Seroquel XR® (quetiapine fumarate) for Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD)

United States Food and Drug Administration
Psychopharmacologic Drugs Advisory Committee

April 8, 2009

Seroquel XR® (quetiapine fumarate) for Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD)

Introduction and Background on Quetiapine

Mark Scott, PhD

Executive Director
Clinical Development
AstraZeneca Pharmaceuticals LP

Proposed New Indications and Dosing for Quetiapine XR

- sNDA submissions in 2008
  - Seroquel XR® is indicated for monotherapy, adjunct therapy, and maintenance treatment for adult patients with Major Depressive Disorder (MDD)
  - Seroquel XR® is indicated for monotherapy and maintenance treatment for adult patients with Generalized Anxiety Disorder (GAD)
  - Dosing in the range of 50 - 300 mg; once daily

Context for Advisory Committee Meeting

- Based on the FDA's complete response letters and FDA Briefing Document
  - Efficacy is established in Major Depressive Disorder and Generalized Anxiety Disorder
  - Further discussion is needed for
    - Long-term metabolic safety
    - Tardive dyskinesia (TD)
    - Sudden cardiac death (SCD)[a]
    - Benefit/Risk assessment for MDD and GAD

[a] Ray WA, et al. *N Engl J Med*. 2009;360:225-35.

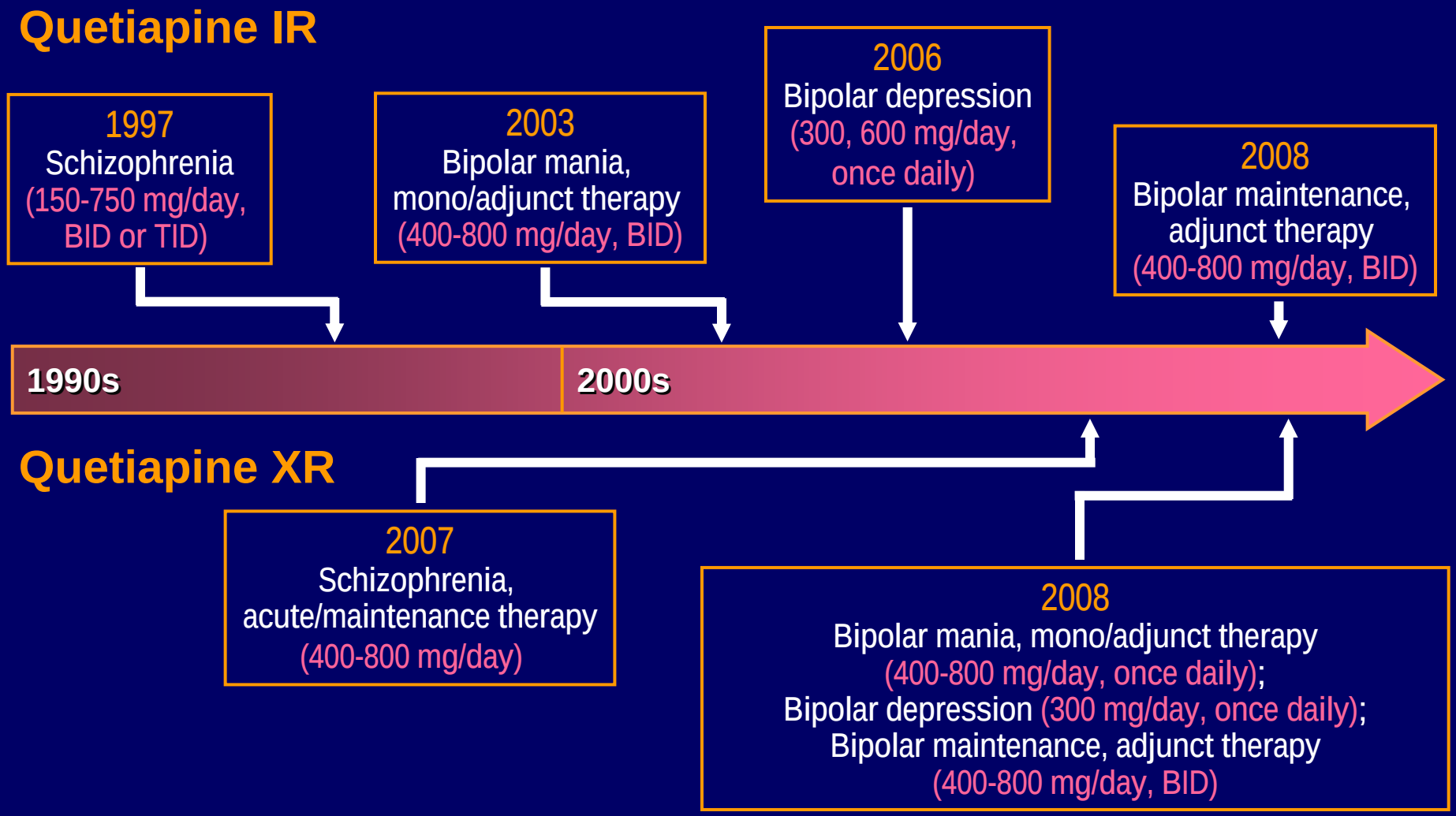
Today's Agenda

Introduction and Background on Quetiapine	Mark Scott, PhD AstraZeneca Pharmaceuticals LP
Efficacy and General Safety Profile in MDD and GAD	Hans Eriksson, MD, PhD AstraZeneca Pharmaceuticals LP
Safety Topics of Interest—Tardive Dyskinesia, Metabolic Risks, Sudden Cardiac Death	Ihor Rak, MD AstraZeneca Pharmaceuticals LP
Risk Management Benefit/Risk Assessment	Howard G. Hutchinson, MD, FACC AstraZeneca Pharmaceuticals LP
Clinical Perspective	Alan J. Gelenberg, MD University of Wisconsin
Concluding Remarks	Mark Scott, PhD AstraZeneca Pharmaceuticals LP

Introduction and Essential Background Information—Points to be Covered

- Regulatory development and safety profile
- Major Depressive Disorder and Generalized Anxiety Disorder are serious disorders with high unmet clinical need
- Rationale for development of quetiapine XR in MDD and GAD

Quetiapine US Regulatory Approvals



Extensive Worldwide Use of Quetiapine

- Quetiapine or quetiapine XR currently approved worldwide in
  - 94 countries for schizophrenia
  - 92 countries for bipolar mania
  - 41 countries for bipolar depression
- Quetiapine has been extensively researched
  - More than 26,000 subjects in 118 clinical studies
    - Including pediatric and elderly populations
  - Data from all these studies form database for extensive safety evaluations
- More than 22 million patients have received quetiapine

Quetiapine Safety Profile[a] in Approved Indications

- Potential safety risks well characterized and reflected in approved product label
- Boxed Warnings
  - Increased mortality in elderly patients with dementia-related psychoses
  - Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for Major Depressive Disorder and other psychiatric disorders

[a] For complete prescribing information see full product label.

Quetiapine Safety Profile[a] in Approved Indications

- **Warnings and Precautions**
  - Hyperglycemia and Diabetes Mellitus
  - Hyperlipidemia and weight gain
  - Neuroleptic Malignant Syndrome (NMS)
  - Tardive dyskinesia (TD)
  - Orthostatic hypotension
  - Leukopenia, neutropenia, and agranulocytosis
  - Cataracts
  - Suicide
- **Most common adverse reactions (IR and XR formulations) include**
  - Somnolence, dry mouth, hyperlipidemia, dizziness, constipation, dyspepsia, asthenia, abdominal pain, postural hypotension, orthostatic hypotension, pharyngitis, weight gain, increased appetite, fatigue, lethargy, hyperglycemia, dysarthria, nasal congestion, ALT increased, and dyspepsia

[a] For complete prescribing information see full product label.

Introduction and Essential Background Information—Points to Be Covered

- Regulatory development and safety profile
- Major Depressive Disorder and Generalized Anxiety Disorder are serious disorders with high unmet clinical need
- Rationale for development of quetiapine XR in MDD and GAD

Major Depressive Disorder and Generalized Anxiety Disorder Are Serious

- Highly prevalent and highly disabling
  - Increased morbidity and mortality
  - Lead to functional impairment (eg, social and occupational)
- Symptoms are complex and varied
  - Comorbid conditions challenge diagnostic certainty
  - Treatment recommendations available
- Physicians use many treatment options to achieve the appropriate balance between efficacy and tolerability with safety in mind

Introduction and Essential Background Information—Points to Be Covered

- Regulatory development and safety profile
- Major Depressive Disorder and Generalized Anxiety Disorder are serious disorders with high unmet clinical need
- **Rationale for development of quetiapine XR in MDD and GAD**

Quetiapine XR Extends Treatment Options for Patients With Major Depressive Disorder and Generalized Anxiety Disorder

- Quetiapine engages well-established targets for antidepressant and anxiolytic treatments
  - Distinct from currently available pharmacotherapy
    - Low D_2 dopamine receptor occupancy
    - Serotonin 5-HT_{2A}, 5-HT_{2C} antagonism, and 5-HT_{1A} partial agonism
    - Norepinephrine reuptake inhibition
- Treatment guidelines recommend changing to drug with different MOA for patients with poor response or intolerance
- Quetiapine XR offers physicians and patients a unique treatment for MDD and GAD

Development in MDD and GAD

- Rationale
  - Effects on anxiety and depressive symptoms seen in development programs for schizophrenia and mania
  - Effects seen in depressive episodes associated with bipolar disorder
  - Prevalence and seriousness of both disorders
  - Need for additional options in both disorders
- End of Phase II Meeting—May 2005
  - FDA agreed to scope of program, but not the inclusion of severity as part of the indication
- sNDA submissions in 2008

Quetiapine XR Is Not for All Patients

- The development programs enrolled with moderate to severe MDD or GAD were included
- In MDD, quetiapine was also evaluated as an adjunct therapy for patients with inadequate response to another antidepressant
- Use of quetiapine in MDD and GAD should be based on medical history, symptom presentation, and previous treatment
- Quetiapine XR will not replace SSRI/SNRIs within the treatment cascade but is a valuable additional treatment option for patients for whom first-line therapies are not appropriate

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Seroquel XR® (quetiapine fumarate) for Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD)

Efficacy and General Safety Profile in MDD and GAD

Hans Eriksson, MD, PhD

Medical Science Senior Director
Research and Development
AstraZeneca Pharmaceuticals LP

Presentation Overview—MDD and GAD

- Clinical development program in MDD and GAD
  - Patient characteristics
  - Key study endpoints
  - Key efficacy data
  - General safety data in short-term and longer-term studies

Clinical Development Program in MDD

Overview of MDD Studies

	No	Duration, wk	Randomized	Treatments
Acute mono	1	6[a]	723	QTP XR 50, 150, 300 mg; placebo
	2	6[a]	612	QTP XR 150, 300 mg; duloxetine 60 mg; placebo
	3	8[a]	310	QTP XR 150/300 mg; placebo
	4	8[a]	471	QTP XR 150/300 mg; escitalopram 10/20 mg; placebo
Maintenance	5	Up to 52	Open-label: 1876 Randomized: 787	QTP XR 50-300 mg; placebo
Acute adjunct	6	6[a]	446	QTP XR 150, 300 mg + AD; placebo + AD
	7	6	493	QTP XR 150, 300 mg + AD; placebo + AD
Acute mono elderly	14	9[a]	338	QTP XR 50-300 mg; placebo

AD, antidepressant.

[a] Randomized phase followed by 2-wk post-treatment drug discontinuation phase.

Patient Characteristics—MDD

- **Key inclusion criteria**
  - DSM-IV diagnosis of MDD, single episode or recurrent
  - HAM-D score ≥ 22[a] or ≥ 20[b]
  - Inadequate response[c] to antidepressant (adjunct studies)
- **Baseline disease characteristics**
  - Mean HAM-D = 25.8
  - Mean MADRS = 30.7

