|-------------------------------|-----------------------|-----------------------------------|
| | Placebo (n = 1380) | Mirabegron 50 mg (n = 1375) |
| Patients | | |
| UTI | 25 (1.8%) | 40 (2.9%) |
| Dry mouth | 29 (2.1%) | 23 (1.7%) |
| Tachycardia | 8 (0.6%) | 17 (1.2%) |

| Long-Term (52-Week) Controlled Study | | |
|--------------------------------------|----------------------------------|--------------------------|
| | Mirabegron 50 mg (n = 812) | Tolterodine (n = 812) |
| Patients | | |
| UTI | 48 (5.9%) | 52 (6.4%) |
| Dry mouth | 23 (2.8%) | 70 (8.6%) |
| Tachycardia | 8 (1.0%) | 25 (3.1%) |

- Comprehensive data review support the cardiovascular safety of mirabegron 50 mg
- Mirabegron is safe and well tolerated in the treatment of patients suffering from OAB

Agenda

Steven Ryder, MD FACP

Introduction

Prof. Christopher Chapple MD,
FRCS (Urol)

Medical Need

Leticia Delgado-Herrera, RPh MS

Overview and Efficacy

William Fitzsimmons, PharmD MS

Safety

Steven Ryder, MD FACP

Benefit and Managing the Risk

Benefit

- **Consistently improved urinary frequency and urge incontinence in OAB controlled clinical trials**
- **Efficacy**
 - **Comparable to antimuscarinics**
 - **Clinically relevant**
- **Efficacy established in**
 - **OAB-representative population**
 - **Treatment-naïve patients**
 - **Patients who received prior antimuscarinic therapy**
- **Well tolerated with a frequency of anticholinergic side effects (e.g. dry mouth) similar to placebo**
- **Fulfills the unmet medical need of providing OAB patients with a MoA distinctly different from the antimuscarinics, addressing the important issues of**
 - **Toleration**
 - **Low persistence on therapy**

Risk

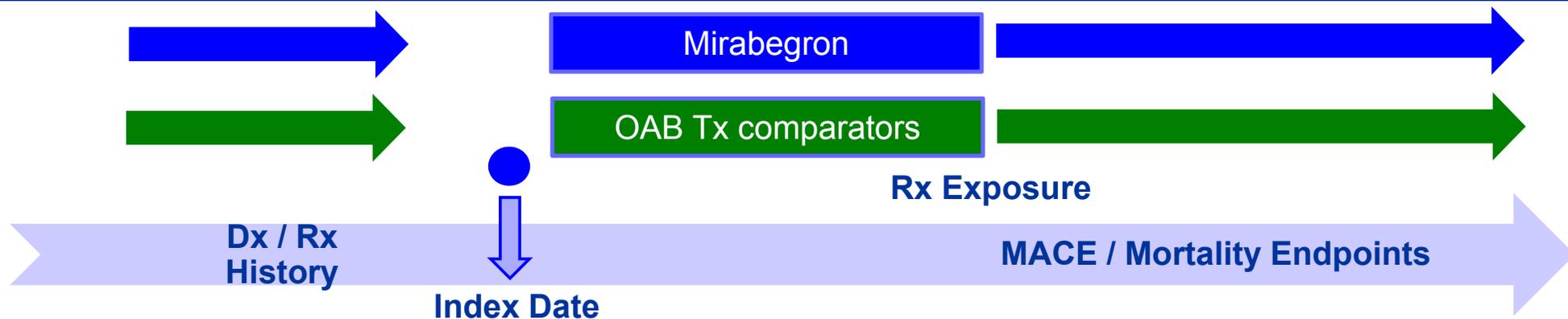
- **Cardiovascular effects**
 - Mirabegron 50 mg ↑ mean pulse (~1 bpm) and tachycardia (1.2% vs. 0.6% placebo); clinically relevant categorical changes in pulse similar to active control
 - Mirabegron 50 mg ↑ mean BP (~0.4-0.6 mmHg) with no increase in clinically relevant categorical changes or clinical hypertension compared to placebo
 - No QTc increase at therapeutically recommended dose in TQT or in OAB clinical trials
 - No increase in cardiovascular MACE events
- **Non-immediate, primarily cutaneous hypersensitivity**
 - Low frequency, generally mild/moderate, reversible, more often in doses ≥100 mg
- **Urinary tract infections**
 - Reported with a frequency higher in the mirabegron 50 mg group (2.9%) compared to placebo (1.8%); comparable to other OAB treatments
- **Pregnancy**
 - The use of mirabegron in pregnancy should be avoided unless the benefit to the patient outweighs the risk to the fetus; embryo-fetal toxicity

Risk Minimization and Proposed Studies

| | Activities to Minimize Risk | Ongoing/Proposed Studies and Activities to Assess Risk | | | |
|--|------------------------------------|--|--|-----------|---|
| | Informative Labeling and Education | Enhanced Pharmacovigilance with Targeted Data Capture | Post-authorization Cardiovascular Observational Cohort Study | Pediatric | Concomitant Antimuscarinic Administration |
| Important Identified Risks | | | | | |
| Hypersensitivity reactions | √ | √ | | | |
| Increased pulse and tachycardia | √ | √ | √ | | |
| Important Potential Risks | | | | | |
| Increased BP | √ | √ | √ | | |
| QT Prolongation | √ | √ | √ | | |
| Urinary tract infection | √ | √ | | | |
| Embryo-fetal toxicity | √ | √ | | | |
| Limited Information | | | | | |
| Severe uncontrolled hypertension | √ | √ | | | |
| Congestive heart failure | √ | √ | | | |
| End-stage renal disease | √ | √ | | | |
| Severe hepatic impairment | √ | √ | | | |
| Children and Adolescents | √ | √ | | √ | |
| Concomitant Administration with Antimuscarinic Agent | √ | √ | | | √ |

Post-authorization CV Observational Cohort Study

| | |
|-----------------------------------|---|
| Study Objective | Post-authorization cardiovascular observational study |
| Study Design and Rationale | Observational cohort study based on electronic healthcare databases <ul style="list-style-type: none"> • Ability to capture information from patients in a real-world setting without interfering in clinical care and with longitudinal f/u • Focus on a set of targeted medical events (CV) with the capacity to extend the evaluation to other relevant events |
| Research Units | OptumInsight Epidemiology and RTI Health Solutions |
| Potential Data Sources | US: OptumInsight Life Sciences Research Database Europe: Databases to be considered include General population data sources in the UK (General Practitioners Research Database) |
| Study Groups | <ol style="list-style-type: none"> 1. Mirabegron initiators 2. Other OAB treatment initiators |
| Follow-up | In naturalistic settings through the duration of the study period to achieve sufficient study size |



Post-authorization CV Observational Cohort Study

| | |
|---|--|
| Primary Analysis | Mirabegron vs. active comparator in a Cox model for individual components (AMI, stroke, CV mortality) and composite MACE endpoint |
| Endpoint Validation | Scientific Advisory Board including clinical (Urology, CV) and pharmacoepidemiology expertise |
| Study Size and Statistical Power | <ul style="list-style-type: none">• Estimated MACE occurrence of ~0.5 events per 100 patient-years• Estimated number of targeted MACE events: ~ 250• Estimated number of patients followed for 1 year ~ 75,000 (mirabegron and active comparator; 1:1)• Based on a true RR of 1.0 (mirabegron compared to active control) estimated 95% power for RR 95% CI to exclude 1.5 estimated 80% power for RR 95% CI to exclude 1.3 |
| Estimated Timing | <ul style="list-style-type: none">• Initiation upon authorized introduction of mirabegron into practice• Based on anticipated mirabegron use and MACE occurrence ~ 2-3 years for patient accrual ~ at least 1 year follow-up |

Benefit/Risk Balance

- **Consistently effective in the treatment of OAB, comparable to antimuscarinics and clinically relevant**
- **Mirabegron 50 mg fulfills the unmet medical need of providing OAB patients with a MoA distinctly different from the antimuscarinics, addressing the important issues of**
 - **Toleration**
 - **Low persistence on therapy**
- **Well tolerated and safe under the conditions in the proposed labeling**
- **Program of enhanced pharmacovigilance and continued investigation to monitor safety in real-world medical use**
- **Benefits of treatment exceed any risk associated with use of mirabegron**

