



U.S. Food and Drug Administration

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Serdolect[®] (Sertindole) Tablets for Treatment of Schizophrenia

United States Food and Drug
Psychopharmacologic Drugs Advisory Committee
April 7, 2009

Serdolect[®] (Sertindole) Tablets for Treatment of Schizophrenia

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Head of Drug Development
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Proposed Indications for Sertindole

- NDA 20-644 (4, 12, 16 and 20 mg tablets)
- Treatment of schizophrenia
- Reducing the risk of fatal plus non-fatal suicide attempts in patients with schizophrenia

Sertindole Pharmacology

- Antipsychotic with unique limbic selectivity
 - balanced DA D_2 , 5-HT $_{2A}$, 5-HT $_6$ and α_1 affinity
- No H $_1$ antihistamine or anticholinergic activity
 - low potential for sedation and cognitive disturbances

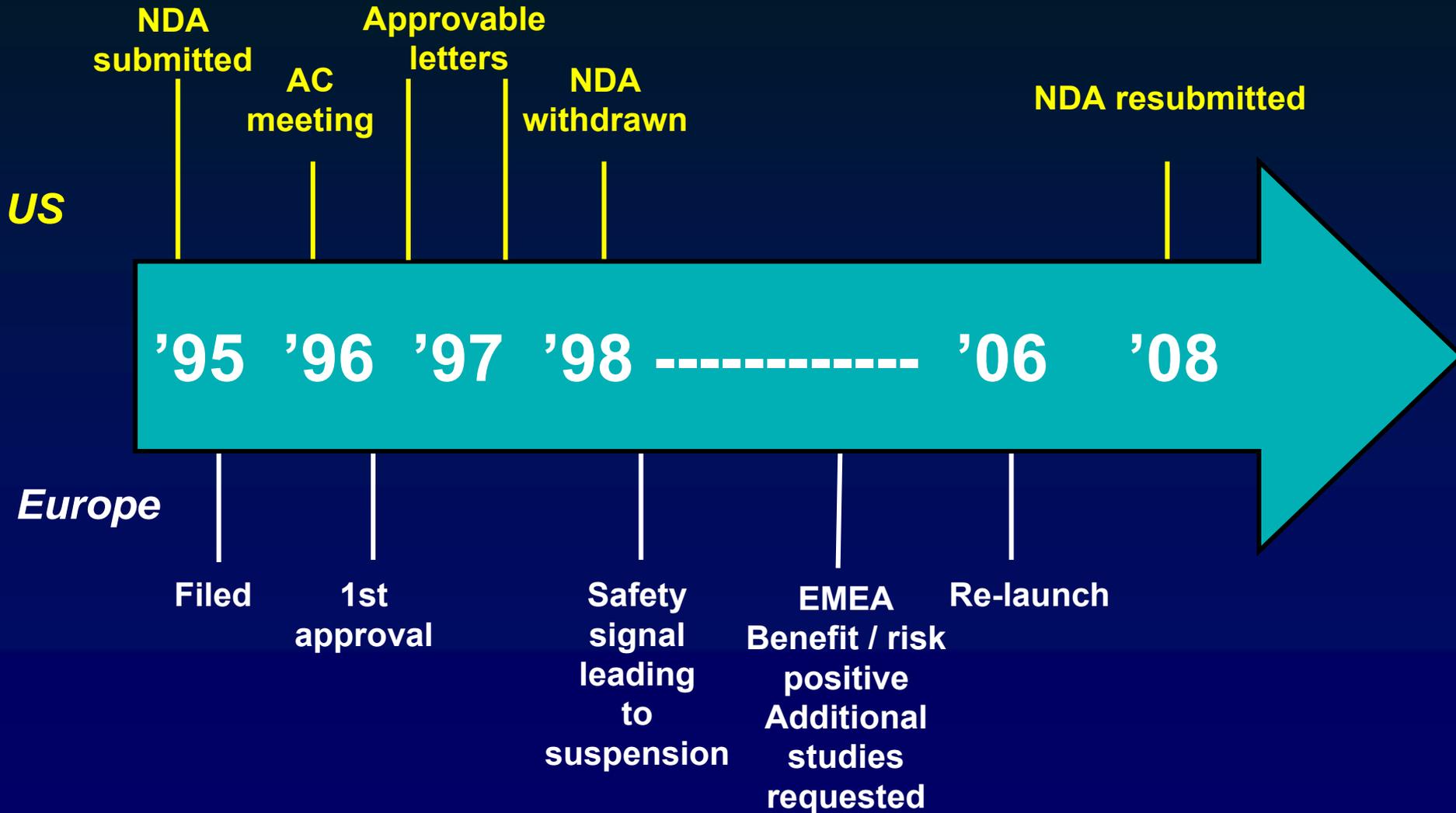
Schizophrenia is Chronic & Disabling – Need for Additional Treatments

- 2- to 3-fold increase in mortality compared with general population
- Suicide is a major contributor to mortality
 - 50% of patients attempt suicide
 - approximately 10% die from suicide
 - any improvement in suicide risk is meaningful
- No treatment is effective in all patients
 - need for additional treatment options

Sertindole Offers a Safe and Effective Treatment Option

- Effective in short-term and long-term treatment
 - 40% to 50% response
- Large body of evidence
- Approved in Europe, Asia and Latin America
- Well tolerated with placebo-level EPS
- Risk is well defined

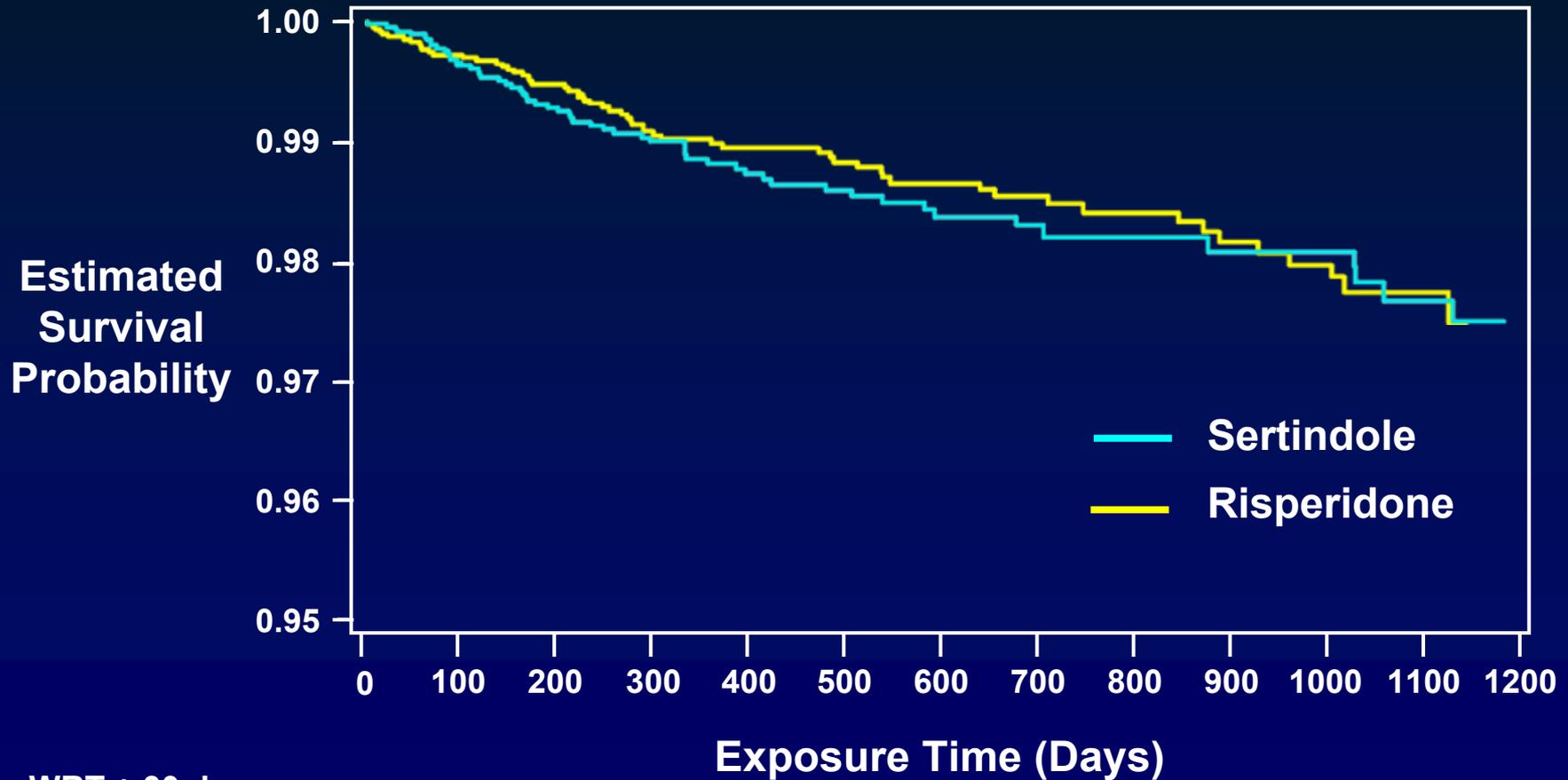
Regulatory Event Chronology



SCoP – Overview

- 10,000 patients
- Well-controlled, prospective, randomized, “simple” study
- One of the largest prospective studies ever in schizophrenia

SCoP – All-cause Mortality Similar to Risperidone

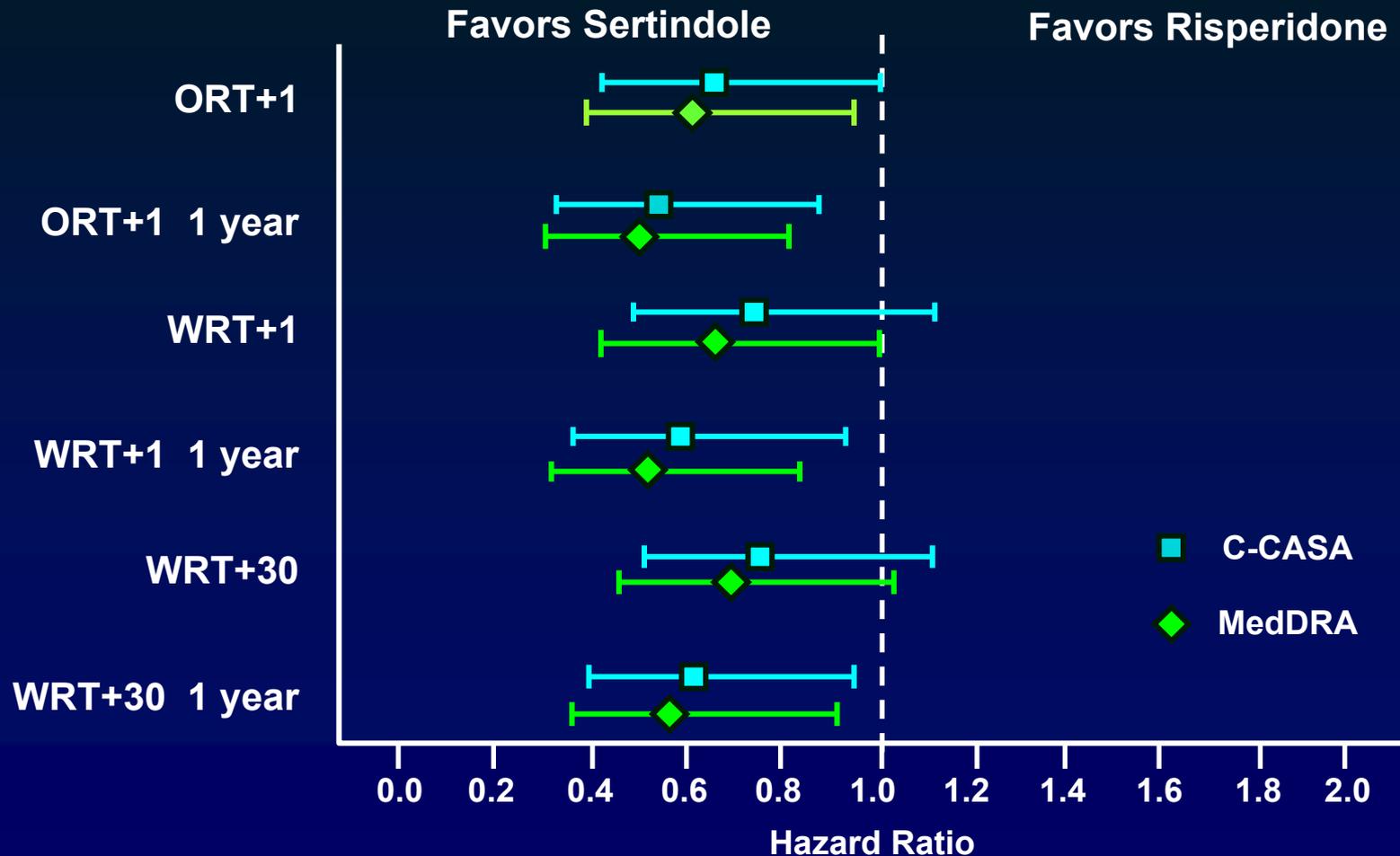


WRT + 30 days

SCoP – Sertindole Superior to Risperidone in Reducing the Risk of Suicide Attempts

- Addresses earlier request from FDA for large safety study
- Showed superiority to risperidone in reducing the risk of suicide attempts (fatal plus non-fatal)
- Columbia Classification Algorithm of Suicide Assessment (C-CASA)

Similar Hazard Ratios Using C-CASA and MedDRA



Cox's Proportional Hazards Model
95% CI

Agenda & Presenters

Medical Need

Carol A. Tamminga, MD

Professor of Psychiatry and Neuroscience
University of Texas Southwestern Medical School