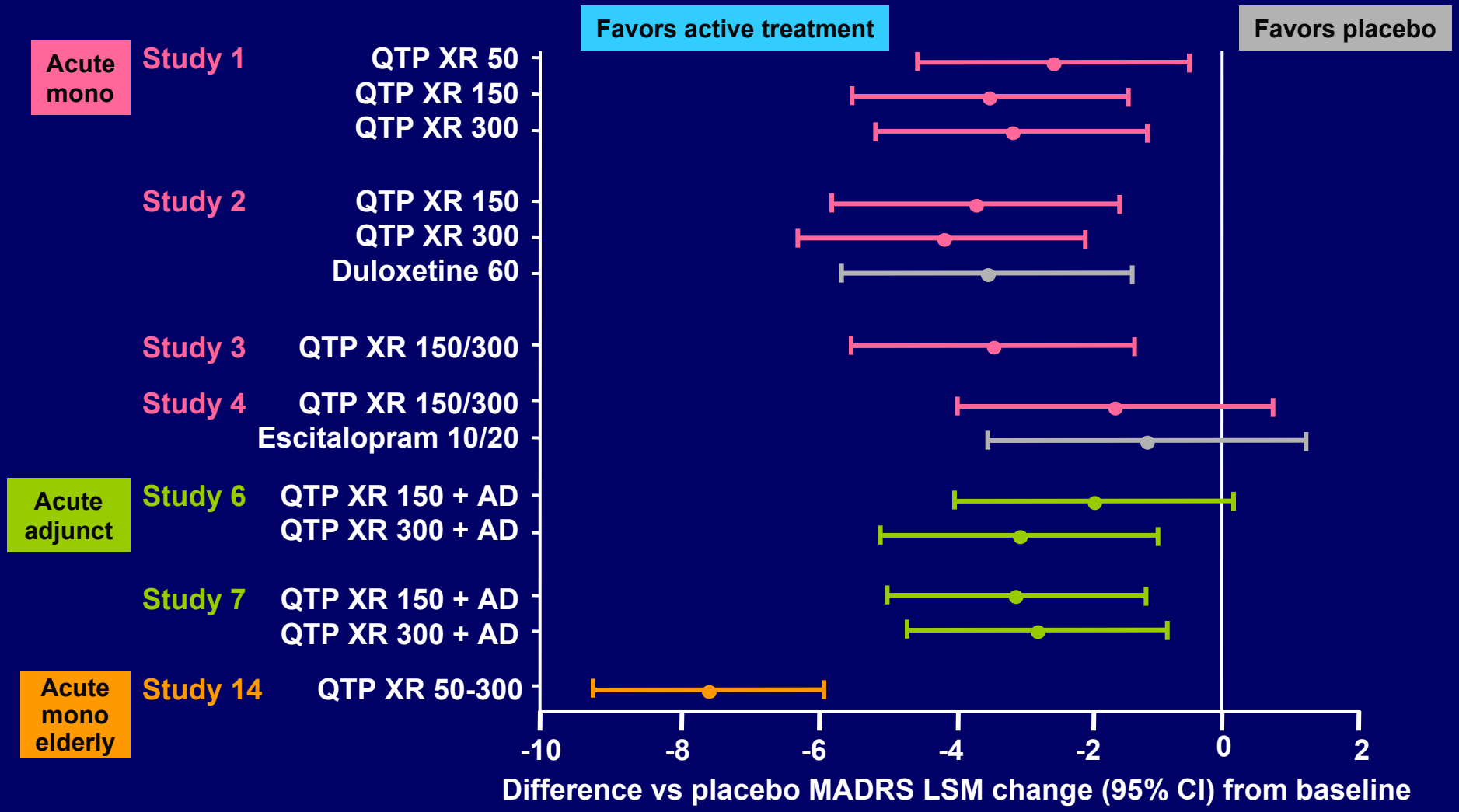
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (4th ed); HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale.
[a] Studies 1, 2, 3, and 4. [b]Studies 5, 6, and 7. [c] Having at least minimum effective antidepressant dose for 6 weeks including at least 1 dose increase when permitted.

Key Study Endpoints—MDD

- Primary
  - Mean change from baseline depression symptoms based on MADRS total score (acute studies)
  - Time to recurrence of depressive symptoms (maintenance study)
- Secondary
  - Response (≥ 50% reduction in MADRS total)
  - Remission (MADRS ≤ 8)

MADRS, Montgomery-Asberg Depression Rating Scale.

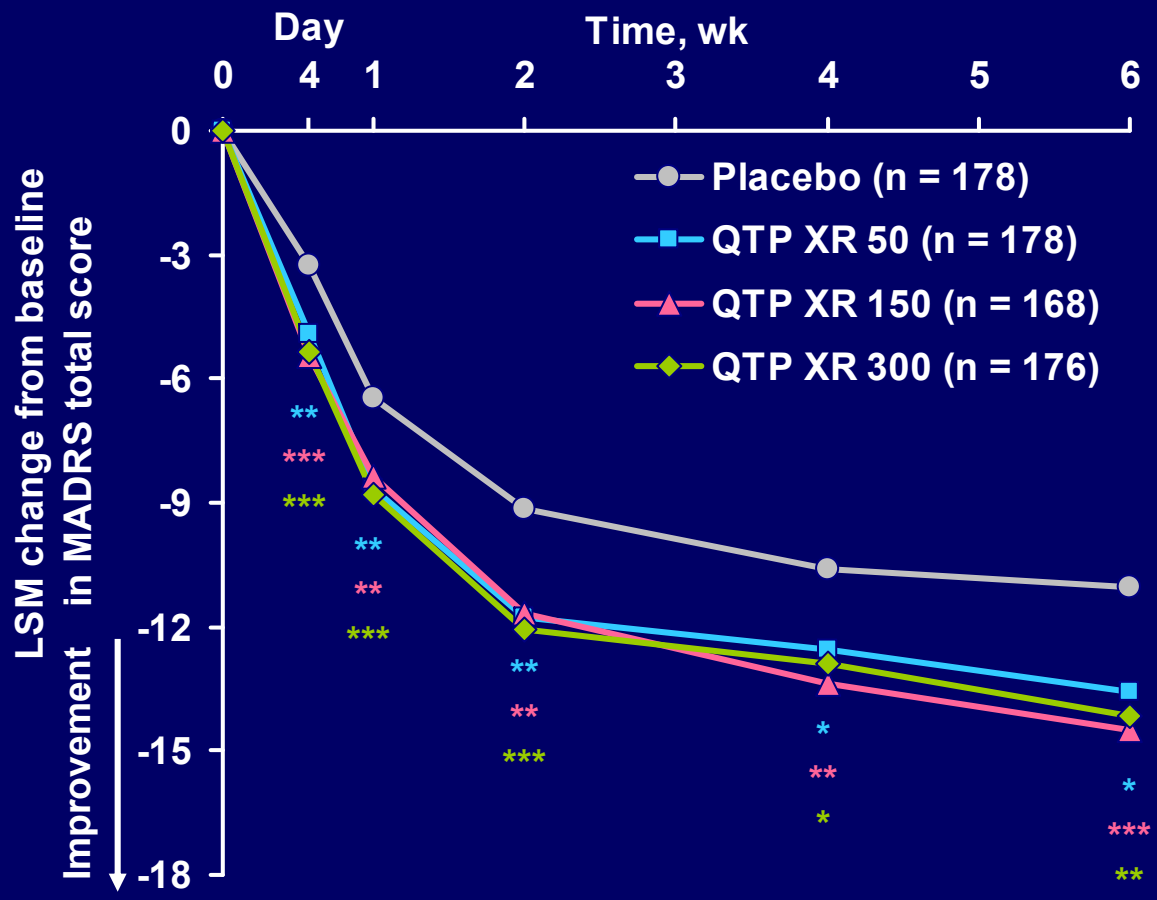
Consistent Efficacy Demonstrated Based on Change From Baseline MADRS Score vs Placebo



LSM, least-squares means; AD, antidepressant.

Early Effect on MADRS Score Maintained Over Time

Study 1—Acute Monotherapy



*p < 0.05; **p < 0.01; ***p < 0.001 vs placebo
MITT; LOCF

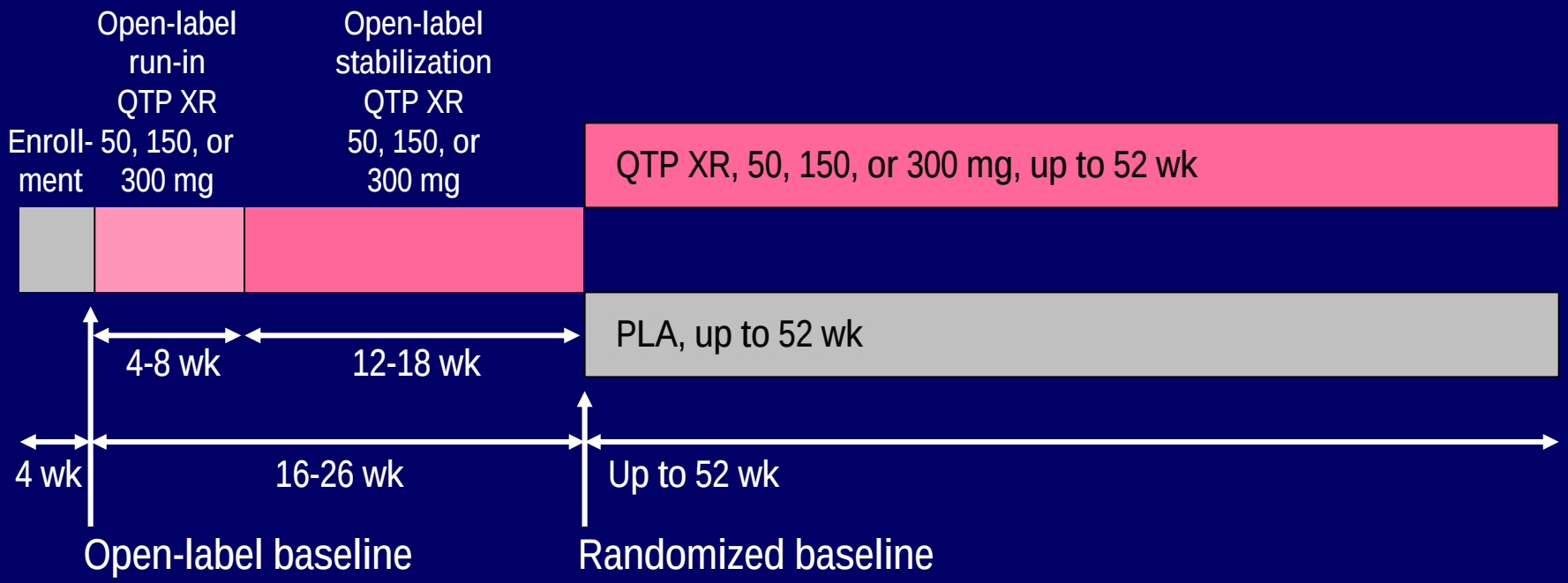
Effects on Secondary Parameters Support the Findings on the Primary Variable in MDD

- Statistically significant and clinically relevant
  - Separation from placebo for MADRS observed within the first week in all 6 positive short-term studies in MDD
  - Effects on response (MADRS improvement ≥ 50%) for quetiapine in fixed-dose, modified fixed-dose, adjunct, and elderly studies
  - Effects on remission (MADRS ≤ 8) for quetiapine in fixed-dose, adjunct, and elderly studies

MADRS, Montgomery-Asberg Depression Rating Scale.

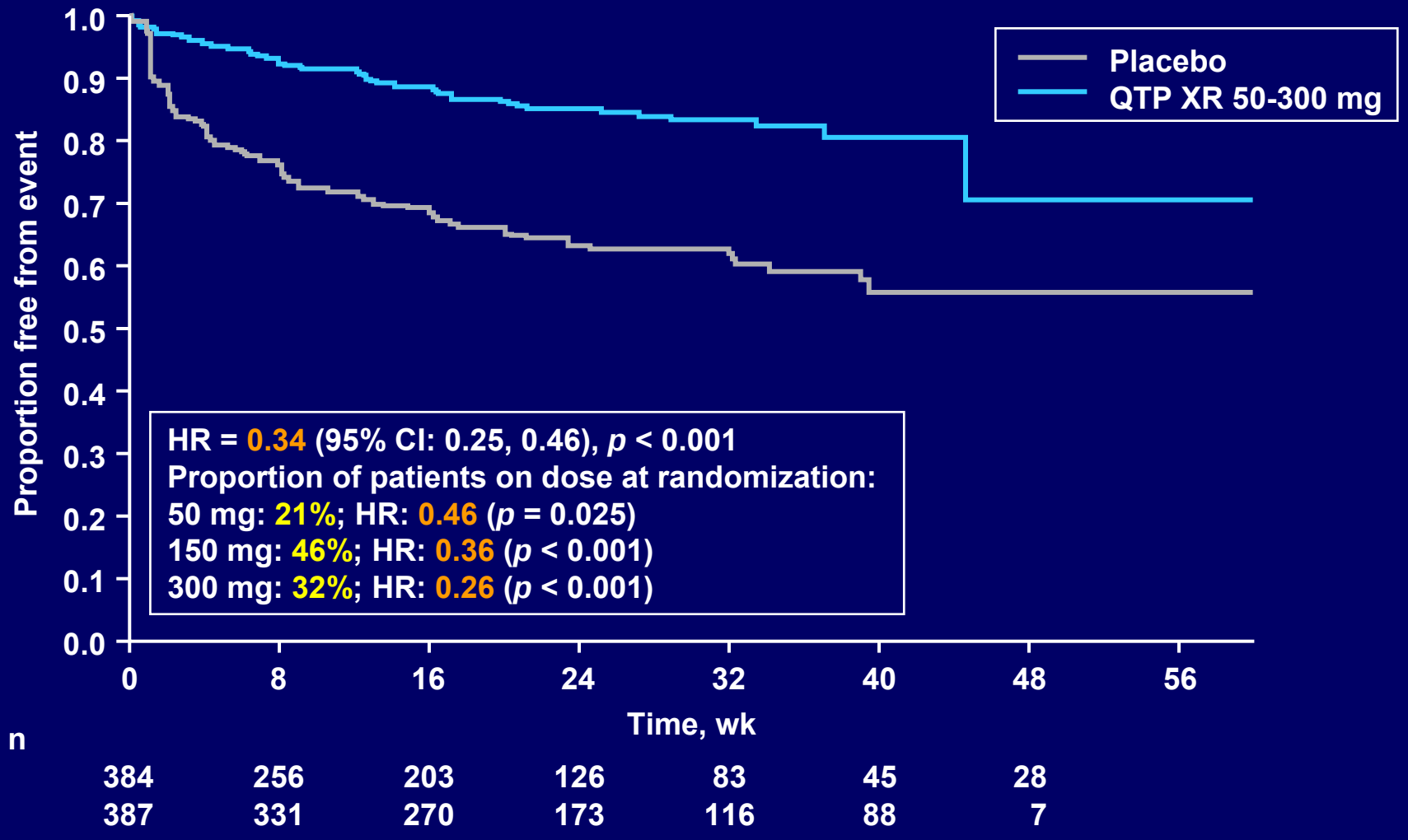
Study Flow for Randomized Withdrawal Studies

Study 5 (MDD) and Study 12 (GAD)



Quetiapine XR Significantly Reduces Risk of Relapse in MDD

Study 5—Maintenance Therapy



HR, hazard ratio; CI, confidence interval.