Agenda

Steven Ryder, MD FACP

Introduction

**Prof. Christopher Chapple MD,
FRCS (Urol)**

Medical Need

Leticia Delgado-Herrera, RPh MS

Overview and Efficacy

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Safety

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Benefit and Managing the Risk

Backup Slides Shown

BD-APP 1 – TBL 9: Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Characteristics of OAB, Pooled Primary Phase 3 Studies (4 of 5)

| Sub-population and Category | | Mean Number of Incontinence Episodes per 24 hours, FAS-I | | | | | Mean Number of Micturitions per 24 hours, FAS | | |
|--|---------------------------|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---|---------------------------------|---------------------------------|
| | | | | Placebo | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Mirabegron 50 mg | Mirabegron 100 mg |
| Previous Treatment with OAB Medication | Previous OAB med | n | | 518 | 506 | 336 | 704 | 688 | 460 |
| | | Baseline | Mean (SE) | 2.93 (0.118) | 2.98 (0.120) | 2.99 (0.141) | 11.53 (0.110) | 11.78 (0.119) | 11.60 (0.144) |
| | | Adjusted Diff. from Baseline | Mean (SE) 95% 2-sided CI | -0.92 (0.087) (-1.09, -0.75) | -1.49 (0.088) (-1.66, -1.32) | -1.42 (0.110) (-1.64, -1.21) | -0.93 (0.097) (-1.12, -0.74) | -1.67 (0.098) (-1.86, -1.48) | -1.61 (0.122) (-1.85, -1.37) |
| | Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | -0.57 (-0.81, -0.33) | -0.50 (-0.77, -0.22) | -- | -0.74 (-1.01, -0.47) | -0.69 (-0.99, -0.38) | |
| | No Previous OAB med | n | | 360 | 356 | 241 | 624 | 636 | 430 |
| | | Baseline | Mean (SE) | 2.44 (0.137) | 2.33 (0.131) | 2.50 (0.144) | 11.62 (0.132) | 11.61 (0.131) | 11.55 (0.144) |
| Adjusted Diff. from Baseline | | Mean (SE) 95% 2-sided CI | -1.35 (0.104) (-1.55, -1.14) | -1.50 (0.105) (-1.71, -1.29) | -1.62 (0.129) (-1.87, -1.36) | -1.51 (0.103) (-1.71, -1.31) | -1.84 (0.102) (-2.04, -1.64) | -1.87 (0.126) (-2.12, -1.63) | |
| | | Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | -0.15 (-0.44, 0.14) | -0.27 (-0.60, 0.06) | -- | -0.33 (-0.62, -0.05) | -0.36 (-0.68, -0.04) |
| | | Interaction P value: | | | 0.095 | 0.10 | | | |

BD-APP 1 – TBL 9: Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Characteristics of OAB, Pooled Primary Phase 3 Studies (5 of 5)

| Sub-population and Category | | Mean Number of Incontinence Episodes per 24 hours, FAS-I | | | | Mean Number of Micturitions per 24 hours, FAS | | | |
|---|------------------------------|--|----------------|------------------|-------------------|---|------------------|-------------------|----------------|
| | | | Placebo | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Mirabegron 50 mg | Mirabegron 100 mg | |
| Reason for Discontinuing Prior OAB Medication | Insufficient Effect Yes | n | 336 | 335 | 224 | 466 | 464 | 296 | |
| | | Baseline | Mean (SE) | 3.03 (0.151) | 2.94 (0.141) | 3.20 (0.183) | 11.60 (0.142) | 11.67 (0.142) | 11.87 (0.196) |
| | | Adjusted Diff. from Baseline | Mean (SE) | -0.86 (0.113) | -1.56 (0.114) | -1.50 (0.142) | -0.86 (0.115) | -1.54 (0.116) | -1.65 (0.148) |
| | | | 95% 2-sided CI | (-1.09, -0.64) | (-1.78, -1.34) | (-1.78, -1.22) | (-1.09, -0.64) | (-1.77, -1.31) | (-1.94, -1.36) |
| | | Adjusted Diff. vs Placebo | Mean | -- | -0.70 | -0.63 | -- | -0.67 | -0.79 |
| | | | 95% 2-sided CI | -- | (-1.01, -0.38) | (-0.99, -0.27) | -- | (-0.99, -0.36) | (-1.16, -0.42) |
| | Insufficient Effect No | n | 182 | 171 | 112 | 238 | 224 | 164 | |
| | | Baseline | Mean (SE) | 2.74 (0.188) | 3.07 (0.225) | 2.57 (0.206) | 11.41 (0.171) | 12.01 (0.216) | 11.12 (0.191) |
| | | Adjusted Diff. from Baseline | Mean (SE) | -1.33 (0.154) | -1.69 (0.159) | -1.59 (0.199) | -1.13 (0.162) | -2.06 (0.166) | -1.74 (0.197) |
| | | | 95% 2-sided CI | (-1.64, -1.03) | (-2.00, -1.38) | (-1.98, -1.20) | (-1.44, -0.81) | (-2.38, -1.73) | (-2.13, -1.36) |
| | | Adjusted Diff. vs Placebo | Mean | -- | -0.35 | -0.26 | -- | -0.93 | -0.61 |
| | | | 95% 2-sided CI | -- | (-0.79, 0.08) | (-0.75, 0.24) | -- | (-1.38, -0.47) | (-1.12, -0.11) |
| Interaction P value: | | | 0.34 | | | 0.38 | | | |
| Poor Tolerability Yes | n | 136 | 138 | 80 | 185 | 173 | 113 | | |
| | Baseline | Mean (SE) | 2.80 (0.226) | 3.00 (0.234) | 2.75 (0.234) | 11.55 (0.187) | 11.70 (0.223) | 11.77 (0.337) | |
| | Adjusted Diff. from Baseline | Mean (SE) | -1.09 (0.179) | -1.59 (0.178) | -1.65 (0.235) | -0.93 (0.183) | -1.81 (0.190) | -2.00 (0.236) | |
| | | 95% 2-sided CI | (-1.44, -0.74) | (-1.94, -1.24) | (-2.11, -1.19) | (-1.29, -0.57) | (-2.19, -1.44) | (-2.46, -1.53) | |
| | Adjusted Diff. vs Placebo | Mean | -- | -0.50 | -0.56 | -- | -0.88 | -1.07 | |
| | | 95% 2-sided CI | -- | (-1.00, -0.01) | (-1.14, 0.02) | -- | (-1.40, -0.37) | (-1.66, -0.48) | |
| Poor Tolerability No | n | 382 | 368 | 256 | 519 | 515 | 347 | | |
| | Baseline | Mean (SE) | 2.97 (0.139) | 2.98 (0.140) | 3.07 (0.170) | 11.53 (0.134) | 11.81 (0.140) | 11.55 (0.157) | |
| | Adjusted Diff. from Baseline | Mean (SE) | -1.01 (0.107) | -1.61 (0.109) | -1.49 (0.134) | -0.96 (0.110) | -1.67 (0.110) | -1.58 (0.138) | |
| | | 95% 2-sided CI | (-1.22, -0.80) | (-1.82, -1.39) | (-1.76, -1.23) | (-1.18, -0.75) | (-1.89, -1.46) | (-1.85, -1.31) | |
| | Adjusted Diff. vs Placebo | Mean | -- | -0.60 | -0.49 | -- | -0.71 | -0.62 | |
| | | 95% 2-sided CI | -- | (-0.90, -0.30) | (-0.82, -0.15) | -- | (-1.01, -0.41) | (-0.97, -0.27) | |
| Interaction P value: | | | 0.87 | | | 0.43 | | | |

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All patients in the FAS who had least one incontinence episode in the baseline diary (Full Analysis Set-Incontinence [FAS-I]).

OAB: overactive bladder; --: not applicable.

Descriptive statistics for adjusted changes from baseline are generated from the analysis of covariance (ANCOVA) model with treatment group, gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. P value is from treatment by subpopulation interaction in the ANCOVA model described above.