Efficacy and Reduction of Risk of Suicide Attempts

Raimund Buller, MD

Director, Clinical Research, Psychosis

Tolerability and Safety

Lasse Ravn, MD, PhD

Department Head, Psychiatric Safety

Concluding Remarks Benefit / Risk Assessment

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Additional Experts

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Pharmacologist
The Degge Group, Ltd

Medical Need

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Professor of Psychiatry and Neuroscience

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Schizophrenia – One of the Most Serious Psychiatric Disorders

- Affects 1% of the population
 - average age of onset – early 20s
 - strikes the most productive period of life
- Symptoms affect all aspects of psychosocial function
 - less than 20% of individuals work productively
 - less than 15% of individuals marry
- Disease manifestations last a life-time with high relapse rates

Schizophrenia Causes Significant Suffering for Patients and Families

- Complex, multi-symptom disorder
 - psychosis
 - negative symptoms
 - cognition dysfunction
 - mood dysregulation

- Causes significant social impairment
 - usually unemployed
 - often homeless or incarcerated
 - always socially isolated

Psychiatrists Consider Many Factors When Prescribing Treatment for Schizophrenia

- Individual risk profile of patient
 - age
 - medical health
 - mood regulation
- Relative risks in individual patient
- Benefit / risk profile of medication
- Tolerability of medicine

Current Treatments for Schizophrenia are Limited

- Not all treatments are effective in all symptom domains
- Effectiveness of treatment varies
 - individuals respond differently
 - potency within domains varies

Side Effects Often Lead to Non-compliance

- Excessive sedation, somnolence, lethargy
- Motor side effects
- Cardiac and metabolic risks
- Cognitive impairment
- Limited treatment options for suicide risk

High Risk of Suicide in People with Schizophrenia

- Risk of suicide in schizophrenia is high – “unbearably frequent”
- Finnish study^a
 - probands between 16 and 39 years
 - 50% of all deaths were by suicide
 - 2.9% for women
 - 9.2% for men
- 90% of people who commit suicide made previous attempt(s)^b

^aAlaraisanen *et al.*, 2009

^bKelly *et al.*, 2004

Multiple Risk Factors for Suicide Attempts and Suicide

- Risk factors
 - hopelessness, gender, depression, prior attempts, substance abuse, higher education, young age
- Average age of death in schizophrenia
 - overall – 60 years
 - by suicide – late 30s
- Targeting young, male, suicide-prone patients could offer opportunities for better treatment

Clozapine – Only Treatment Option for Suicidality has Significant Side Effects

- Medically serious conditions
 - agranulocytosis
 - cardiomyopathies
 - seizures

- Troublesome side effects
 - hypotension
 - blurred vision
 - excessive sedation

Unmet Medical Need for Additional Treatments for Schizophrenia

- Incomplete efficacy / limited tolerability of current options
- No one treatment is best for all patients
- Psychiatrists balance risks and benefits to individualize treatment
- Critical to bring more treatment options to patients with schizophrenia
 - particular need in suicide risk

Sertindole Efficacy and Reduction of Risk of Suicide Attempts

Raimund Buller, MD

Director, Clinical Research, Psychosis

H. Lundbeck A/S

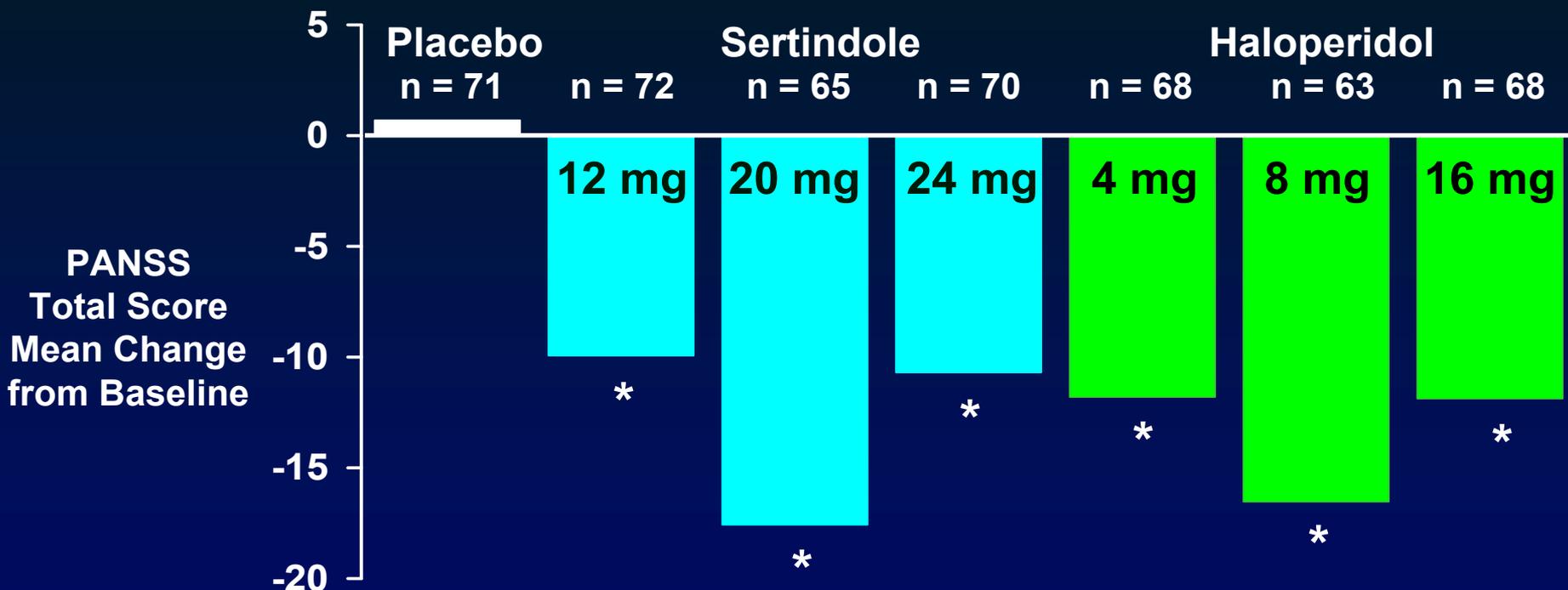
Sertindole is an Effective Antipsychotic

- Efficacy similar to 1st and 2nd generation antipsychotics
 - antipsychotic effect
 - responder rates
 - time to response
 - effective in long-term use
- Reduction of suicide risk
 - fatal plus non-fatal attempts
 - high-risk population

Sertindole Key Efficacy Studies

Study number	Study name	Patients (n)	Duration	Reference therapy	Sertindole doses (mg)
M93-113	US Landmark study	497	8 weeks	Placebo Haloperidol	12, 20, 24
M93-098	US study	462	8 weeks	Placebo Haloperidol	20, 24
M95-342	European study	617	8 weeks	Haloperidol	8, 16, 20, 24
97203	French study	186	12 weeks	Risperidone	12-24 flexible
M92-762	US study	157	6 weeks	Placebo	8, 12, 20
M93-132	US 1-year study	282	12 months	Haloperidol	24

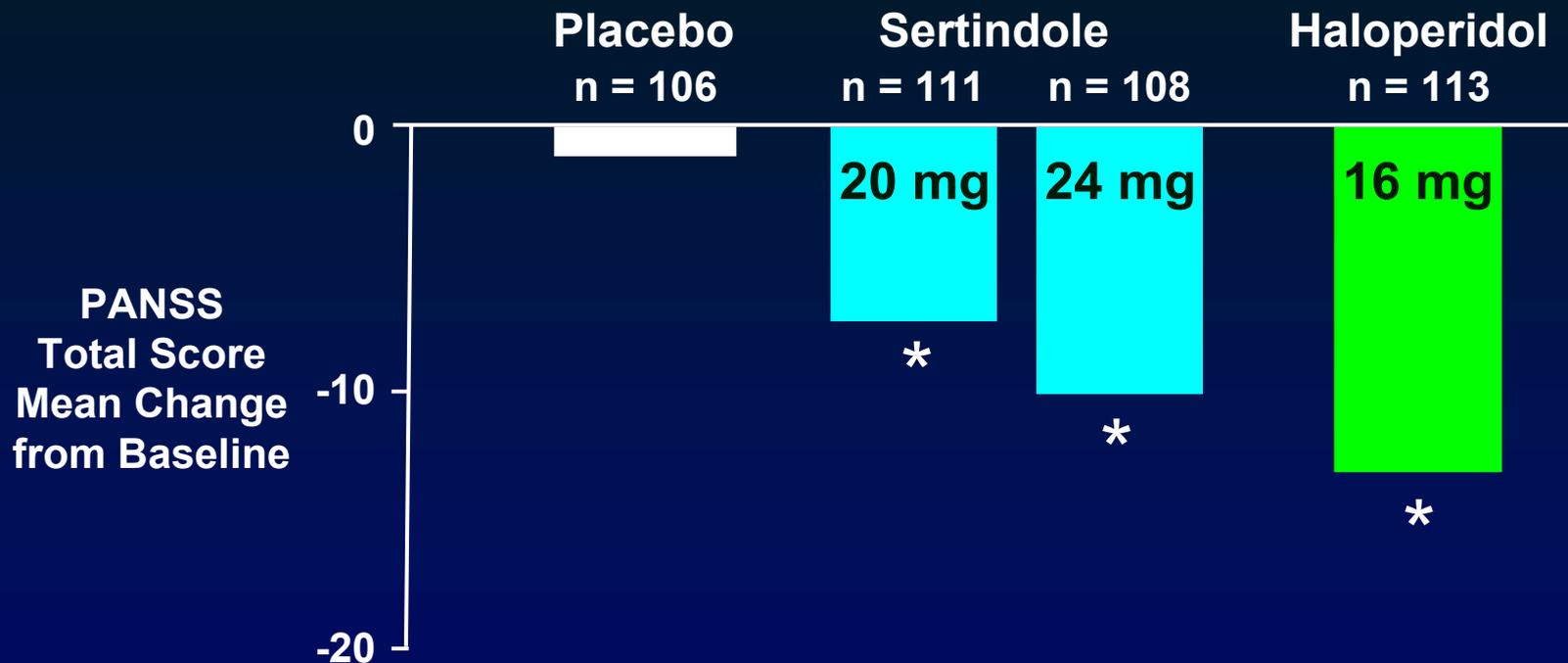
Antipsychotic Effect Similar with Sertindole and Haloperidol



* $p \leq 0.05$ vs placebo, LOCF

Landmark Study M93-113
Zimbroff *et al.*, 1997

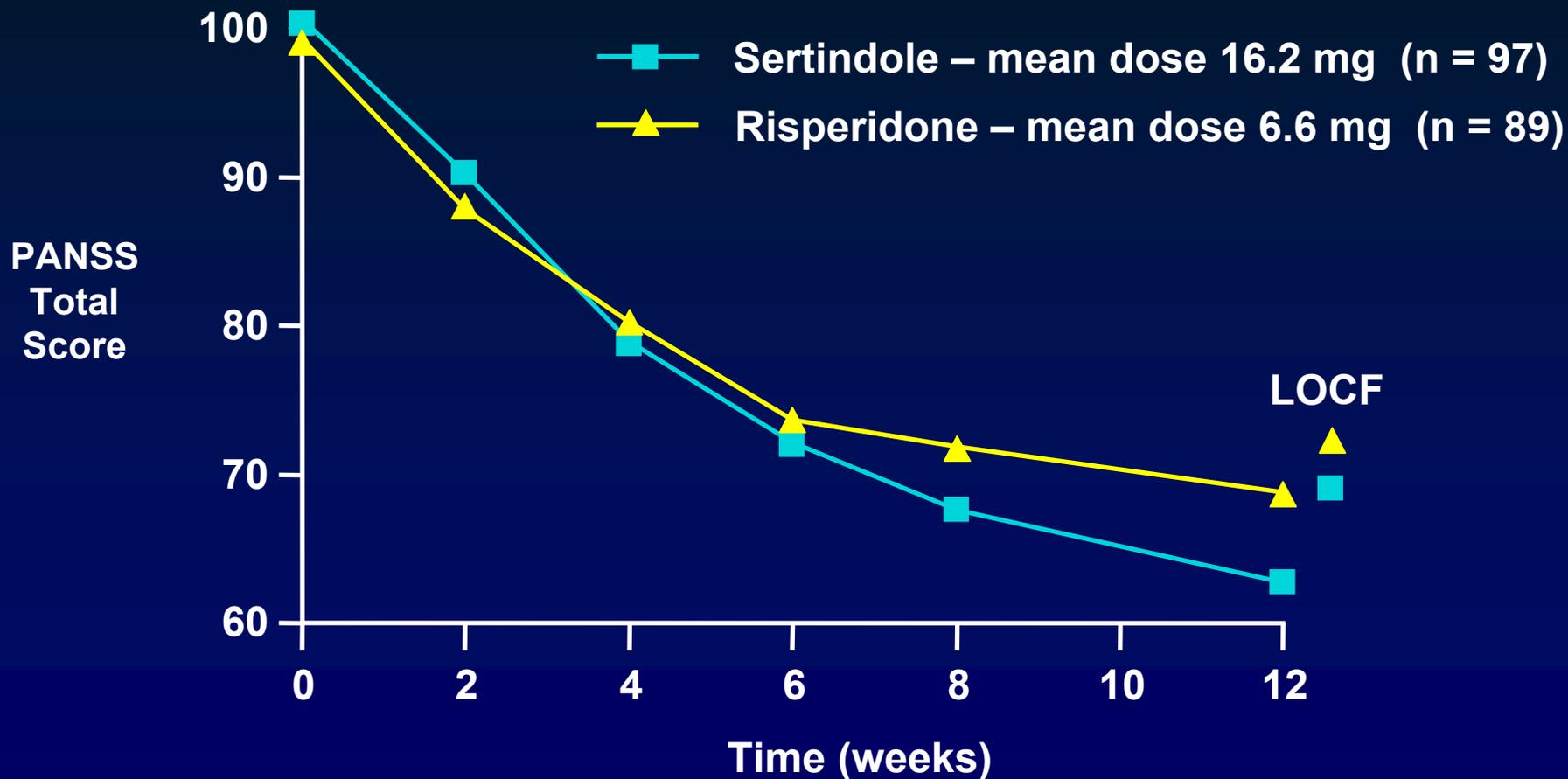
Antipsychotic Effect Supported in Second Adequate and Well-controlled Study