Quetiapine XR Is Efficacious in the Treatment of MDD

- At low doses (50 - 300 mg/day), quetiapine XR is an efficacious antidepressant
- Consistently reduces level of depressive symptoms
  - As monotherapy
  - As adjunctive therapy in patients with inadequate response to antidepressant drug therapy
  - In elderly patients
- Symptom improvement seen within 1 week
- Consistently effective based on response and remission rates
- Delays recurrence of a depressed event during maintenance therapy

Clinical Development Program in GAD

Overview of GAD Studies

	No.	Duration, wk	Randomized	Treatments
Acute mono	9	8[a]	951	QTP XR 50, 150, 300 mg; placebo
	10	8[a]	854	QTP XR 150, 300 mg; escitalopram 10 mg; placebo
	11	8[a]	873	QTP XR 50, 150 mg; paroxetine 20 mg; placebo
Maintenance	12	Up to 52	Open-label: 1224 Randomized: 432	QTP XR 50-300 mg; placebo
Acute mono elderly	15	9[a]	338	QTP XR 50-300 mg; placebo

[a] Randomized phase followed by 2-wk post-treatment drug discontinuation phase.

Patient Characteristics—GAD

- **Key inclusion criteria**
  - DSM-IV TR diagnosis of GAD
  - HAM-A total score ≥ 20
  - MADRS total score ≤ 16[a]
- **Baseline disease characteristics**
  - Mean HAM-A = 25.5

DSM-IV TR, Diagnostic and Statistical Manual of Mental Disorders (4th ed) text revision; HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Asberg Depression Rating Scale.

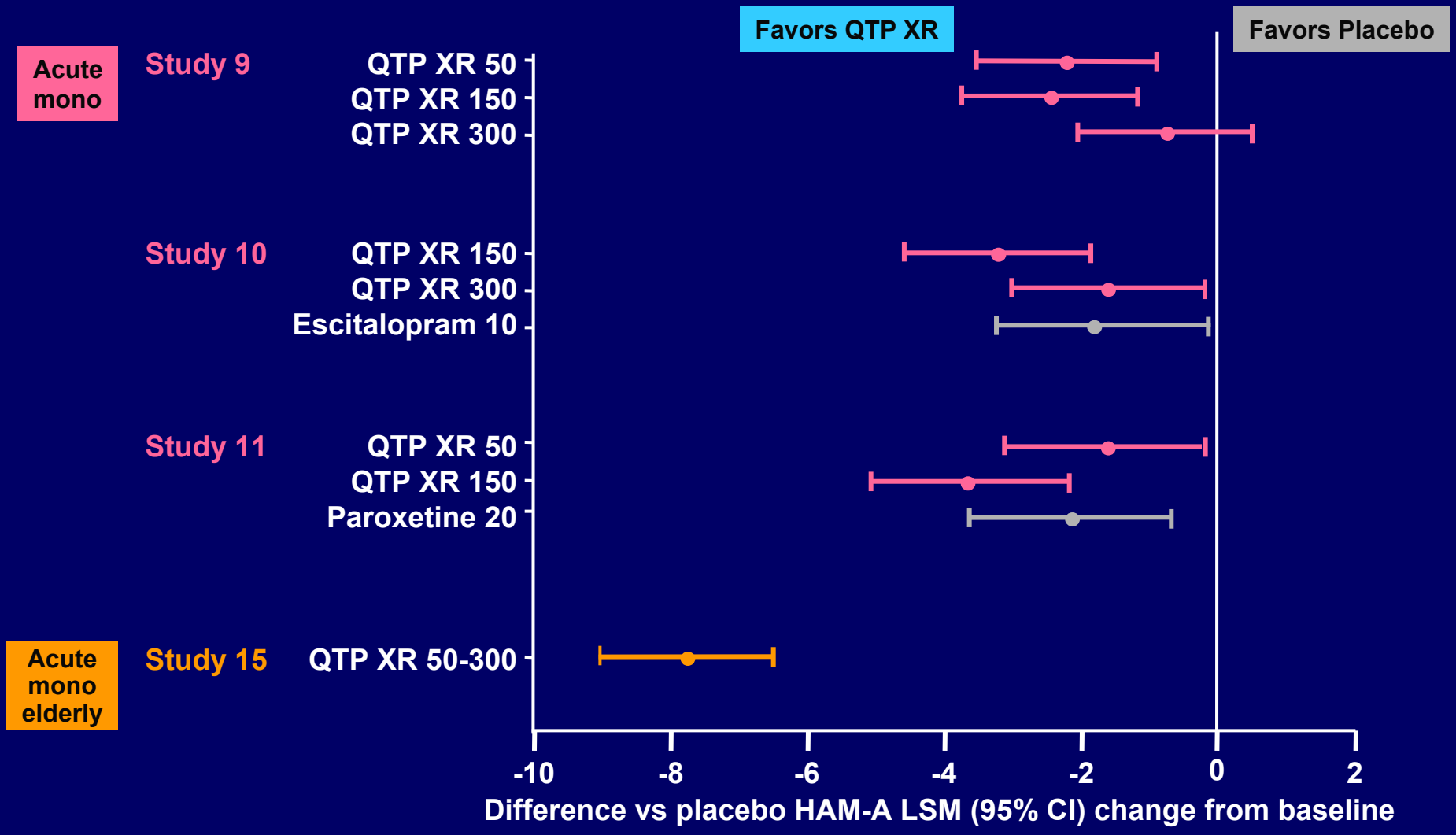
[a] Studies 9, 10, and 11.

Key Study Endpoints—GAD

- **Primary**
  - Mean change from baseline anxiety symptoms based on HAM-A total score (acute studies)
  - Time to recurrence of anxiety symptoms (maintenance study)
- **Secondary**
  - Response (≥ 50% reduction in HAM-A total score)
  - Remission (HAM-A total score ≤ 7)

HAM-A, Hamilton Rating Scale for Anxiety.

Consistent Efficacy Demonstrated Based on Change From Baseline HAM-A Score vs Placebo



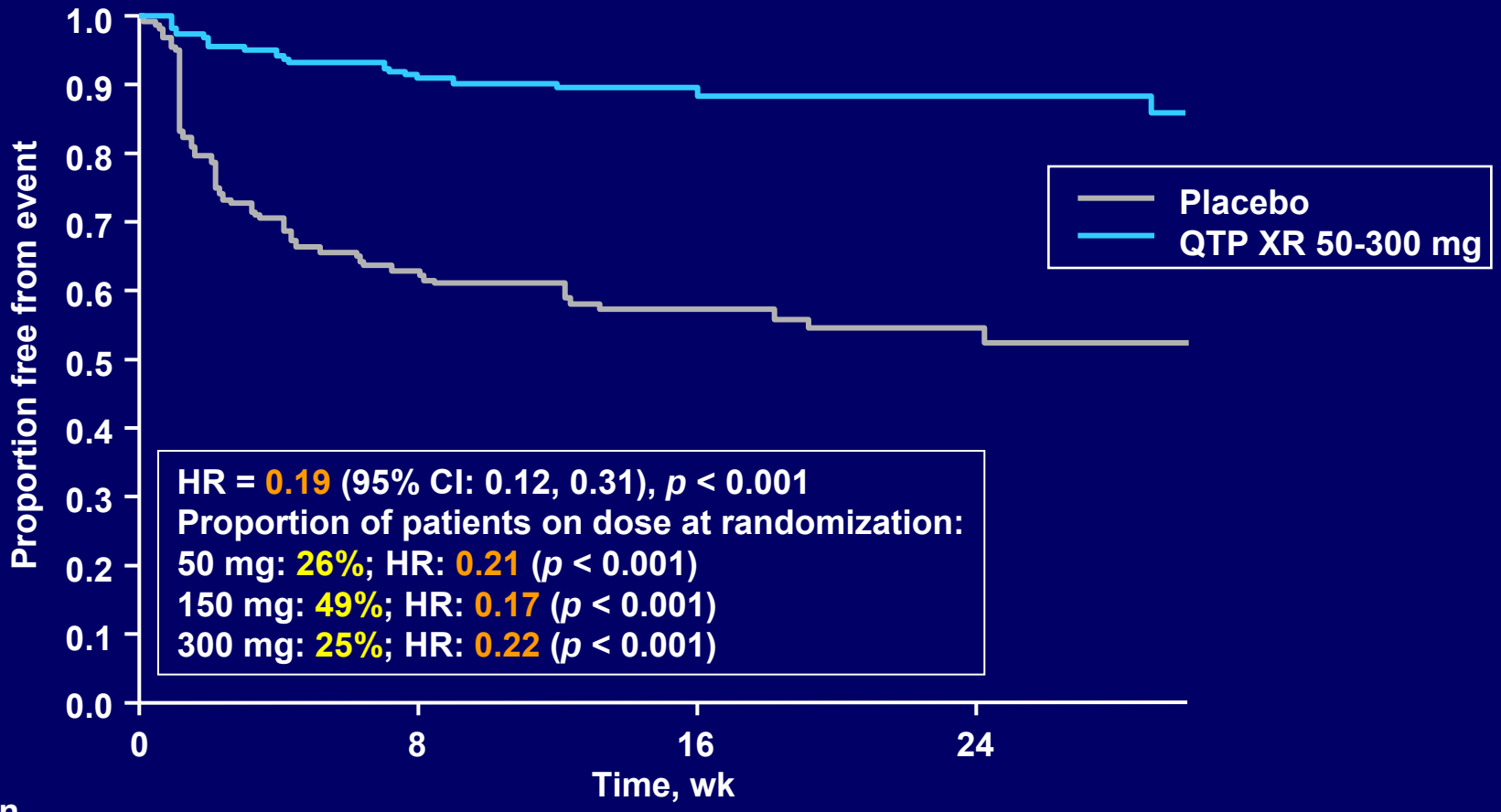
Effects on Secondary Parameters Support the Findings on the Primary Variable in GAD

- Statistically significant and clinically relevant
  - Separation from placebo for HAM-A observed within the first week in all 4 short-term studies in GAD
  - Effects on response (HAM-A improvement ≥ 50%) for quetiapine in fixed-dose and elderly studies
  - Effects on remission (HAM-A ≤ 7) for quetiapine in fixed-dose and elderly studies

HAM-A, Hamilton Rating Scale for Anxiety.

Quetiapine XR Significantly Reduces Risk of Relapse in GAD

Study 12—Maintenance Therapy



At risk, n				
PLA	216	91	41	26
QTP	216	151	92	92

HR, hazard ratio; CI, confidence interval.

Quetiapine XR Is Efficacious in the Treatment of GAD

- At low doses (50 - 300 mg/day), quetiapine XR is an efficacious anxiolytic agent
- Consistently reduces level of anxiety symptoms
  - As monotherapy
  - In elderly patients
- Symptom improvement seen within 1 week
- Consistently effective based on response and remission rates
- Delays recurrence of an anxiety event during maintenance therapy

Overall Summary of Efficacy in MDD and GAD

- In a population of patients with moderate to severe MDD or GAD quetiapine XR was consistently demonstrated within the dose range of 50-300 mg
  - In acute treatment in adults
  - In acute treatment in elderly patients
  - In longer-term maintenance treatment
- Efficacy of quetiapine XR was also demonstrated in adjunct treatment of MDD together with an antidepressant
- Efficacy was consistently seen within the first week of treatment

General Safety Data From Studies in MDD and GAD

AEs ≥ 5%—Short-term Monotherapy
Studies 1, 2, 3, 4, 9, 10, and 11

	Patients, %							
MedDRA preferred term	PLA n = 1313	All QTP n = 2718	QTP 50 n = 633	QTP 150 n = 1268	QTP 300 n = 818	ESC n = 365	PAR n = 215	DUL n = 149
Any AE	53.7	77.3	68.1	78.9	81.9	73.4	65.1	81.2
Dry mouth	9.2	32.9	21.6	34.2	39.7	17.0	9.8	20.8
Somnolence	8.8	28.1	23.7	28.6	30.6	12.6	11.2	13.4
Sedation	4.7	24.1	16.6	23.7	30.6	9.9	2.3	16.1
Dizziness	8.8	14.8	12.2	15.3	16.0	14.8	21.4	20.8
Headache	17.8	13.7	13.1	15.3	11.8	28.2	20.9	21.5
Nausea	9.4	11.1	7.9	12.2	11.8	27.1	22.3	37.6
Fatigue	4.9	9.4	10.4	9.9	8.0	9.9	10.2	7.4
Constipation	3.4	7.7	5.4	7.3	9.9	7.4	3.7	11.4
Insomnia	6.9	6.8	5.1	8.2	6.1	11.8	11.6	16.1
Diarrhea	7.1	6.0	5.5	6.5	5.6	13.7	7.0	12.8
Increased appetite	3.4	5.1	4.4	5.3	5.4	1.6	1.4	2.0
Vomiting	2.7	4.1	2.1	4.3	5.4	4.1	6.0	4.7
Dyspepsia	1.9	3.6	1.7	3.5	5.0	2.5	4.7	5.4
Nasopharyngitis	4.0	3.3	2.8	3.7	3.2	3.0	6.0	1.3
Anxiety	2.1	2.2	1.4	2.6	2.3	3.0	6.5	3.4
Decreased appetite	1.8	2.0	1.6	1.9	2.4	4.9	1.4	5.4
Hyperhidrosis	1.4	1.5	1.4	1.7	1.2	4.7	3.7	7.4
Tremor	1.4	1.5	1.4	1.3	1.7	2.2	5.1	5.4
Pollakiuria	1.5	1.0	0.6	1.0	1.3	1.1	0.9	5.4

AE Incidence—Short-term Monotherapy
Studies 1, 2, 3, 4, 9, 10, and 11

	Patients, n (%)							
Type of AE[a]	PLA n = 1313	ALL QTP n = 2718	QTP 50 n = 633	QTP 150 n = 1268	QTP 300 n = 817	ESC 10/20 n = 365	PAR 20 n = 215	DUL 60 n = 149
SAE	9 (0.7)	28 (1.0)	4 (0.6)	9 (0.7)	15 (1.8)	6 (1.6)	0	3 (2.0)
AE leading to death	0	1 (0.0)	0	1 (0.1)	0	0	0	0
Withdrawals due to AE	72 (5.5)	461 (17.0)	79 (12.5)	211 (16.6)	171 (20.9)	32 (8.8)	17 (7.9)	27 (18.1)

AE, adverse event; SAE, serious adverse event.