BD-APP 1 – TBL 10: Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Intrinsic/Extrinsic Factors, Pooled Primary Phase 3 Studies (1 of 7)

| Sub-population and Category | | Mean Number of Incontinence Episodes per 24 hours, FAS-I | | | | | Mean Number of Micturitions per 24 hours, FAS | | |
|------------------------------|---------------------------|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---|---------------------------------|---------------------------------|
| | | | | Placebo | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Mirabegron 50 mg | Mirabegron 100 mg |
| History of BPHT | Yes | n | | 60 | 56 | 36 | 147 | 142 | 95 |
| | | Baseline | Mean (SE) | 1.84 (0.237) | 2.27 (0.338) | 2.24 (0.320) | 11.94 (0.280) | 11.89 (0.291) | 11.73 (0.339) |
| | | Adjusted Diff. from Baseline | Mean (SE) 95% 2-sided CI | -0.84 (0.251) (-1.33, -0.34) | -0.70 (0.260) (-1.21, -0.18) | -0.81 (0.329) (-1.45, -0.16) | -0.82 (0.218) (-1.25, -0.39) | -0.99 (0.223) (-1.42, -0.55) | -1.69 (0.277) (-2.24, -1.15) |
| | Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | 0.14 (-0.57, 0.85) | 0.03 (-0.79, 0.85) | -- | -0.16 (-0.77, 0.45) | -0.87 (-1.57, -0.17) | |
| | No | n | | 94 | 112 | 58 | 215 | 240 | 146 |
| | | Baseline | Mean (SE) | 2.30 (0.333) | 2.24 (0.228) | 1.87 (0.234) | 11.50 (0.233) | 12.12 (0.216) | 11.35 (0.256) |
| Adjusted Diff. from Baseline | | Mean (SE) 95% 2-sided CI | -1.36 (0.200) (-1.76, -0.97) | -1.45 (0.183) (-1.81, -1.09) | -1.33 (0.261) (-1.84, -0.82) | -1.10 (0.181) (-1.46, -0.75) | -1.58 (0.171) (-1.91, -1.24) | -1.60 (0.226) (-2.04, -1.15) | |
| Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | -0.09 (-0.62, 0.44) | 0.04 (-0.62, 0.69) | -- | -0.48 (-0.97, 0.01) | -0.50 (-1.07, 0.08) | | |
| Interaction P value: | | | | 0.85 | | 0.30 | | | |

BD-APP 1 – TBL 10: Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Intrinsic/Extrinsic Factors, Pooled Primary Phase 3 Studies (2 of 7)

| Sub-population and Category | | Mean Number of Incontinence Episodes per 24 hours, FAS-I | | | | | Mean Number of Micturitions per 24 hours, FAS | | |
|------------------------------|---------------------------|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---|---------------------------------|---------------------------------|
| | | | | Placebo | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Mirabegron 50 mg | Mirabegron 100 mg |
| History of Diabetes | Yes | n | | 76 | 79 | 59 | 105 | 115 | 75 |
| | | Baseline | Mean (SE) | 2.68 (0.228) | 2.86 (0.314) | 2.59 (0.325) | 11.65 (0.298) | 11.37 (0.256) | 11.25 (0.342) |
| | | Adjusted Diff. from Baseline | Mean (SE) 95% 2-sided CI | -0.99 (0.227) (-1.43, -0.54) | -1.54 (0.222) (-1.98, -1.11) | -1.34 (0.258) (-1.85, -0.83) | -0.93 (0.250) (-1.42, -0.44) | -1.71 (0.239) (-2.18, -1.24) | -1.76 (0.296) (-2.34, -1.18) |
| | Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | -0.55 (-1.18, 0.07) | -0.35 (-1.03, 0.32) | -- | -0.78 (-1.45, -0.10) | -0.83 (-1.59, -0.06) | |
| | No | n | | 802 | 783 | 518 | 1223 | 1209 | 815 |
| | | Baseline | Mean (SE) | 2.74 (0.096) | 2.70 (0.093) | 2.81 (0.107) | 11.57 (0.089) | 11.73 (0.094) | 11.61 (0.107) |
| Adjusted Diff. from Baseline | | Mean (SE) 95% 2-sided CI | -1.11 (0.070) (-1.25, -0.97) | -1.49 (0.071) (-1.63, -1.35) | -1.52 (0.090) (-1.70, -1.35) | -1.22 (0.073) (-1.37, -1.08) | -1.75 (0.074) (-1.90, -1.61) | -1.74 (0.093) (-1.92, -1.56) | |
| Adjusted Diff. vs Placebo | Mean 95% 2-sided CI | -- | -0.38 (-0.57, -0.19) | -0.41 (-0.64, -0.19) | -- | -0.53 (-0.73, -0.33) | -0.52 (-0.75, -0.28) | | |
| Interaction P value: | | | | 0.78 | | 0.69 | | | |

BD – TBL 18: Responders Analysis Based on Incontinence Episodes, Primary Phase 3 Studies, FAS-I

| | Placebo (n = 878) | Mirabegron 50 mg (n = 862) | Mirabegron 100 mg (n = 577) |
|---|----------------------|----------------------------------|--------------------------------|
| Responders for Zero Incontinence Episodes at Final Visit † | | | |
| Responders (n [%]) | 332 (37.8%) | 380 (44.1%) | 268 (46.4%) |
| Difference vs Placebo (%) | | 6.3% | 8.6% |
| 95% 2-sided CI for Difference‡ | | (1.7%, 10.9%) | (3.5%, 13.8%) |
| Odds Ratio§ | -- | 1.32 | 1.58 |
| 95% 2-sided CI for Odds Ratio | | (1.08, 1.61) | (1.25, 2.00) |
| P value | | 0.008* | < 0.001* |
| Responders for ≥ 50% Reduction from Baseline to Final Visit in Incontinence Episodes ¶ | | | |
| Responders (n [%]) | 523 (59.6%) | 599 (69.5%) | 407 (70.5%) |
| Difference vs Placebo (%) | | 9.9% | 11.0% |
| 95% 2-sided CI for Difference‡ | | (5.5%, 14.4%) | (6.0%, 15.9%) |
| Odds Ratio§ | -- | 1.54 | 1.64 |
| 95% 2-sided CI for Odds Ratio | | (1.26, 1.89) | (1.29, 2.07) |
| P value | | < 0.001* | < 0.001* |

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

--: not applicable.

† A responder was defined as a patient with zero incontinence episodes at final visit.

‡ 95% CIs for the difference of the proportions were based on normal approximation.

§ Odds ratios of mirabegron over placebo, corresponding 95% CIs and P values were derived from a logistic regression model including treatment group, gender, study and baseline measurement.

¶ A responder was defined as a patient with a ≥ 50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment

BD – TBL 19: Responders for 8 or Fewer Micturitions per 24 Hours at Final Visit, Pooled Primary Phase 3 Studies, FAS

| | Placebo (n = 1328) | Mirabegron 50 mg (n = 1324) | Mirabegron 100 mg (n = 890) |
|---------------------------------------|-----------------------|-----------------------------------|--------------------------------|
| Final Visit | | | |
| Responders (n [%]) | 327 (24.6%) | 419 (31.6%) | 303 (34.0%) |
| Difference vs Placebo (%) | | 7.0% | 9.4% |
| 95% 2-sided CI for Difference† | | (3.6%, 10.4%) | (5.5%, 13.3%) |
| Odds Ratio‡ | | 1.57 | 1.69 |
| 95% 2-sided CI for Odds Ratio | -- | (1.30, 1.89) | (1.37, 2.09) |
| P value | | < 0.001* | < 0.001* |

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074. All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). A responder is defined as a patient with a value ≤ 8 for mean number of micturition per 24 hours at final visit.

--: not applicable.

† 95% CIs for the difference of the proportions were based on normal approximation.