*p <0.05 vs placebo, LOCF

Second US Study M93-098
Kane, 1998

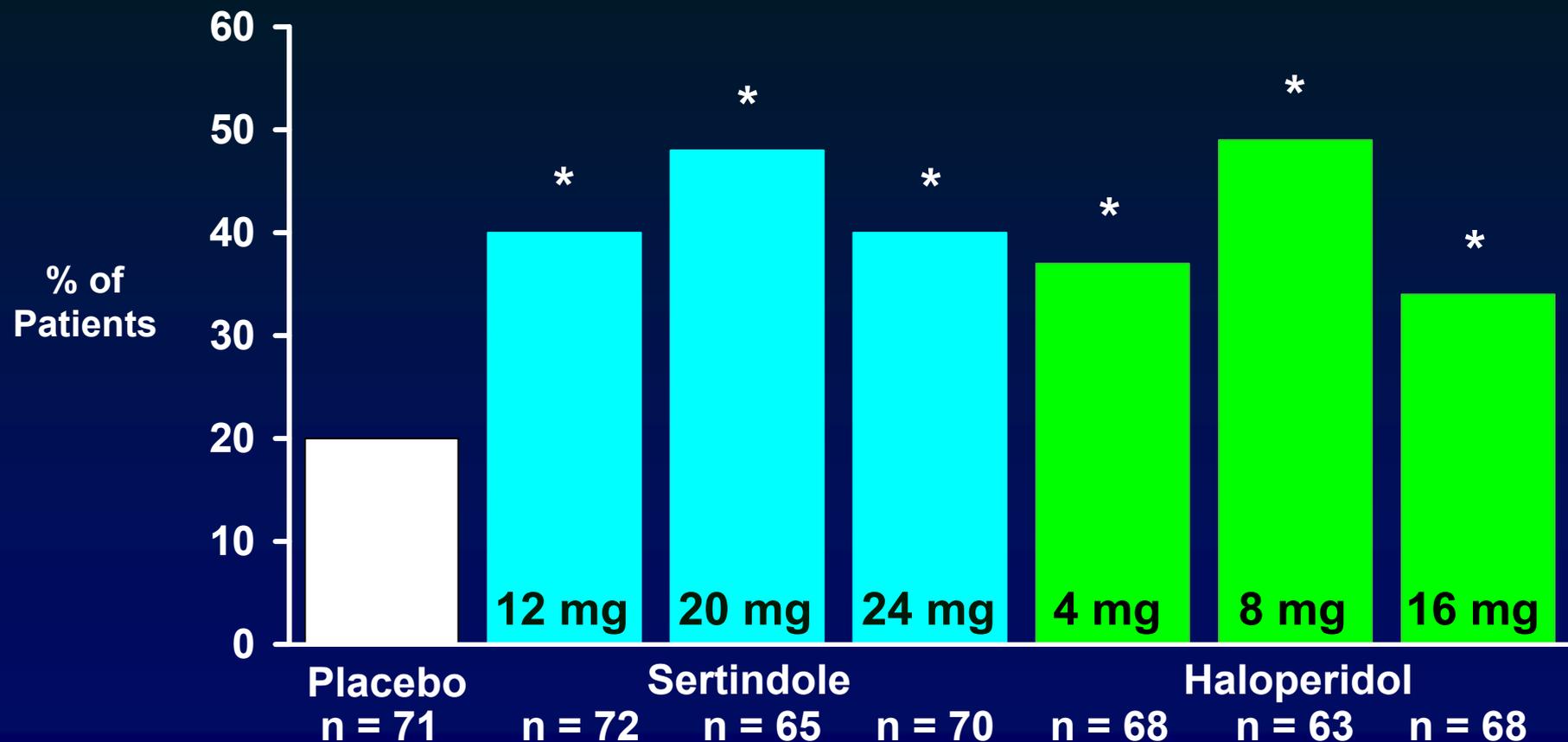
Sertindole and Risperidone Similar in Reducing PANSS Total Score



Observed cases

French Study 97203
Azorin *et al.*, 2006

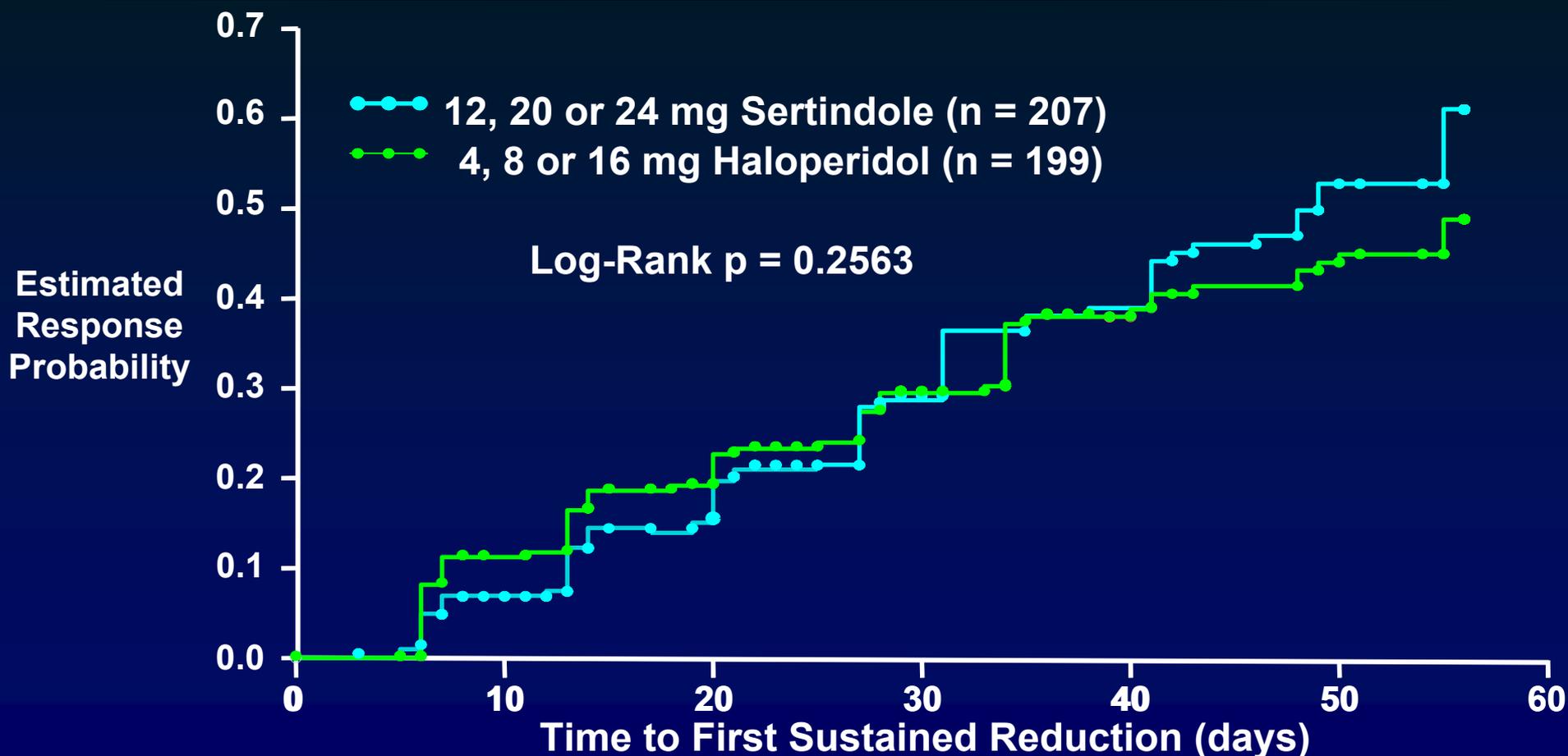
Similar Responder Rates with Sertindole and Haloperidol



Response defined as $\geq 30\%$ reduction from baseline in PANSS total score
 * $p \leq 0.05$ vs placebo (Cochran-Mantel-Haenszel, LOCF)

Landmark Study M93-113
 Zimbroff *et al.*, 1997

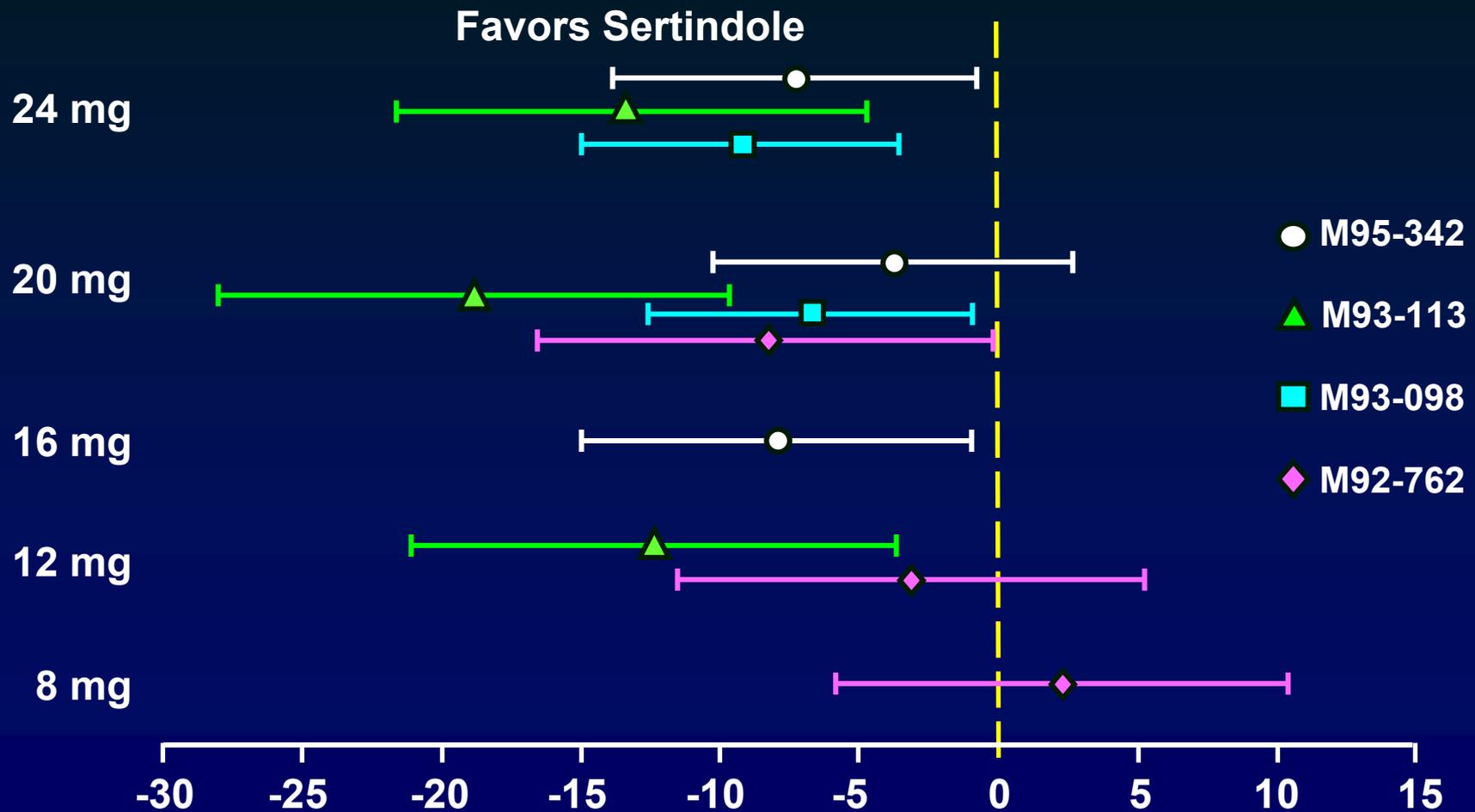
Time to Response Similar Between Sertindole and Haloperidol



Sertindole 12, 20 & 24 mg pooled vs haloperidol 4, 8 & 16 mg pooled
Response defined as $\geq 30\%$ sustained reduction in PANSS total score