[a] Patients with multiple events in the same category are counted only once.

Common AEs ≥ 5%
Studies 5 and 12—Open-label Phase

MedDRA preferred term[a]	QTP N = 3078, n (%)
Dry mouth	859 (27.9)
Somnolence	955 (31.0)
Sedation	673 (21.9)
Dizziness	399 (13.0)
Fatigue	406 (13.2)
Constipation	260 (8.4)
Headache	295 (9.6)
Weight increased	190 (6.2)
Nausea	195 (6.3)
Increased appetite	145 (4.7)
Nasopharyngitis	114 (3.7)
Irritability	181 (5.9)
Upper respiratory tract infection	81 (2.6)

Note: Common adverse event (AE) is defined as an event occurring at a rate of ≥ 5% in any treatment group.
Note: Events reported during randomized phase are sorted by decreasing frequency in the QTP XR group.
[a] Patients with multiple events falling under the same preferred term are counted only once in that term during each phase (open-label or randomized).

Common AEs ≥ 5%
Studies 5 and 12—Randomized Phase

MedDRA preferred term[a]	Patients, n (%) PLA n = 601	QTP n = 607
Weight increased	7 (1.2)	47 (7.7)
Headache	71 (11.8)	46 (7.6)
Nasopharyngitis	32 (5.3)	39 (6.4)
Dizziness	23 (3.8)	32 (5.3)
Insomnia	87 (14.5)	29 (4.8)
Diarrhea	33 (5.5)	28 (4.6)
Nausea	70 (11.6)	22 (3.6)

Note: Common adverse event (AE) is defined as an event occurring at a rate of ≥ 5% in any treatment group.
Note: Events reported during randomized phase are sorted by decreasing frequency in the QTP XR group.
[a] Patients with multiple events falling under the same preferred term are counted only once.

General Safety Profile Summary

- Most common adverse events were
  - Sedation, somnolence, dizziness, and dry mouth
- Weight gain was reported more frequently for quetiapine than for placebo during longer-term treatment
- Adverse event profile seen in the MDD and GAD programs similar to those that are seen in approved indications

Seroquel XR® (quetiapine fumarate) for Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD)

Safety Topics of Interest

Ihor W. Rak, MD

Vice President
Clinical Neuroscience
AstraZeneca Pharmaceuticals LP

Presentation Overview

- Well-characterized, longer-term safety data
  - Pooled Safety Populations
- Safety topics of special interest
  - Tardive dyskinesia
  - Metabolic and cardiovascular assessments
  - Sudden cardiac death

Pooled Safety Populations

	Quetiapine			Placebo		
	N	Exposure, pt-yr	Mean time on treatment, wk (max)	N	Exposure, pt-yr	Mean time on treatment, wk (max)
Pool A: all studies	26,454	7890	15.5 (322)	6375	1197	9.8 (103)
Pool B: all short-term, placebo-controlled studies	8853	982	5.8 (14)	4359	492	5.6 (14)
Pool C: all longer-term, randomized withdrawal studies	2043	1026	26.1(104)	2016	702	18.1 (103)
Pool D: all MDD/GAD studies	6816	1405	10.7 (72)	2622	438	8.7 (53)
Pool E: MDD/GAD longer-term, randomized withdrawal studies	607	242	20.7 (53)	601	178	15.4 (53)

Tardive Dyskinesia

Current Label for Approved Indications
Tardive Dyskinesia (1)

"**A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs including quetiapine.** Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown."

Current Label for Approved Indications
Tardive Dyskinesia (2)

- "The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.
- "There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown."

Incidence of Tardive Dyskinesia Is Low (0.2%)

	N	Events, n (%)	Pt-yr exposure	Event rate per 100 pt-yr	Relative risk QTP vs PLA (95%CI)[a]
Pool A, all studies					
Quetiapine	26,454	53 (0.20)	7862	0.7	
Placebo	6375	2 (0.03)	1196	0.2	
Comparator	4,001	7 (0.2)	787	0.9	
Pool B, all short-term placebo-controlled studies					
Quetiapine	8853	8 (0.09)	982	0.6	2.26 (0.28, 107.53)
Placebo	4359	1 (0.02)	492	0.3	
Pool C, all longer-term placebo-controlled randomized withdrawal studies					
Quetiapine	2043	1 (0.05)	1026	0.1	0.63 (0.01, 49.77)
Placebo	2016	1 (0.05)	704	0.1	
Pool D, all MDD and GAD studies					
Quetiapine	6816	0	1405	0.0	
Placebo	2622	0	438	0.0	
Pool E, MDD/GAD longer-term, randomized withdrawal studies					
Quetiapine	607	0	242	0.0	—
Placebo	601	0	174	0.0	

[a] Exact RR estimate and 95% CI.

Risk of TD Present and Low in MDD and GAD

Evaluation of AIMS data using Schooler-Kane criteria	Incidence
Schizophrenia	
Long-term studies	2.4%
Bipolar disorder	
Randomized withdrawal studies	0.58%
MDD and GAD	
Longer-term studies	0.21%
Studies in elderly patients	0.26%

Guy 1976; Schooler and Kane 1982.

Current Label for Approved Indications
Tardive Dyskinesia (3)

"Given these considerations, SEROQUEL XR should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically."

"If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome."

Metabolic and Cardiovascular Assessments

Metabolic and Cardiovascular Assessments Overview

- Weight
- Glucose control
  - Fasting plasma glucose
  - HbA1C
  - Glycosuria
  - Reported adverse events potentially related to diabetes mellitus
- Lipids
  - Total cholesterol
  - Triglycerides
  - LDL-C, HDL-C, LDL/HDL ratio
  - Reported adverse events potentially related to atherosclerotic cardiovascular disease

Mean Weight Changes (kg) by Dose
Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	400	600	800
All indications, mean (SD)	n = 2319	n = 656	n = 1286	n = 1915	n = 340	n = 1182	n = 451
Baseline	81.0 (21.9)	78.3 (19.8)	79.8 (20.9)	82.8 (20.6)	73.9 (22.8)	81.4 (21.7)	83.3 (23.4)
Change	0.2 (3.4)	0.8 (2.2)	1.0 (2.5)	1.1 (2.9)	1.1 (2.8)	1.4 (4.4)	1.2 (5.0)
p value	—	0.053	< 0.001	< 0.001	0.004	< 0.001	< 0.001

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	Dul 60	Esc 10	Par 20
MDD + GAD, mean (SD)	n = 1301	n = 627	n = 1257	n = 816	n = 149	n = 209	n = 215
Baseline	80.7 (22.2)	78.4 (19.9)	79.8 (20.9)	82.6 (20.9)	84.8 (19.5)	79.7 (19.7)	74.4 (17.1)
Change	0.3 (3.8)	0.7 (2.1)	1.0 (2.4)	1.2 (2.5)	–0.2 (2.7)	0.2 (2.0)	0.2 (2.3)
p value	—	0.176	< 0.001	< 0.001	0.734	0.813	0.980

Proportion of Patients Gaining ≥ 7% Body Weight

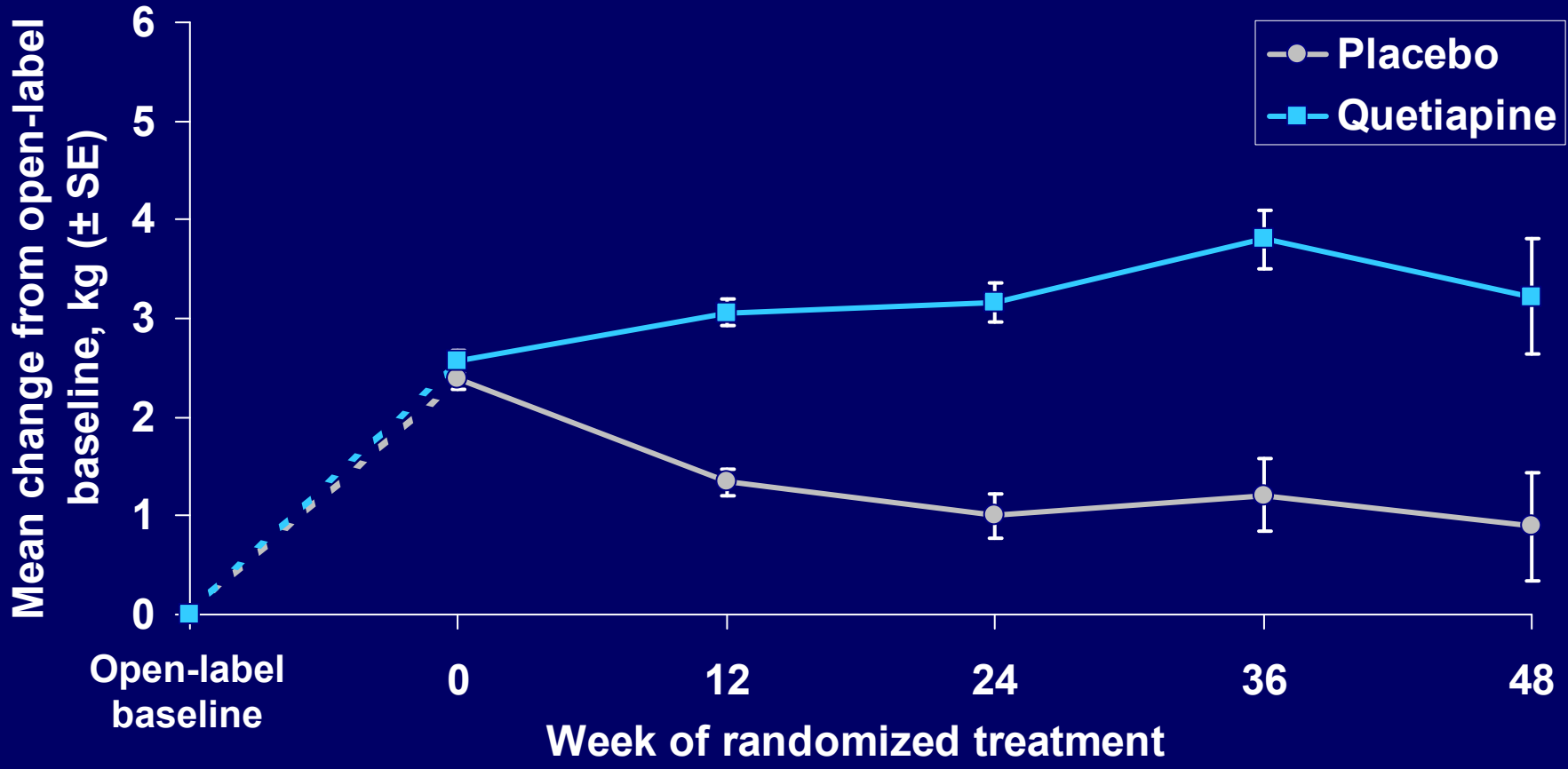
Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	400	600	800
All indications, n	2328	657	1287	1926	341	1192	451
≥ 7% increase, %	3.7	5.3	6.6	7.7	15.5	12.5	14.2
p value	—	0.074	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	Dul 60	Esc 10	Par 20
MDD + GAD, n	1303	628	1258	818	149	209	215
≥ 7% increase, %	2.9	4.6	6.1	6.7	1.3	2.4	5.6
p value	—	0.063	< 0.001	< 0.001	0.425	0.824	0.060

Weight Change (kg) From Open-label Baseline

Pool C: Longer-term, Randomized Withdrawal Studies



N =					
Placebo	1894	1740	698	333	120
Quetiapine	1953	1758	1044	544	152

Summary of Weight Changes

- Small mean weight increases were seen at all doses in short-term studies
- The largest incidence of weight gain ≥ 7% was observed in patients treated with 400 mg/day
- In longer-term studies, mean weight plateaued with continued treatment and decreased towards baseline after drug withdrawal

Fasting Glucose (mg/dL)—Mean Change by Dose

Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	400	600	800
All indications, mean (SD)	n = 1489	n = 439	n = 832	n = 1004	n = 287	n = 578	n = 266
Baseline	91.7 (13.6)	91.0 (11.4)	91.8 (13.0)	91.2 (12.3)	92.1 (15.7)	93.1 (16.6)	95.4 (21.3)
Change	1.7 (13.8)	0.2 (13.6)	1.8 (13.6)	3.3 (16.4)	1.7 (17.2)	3.4 (19.9)	2.4 (23.4)
p value	—	0.188	0.609	0.075	0.094	0.020	0.272

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	Dul 60	Esc 10	Par 20
MDD + GAD, mean (SD)	n = 941	n = 439	n = 832	n = 506	n = 94	n = 132	n = 161
Baseline	91.4 (13.3)	91.0 (11.4)	91.8 (13.0)	90.2 (11.2)	91.2 (9.8)	89.4 (12.1)	93.7 (12.8)
Change	1.5 (12.5)	0.2 (13.6)	1.8 (13.6)	2.6 (14.0)	1.1 (14.4)	1.6 (11.2)	1.6 (12.6)
p value	—	0.159	0.589	0.189	0.858	0.801	0.491