‡ Odds ratios of mirabegron over placebo, corresponding 95% CIs and P values were derived from a logistic regression model including treatment group, gender, study and baseline measurement.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

BD – TBL 21: Change from Baseline to Final Visit in TS-VAS, Primary Phase 3 Studies, FAS

| | Study 178-CL-046 | | | | Study 178-CL-047 | | | Study 178-CL-074 | | |
|--|----------------------|----------------------------------|-----------------------------------|------------------------------|----------------------|----------------------------------|-----------------------------------|----------------------|----------------------------------|----------------------------------|
| | Placebo (n = 480) | Mirabegron 50 mg (n = 473) | Mirabegron 100 mg (n = 478) | Tolt ER 4 mg (n = 475) | Placebo (n = 433) | Mirabegron 50 mg (n = 425) | Mirabegron 100 mg (n = 412) | Placebo (n = 415) | Mirabegron 25 mg (n = 410) | Mirabegron 50 mg (n = 426) |
| Adjusted Change from Baseline† | | | | | | | | | | |
| Mean (SE) | 1.89 (0.146) | 2.55 (0.149) | 2.66 (0.146) | 2.44 (0.147) | 0.7 (0.16) | 1.5 (0.16) | 2.1 (0.16) | 1.05 (0.154) | 1.54 (0.152) | 1.88 (0.152) |
| 95% 2-sided CI | (1.60, 2.18) | (2.26, 2.85) | (2.37, 2.94) | (2.15, 2.73) | (0.4, 1.0) | (1.2, 1.9) | (1.8, 2.4) | (0.75, 1.35) | (1.24, 1.84) | (1.58, 2.18) |
| Adjusted Difference vs Placebo‡ | | | | | | | | | | |
| Mean (SE) | -- | 0.66 (0.208) | 0.77 (0.207) | 0.55 (0.207) | -- | 0.8 (0.22) | 1.4 (0.22) | -- | 0.49 (0.216) | 0.83 (0.216) |
| 95% 2-sided CI | -- | (0.25, 1.07) | (0.36, 1.17) | (0.14, 0.95) | -- | (0.4, 1.3) | (1.0, 1.8) | -- | (0.07, 0.91) | (0.41, 1.25) |
| P value‡ | -- | 0.001* | < 0.001* | 0.008* | -- | < 0.001* | < 0.001* | -- | 0.024* | < 0.001* |

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).

Treatment satisfaction was assessed by patients on a 10 cm VAS. A score of 10 indicated complete satisfaction. A positive change from baseline in TS-VAS indicated improvement in patient satisfaction.

TS-VAS: Treatment satisfaction visual analog scale; ER: extended release; Tolt: tolterodine; --: not applicable.

† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate.

‡ P values were from pairwise comparisons vs placebo within the ANCOVA model.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

BD – TBL 26: Efficacy Results, Supportive Study 178-CL-048, FAS

| | Placebo | Mirabegron 50 mg | Tolterodine ER 4 mg |
|--|-------------------|---------------------|------------------------|
| Change from Baseline to Endpoint Visit in Mean Number of Incontinence Episodes per 24 Hours (FAS) | | | |
| n | 264 | 266 | 240 |
| Mean baseline (SD) | 1.91 (1.760) | 1.99 (2.054) | 1.89 (1.826) |
| Adjusted mean difference from baseline† | -0.67 | -1.09 | -0.99 |
| Adjusted mean difference from placebo† | -- | -0.42 | -0.32 |
| 95% CI | -- | (-0.67, -0.17) | (-0.57, -0.06) |
| Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours | | | |
| n | 368 | 369 | 368 |
| Mean baseline (SD) | 11.29 (2.748) | 11.15 (2.650) | 11.10 (2.567) |
| Adjusted mean difference from baseline† | -0.82 | -1.68 | -1.43 |
| Adjusted mean difference from placebo† | -- | -0.86 | -0.61 |
| 95% CI | -- | (-1.16, -0.57) | (-0.90, -0.32) |
| Change from Baseline to Endpoint Visit in Mean Volume Voided per Micturition (FAS) | | | |
| n | 366 | 368 | 367 |
| Mean baseline (SD) | 146.791 (44.2336) | 149.591 (46.3775) | 145.863 (46.8973) |
| Adjusted mean difference from baseline† | 9.675 | 24.450 | 28.724 |
| Adjusted mean difference from placebo† | -- | 14.775 | 19.049 |
| 95% CI | -- | (9.974, 19.576) | (14.246, 23.852) |

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). While FAS-I was not defined as a separate population, analyses of incontinence endpoints were limited to the subset of the FAS that reported incontinence at baseline.

--: not applicable; ER: extended release.

† Analysis of variance with treatment group as a fixed factor and baseline as a covariate.

BD – TBL 56: Concomitant Medications During the Double-Blind Period in Mirabegron OAB Studies

| | EU/NA OAB 12-week Phase 3 Population (n = 4611) | EU/NA Long-Term Controlled Population (n = 2444) |
|---------------------------------|---|--|
| ACE/ARB | 1311 (28.4%) | 714 (29.2%) |
| Beta Blockers | 778 (16.9%) | 451 (18.5%) |
| Calcium Channel Blockers | 552 (12.0%) | 317 (13.0%) |
| Diuretics | 477 (10.3%) | 289 (11.8%) |
| Lipid Lowering Agents | 1317 (28.6%) | 631 (25.8%) |
| Antithrombotics | 963 (20.9%) | 501 (20.5%) |
| Antidiabetics | 409 (8.9%) | 217 (8.9%) |

OAB: overactive bladder; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers.

BD – TBL 67: Patients With AM or PM SBP Increase from Baseline ≥ 5 mm Hg and Actual Value ≥ 140 mm Hg, EU/NA OAB 12-week Phase 3 Population

| Parameter n (%) of Patients | Mirabegron | | | | Tolterodine ER 4 mg |
|---|-------------------|------------------|-------------------|------------------|------------------------|
| | Placebo | 25 mg | 50 mg | 100 mg | |
| Final Visit (AM) | 57/1067 (5.3%) | 21/311 (6.8%) | 73/1057 (6.9%) | 42/726 (5.8%) | 26/378 (6.9%) |
| 3 Consecutive Postbaseline visits (AM) | 8/961 (0.8%) | 4/293 (1.4%) | 14/965 (1.5%) | 9/673 (1.3%) | 4/351 (1.1%) |
| 2 Consecutive Postbaseline visits (AM) | 25/999 (2.5%) | 9/301 (3.0%) | 43/999 (4.3%) | 24/697 (3.4%) | 10/368 (2.7%) |
| Final Visit (PM) | 78/1127 (6.9%) | 21/324 (6.5%) | 91/1114 (8.2%) | 53/785 (6.8%) | 29/394 (7.4%) |
| 3 Consecutive Postbaseline visits (PM) | 12/1022 (1.2%) | 4/305 (1.3%) | 12/1012 (1.2%) | 11/724 (1.5%) | 6/366 (1.6%) |
| 2 Consecutive Postbaseline visits (PM) | 40/1061 (3.8%) | 12/314 (3.8%) | 36/1053 (3.4%) | 29/750 (3.9%) | 16/382 (4.2%) |