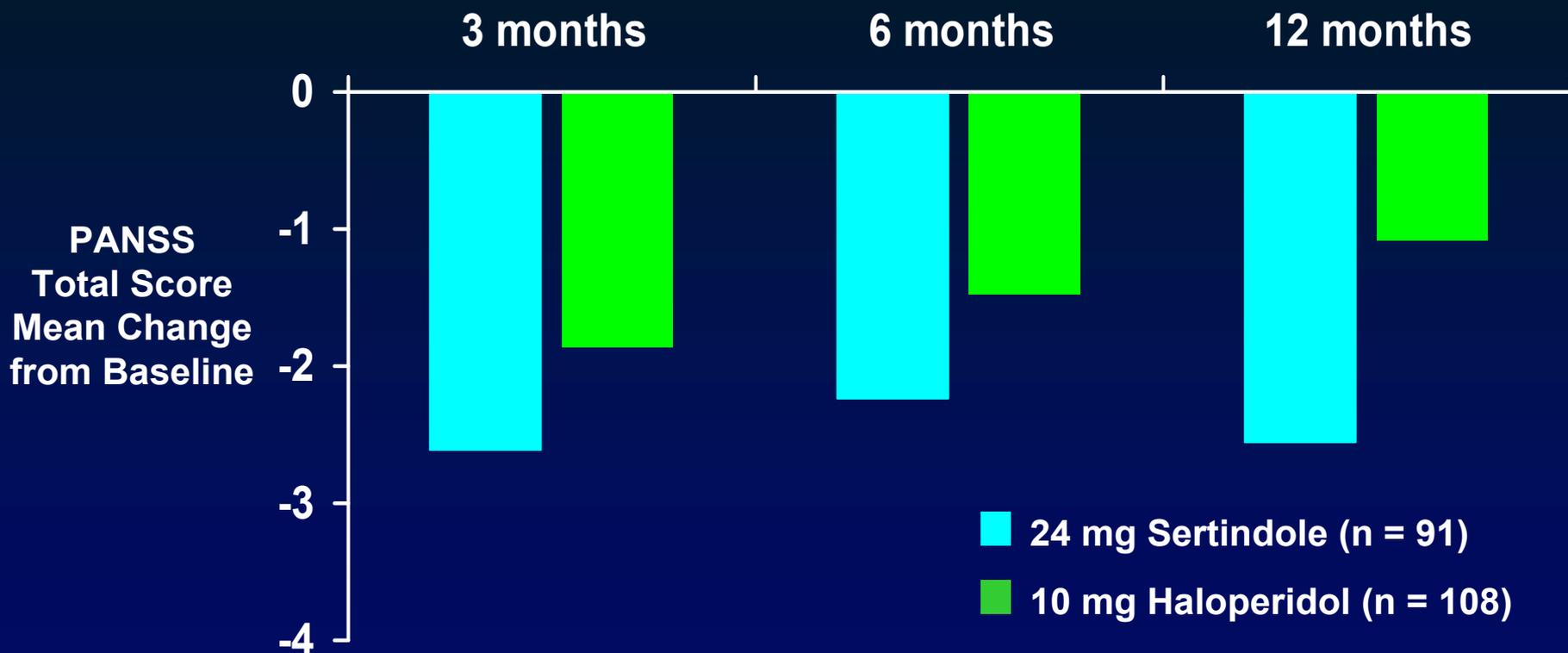
Landmark Study M93-113

Effective Dose Range of Sertindole is 12 to 24 mg/day



Mean change from baseline in PANSS total score vs placebo (Studies M92-762, M93-098 and M93-113) or vs sertindole 8 mg (Study M95-342) with 95% CI (LOCF)

Sertindole Maintained Antipsychotic Effect up to 12 Months



Sertindole Reduces the Risk of Suicide Attempts

Low Suicide Rate in Sertindole NDA

	Suicide mortality / 100 PYE	95% CI
Sertindole 1995 NDA	0.42	0.11 – 1.68
Olanzapine SBA	0.89	0.43 – 1.64
Risperidone SBA	1.17	0.56 – 2.14

SBA: Summary Basis of Approval; PYE: patient years of exposure; CI: confidence interval

Low Suicide Rates in Sertindole Epidemiological Studies

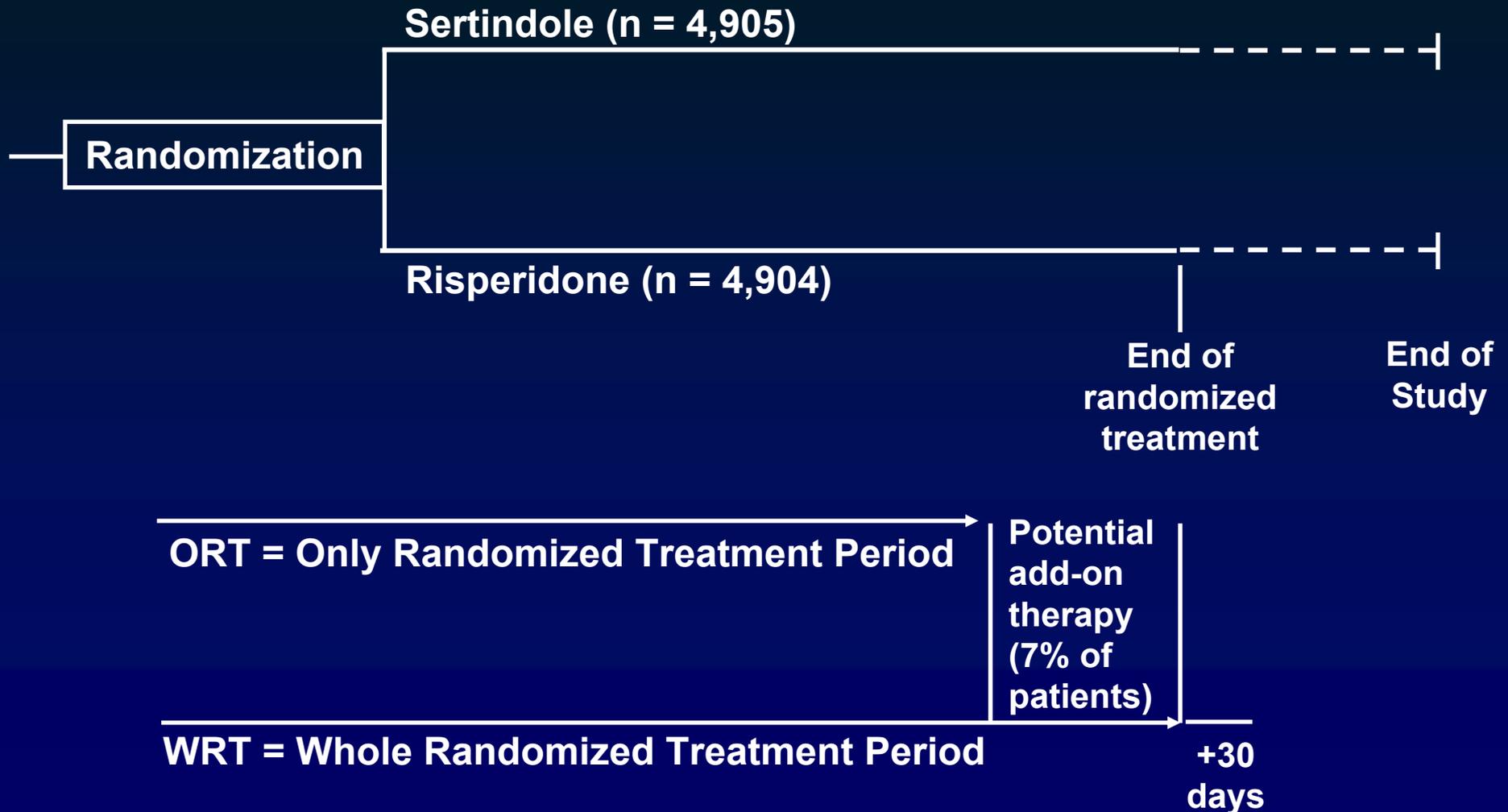
Study	Suicide mortality / 100 PYE	95% CI
ESES (n = 8,608)	0.21	0.09 – 0.41
Sertindole Safety Survey (n = 1,439)	0.11	0.01 – 0.41
ESES Crossover Sub-study (n = 1,112)		
During sertindole treatment	0.10	0.001 – 0.57
Post-sertindole treatment	0.71	0.35 – 1.27

PYE: patient years of exposure; CI: confidence interval

SCoP – Amended to Assess Suicidality

- Suicide data presented to FDA in 2003
- Definition of suicide attempts (fatal and non-fatal) discussed with the FDA
 - observable events with intent to commit suicide confirmed by clinicians
 - suicide attempt history collected and suicide attempts followed during the study
- Suicide attempts compared to risperidone

SCoP – Study Design



SCoP – Study Conduct

- Randomization 1:1
- Open-label treatment
- Investigators followed their individual clinical routine
- Study assessments performed monthly for 3 months, then quarterly

SCoP – Broad Inclusion Criteria

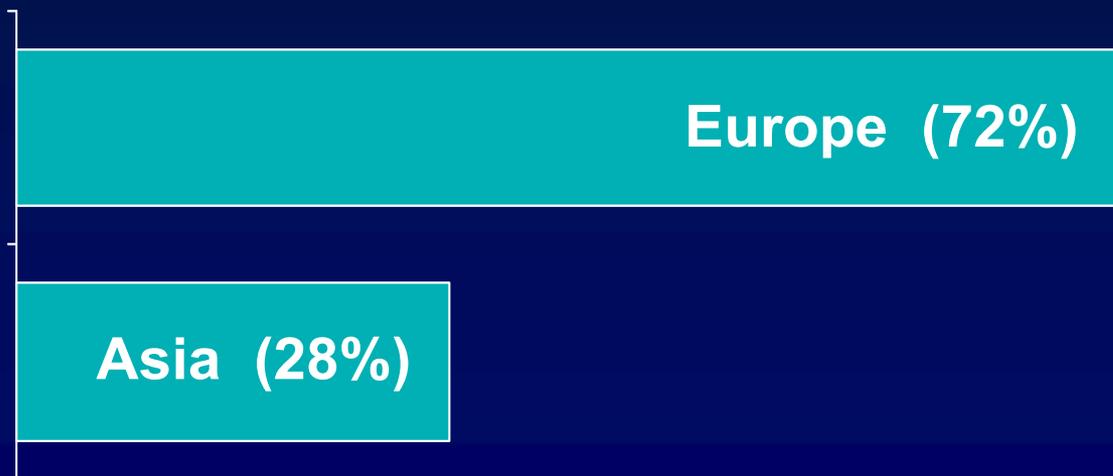
- Clinical diagnosis of schizophrenia
- Need to switch patient to new antipsychotic treatment
- Patient at least 18 years of age
- Patient meets criteria described in the labels of both sertindole and risperidone

SCoP – Limited Exclusion Criteria

- On sertindole or risperidone before entry
- Antipsychotic drug naive
- Needs combination treatment
- Homeless
- Unlikely to comply with study protocol

SCoP – Recruitment and Exposure

	Sertindole	Risperidone	Total
Patients treated	4,905	4,904	9,809
Total exposure (years)	6,978	7,975	14,953
Exposure (days, median)	360	476	415



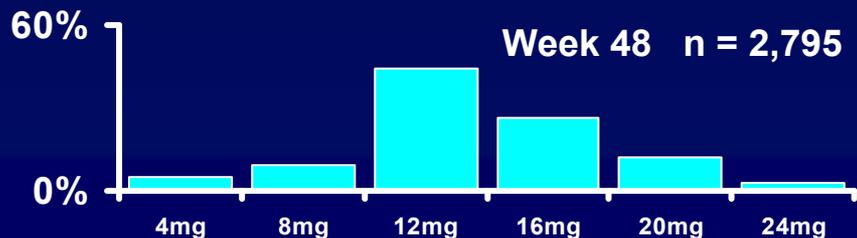
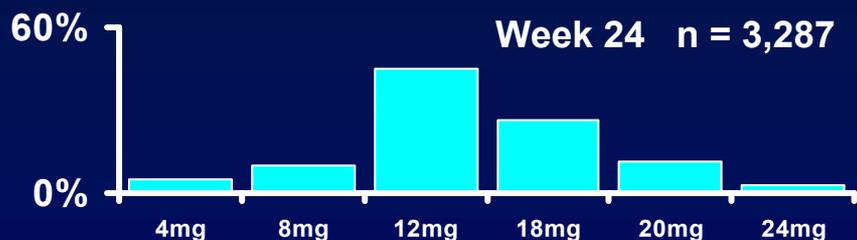
WRT + 30 days

SCoP – Treatment-related Reasons for Discontinuation of Study Drug

Reason	Sertindole n = 4,905	Risperidone n = 4,904
Lack of efficacy	8%	8%
Serious adverse event	2%	1%
Non-serious adverse event	8%	4%
Non-compliance	6%	5%
Patient / relative decision	22%	19%
Investigator decision	1%	2%

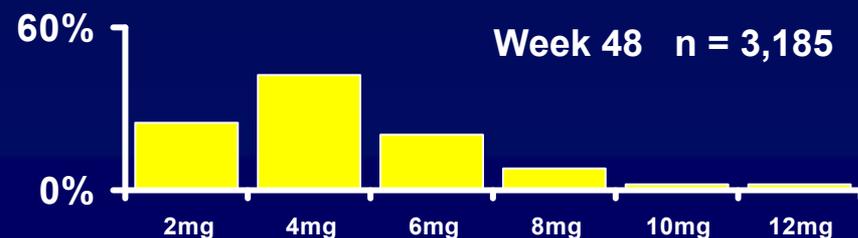
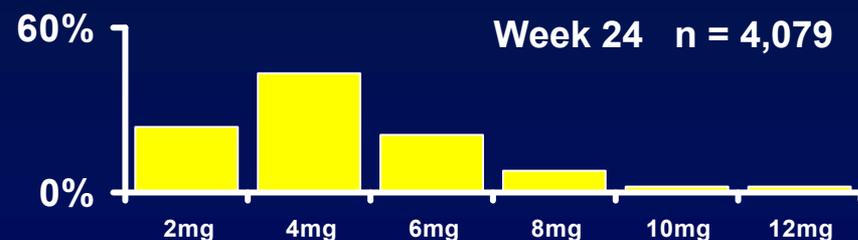
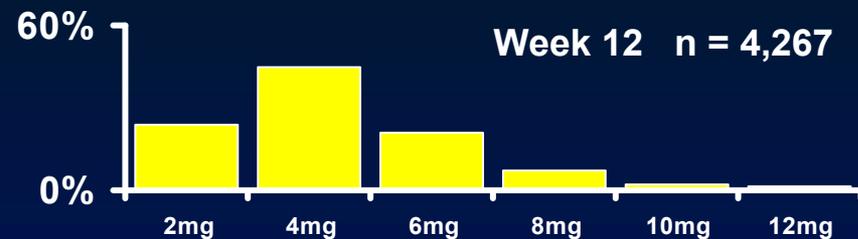
SCoP – Dosing Pattern Stable Over Time