Fasting Glucose—Proportion of Patients Shifting to ≥ 126 mg/dL

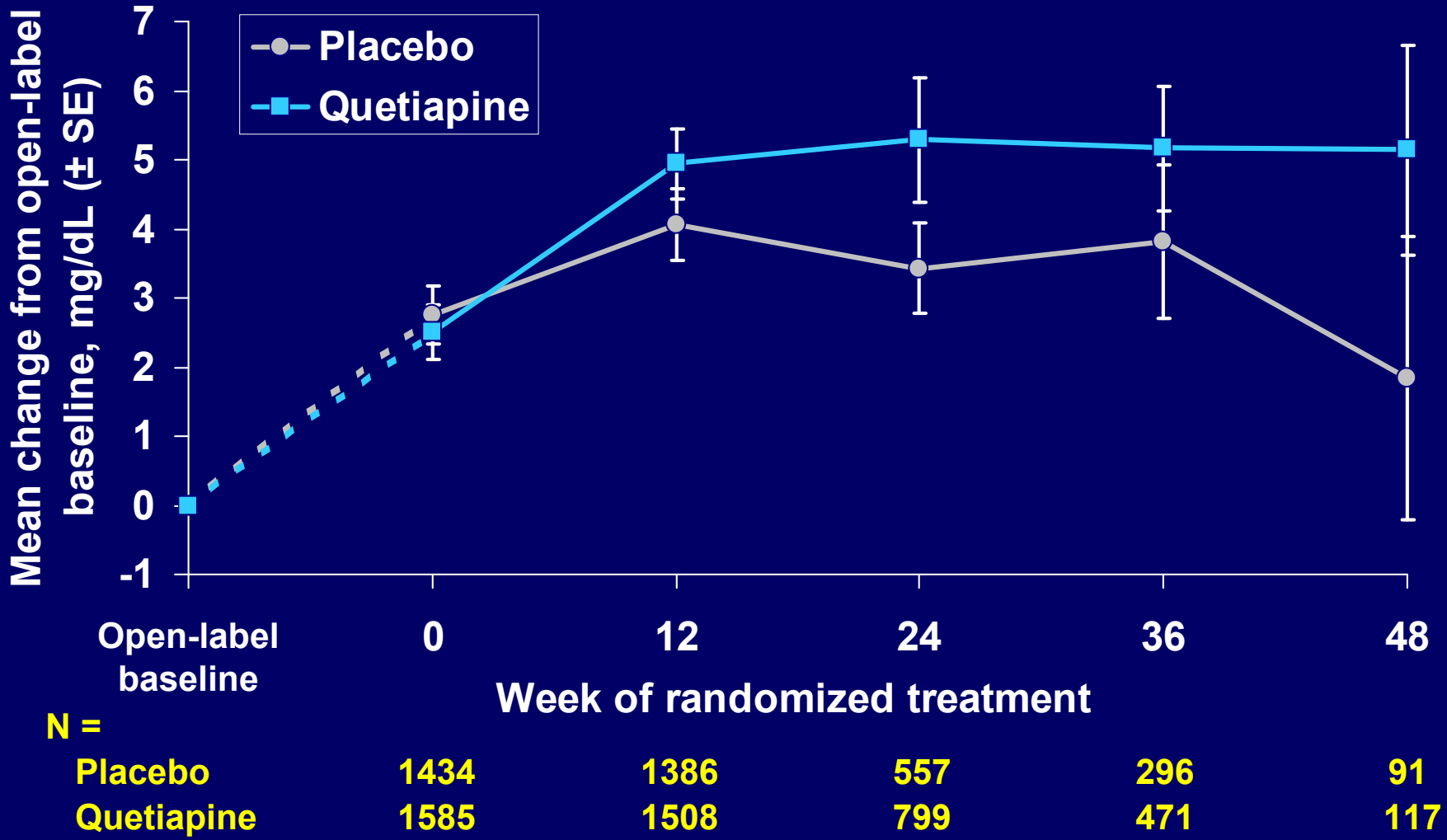
Pool B: Fixed-Dose, Placebo-Controlled Studies

All indications	Placebo	QTP fixed dose, mg/day 50	150	300	400	600	800
Normal baseline < 100 mg/dL							
N	1210	368	689	835	242	452	196
% shifting	1.4	0.5	2.6	2.8	3.3	2.9	1.0
p value	—	0.275	0.075	0.035	0.053	0.060	1.000
Borderline baseline ≥ 100 to < 126 mg/dL							
N	248	65	126	155	40	104	52
% shifting	12.5	10.8	4.8	14.2	20.0	12.5	15.4
p value	—	0.833	0.017	0.651	0.214	1.000	0.650

MDD + GAD	Placebo	QTP fixed dose, mg/day 50	150	300	Dul 60	Esc 10	Par 20
Normal baseline < 100 mg/dL							
N	779	368	689	433	77	111	125
% shifting	1.3	0.5	2.6	3.7	2.6	0.9	2.4
p value	—	0.357	0.084	0.007	0.295	1.000	0.406
Borderline baseline ≥ 100 to < 126 mg/dL							
N	146	65	126	68	16	19	31
% shifting	11.6	10.8	4.8	17.6	6.3	5.3	3.2
p value	—	1.000	0.050	0.284	1.000	0.697	0.205

Fasting Glucose (mg/dL)—Change From Open-label Baseline

Pool C: Longer-Term, Randomized Withdrawal Studies



N =	Open-label baseline	0	12	24	36	48
Placebo		1434	1386	557	296	91
Quetiapine		1585	1508	799	471	117

HbA1c (%)—Proportion of Patients Shifting to ≥ 6.1%

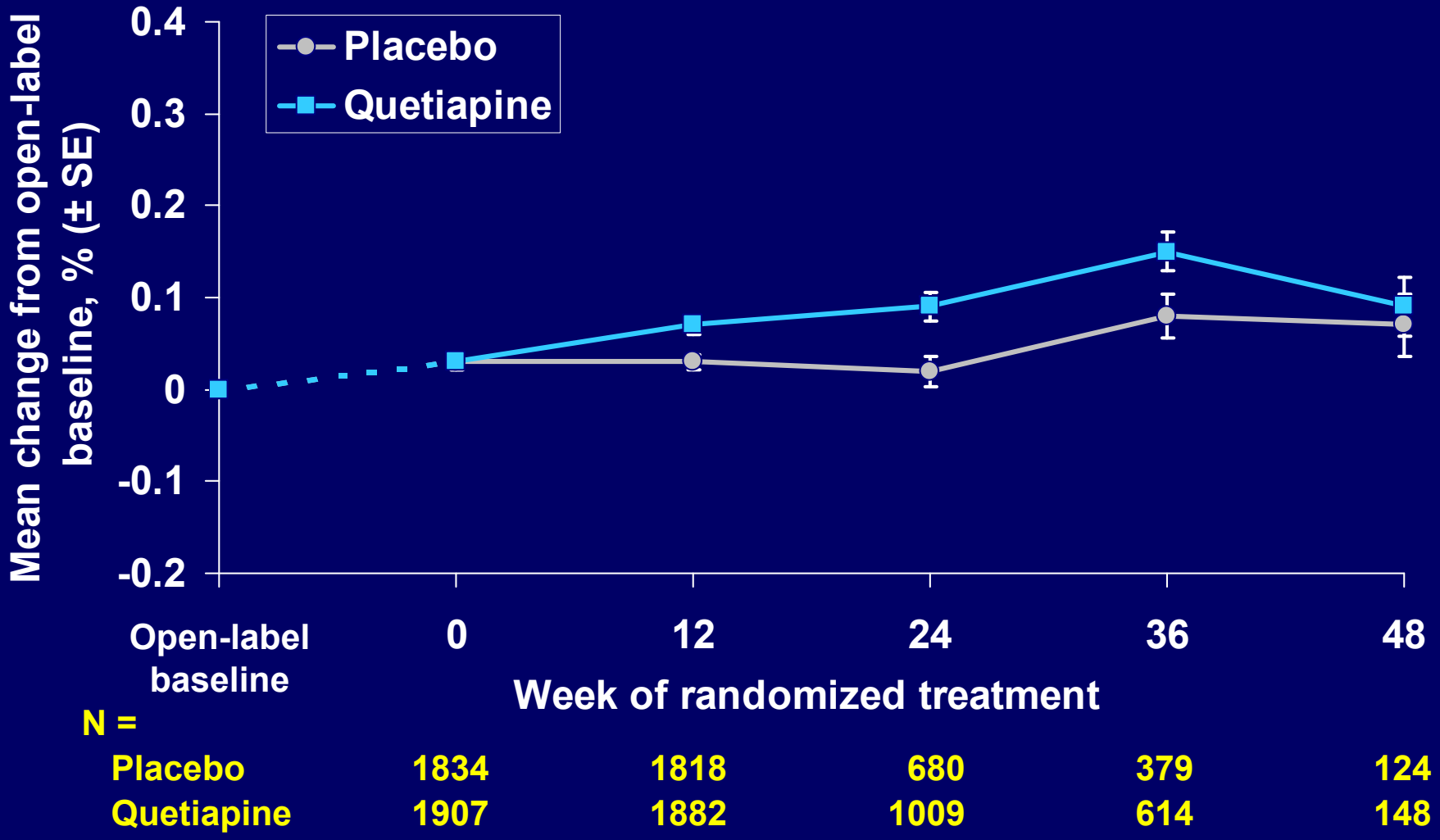
Pool B: Fixed-Dose, Placebo-Controlled Studies

		QTP fixed-dose, mg/day					
All indications	Placebo	50	150	300	400	600	800
Baseline < 6.1 (%)							
N	1473	399	799	1024	277	622	261
% shifting	2.5	3.3	3.9	3.3	1.1	5.1	7.7
p value	—	0.386	0.072	0.271	0.188	0.003	< 0.001

		QTP fixed-dose, mg/day					
MDD + GAD	Placebo	50	150	300	Dul 60	Esc 10	Par 20
Baseline < 6.1 (%)							
N	916	399	799	493	93	142	145
% shifting	2.7	3.3	3.9	2.4	3.2	1.4	2.1
p value	—	0.594	0.220	0.862	0.738	0.566	1.000

HbA1c (%)—Mean Change (± SE) From Open-Label Baseline

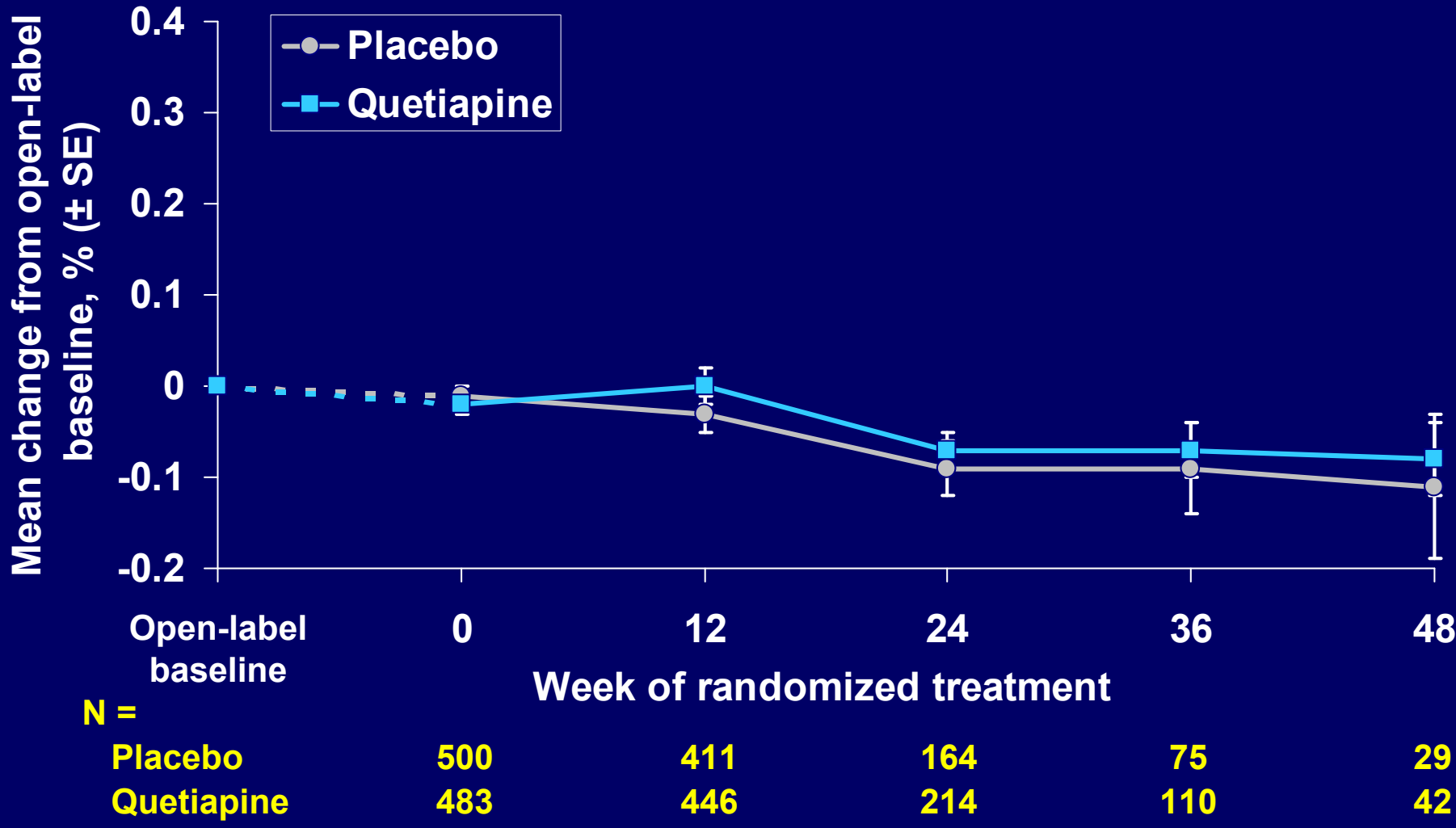
Pool C: Longer-Term, Randomized Withdrawal Studies