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

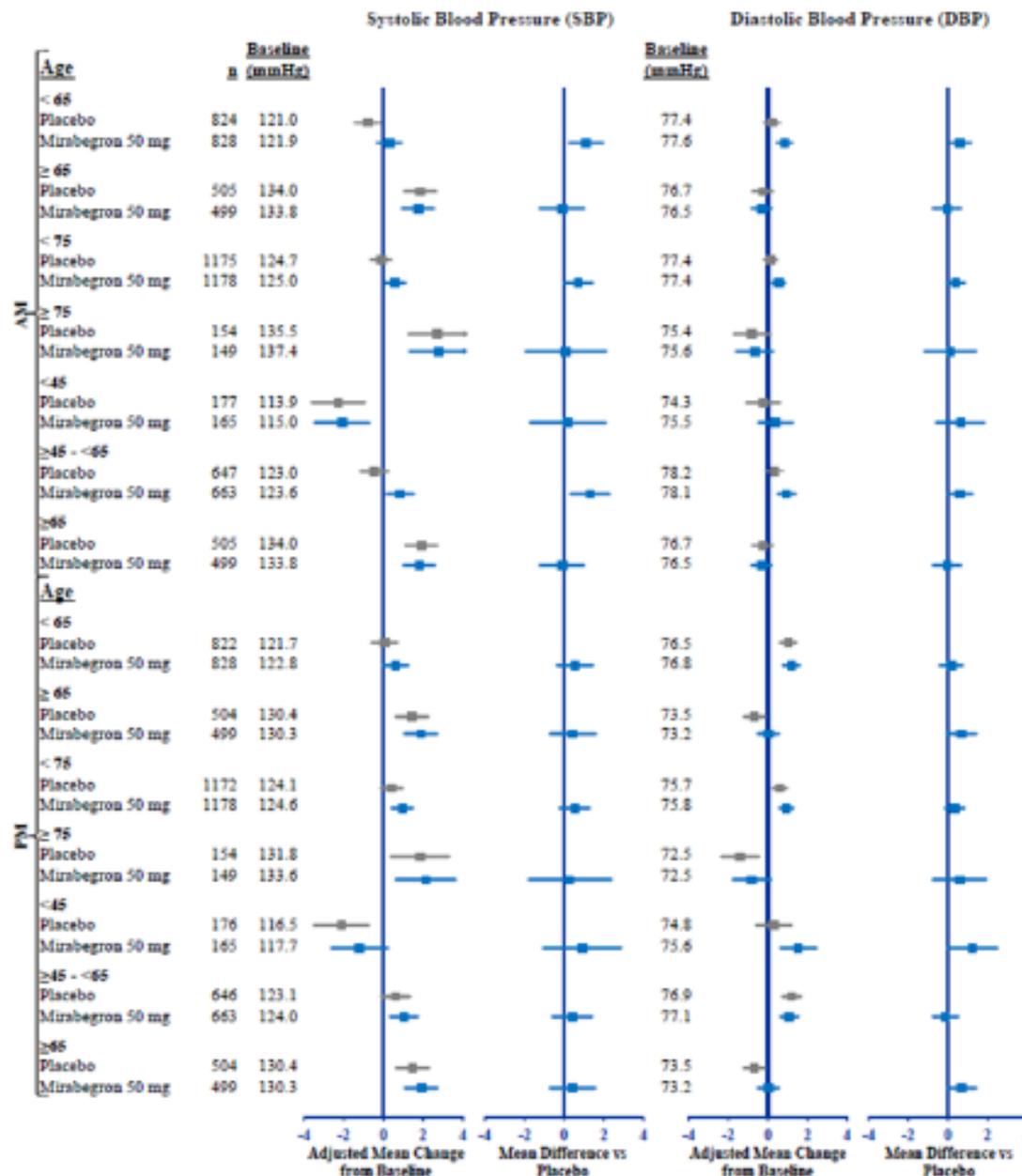
BD – TBL 103: Overview of Coprimary and Key Secondary Efficacy Results (1 of 2)

| | Study 178-CL-074 | | Pooled Primary Studies | |
|---|---------------------|---------------------|------------------------|----------------------|
| | Mirabegron 25 mg | Mirabegron 50 mg | Mirabegron 50 mg | Mirabegron 100 mg |
| Coprimary Efficacy Results | | | | |
| Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours (FAS-I) | | | | |
| n | 254 | 257 | 862 | 577 |
| Adjusted mean difference vs placebo (SE) | -0.40 (0.17) | -0.42 (0.17) | -0.40 (0.09) | -0.41 (0.11) |
| 95% 2-sided CI | (-0.74, -0.06) | (-0.76, -0.08) | (-0.58, -0.21) | (-0.62, -0.19) |
| P value† | 0.005# | 0.001# | < 0.001# | < 0.001# |
| Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours (FAS) | | | | |
| n | 410 | 426 | 1324 | 890 |
| Adjusted mean difference vs placebo (SE) | -0.47 (0.18) | -0.42 (0.17) | -0.55 (0.10) | -0.54 (0.12) |
| 95% 2-sided CI | (-0.82, -0.13) | (-0.76, -0.08) | (-0.75, -0.36) | (-0.77, -0.31) |
| P value‡ | 0.007# | 0.015# | < 0.001# | < 0.001# |
| Key Secondary Efficacy Results | | | | |
| Change from Baseline to Final Visit in Mean Volume Voided per Micturition (FAS) | | | | |
| n | 410 | 426 | 1322 | 890 |
| Adjusted mean difference vs placebo (SE) | 4.6 (3.16) | 12.4 (3.13) | 11.9 (1.82) | 12.3 (2.12) |
| 95% 2-sided CI | (-1.6, 10.8) | (6.3, 18.6) | (8.3, 15.5) | (8.1, 16.5) |
| P value‡ | 0.15 | < 0.001# | < 0.001# | < 0.001# |

BD – TBL 103: Overview of Coprimary and Key Secondary Efficacy Results (2 of 2)

| | Study 178-CL-074 | | Pooled Primary Studies | |
|---|---------------------|---------------------|------------------------|----------------------|
| | Mirabegron 25 mg | Mirabegron 50 mg | Mirabegron 50 mg | Mirabegron 100 mg |
| Key Secondary Efficacy Results (continued) | | | | |
| Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours (FAS-I) | | | | |
| n | 254 | 255 | 857 | 574 |
| Adjusted mean difference vs placebo (SE) | -0.34 (0.17) | -0.51 (0.17) | -0.45 (0.10) | -0.42 (0.12) |
| 95% 2-sided CI | (-0.68, -0.01) | (-0.85, -0.17) | (-0.64, -0.26) | (-0.65, -0.20) |
| P value† | 0.039§ | < 0.001#§ | < 0.001# | < 0.001# |
| Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours (FAS) | | | | |
| n | 410 | 424 | 1317 | 886 |
| Adjusted mean difference vs placebo (SE) | -0.18 (0.18) | -0.37 (0.17) | -0.40 (0.09) | -0.56 (0.11) |
| 95% 2-sided CI | (-0.53, 0.16) | (-0.71, -0.03) | (-0.59, -0.22) | (-0.78, -0.35) |
| P value‡ | 0.30§ | 0.035§ | < 0.001# | < 0.001# |
| Change from Baseline to Final Visit in Mean Level of Urgency (FAS) | | | | |
| n | 410 | 426 | 1323 | 886 |
| Adjusted mean difference vs placebo (SE) | -0.07 (0.04) | -0.14 (0.04) | -0.11 (0.02) | -0.11 (0.03) |
| 95% 2-sided CI | (-0.15, 0.01) | (-0.22, -0.06) | (-0.16, -0.07) | (-0.16, -0.06) |
| P value‡ | 0.083§ | < 0.001§ | < 0.001# | < 0.001# |
| Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 hours (FAS-I) | | | | |
| n | 247 | 251 | 834 | 567 |
| Adjusted mean difference vs placebo (SE) | -0.36 (0.16) | -0.39 (0.16) | -0.40 (0.09) | -0.40 (0.10) |
| 95% 2-sided CI | (-0.67, -0.05) | (-0.69, -0.08) | (-0.57, -0.23) | (-0.60, -0.20) |
| P value† | 0.004 | 0.002§ | < 0.001# | < 0.001# |
| Change from Baseline to Final Visit in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 hours (FAS) | | | | |
| n | 410 | 426 | 1320 | 885 |
| Adjusted mean difference vs placebo (SE) | -0.33 (0.22) | -0.59 (0.22) | -0.64 (0.13) | -0.60 (0.15) |
| 95% 2-sided CI | (-0.76, 0.10) | (-1.01, -0.16) | (-0.89, -0.39) | (-0.89, -0.31) |
| P value‡ | 0.13 | 0.007§ | < 0.001# | < 0.001# |

BD-APP 2 – FIG 23: Change from Baseline to Final Visit for SBP/DBP by Age, EU/NA OAB 12-week Phase 3 Population