Sertindole



Dose

Risperidone



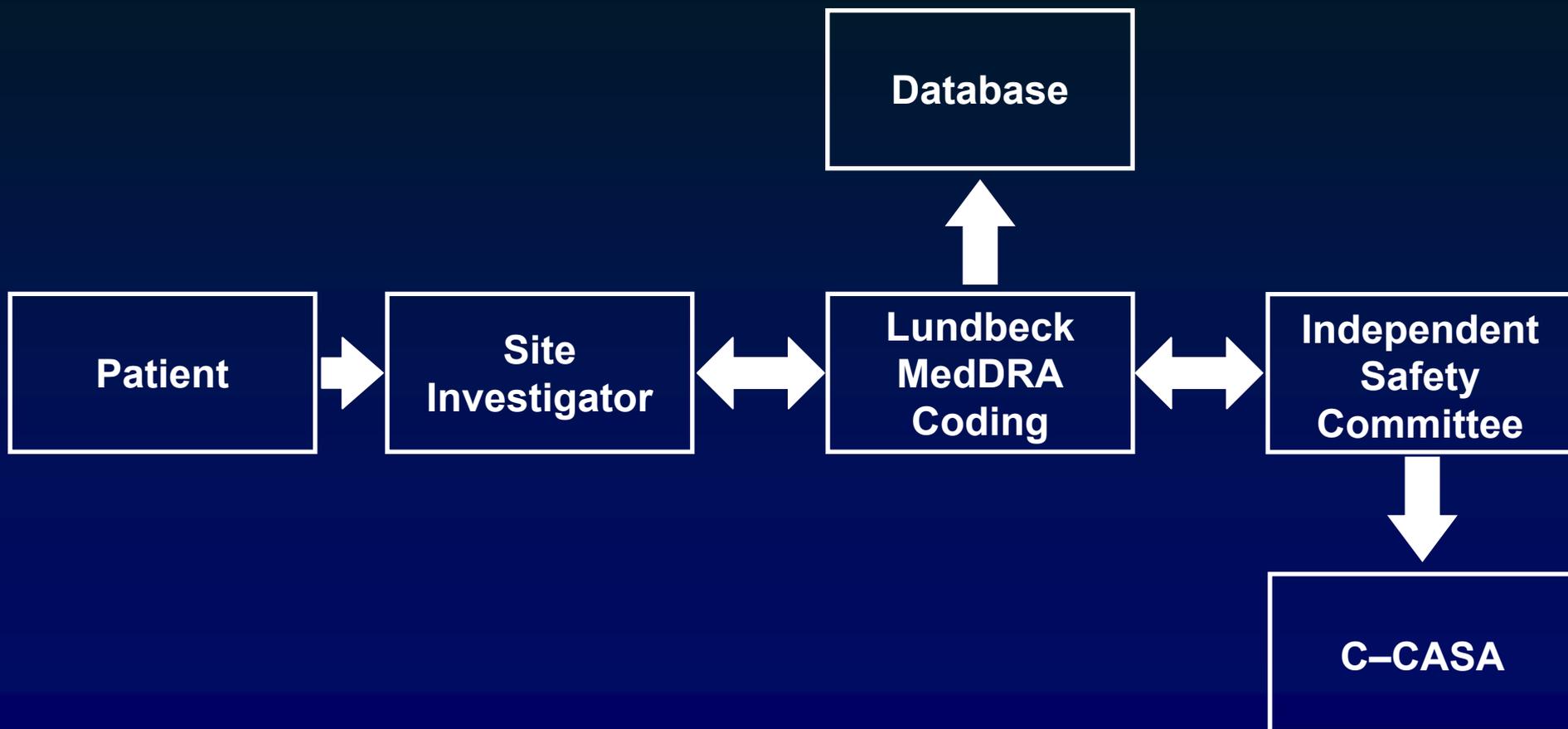
Dose

SCoP – Study Endpoints

- Primary endpoints
 - all-cause mortality (survival)
 - cardiac events leading to hospitalizations

- Secondary endpoints
 - suicide attempts (fatal plus non-fatal)
 - cause-specific mortality (cardiac, suicide, other)
 - hospitalizations (excluding hospitalizations related to the primary psychiatric disease)

SCoP – Safety Data Review



MedDRA: Medical Dictionary for Regulatory Activities

C-CASA: Columbia Classification Algorithm of Suicide Assessment

C-CASA Definitions

Suicidal events		
Code	Category	Definition
1	Completed suicide	A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act.
2	Suicide attempt	A potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him-/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.
3	Preparatory act toward imminent suicidal behavior	The individual takes steps to injure him- or herself, but is stopped by self or others from starting the self-injurious act before the potential for harm has begun.

SCoP – Characteristics of Suicide Attempts

Type of attempt	Sertindole n = 36		Risperidone n = 54	
	n	%	n	%
Non-violent	23	64	25	46
Violent	13	36	28	52
Unknown	0	0	1	2

SCoP – No Increase in Number of Suicides during First 3 Months Post-treatment

	Sertindole	Risperidone
Patient discontinuation (n)	3,137	2,597
Post-treatment exposure (PYE)	2,672	2,170
Time to suicide after stopping randomized treatment		
Day 2 - 14	2	3
Day 15 - 30	2	0
Day 31 - 60	0	1
Day 61 - 90	1	0

SCoP – Time to Suicide Attempt Analyses Based on Cox Regression

Baseline Variables Included in Final Models

Pre-defined

- Age
- Gender
- Duration of schizophrenia
- Time since last suicide attempt

Added

- Study accrual time

SCoP – Lower Risk of Suicide Attempts (Fatal plus Non-fatal) with Sertindole

Events	Sertindole n = 4,905		Risperidone n = 4,904		Hazard ratio ^a	Two-sided p-value
	n	Rate / 100 PYE	n	Rate / 100 PYE		
Suicide attempts (fatal plus non-fatal)	36	0.57	54	0.75	0.66	0.06

C-CASA; ORT + 1 day

a: Cox's Proportional Hazards Model

SCoP – Lower Risk of Suicide Attempts (Fatal plus Non-fatal) with Sertindole

Events	Sertindole n = 4,905		Risperidone n = 4,904		Hazard ratio ^a	Two-sided p-value
	n	Rate / 100 PYE	n	Rate / 100 PYE		
Suicide attempts (fatal plus non-fatal)	36	0.57	54	0.75	0.66	0.06
Completed suicides	9	0.14	19	0.26	0.50	0.09

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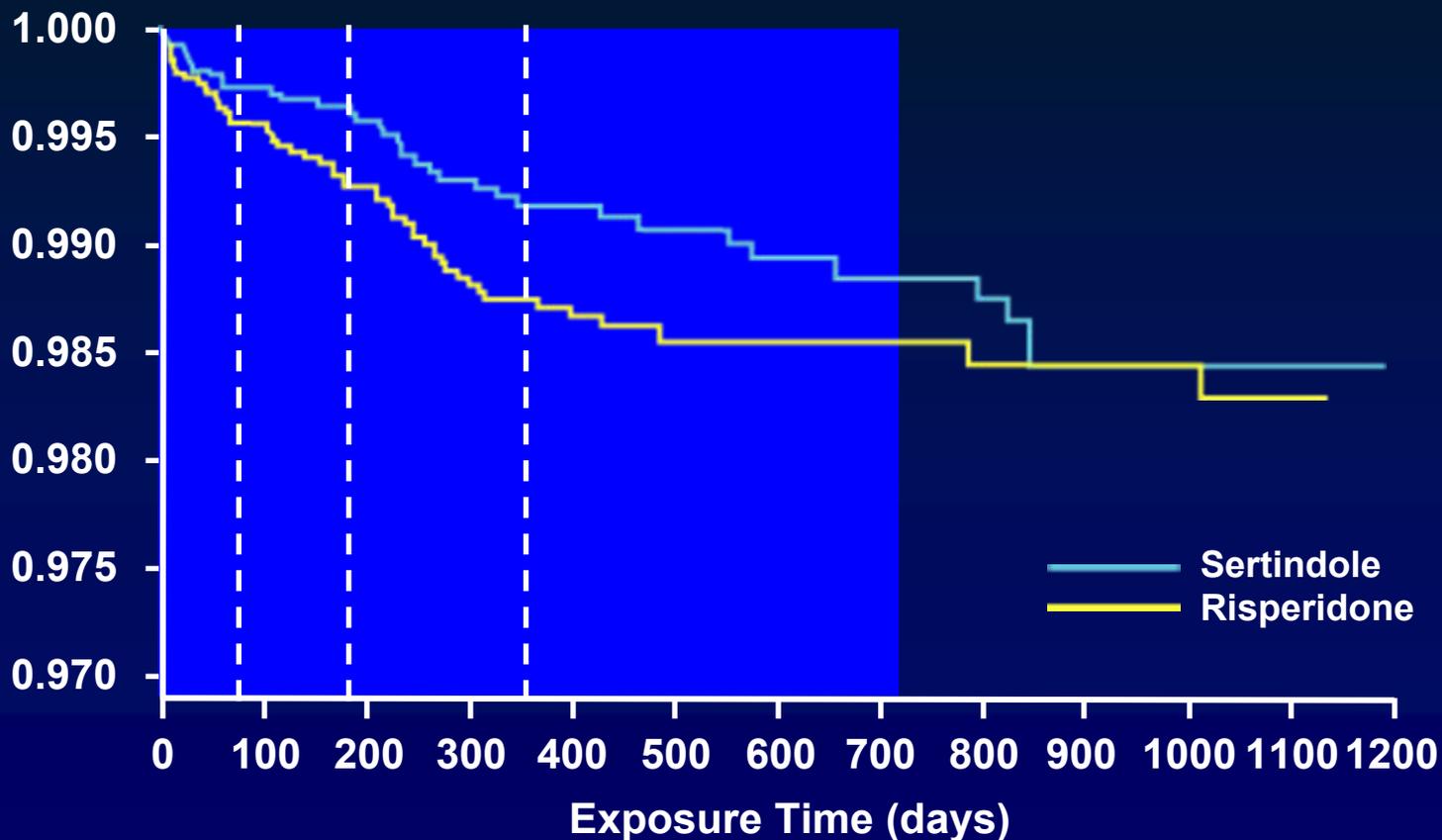
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	n	Rate / 100 PYE	n	Rate / 100 PYE		
Suicide attempts (fatal plus non-fatal)	36	0.57	54	0.75	0.66	0.06
Completed suicides	9	0.14	19	0.26	0.50	0.09
Suicide attempts (fatal plus non-fatal) during first year	27	0.81	47	1.28	0.54	0.01

C-CASA; ORT + 1 day

a: Cox's Proportional Hazards Model

SCoP – Early Reduction of Risk of Suicide Attempts with Sertindole

Estimated Attempt-free Probability



C-CASA; ORT + 1 day

Hazard ratio = 0.661; CI = 0.43 – 1.01

SCoP – Demographics of High-risk Patients for Suicide Attempts

	High-risk patients n = 683	All patients n = 9,809
Gender, male	54%	55%
Mean age (years)	35	38
European region	71%	72%
Duration of schizophrenia >10 years	29%	42%
At least one previous suicide attempt	100%	12%
Suicide attempt during last year before study entry	35%	2%

SCoP – Effect of Sertindole on Suicide Attempts (Fatal plus Non-fatal) Retained in High-risk Group

	(Rate / 100 PYE)		Hazard ratio^a	Two-sided p-value
	Sertindole	Risperidone		
High-risk patients^b (n)	348	335		
Suicide attempts (fatal plus non-fatal)	14 (3.25)	21 (5.15)	0.58	0.12
Suicide attempts (fatal plus non-fatal) during first year	13 (5.65)	20 (9.22)	0.56	0.11

C-CASA; ORT + 1 day

a: Cox's Proportional Hazards Model

b: Patients who had a suicide attempt within the last 5 years before entering the study.