N =	Open-label baseline	0	12	24	36	48
Placebo		1834	1818	680	379	124
Quetiapine		1907	1882	1009	614	148

HbA1c (%)—Mean Change (± SE) From Open-Label Baseline (MDD/GAD)

Pool E: Longer-Term, Randomized Withdrawal Studies



N =	Open-label baseline	0	12	24	36	48
Placebo		500	411	164	75	29
Quetiapine		483	446	214	110	42

Treatment-Emergent Glycosuria by Dose
Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine dose, mg/day					
All indications	Placebo	50	150	300	400	600	800
n	283	4	7	275	293	450	276
%	0.4	0.0	0	1.8	1.7	2.4	4.7

Rates of Reported Adverse Events Potentially Related to Diabetes Mellitus

	N	Events, n (%)	Pt-yr exposure	Event rate per 100 pt-yr[a]	
Pool A: all studies					
Quetiapine	26,454	199 (0.75)	7,843.0	2.5	
Placebo	6,375	34 (0.53)	1,193.7	2.8	
Comparator	4,001	20 (0.50)	785.0	2.5	
Pool B: all short term, placebo-controlled studies					**Relative risk QTP vs PLA (95%CI)**
Quetiapine	8,853	38 (0.43)	980.6	4.1	0.87 (0.51, 1.48)
Placebo	4,359	23 (0.53)	491.3	4.7	
Pool C: all long term, placebo-controlled, randomized withdrawal studies					
Quetiapine	2,043	31 (1.52)	1,017.5	3.1	1.98 (1.00, 3.95)
Placebo	2,016	11 (0.55)	702.4	1.5	
Pool D: all MDD and GAD studies					
Quetiapine	6,816	42 (0.62)	1,399.7	3.0	
Placebo	2,622	19 (0.72)	436.2	4.4	
Pool E: MDD and GAD longer-term randomized withdrawal studies					
Quetiapine	607	7 (1.15)	240.8	2.9	1.01 (0.32, 3.17)
Placebo	601	5 (0.83)	172.9	2.9	

[a] Pool A:incidence rate per 100 pt-yr; Pool B and C:MH incidence rate per 100 pt-yr.

Reported Adverse Events Potentially Related to Diabetes Mellitus

Pool C: Randomized Withdrawal Studies

Quetiapine-treated patients N = 31
34 events

1 - Diabetic ketoacidosis
4 – Diabetes mellitus
6 – Type 2 diabetes mellitus

→ 11*- Either had a history of DM or had conventional risk factors for DM (eg, obesity, IFG, and/or family history for DM)

5 – HbA1c increased
4 - Hyperglycemia
3 – Hyperinsulinemia
3 - Blood glucose increased
2 - Insulin resistance
2 - Blood insulin increased

→ For patients with remaining less specific MedDRA terms related to DM:

- 16* – Either had a history of DM or had conventional risk factors for DM (eg, obesity, IFG, and/or family history for DM)
- 1 - Had treatment with confounding medication valproate

1 – Insulin resistance
1 – Hyperinsulinemia
1 – Blood insulin decreased
1 – Polyuria

→ 4 - Without risk factors at baseline had fasting blood glucose <100 mg/dl at baseline and at time of event

*1 patient with events of type 2 DM and hyperinsulinemia.

Glucose Control Summary

- Small increases in fasting plasma glucose observed
  - Doses ≥ 300 mg/day
  - Not progressive over time
  - Decreased toward baseline after drug withdrawal
- Small increases in fasting plasma glucose observed with placebo and other antidepressants
- Significant shifts above 6.1% in HbA1c observed at doses of quetiapine of ≥ 600 mg/day
- Glycosuria observed at doses of ≥ 300 mg/day
- In longer-term studies, an evaluation of reported adverse events potentially related to DM revealed that 27 of 31 had established DM or risk factors, and the 4 remaining patients had normal fasting plasma glucose at the time of the reported event

Lipids—Total Cholesterol, Triglycerides, LDL-C, HDL-C, and LDL/HDL Ratio

Total Cholesterol (mg/dL)—Changes by Dose

Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	400	600	800
All indications, mean (SD)	n = 1821	n = 452	n = 902	n = 1408	n = 302	n = 913	n = 351
Baseline	194.0 (42.7)	195.3 (42.4)	195.9 (41.8)	196.1 (42.3)	186.5 (42.4)	198.5 (45.4)	192.6 (43.8)
Change	–3.6 (27.6)	–1.0 (26.7)	–1.5 (26.5)	0.8 (30.6)	7.0 (31.4)	3.3 (33.8)	7.1 (32.4)
p value	—	0.021	0.046	< 0.001	< 0.001	< 0.001	< 0.001

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	Dul 60	Esc 10	Par 20
MDD + GAD, mean (SD)	n = 1027	n = 452	n = 902	n = 565	n = 106	n = 161	n = 154
Baseline	193.3 (40.8)	195.3 (42.4)	195.9 (41.8)	192.4 (39.0)	195.1 (40.7)	189.3 (36.5)	201.8 (44.2)
Change	–4.0 (25.5)	–1.0 (26.7)	–1.5 (26.5)	0.3 (25.9)	–0.3 (27.8)	1.9 (28.5)	2.3 (26.0)
p value	—	0.015	0.036	< 0.001	0.227	0.494	0.636

Total Cholesterol—Proportion of Patients Shifting to ≥ 240 mg/dL

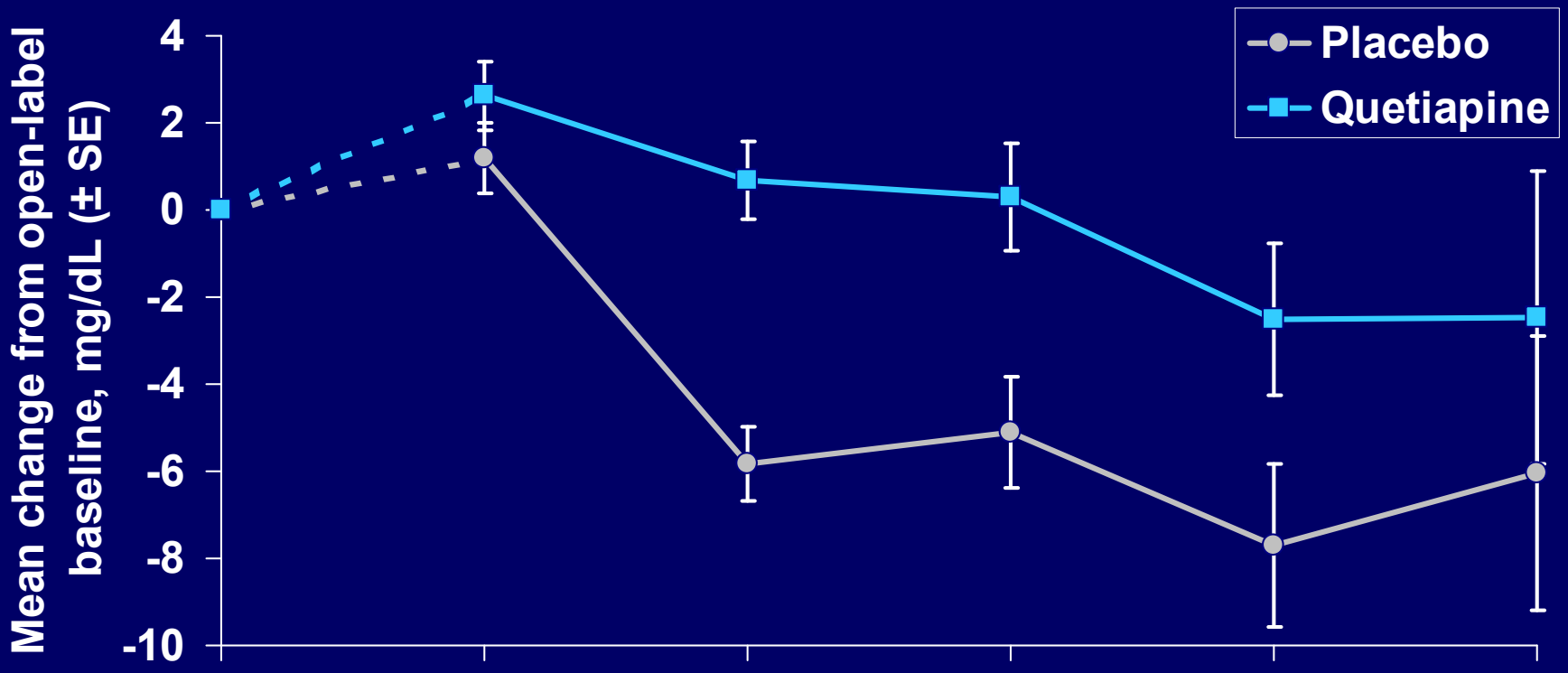
Pool B: Fixed-Dose, Placebo-Controlled Studies

		QTP fixed dose, mg/day					
All indications	**Placebo**	**50**	**150**	**300**	**400**	**600**	**800**
Normal baseline < 200 mg/dL							
N	1079	259	534	804	199	510	224
% shifting	1.0	1.2	2.2	2.9	2.0	4.1	3.6
p value	—	0.741	0.072	0.004	0.272	< 0.001	0.009
Borderline baseline ≥ 200 to < 240 mg/dL							
N	495	126	234	402	70	246	87
% shifting	13.7	15.9	12.0	21.4	20.0	21.1	36.8
p value	—	0.567	0.559	0.003	0.202	0.011	< 0.001

		QTP fixed dose, mg/day					
MDD + GAD	**Placebo**	**50**	**150**	**300**	**Dul 60**	**Esc 10**	**Par 20**
Normal baseline < 200 mg/dL							
N	625	259	534	339	67	99	78
% shifting	1.0	1.2	2.2	1.8	1.5	2.0	1.3
p value	—	0.726	0.096	0.362	0.511	0.301	0.563
Borderline baseline ≥ 200 to < 240 mg/dL							
N	268	126	234	164	26	43	52
% shifting	9.3	15.9	12.0	18.3	15.4	11.6	25.0
p value	—	0.063	0.383	0.011	0.304	0.584	0.004

Total Cholesterol (mg/dL)—Change (± SE) From Open-label Baseline

Pool C: Longer-term, Randomized Withdrawal Studies



N =	Open-label baseline	0	12	24	36	48
Placebo		1782	1616	686	326	127
Quetiapine		1885	1669	1011	538	155

Fasting Triglycerides (mg/dL) by Dose
Pool B: Fixed-Dose, Placebo-Controlled Studies

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	400	600	800
All indications, mean (SD)	n = 887	n = 241	n = 437	n = 616	n = 169	n = 386	n = 151
Baseline	137.1 (93.2)	128.2 (86.7)	135.1 (94.3)	142.2 (99.3)	140.4 (90.2)	146.2 (104.8)	150.6 (111.2)
Change	–5.0 (76.5)	0.0 (58.5)	13.2 (105.8)	17.4 (106.4)	15.8 (80.8)	8.7 (84.4)	16.3 (103.5)
p value	—	0.365	0.003	< 0.001	0.004	0.005	0.003

		Quetiapine fixed dose, mg/day					
	Placebo	50	150	300	Dul 60	Esc 10	Par 20
MDD + GAD, mean (SD)	n = 538	n = 241	n = 437	n = 281	n = 56	n = 72	n = 86
Baseline	130.5 (80.8)	128.2 (86.7)	135.1 (94.3)	136.3 (97.9)	125.2 (57.1)	124.1 (78.4)	114.0 (57.9)
Change	–3.7 (57.6)	0.0 (58.5)	13.2 (105.8)	16.5 (73.5)	–3.7 (58.8)	19.9 (168.8)	–4.7 (58.8)
p value	—	0.253	0.002	< 0.001	0.971	0.177	0.767