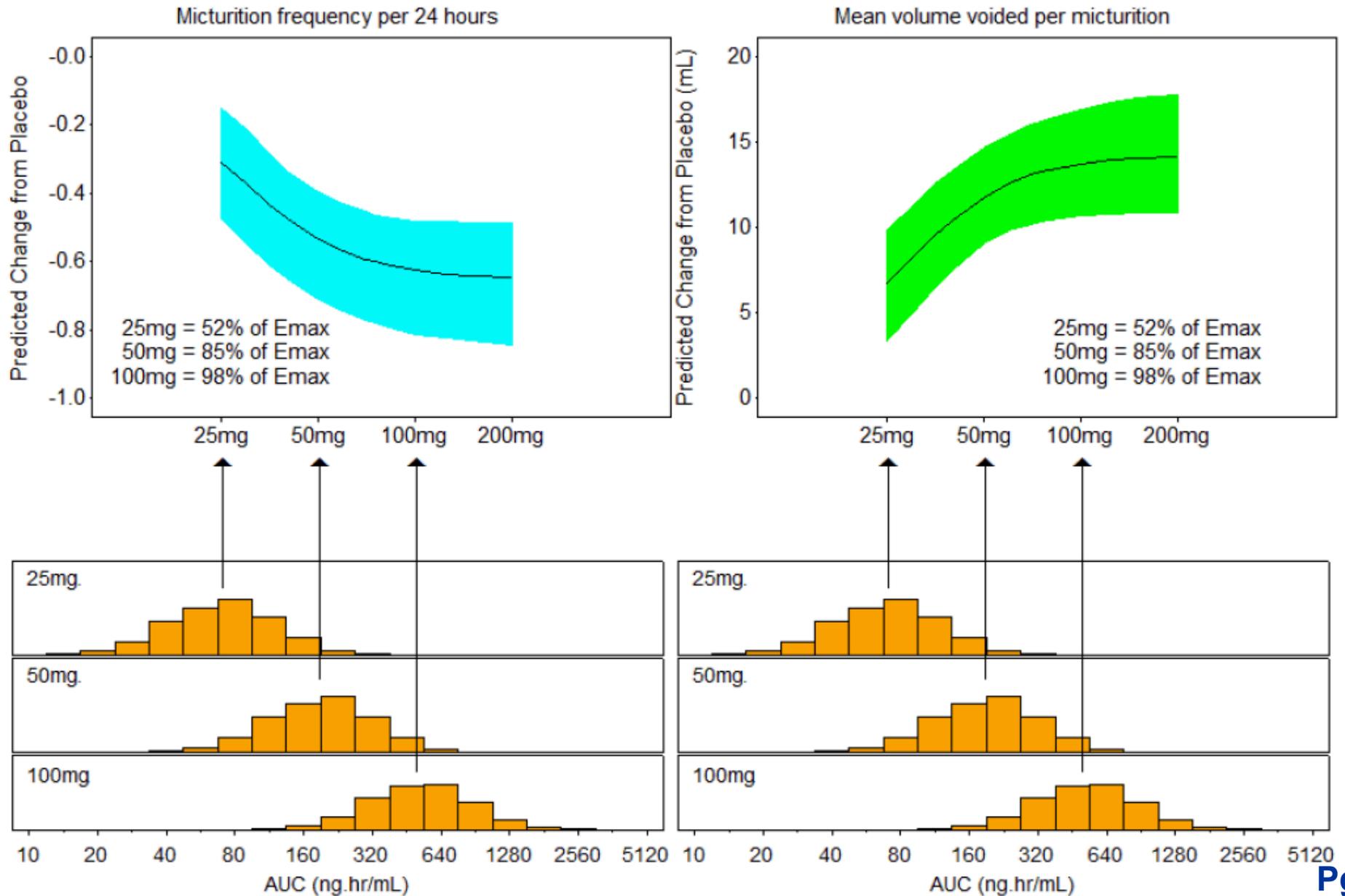
Studies included: 175-CL-046, 175-CL-047 and 175-CL-074.

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAS]).

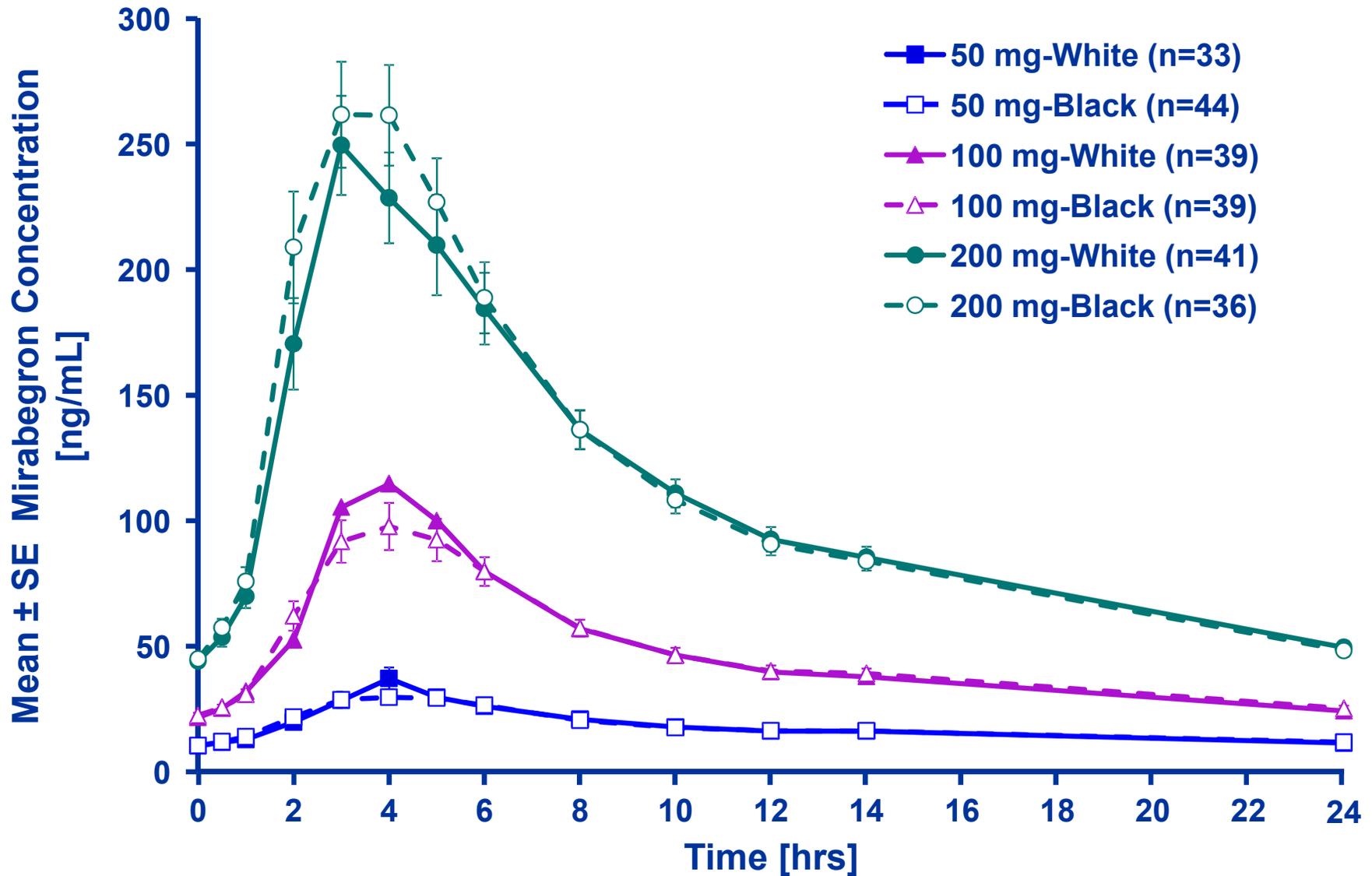
Age is presented in years. Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subgroup analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subgroup, and treatment by subgroup interaction as fixed factors and baseline as a covariate.

ANCOVA, analysis of covariance; DBP, diastolic blood pressure; OAB, overactive bladder; SBP, systolic blood pressure.