Benefit of Reduction in Suicide Attempts for Sertindole Comparable to Clozapine

Study	Suicide attempts			Suicide			Overall mortality		
	n	Hazard ratio	p-value	n	Hazard ratio	p-value	n	Hazard ratio	p-value
InterSePT^a CLZ / OLZ n = 956	34/55	~0.62	0.03	5/3	~1.7	0.73	12/8	~1.5	0.50
SCoP^b SER / RIS n = 9,809	32/51	0.61	0.03	8/17	0.50	0.10	34/40	0.91	1.43

^aMeltzer *et al.*, 2003

^bC-CASA ORT +1, 2 years

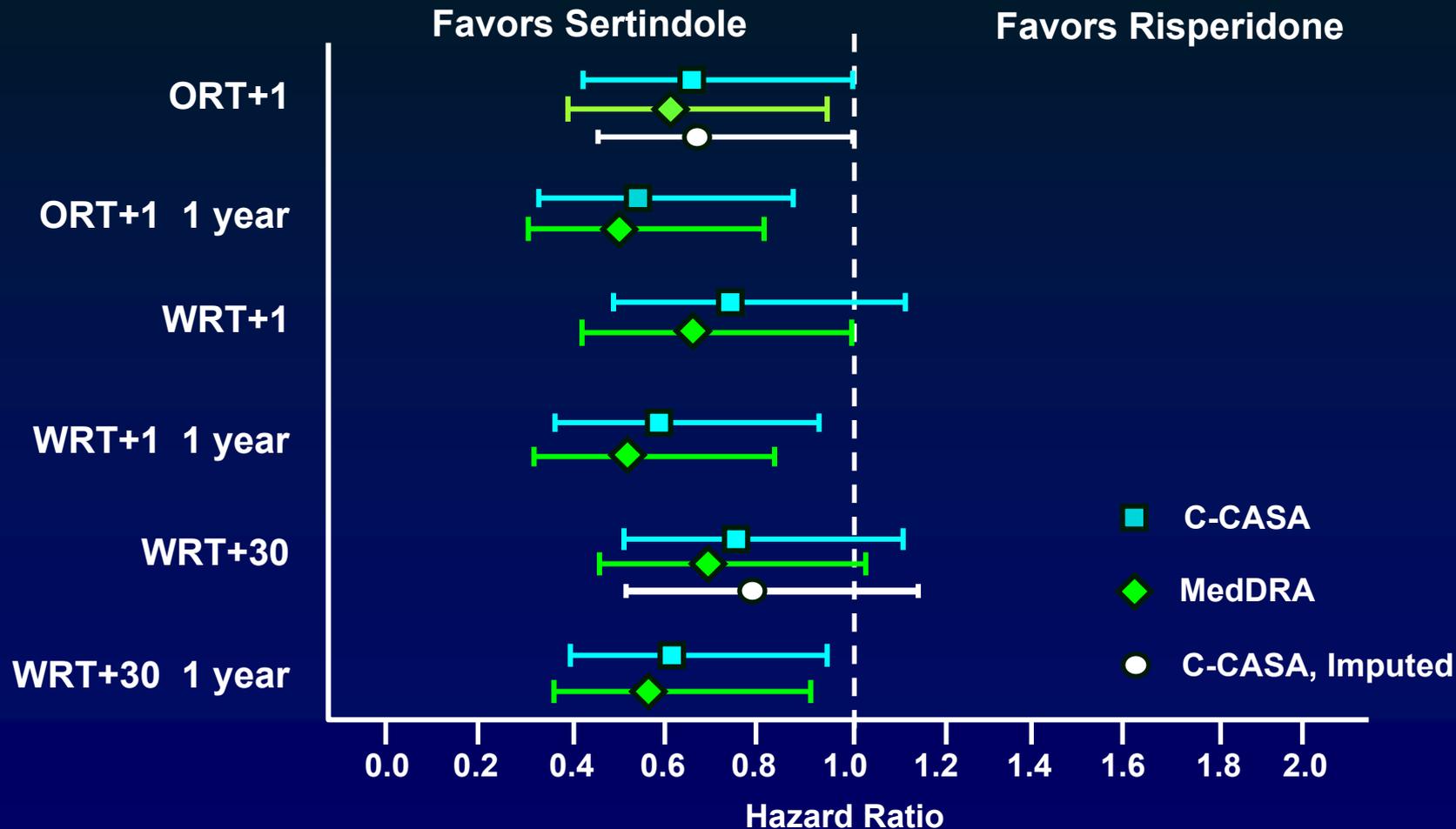
Benefit of Reduction in Suicide Attempts for Sertindole Comparable to Clozapine

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InterSePT^a CLZ / OLZ n = 956	34/55	~0.62	0.03	5/3	~1.7	0.73	12/8	~1.5	0.50
SCoP^b SER / RIS n = 9,809	32/51	0.61	0.03	8/17	0.50	0.10	34/40	0.91	1.43
SCoP High-risk^b SER / RIS n = 683	14/20	0.61	0.16	4/5	0.70	0.60	5/10	0.48	1.41

^aMeltzer *et al.*, 2003

^bC-CASA ORT +1, 2 years

SCoP – Similar Hazard Ratios using C-CASA and MedDRA



Cox's Proportional Hazards Model
95% CI

SCoP – Sertindole is Efficacious in Reducing Risk of Suicide Attempts

- Reduced risk of suicide attempts (fatal plus non-fatal)
 - especially in high-risk group
- Effect already observed during first year
 - clinically significant reduction at 6 and 12 months
- Reduced risk of completed suicides
- Confirms observation of low suicide mortality in clinical and epidemiological studies

Sertindole – Effective in Treatment of Schizophrenia and Reduction of Suicide Attempts

- Efficacious antipsychotic treatment at doses of 12 to 20 mg/day
- Antipsychotic effect similar to that of other antipsychotics
- Antipsychotic effect maintained in long-term treatment
- Reduction of suicide attempts (fatal plus non-fatal) in the broad population with schizophrenia and in high-risk patients

Sertindole Safety and Tolerability

Lasse Steen Ravn, MD, PhD

Department Head, Psychiatric Safety

H. Lundbeck A/S

Agenda – Safety and Tolerability

- All-cause and cause-specific mortality
- Arrhythmias
- Overdose
- QT prolongation
 - mechanism behind QT prolongation
 - non-clinical investigations
 - clinical trials
- Tolerability
 - EPS, akathisia, sedation

Mortality in Global Safety Database

Extensive Experience with Sertindole

Source	Number of Patients	PYE
Clinical studies	3,390	1,983
Epidemiological studies	9,672	4,222
SCoP study^a	4,905	6,978
Post-marketing surveillance	-	27,450

^aWRT + 30 days

Sertindole Mortality Rates in Clinical Studies

	All-cause mortality rate / 100 PYE	CI
Sertindole	0.82	0.5 – 1.3
Sertindole + 30 days	1.47	1.0 – 2.1

CI = 95% Poisson's confidence interval
Sertindole Core Clinical Studies

Sertindole Mortality Rates Similar to Other Antipsychotics

	All-cause mortality rate / 100 PYE	CI
Sertindole	1.47	1.0 – 2.1
Risperidone	1.86	1.1 – 3.0
Olanzapine	1.87	1.2 – 2.9
Aripiprazole	0.90	–
Ziprasidone	1.62	–
Quetiapine	1.09	–

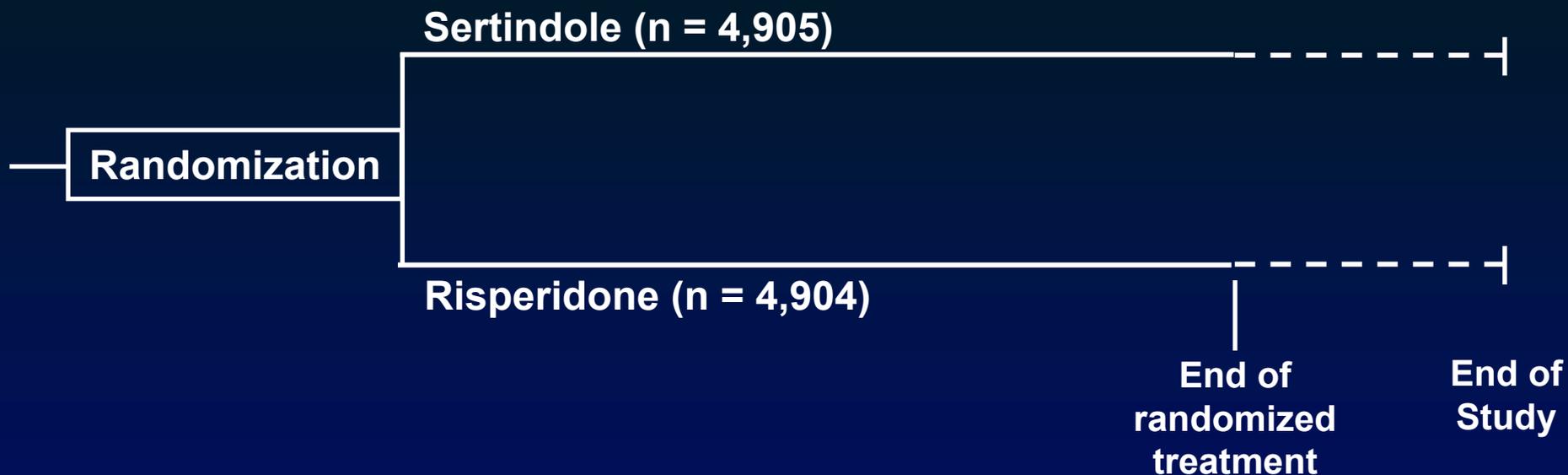
CI = 95% Poisson's confidence interval

Sertindole Core Clinical Studies; Summary Basis of Approval of individual compounds

Extensive Epidemiology Study Database

Study	All-cause mortality rate / 100 PYE	CI
ESES (n = 8,608)	0.76	0.51 – 1.10
SSS (n = 1,439)	0.51	0.23 – 0.97
Crossover Sub-study (n = 1,112)	0.72	0.29 – 1.49

SCoP – Study Design



ORT = Only Randomized Treatment Period

Potential
add-on
therapy
(7% of
patients)

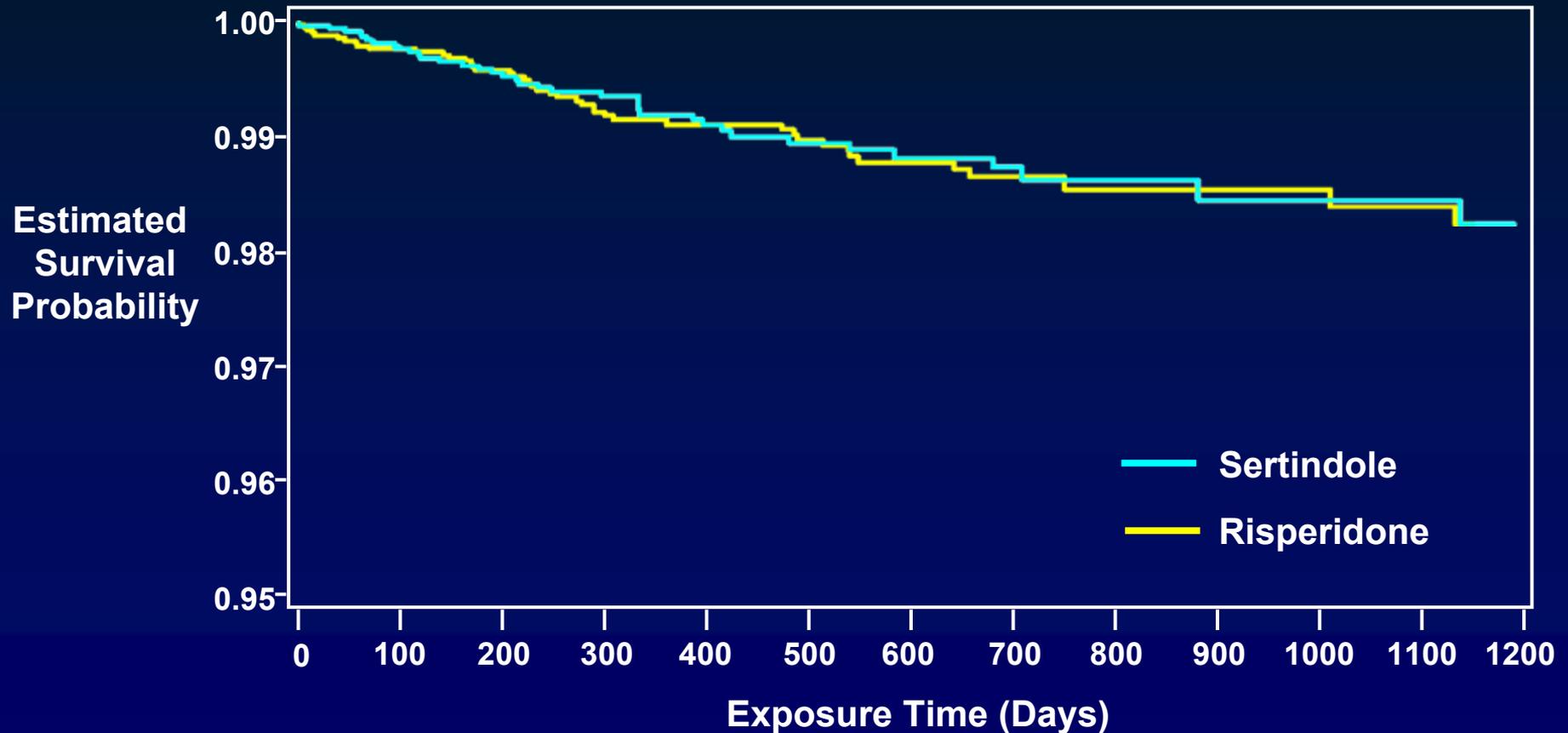
WRT = Whole Randomized Treatment Period

+30
days

SCoP – All-cause Mortality Similar in Both Treatment Groups

ORT + 1 day	Sertindole n = 4,905	Risperidone n = 4,904
Fatal events, n (%)	40 (0.82%)	44 (0.90%)
Mortality rate / 100 PYE	0.63	0.61
Hazard ratio (90% CI)	0.98 (0.68-1.41)	

SCoP – No Difference in All-cause Mortality Between Sertindole and Risperidone



ORT + 1 day

SCoP – All-cause Mortality Similar in Both Treatment Groups

ORT + 1 day	Sertindole n = 4,905	Risperidone n = 4,904
Fatal events, n (%)	40 (0.82%)	44 (0.90%)
Mortality rate / 100 PYE	0.63	0.61
Hazard ratio (90% CI)	0.98 (0.68-1.41)	

WRT + 30 days

Fatal events, n (%)	64 (1.30%)	61 (1.24%)
Mortality rate / 100 PYE	0.92	0.76
Hazard ratio (90% CI)	1.12 (0.83-1.50)	

Cause-specific Mortality is Difficult to Determine with Reliability

- Cause of death can be difficult to determine
 - few autopsies are performed
 - classification often based on medical history
 - limited observation at time of death by trained observer
- All-cause mortality is the most reliable endpoint

The Challenge of Classifying Mortality

Case ID	Case detail	ISC classification
1016470	Muscle spasm and twitch during sleep. Resuscitation unsuccessful.	Documented Sudden Death
1026659	Seizure described as rigidity of extremities and loss of consciousness. Declared dead upon arrival at hospital. Diagnosed with low potassium the day before death.	Other