Fasting Triglycerides—Proportion of Patients Shifting to ≥ 200 mg/dL

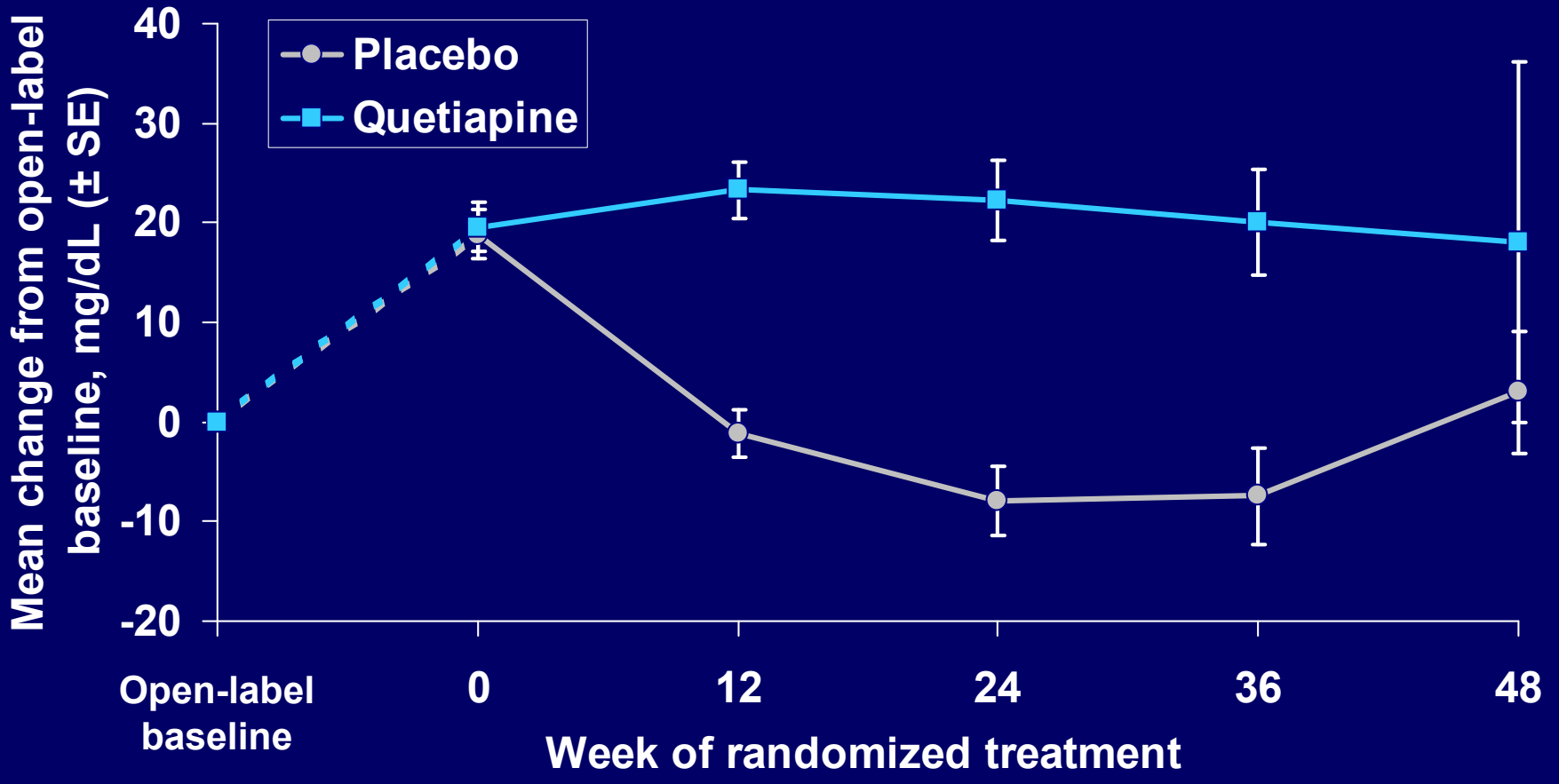
Pool B: Fixed-Dose, Placebo-Controlled Studies

All indications	Placebo	QTP fixed dose, mg/day 50	150	300	400	600	800
Normal baseline < 150 mg/dL							
N	615	173	308	417	113	259	96
% shifting	4.1	3.5	8.1	8.9	8.8	7.7	7.3
p value	—	0.828	0.013	0.002	0.051	0.030	0.180
Borderline baseline ≥ 150 to < 200mg/dL							
N	125	36	62	84	32	52	26
% shifting	18.4	19.4	32.3	35.7	34.4	30.8	38.5
p value	—	1.000	0.042	0.006	0.058	0.077	0.036

MDD + GAD	Placebo	QTP fixed dose, mg/day 50	150	300	Dul 60	Esc 10	Par 20
Normal baseline < 150 mg/dL							
N	388	173	308	199	43	54	62
% shifting	3.9	3.5	8.1	10.6	2.3	7.4	3.2
p value	—	1.000	0.021	0.003	1.000	0.271	1.000
Borderline baseline ≥ 150 to < 200mg/dL							
N	69	36	62	37	7	7	17
% shifting	18.8	19.4	32.3	45.9	28.6	14.3	11.8
p value	—	1.000	0.106	0.006	0.619	1.000	0.725

Triglycerides (mg/dL)—Change From Open-label Baseline

Pool C: Longer-term, Randomized Withdrawal Studies



N =					
Placebo	1782	1616	686	326	127
Quetiapine	1885	1669	1011	538	155

LDL-C, HDL-C, and LDL/HDL Ratio Summary

- Short-term studies
  - Small decreases in HDL at all doses including placebo
  - No clear change in LDL
  - No clear change in LDL/HDL ratio
- Longer-term studies
  - With continued therapy, changes did not appear to progress
  - Upon discontinuation, changes trended toward baseline

Reported Adverse Events Potentially Related to Atherosclerotic Cardiovascular Disease

Rates of Reported Adverse Events Potentially Related to Atherosclerotic Cardiovascular Disease

	N	Events, n (%)	Pt-yr exposure	Event rate per 100 pt-yr[a]	
Pool: all studies					
Quetiapine	26,454	149 (0.56)	7,889.97	1.9	
Placebo	6,375	29 (0.45)	1,196.69	2.4	
Comparator	4,001	16 (0.40)	787.43	2.0	
Pool B: all short term, placebo-controlled studies					**Relative risk QTP vs PLA (95%CI)**
Quetiapine	8,853	32 (0.36)	981.74	3.36	0.73 (0.42, 1.25)
Placebo	4,359	24 (0.55)	492.41	4.63	
Pool C: all long term, placebo-controlled, randomized withdrawal studies					
Quetiapine	2,043	1 (0.05)	1,025.95	0.10	0.14 (0.02, 1.21)
Placebo	2,016	5 (0.25)	704.27	0.71	
Pool D: all MDD and GAD studies					
Quetiapine	6,816	13 (0.19)	1,404.8	0.9	
Placebo	2,622	4 (0.15)	437.6	0.9	
Pool E: MDD and GAD longer- term randomized withdrawal studies					
Quetiapine	607	0	242.0	0	0.00 (0.00, 29.04)[b]
Placebo	601	1 (0.16)	173.7	0.57	

[a]Pool A: incidence rate per 100 pt-years; Pool B and C: MH incidence rate per 100 pt-yrs. [b]Exact RR estimate and 95% CI.

Summary of Lipids Parameters and Reported Atherosclerotic Adverse Events

- Short-term studies
  - Total cholesterol increased at doses ≥ 300 mg/day
  - Triglycerides increased at doses ≥ 150 mg/day
  - Small decreases in HDL at all doses including placebo
  - No clear change in LDL
- Longer-term studies
  - With continued therapy, changes did not appear to progress
  - Upon discontinuation, changes trended toward baseline
- No evidence of an increased risk of reported adverse events potentially related to atherosclerotic cardiovascular disease for quetiapine compared to placebo

Sudden Cardiac Death

Sudden Cardiac Death (SCD)

- Unexpected pulseless condition from a cardiac cause occurring within 1 hour of symptom onset in absence of a prior condition that would appear fatal
- Ventricular tachyarrhythmia often the proximate cause
  - > 80% of cases occurring in patients with significant coronary artery disease, either symptomatic or previously silent
  - QT prolongation is one of many risk factors for ventricular tachyarrhythmia (eg, torsade de pointes)
  - Many drugs recognized to prolong QT interval
- Patients with depression have increased risk for SCD
  - 2 observational studies[a] found increased risk of SCD among patients with depressive symptoms

[a] Luukinen et al, 2003; Whang et al, 2009.

Risk of SCD in Clinical Studies—Evaluated by Multiple Approaches

- All-cause mortality across clinical program
- Preferred adverse event terms reported by investigators potentially related to SCD (non-adjudicated)
- Blinded adjudication of fatal cases by external cardiologist as "sudden cardiac death" or "not sudden cardiac death" (Ray et al. *N Engl J Med*. 2009 definition)
  - Excluding reports of homicide, non-overdose suicides, accidental injuries
- Potential for QTc prolongation based on centrally read ECG measurements
- Adverse events related to a potential proarrhythmic effect

No Difference in All Cause Mortality Between Quetiapine and Placebo

	N	Events, n (%)	Pt-yr exposure	Event rate per 100 pt-yr[a]	
Pool A: all studies					
Quetiapine	26,454	119 (0.45)	7,890	1.51	
Placebo	6,375	18 (0.28)	1,196.7	1.50	
Comparator	4,001	19 (0.47)	787.4	2.41	
Pool B: all short term, placebo-controlled studies					**Relative risk QTP vs PLA (95%CI)**
Quetiapine	8,853	24 (0.27)	981.7	2.5	1.08 (0.53, 2.20)
Placebo	4,359	12 (0.27)	492.4	2.3	
Pool C: all longer term, placebo-controlled, randomized withdrawal studies					
Quetiapine	2,043	2 (0.09)	1,025.0	0.20	0.24 (0.05, 1.16)
Placebo	2,016	6 (0.30)	704.3	0.85	
Pool D: all MDD and GAD studies					
Quetiapine	6,816	5 (0.07)	1,404.8	0.36	
Placebo	2,622	2 (0.07)	437.6	0.46	
Pool E: MDD and GAD longer- term randomized withdrawal studies					
Quetiapine	607	0	242.0	0	0.00 (0.00, 29.04)[b]
Placebo	601	1 (0.16)	173.7	0.57	

[a] Pool A: incidence rate per 100 pt-yr; Pool B and C: MH incidence rate per 100 pt-yr.
[b] Exact RR estimate and 95% CI.

No Evidence of Increased Risk for SCD (Adjudicated Events) in Clinical Studies

	N	Events, n (%)	Pt-yr exposure	Event rate per 100 pt-yr[a]	Relative risk QTP vs PLA (95%CI)[b]
Pool A: all studies					
Quetiapine	26,454	23 (0.08)	7,890	0.29	
Placebo	6,375	8 (0.12)	1,196.7	0.67	
Comparator	4,001	5 (0.1)	787.4	0.64	
Pool B: all short term studies					
Quetiapine	8,853	4 (0.04)	981.7	0.36	0.46 (0.09, 2.24)
Placebo	4,359	5 (0.11)	492.4	0.88	
Pool C: all longer term randomized withdrawal studies					
Quetiapine	2,043	0 (0.09)	1,026	0	0 (0.0, 1.77)
Placebo	2,016	3 (0.29)	704.3	0.42	
Pool D: all MDD and GAD studies					
Quetiapine	6,816	3 (0.04)	1,404.8	0.21	
Placebo	2,622	1 (0.03)	437.6	0.23	
Pool E: MDD and GAD longer term randomized withdrawal studies					
Quetiapine	607	0	242.0	0	0.00 (0.00, 29.04)
Placebo	601	1 (0.1)	173.7	0.57	

[a] Pool A: incidence rate per 100 pt-yr; Pool B and C: MH incidence rate per 100 pt-yr. [b] Exact RR estimate and 95% CI.

Change From Baseline QTcF

Pool B: Short-term, Placebo Controlled Studies[a]

Change from baseline[b]	QTP LS mean, msec (SE)	PLA LS mean, msec (SE)	Difference LS mean, msec (SE)
N	7111	3544	
To final	–0.44 (0.22)	–0.90 (0.28)	0.46 (0.35)
95% CI	–0.87, –0.01	–1.44, –0.34	–0.22, 1.14
To maximum	0.58 (0.22)	0.21 (0.28)	0.37 (0.35)
95% CI	0.15, 1.01	–0.34, 0.76	–0.31, 1.05

[a] Studies since 2001, patients with baseline and ≥ 1 post-baseline assessment; centrally read ECGs.
[b] Baseline is last observation prior to randomization (usually screening).

Incidence of QTcF Shifts Similar Between Quetiapine and Placebo

Pool A: All Studies

Treatment	Patients with ECG finding	Total patients[a]	Exposure[b]	Incidence rate/100 pt-yr[c]
QTcF increase from baseline ≥ 60 ms				
Quetiapine	50	15,470	4256.4	1.174
Placebo	13	5239	1057.6	1.229
QTcF ≥ 500 ms from baseline (baseline < 500 ms)				
Quetiapine	5	15,464	4259.0	0.117
Placebo	2	5237	1057.1	0.189
QTcF ≥ 500 ms with a QTcF increase from baseline ≥ 60 ms				
Quetiapine	2	15,464	4259.1	0.047
Placebo	0	5237	1057.2	0

[a] Patients must have received at least 1 dose of study medication.
[b] Exposure in patient-years.
[c] Values are 100 times the total number of patients with event/total patients-years of exposure.

Reported Adverse Events in Clinical Database Potentially Indicating Proarrhythmic Effect

Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate/ 100 pt-yr[c]
Standard MedDRA query (broad): QT and torsade de pointes terms				
Quetiapine	263	26,454	7890.0	3.3
Placebo	29	6375	1196.7	2.4
Comparator	23	4001	787.4	2.9
Standard MedDRA query (broad): QT and torsade de pointes terms, excluding terms "syncope" and "syncope vasovagal"				
Quetiapine	79	26,454	7890	1.0
Placebo	15	6375	1196.7	1.3
Comparator	12	4001	787.4	1.5

No reports of torsade de pointes or ventricular fibrillation

[a] Patients must have received at least 1 dose of study medication.
[b] Exposure in patient-years.
[c] Values are 100 times the total number of patients with event/total patients-years of exposure.