BD -- FIG 44: Mirabegron Exposure-Efficacy Response Model, Micturition Frequency per 24 Hours and Mean Volume Voided per Micturition



Mean Concentration-Time Profiles by Race in 178-CL-077



Specifications: Home Blood Pressure Monitors

Phase 3 Clinical Trials

| Manufacture | Model | Measurement Range | Accuracy |
|---------------------|--------------------------------|---|---|
| Omron® | HEM-711DLX HEM-712C | BP: 0 to 299 mmHg Pulse: 40-180 bpm | BP: ± 3mmHg or $\pm 2\%$ Pulse: $\pm 5\%$ |
| Life Source® | UA-789AC | BP: 20 to 280 mmHg Pulse: 40-200 bpm | BP: ± 3mmHg or $\pm 2\%$, whichever is greater Pulse: $\pm 5\%$ |

Hypertension Adverse Events by Race

| Race, n (%) | 12-Week Phase 3 Studies | | Long-Term (52-Week) Controlled Study | |
|----------------------------------|-------------------------|------------------|--------------------------------------|------------------|
| | Placebo | Mirabegron 50 mg | Mirabegron 50 mg | Tolterodine |
| White | 1274 | 1279 | 778 | 780 |
| Hypertension | 95 (7.5%) | 95 (7.4%) | 71 (9.1%) | 76 (9.7%) |
| Black or African-American | 84 | 66 | 22 | 20 |
| Hypertension | 8 (9.5%) | 6 (9.1%) | 1 (4.5%) | 0 |

Study Results: 178-CL-049

Subject Discontinuation (Randomized Analysis Set)

| Parameter | Mirabegron 50 mg (n=815) | Mirabegron 100 mg (n=824) | Tolterodine ER 4 mg (n=813) |
|---|-----------------------------|------------------------------|--------------------------------|
| Study discontinuation | | | |
| Yes | 186 (22.8%) | 179 (21.7%) | 192 (23.6%) |
| No | 629 (77.2%) | 645 (78.3%) | 621 (76.4%) |
| Primary reason for discontinuation | | | |
| Did not fulfill inclusion or exclusion criteria | 7 (0.9%) | 7 (0.8%) | 10 (1.2%) |
| AE | 52 (6.4%) | 49 (5.9%) | 49 (6.0%) |
| Lack of efficacy | 34 (4.2%) | 25 (3.0%) | 45 (5.5%) |
| Withdrawal of consent | 65 (8.0%) | 75 (9.1%) | 64 (7.9%) |
| Subject lost to follow-up | 14 (1.7%) | 7 (0.8%) | 7 (0.9%) |
| Protocol violation | 6 (0.7%) | 9 (1.1%) | 11 (1.4%) |
| Randomized/registered but never received/dispensed study drug | 1 (0.1%) | 0 | 0 |
| Other | 7 (0.9%) | 7 (0.8%) | 6 (0.7%) |

UTI TEAE Summary OAB EU/NA

TEAE in 12-week

| MedDRA v12.1 PT†, n (%) of Patients | Placebo (n = 1380) | Mirabegron | | | | Total Mira (n = 2736) | Tolterodine ER 4 mg (n = 495) |
|---|-----------------------|--------------------|---------------------|---------------------|-----------|--------------------------|-------------------------------------|
| | | 25 mg (n = 432) | 50 mg (n = 1375) | 100 mg (n = 929) | | | |
| UTI | 25 (1.8%) | 18 (4.2%) | 40 (2.9%) | 25 (2.7%) | 83 (3.0%) | 10 (2.0%) | |
| Mild | 15 (1.1%) | 10 (2.3%) | 27 (2.0%) | 16 (1.7%) | 53 (1.9%) | 5 (1.0%) | |
| Moderate | 9 (0.7%) | 8 (1.9%) | 13 (0.9%) | 9 (1.0%) | 30 (1.1%) | 5 (1.0%) | |
| Severe ‡ | 1 (0.1%) | 0 | 0 | 0 | 0 | 0 | |
| Drug-related | 5 (0.4%) | 5 (1.2%) | 6 (0.4%) | 2 (0.2%) | 13 (0.5%) | 1 (0.2%) | |

TEAE in Long-term

| MedDRA v12.1 PT†, n (%) of Patients | Mirabegron | | | Tolterodine ER 4 mg (n = 812) |
|--|--------------------|---------------------|--------------------------------|-------------------------------------|
| | 50 mg (n = 812) | 100 mg (n = 820) | Total Mirabegron (n = 1632) | |
| UTI | 48 (5.9%) | 45 (5.5%) | 93 (5.7%) | 52 (6.4%) |
| Mild | 31 (3.8%) | 27 (3.3%) | 58 (3.6%) | 44 (5.4%) |
| Moderate | 16 (2.0%) | 16 (2.0%) | 32 (2.0%) | 8 (1.0%) |
| Severe‡ | 1 (0.1%) | 2 (0.2%) | 3 (0.2%) | 0 |
| Drug-related | 5 (0.6%) | 7 (0.9%) | 12 (0.7%) | 9 (1.1%) |

TEAE leading to discontinuation in Long-term

| MedDRA v12.1 SOC PT†, n (%) of Patients | Mirabegron | | | Tolterodine ER 4 mg (n = 812) |
|---|--------------------|---------------------|-----------------------------------|-------------------------------------|
| | 50 mg (n = 812) | 100 mg (n = 820) | Total Mirabegron (n = 1632) | |
| UTI | 3 (0.4%) | 0 | 3 (0.2%) | 1 (0.1%) |

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

Drug relatedness was based on investigator assessment.

ER: extended release; mira: mirabegron; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.

† Sorting order: PT, decreasing frequency of TEAE in total mirabegron group.

‡ Severe category includes TEAE with missing severity.

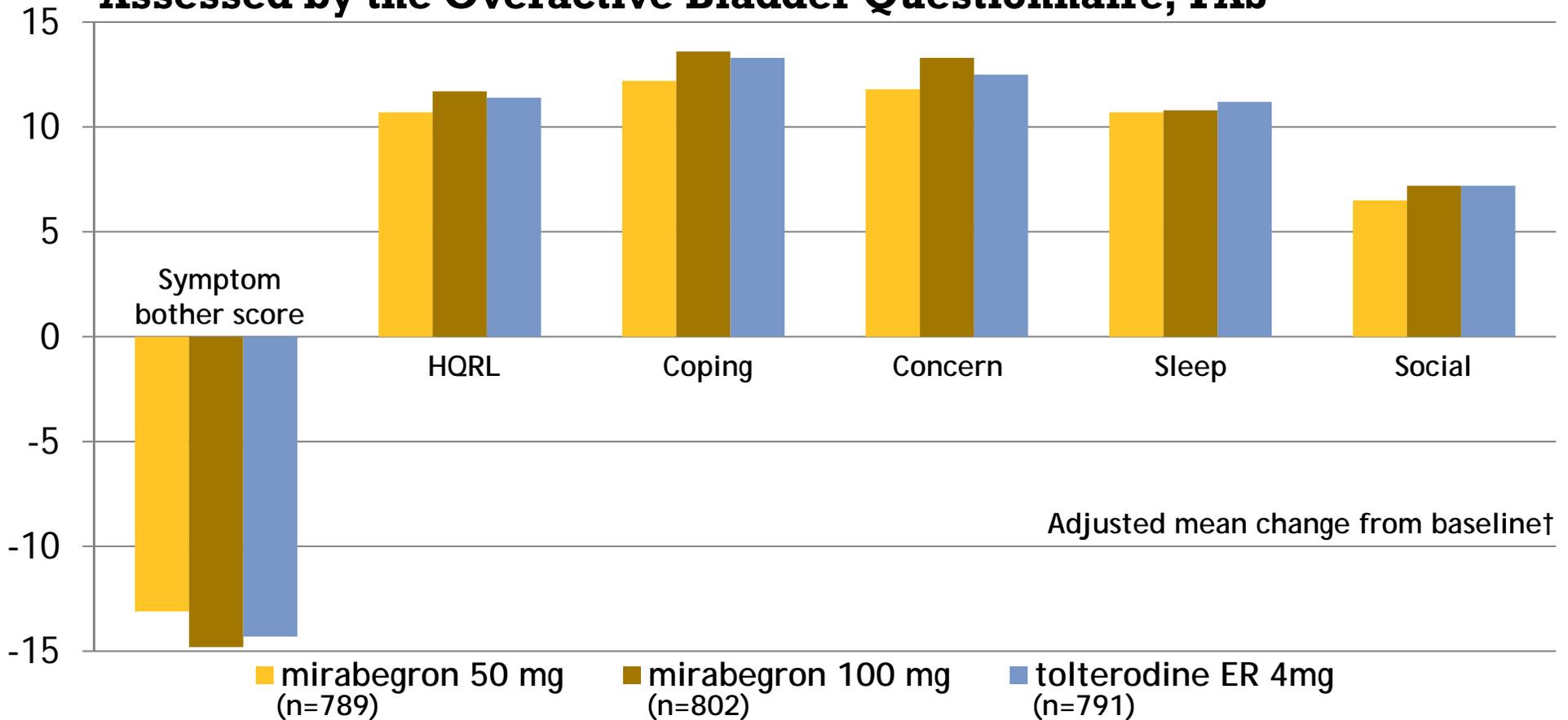
Metabolic Profile of Mirabegron at Steady State