SCoP – Sudden and Unexplained Death – Sertindole vs Risperidone

	Sertindole (n = 64)	Risperidone (n = 61)	Rate Ratio
MedDRA SOC – General disorders	10	6	1.75
ISC sub-classification – Sudden cardiac death	13	3	4.75
Uncertain cause of death	17	16	1.21
Sudden cardiac death occurring in the community	12	8	1.71
Total	23	17	1.55

WRT + 30 days

Conclusions on Mortality

- All-cause mortality with sertindole comparable to risperidone as well as other antipsychotics
- Classifying cause-specific mortality has significant limitations

Arrhythmia and Torsade de Pointes

Two Fatal Cases with Arrhythmia

Age / gender	Duration of sertindole treatment	Dose	Confounding factors	Reported event
79 / F	8.5 months	12 mg	Hypertension, ischaemic heart disease and myocardial damage Concomitant medication: xylocaine, amiodarone, furosemide, perazine	Torsade de Pointes
69 / F	6 months	4 mg	Concomitant medication: verapamil, digoxin, haloperidol	Arrhythmia

Three Non-fatal Cases with Reported TdP

Age / gender	Duration of sertindole treatment	Dose	Concomitant medications	Risk factors
43 / F	18 months	20 mg	Unknown antibiotic, Chinese cough medicine	Low potassium
40 / F	7 weeks	16 mg	Ajmaline	History of palpitations, cardiac irregularity
31 / F	4 months	20 mg	Fluoxetine	History of collapse, family history of sudden death, low potassium

Overdose Experience

All Overdose Cases

Source	Total	Overdose, sertindole only	Mixed overdose, including sertindole	Overdose, not including sertindole
All sources	218	91	42	85
Clinical studies	83	41	18	24
Epidemiological studies	39	13	4	22
SCoP study	67	18	11	38
Spontaneous reports	29	19	9	1

Overdose With Reports of Arrhythmia

Source	Sertindole only		Sertindole and other	
	Total	Arrhythmia	Total	Arrhythmia
All sources	91	3	42	5
Clinical studies	41	1	18	2
Epidemiological studies	13	-	4	-
SCoP study	18	1	11	-
Spontaneous reports	19	1	9	3

Conclusion – Arrhythmias and Overdose

- Reports of TdP are rare
 - clinical trial database: 3 of 8,295 patients
- Extensive overdose experience in clinical trials and post-marketing
 - 8 arrhythmias in 133 reports of overdose
 - majority reported in relation to mixed overdoses

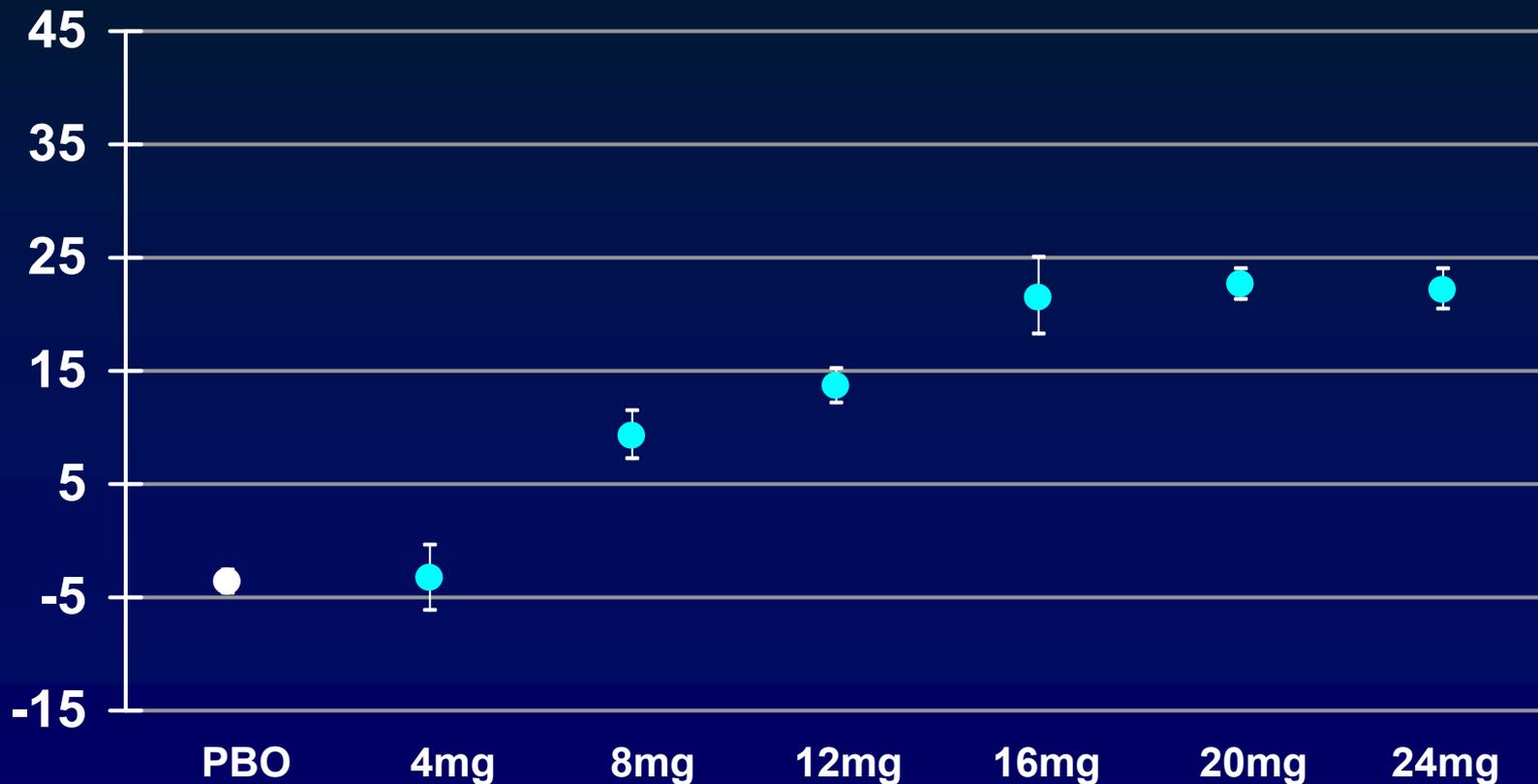
QT Prolongation with Sertindole

QT Prolongation

- QT prolongation is a crude but imperfect biomarker for TdP
- QT prolongation does not always predict TdP
- Other electrophysiological properties including multiple ion channel interactions are important

QT_c Increase with Sertindole is Dose Dependent

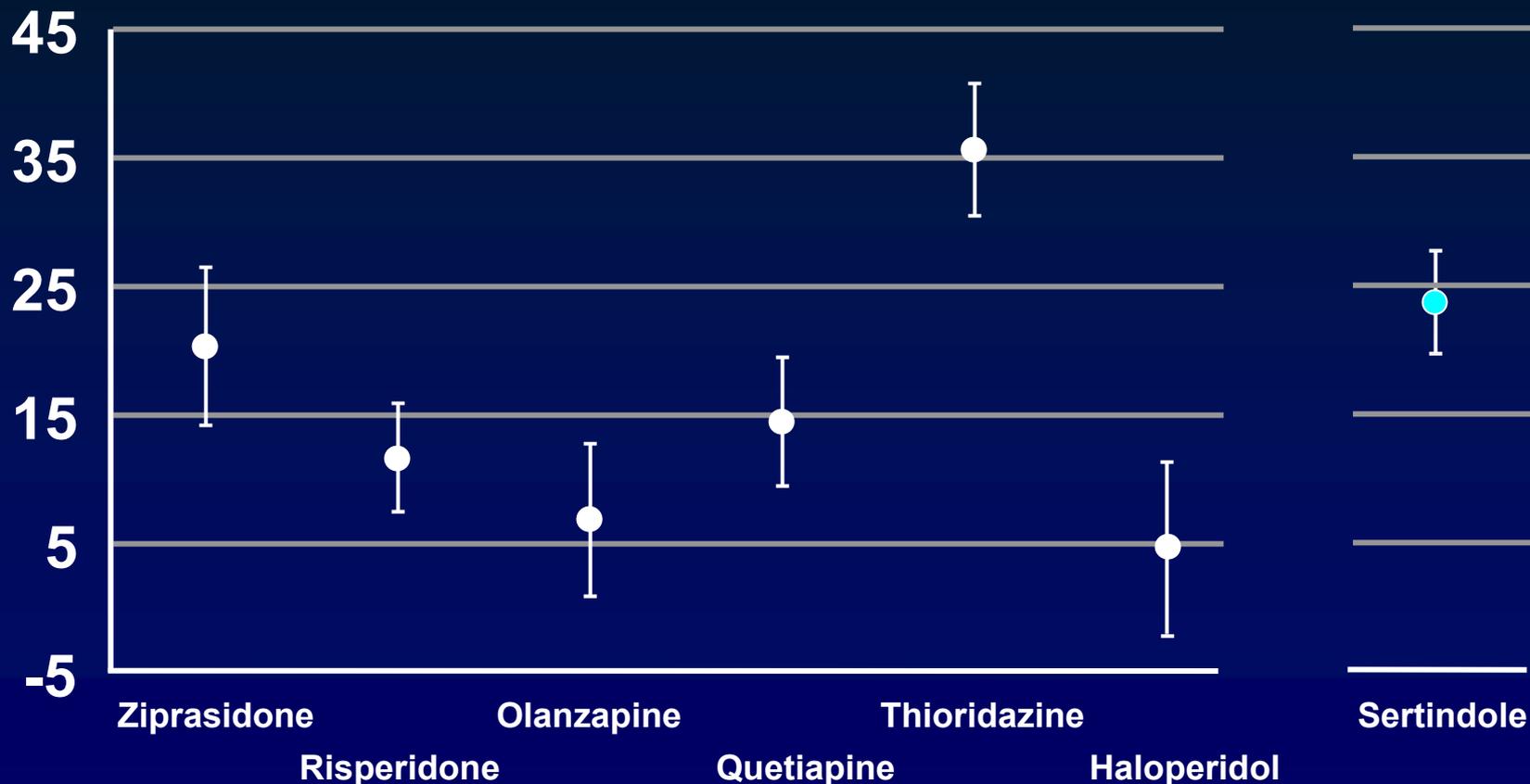
Mean QT_{cF}
Change (msec)



Studies M92-762, M93-817, M93-098, M93-113, and M95-342

Many Antipsychotics Prolong the QT_c Interval

Mean QT_{cB}
Change (msec)



CI = 95% confidence interval; sertindole 20 mg/day
Lindström *et al.*, 2005; Glassman & Bigger, 2001; FDA, 2000

Sertindole Patients with $QT_c > 500$ msec

$QT_{cF} > 500$ msec			
Placebo		Sertindole 20mg/day	
N	n (%)	N	n (%)
137	0 (-)	140	2 (1.4)

N = Number of patients with a post-baseline ECG
 ECG methodology: 2007 re-read.

Studies M93-098 and M93-113

QT_c Change from Baseline to Last Assessment by Category

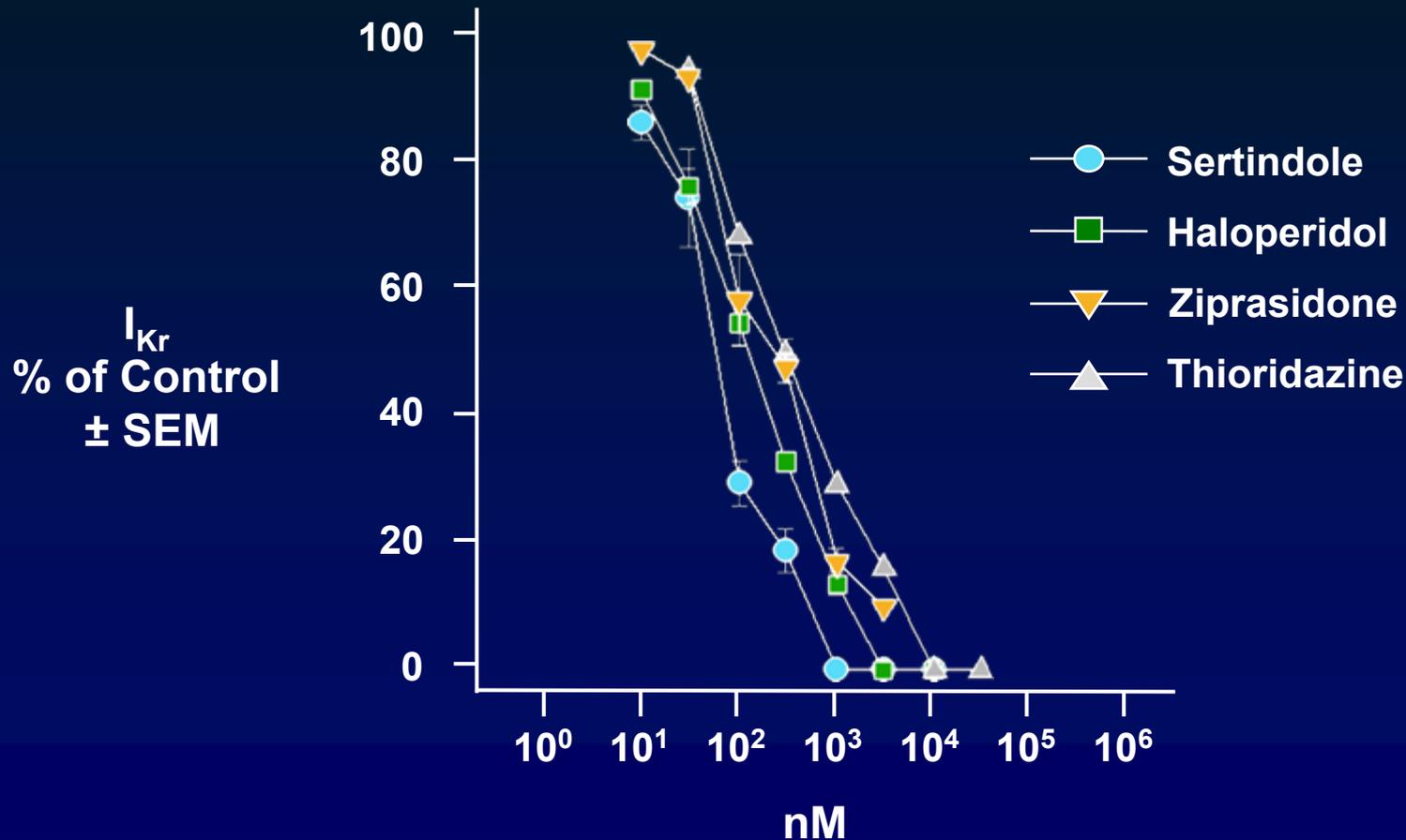
QT _{cF} change category Baseline to last assessment	Placebo (N = 137)		Sertindole 20 mg/day (N = 140)	
	n	%	n	%
<30 msec	132	96.4	77	55.0
≥30 to <60 msec	5	3.6	49	35.0
≥60 msec	0	-	14	10.0