Overall Conclusions on SCD

- No higher risk identified for sudden cardiac death associated with quetiapine compared with placebo using multiple approaches
- No difference in all-cause mortality between quetiapine vs placebo

Safety Topics of Interest Conclusions

- Longer-term safety risks are well characterized
  - Tardive dyskinesia
  - Metabolic and cardiovascular risks
  - Sudden cardiac death
- These data are sufficient to inform the label and medication guide as part of the risk management plan to be discussed

Seroquel XR® (quetiapine fumarate) for Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD)

Risk Management Benefit/Risk Assessment

Howard G. Hutchinson, MD, FACC

Chief Medical Officer
AstraZeneca Pharmaceuticals LP

Benefit/Risk Is Positive

- Extensively studied
- Large post-marketing experience
- Efficacy seen at doses of 50-300 mg in MDD and GAD
- Risks well known and manageable
  - Further managed by comprehensive risk management plan
- Goal: Provide a safe and effective option in patients for whom first-line therapies are not appropriate

Overview of Risk Management Plan

- Risk assessment
  - Pharmacovigilance and post-approval studies
- Risk minimization
  - Label and revised Medication Guide
- Education to reinforce risk management
  - Appropriate use and risk communication

Risk Assessment—Pharmacovigilance

- SAPPHIRE (AstraZeneca's safety database)
  - Additional questionnaires for AEs of special interest
- FDA Adverse Event Reporting System (AERS)
- Review of literature (eg, case reports, clinical studies)
- Benefit/Risk team
  - Signal detection
  - Issue evaluation
  - Updating of labeling
  - Regulatory authority interactions
- Periodic Safety Update Report (PSUR)

Risk Assessment—Post-Approval Study Design Options

- Large Simple Trial (LST)
  - Randomized, open-label comparison of Seroquel and usual care comparator
  - Following randomization, all patients will be treated according to usual clinical practice
- Prospective observational cohort study
  - Patients initiating treatment with Seroquel or usual care comparator
  - All patients will be treated according to usual clinical practice
- Design features
  - Sample size: ~ 3000 - 5000 per arm
  - Length of follow-up: 2 years
  - Community-based general practitioners and psychiatrists
  - Data collection: enrollment, 6, 12, 18, and 24 months

Risk Assessment—Ongoing Observational Cohort Studies in Schizophrenia and Bipolar Disorder

- General Practice Research Database (GPRD) Study—Population-based cohort and nested case-control study
  - Outcomes
    - Death, suicide, acute MI, stroke, diabetes, and hypothyroidism
  - Length: 3 years with 1-year follow-up from the last patient
- Prescription-Event Monitoring Study—Subjects prescribed quetiapine XR by GPs in England
  - Outcomes
    - Incidence of exacerbation of type II diabetes mellitus, hyperglycemia, metabolic syndrome, somnolence/sedation, EPS
  - Length: 4 years; 5000 - 10,000 patients

Risk Minimization—Labeling
Potential Long-term Metabolic Risk

Label[a]

- **Warnings and Precautions**
  - **Weight gain**
  - **Hyperglycemia, hyperlipidemia**
- **Warnings for Diabetes Mellitus, hyperglycemia, weight gain, and hyperlipidemia informs prescriber of following**
  - **Patients with diabetes or with risk factors for diabetes should undergo fasting blood glucose before and during treatment**
  - **All patients should be monitored for symptoms of hyperglycemia (eg, polydipsia, polyuria, polyphagia, and weakness)**
  - **Contains data displays for weight, glucose, total cholesterol, and triglycerides seen in clinical studies, including changes seen in long-term maintenance treatment studies**

[a] For complete prescribing information see full product label.

Risk Minimization—Revisions to the Approved Medication Guide

- Language was tested with patients
- Information on tardive dyskinesia
  - Movements of the face, tongue, or other body parts that cannot be controlled and may not go away
  - Patients are told to tell their doctor if they experience any of these signs
- Information on metabolic parameters
  - Asks patients to tell their doctor about
    - Being very thirsty or hungry, feeling weak, or passing lots of urine
    - Health problems including high cholesterol or triglycerides
  - Patients are also advised that weight gain and increased hunger are common side effects

Education
Health Care Professionals

- In-person communications
  - Sales force and medical liaison
  - Speaker programs
  - Peer-to-peer programs
- Print communications
  - Prescriber education targeted to members of professional societies
  - Education to prescribers and pharmacists
- Toll-free call center
- Computer-based initiatives
- HCP dedicated Web site

Education
Patients, Caregivers, and Friends

- Branded/unbranded print communications
  - Patient support program, patient newsletter, Questions to Ask Your Doctor, Symptom Check Talk Sheet, Adherence Starter Kit, Patient Compliance Package
- Toll-free call center
- Computer-based initiatives
- Multicultural information

Overall Conclusion—Quetiapine Benefits Outweigh Risks

- MDD and GAD are serious disorders with high unmet clinical need
- Benefits and risks of quetiapine XR well characterized in comprehensive clinical development program
- Quetiapine XR provides
  - Distinct mechanism of action
  - Robust efficacy
    - Alleviates depressive and anxiety symptoms
    - Breadth of effects across many treatment domains
  - Well-characterized safety profile with manageable risks
- Quetiapine XR offers patients and prescribers a much-needed and valuable treatment option

Treating MDD & GAD

Is there need for a new agent?

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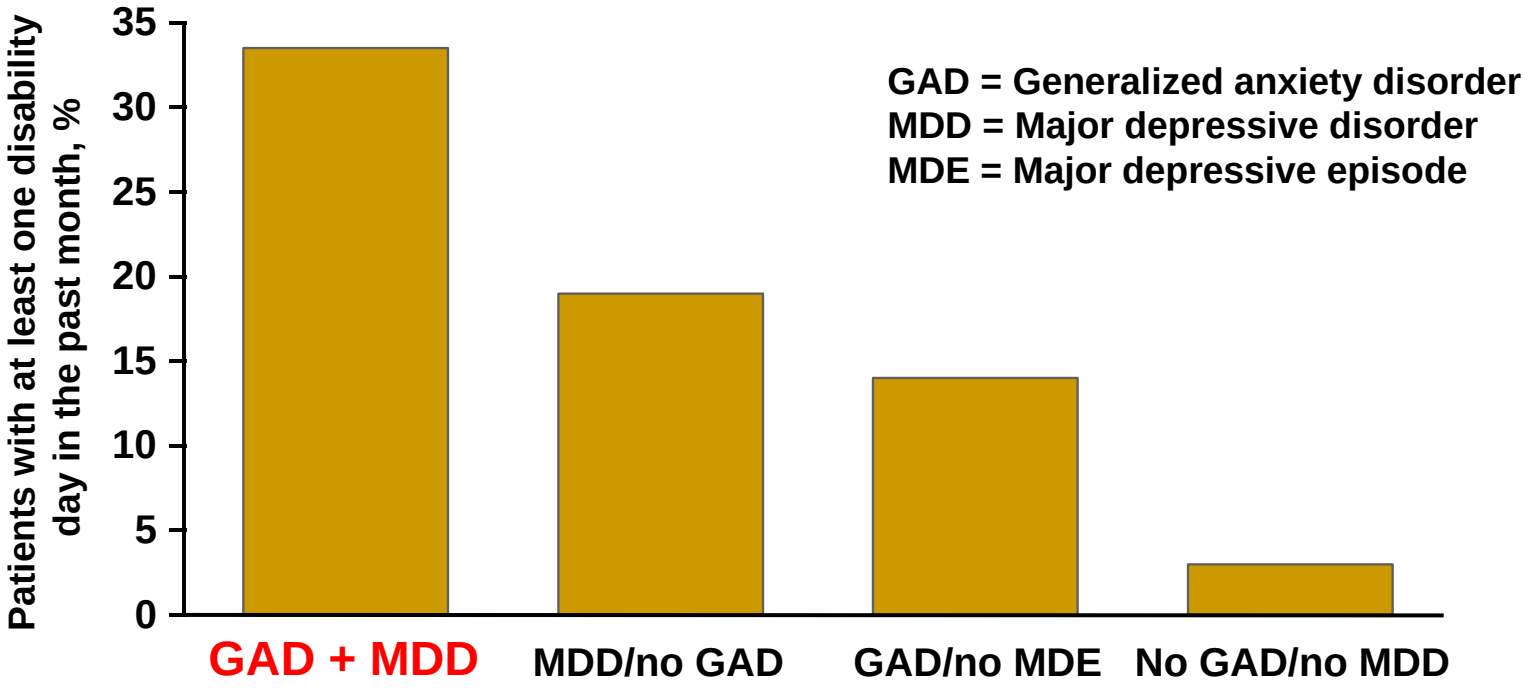
Professor Emeritus, University of Arizona

The Impact of MDD and GAD

- Worldwide, depression is the leading cause of years of health lost to disease in both men and women.[1]
- GAD is as impairing as major depression.[2]
- GAD patients lost 4x as many days of work as people with no mental disorder[3]

1. *Psychiatry News*. Jan 2, 2009.
2. Kessler R, et al. *Am J Psychiatry*. 1999;156:1915-1923.
3. Wittchen HU, et al. *Psychol Med*. 1998;28:109-126.

GAD Causes as Much Impairment as MDD



Allgulander C, *Eur Neuropsychopharmacol*. 2006—adapted from Kessler et al, 1999.

MDD, GAD, and Mortality

- Suicide is the 8th-leading cause of death in the US, 2nd among college students[3]
- 8% -19% of hospitalized MDD patients eventually commit suicide[1,2]
- GAD increases suicide risk[5]
  - Rate Ratio = 2.3 for lifetime attempts, 1.8 for lifetime ideation
- Effective treatment lowers the risk
  - STAR*D patients who achieved remission had a substantially lower risk of treatment-emergent suicidality[6]

1. Bostwick JM, Pankratz VS. *Am J Psychiatry*. 2000;157:1925-1932.
2. Depression Guideline Panel. Depression in Primary Care: Volume 1. Detection and Diagnosis. Clinical Practice Guideline, Number 5. AHCPR publication no. 93-0550. April 1993.
3. National Vital Statistics Reports. Vol 48, No. 11, July 24, 2000.
4. Foley et al, *Arch Gen Psych*, Sep 2006
5. Bernal M et al, *J Affect Disord*. 2006; 101: 27-34.
6. Zizook, S: personal communication

MDD, GAD, and Mortality (2)

- Besides suicide, depression contributes to mortality risk in patients with underlying cardiovascular disease or diabetes
- Depression increases the risk of sudden cardiac death[1,2]
- Depressed people have poor health habits and insufficient medical care

1. Luukinen H, et al. *Euro Heart J*. 2003;24:2021-2026.
2. Whang W, et al. *J Am Coll of Cardiol*. 2009;950-958.

Chronicity and Recurrence in MDD and GAD

MDD:

- From STAR*D[1]:
  - 25% will be chronic
  - 75% will be recurrent
- From Baltimore ECA follow-up[2]:
  - ~ 1/2 of 1st-episode MDD cases recover; no more episodes
  - Chronic, unremitting in 15%
  - Recurrent in 35%

GAD:

- Harvard-Brown Study:[3]
- Symptoms wax and wane
  - Full remission uncommon: 38% at 5 years
  - Relapse is common

1. Rush et al. *Psychiatric Annals*, 2008.
2. Eaton et al. *Arch Gen Psych*, 2008.
3. Keller et al. *J Clin Psychiatry,* 2006.

Unmet Needs

- Limited efficacy and effectiveness of current treatments for MDD & GAD
  - STAR*D
    - Phase 1 remission = 28%
    - Cumulative remission for patients completing all phases = 67%
  - 30% - 60% of GAD patients do not attain remission[1]
- Slow onset of antidepressant benefit

1. Katzman MA. *CNS Drugs*. 2009;23:103-120.

Unmet Needs (2)

- Adverse effects of SSRI & SNRI antidepressants
  - Common and bothersome
    - Sexual dysfunction
    - Weight gain
    - Insomnia
    - Sweating
  - More serious
    - Bleeding*
    - Osteoporosis & fractures*
    - SIADH*
    - Adverse behavioral effects in undiagnosed bipolar patients
    - Diabetes?[1]

***Especially in the elderly.**

1. Andersohn F, et al. *AJP*. 2009; on line

Other Treatments for MDD and GAD

- Aripiprazole as adjunct for MDD
- Olanzapine-fluoxetine combination for treatment-resistant depression
- Stimulation treatments: electroconvulsive therapy, vagus nerve stimulation, repeated transcranial magnetic stimulation, deep brain stimulation
- Psychotherapies
- Complementary and alternative medications
- Off-label agents: eg, modafinil and other stimulants, antipsychotics, benzodiazepines
- Canadian Psych Assoc Guidelines for GAD 2nd-line options: imipramine, buspirone, benzodiazepines, pregabalin

Each has limits and AEs

Widespread Use of an Antipsychotic for Long-term Treatment of MDD & GAD

- Concerns
  - Bad history: widespread use of thioridazine, trifluoperazine, perphenazine-amitriptyline led to TD cases
  - Fears: excessive, unnecessary use of quetiapine could cause unhealthy weight gain, adverse cardiovascular and metabolic effects, TD
- Reality: currently off-label use of antipsychotics is common
- Possible solution: education, monitoring—especially in primary care

What if Quetiapine Receives Approval for MDD & GAD? Is It Worth the Risk?

Yes, Because:

- MDD and GAD are serious, painful, debilitating, and life-threatening disorders
- Current treatments leave many patients suffering and carry their own risks and discomforts
- Non-treatment exposes patients to even greater risks

What if Quetiapine Receives Approval for MDD & GAD? Is It Worth the Risk?

Yes, Because:

- A compound with a distinct MOA expands treatment options for MDD & GAD patients
- Quetiapine appears to be a worthwhile treatment option
  - Earlier onset of benefit
  - Distinct AE profile allows clinician-patient dialogue about treatment options
  - Distinct MOA
- Weighing relative risks
  - Risk of quetiapine
  - Risk of other treatments
  - Risks of no treatment
- Bring knowledge and best practice to current practice

Consultants

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