| Dose | AUC (ng.h/mL) | | | | | | | | |
|------------|--------------------|--------|--------------------|--------|-------------------|-------------------|--------|---------------|--------|
| | Mice | | Rats | | Rabbits | Monkeys | | Human | |
| | 100 mg/kg/d Day 15 | | 100 mg/kg/d Day 15 | | 30 mg/kg/d Day 15 | 30 mg/kg/d Day 15 | | 50 mg/d Day 7 | |
| Gender | Male | Female | Male | Female | Female | Male | Female | Male | Female |
| Mirabegron | 35000 | 23900 | 20500 | 18800 | 3220 | 5710 | 4650 | 341 | 512 |
| M5 | 1300 | 1250 | 2090 | 1630 | 23600 | 102 | 174 | 79.8 | 112 |
| M8 | 1240 | 1380 | 4040 | 2530 | 88.5 | 515 | 528 | 49.4* | 104* |
| M11 | 4150 | 2270 | 153 | 201 | 838 | 124000 | 132000 | 150 | 201 |
| M12 | 0 | 0 | 134 | 137 | 0 | 284 | 321 | 82.9 | 98.5 |
| M13 | 224 | 157 | 45.6 | 51.7 | 199 | 1470 | 1780 | 10.1 | 12.9 |
| M14 | 821 | 582 | 497 | 517 | 890 | 122 | 118 | 68.5 | 75.0 |
| M15 | 49.5 | 90.2 | 0 | 0 | 27.7 | 361 | 376 | 30.9 | 48.5 |
| M16 | 1860 | 1300 | 157 | 158 | 10000 | 59.9 | 70.8 | 41.5 | 69.5 |

* M8 AUC values are for a 100 mg/day dose level as M8 concentrations could not be determined at the 50 mg MRHD. M11 and M12 are major metabolites as defined by ICH M3(R2).

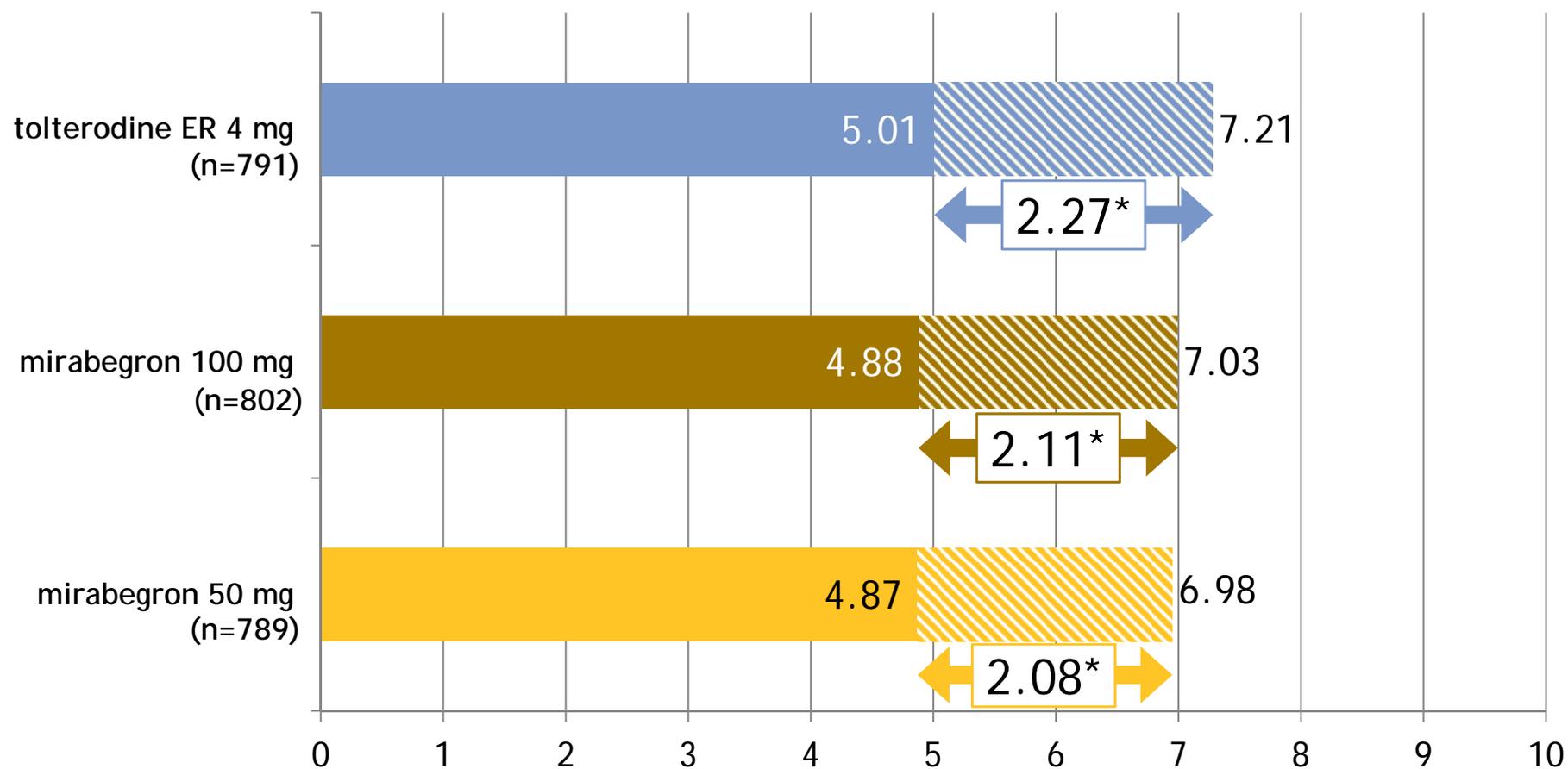
Change from Baseline to Final Visit in Symptom Bother Scale and Health Related Quality of Life Scores

Assessed by the Overactive Bladder Questionnaire, FAS



† The ANCOVA model included treatment group, previous study history, sex and geographical regions as fixed factors and baseline as a covariate.

PROs: Mean Change from Baseline to Final Visit in the Treatment Satisfaction Visual Analog Scale, FAS



*Adjusted mean change from baseline†

† The ANCOVA model included treatment group, previous study history, sex and geographical regions as fixed factors and baseline as a covariate.

Source: Table 12.3.5.6

Vital Signs of Office Device

12-Week Phase 3 Studies

| | Mirabegron 50 mg Adjusted Mean Difference from Placebo (95% CI) | | |
|--------------|--|------------------|-----------------|
| Study Number | DBP (mmHg) | SBP (mmHg) | Pulse (bpm) |
| 178-CL-046 | 0.0 (-0.9, 0.9) | -0.1 (-1.6, 1.3) | 0.8 (-0.3, 1.8) |
| 178-CL-047 | 0.2 (-0.8, 1.3) | 0.8 (-0.8, 2.4) | 0.5 (-0.6, 1.5) |
| 178-CL-074 | 0.9 (-0.1, 1.8) | 2.0 (0.4, 3.6) | 0.2 (-0.9, 1.2) |

Vital Signs of Office Device

Study Long-Term Controlled Study (52 Week)

| | Adjusted Mean Change from Baseline (95% CI) | | |
|-------------|---|------------------|-----------------|
| Dose | DBP (mmHg) | SBP (mmHg) | Pulse (bpm) |
| Mira 50 mg | -0.2 (-0.7, 0.3) | -0.0 (-0.8, 0.8) | 0.4 (-0.1, 1.0) |
| Mira 100 mg | 0.3 (-0.2, 0.8) | 0.4 (-0.4, 1.2) | 1.2 (0.7, 1.8) |
| Tolt | 0.2 (-0.3, 0.7) | -0.1 (-0.9, 0.7) | 1.6 (1.0, 2.1) |