Table includes patients with baseline and at least one post-baseline ECG.
ECG methodology: 2007 re-read

QT Prolongation

- Sertindole prolongs the QT interval
 - 23 msec mean increase at 20 mg/day
 - 1.4% of patients have >500 msec at 20 mg/day
- Prolongation is dose dependent
 - tendency to plateau above 16 mg/day

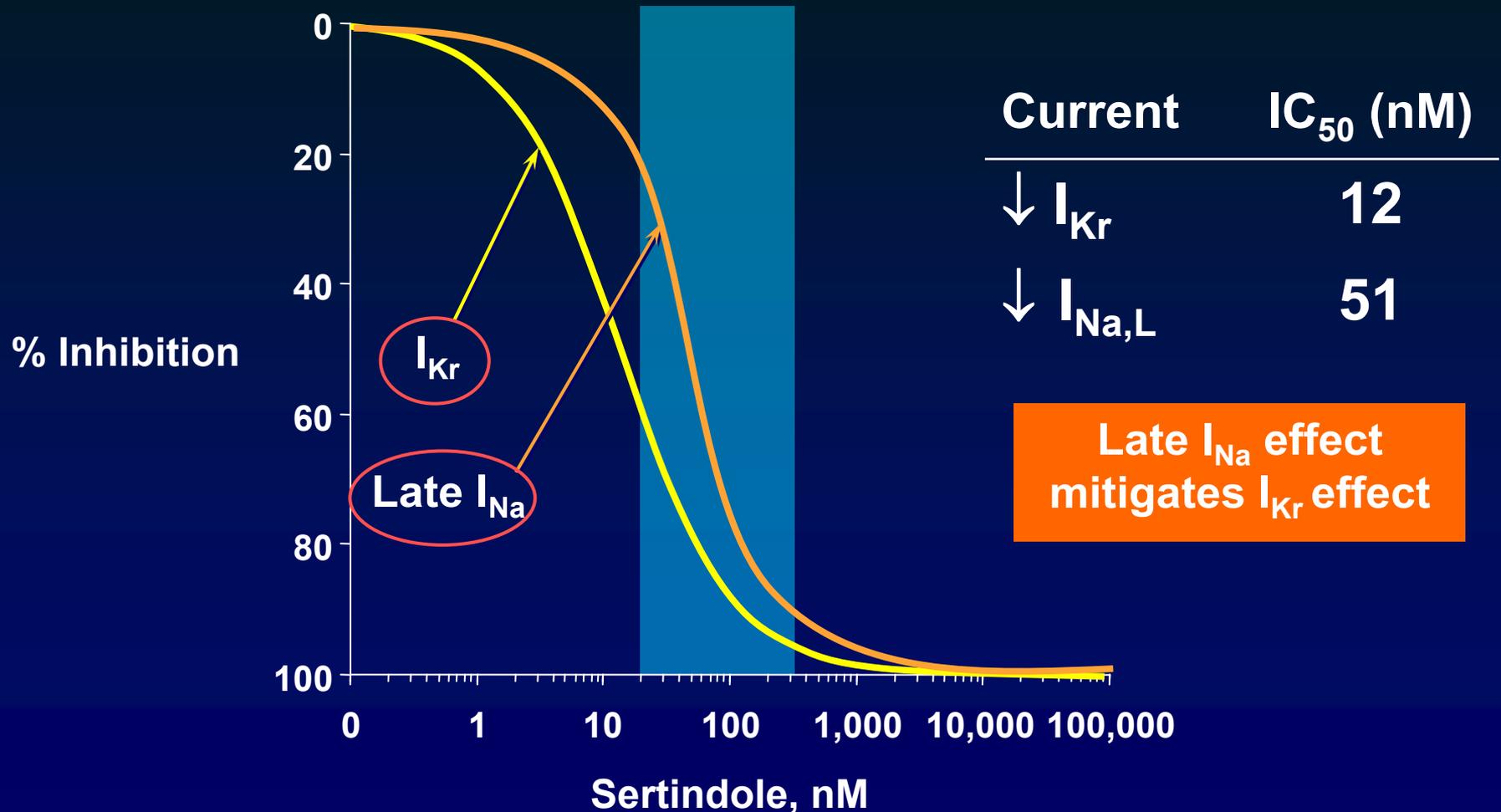
Blockade of I_{Kr} is Common with Antipsychotics



Data from cell cultures transfected with hERG

Haverkamp *et al.*, 2002

Ion Channel Currents – Effects of Sertindole in Myocytes

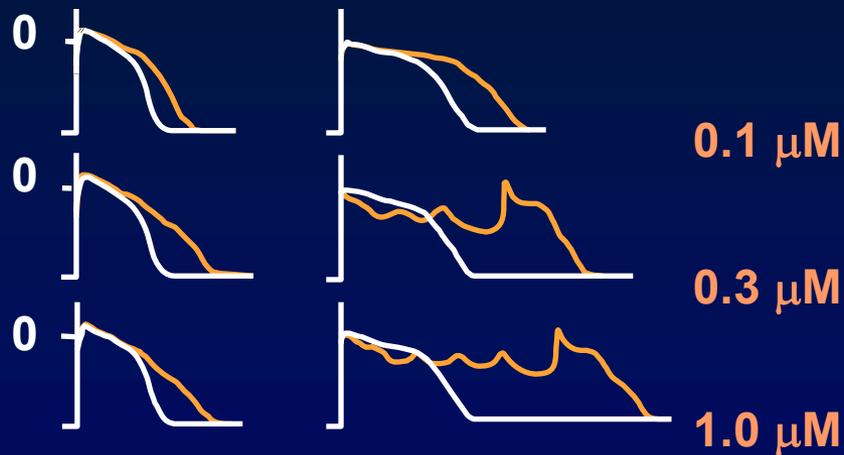


Data obtained in canine LV myocytes
Blue bar = therapeutic range

No Trigger of EADs with Sertindole

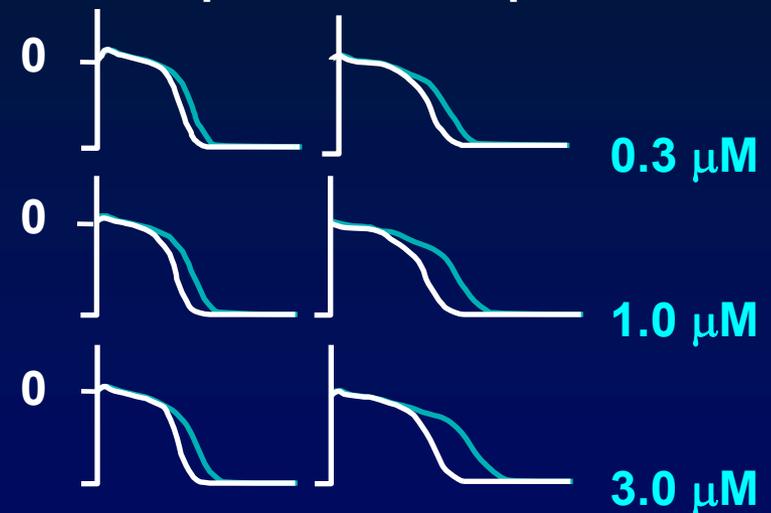
Astemizole

60 bpm → 12 bpm

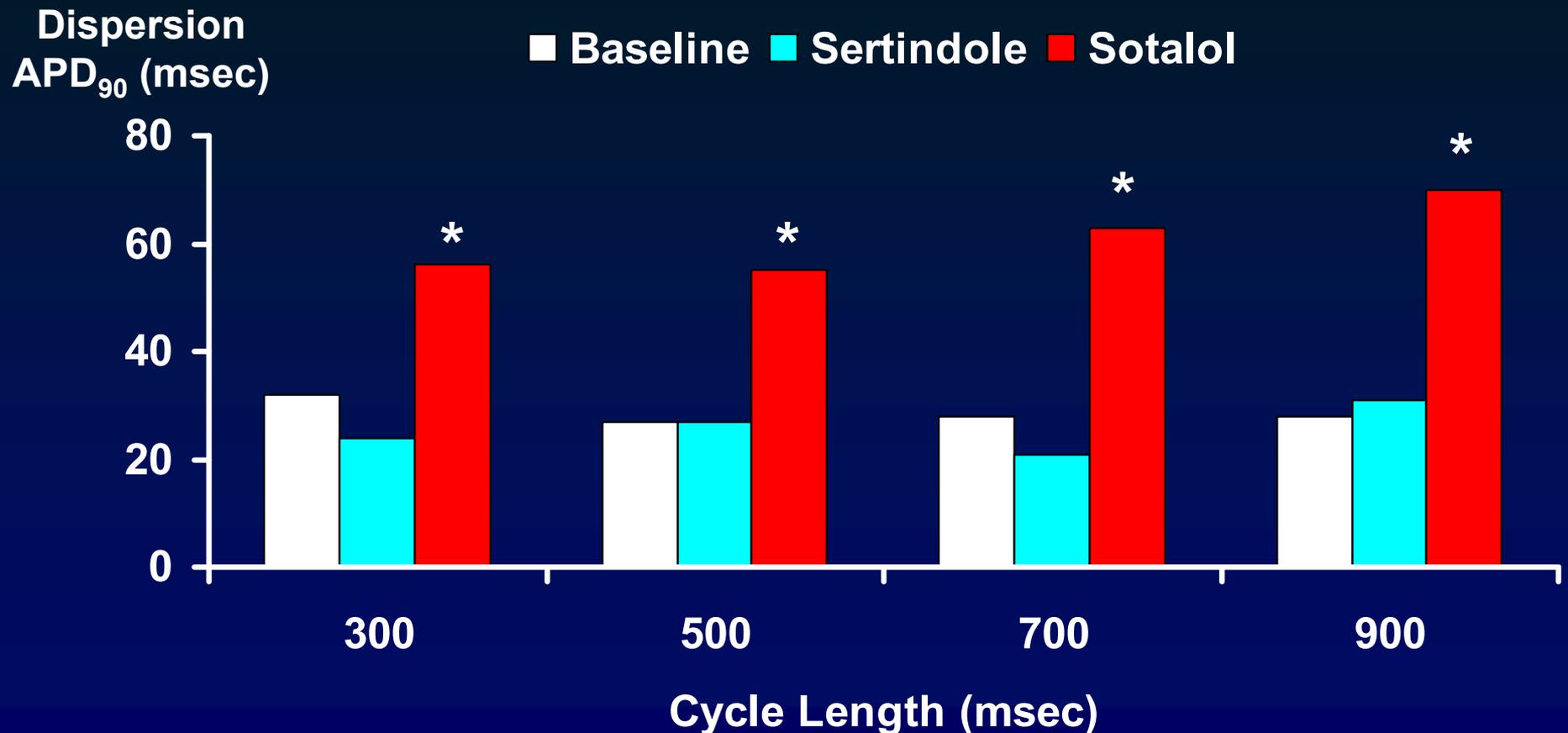


Sertindole

60 bpm → 12 bpm



No Transmural Dispersion of Repolarization with Sertindole



*p-value vs baseline <0.05

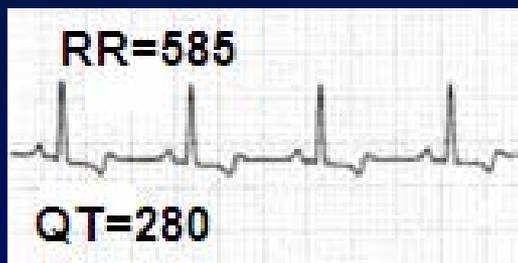
Difference between APD₉₀ from endocardium and epicardium in isolated rabbit hearts

Haverkamp *et al.*, 2002

Effects of Rapid Sertindole IV Infusion on Diseased Hearts

Sinus rhythm
Normal heart

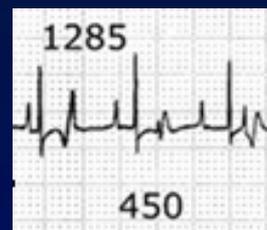
Control



8 weeks after
AV-node
ablation

Idioventricular rhythm
CAVB heart

0.2 mg/kg sertindole, IV



No TdP

1.0 and 2.0 mg/kg sertindole, IV



Animal studies testing sertindole in CAVB canine hearts
Thomsen *et al.*, 2003

QT Prolongation Does Not Translate to Arrhythmia

- Sertindole prolongs the QT interval by blocking I_{Kr}
- The QT prolongation is mitigated by blocking $I_{Na,L}$
- No triggered activity or EADs
- No increased transmural dispersion of repolarization
- Vulnerable animal hearts did not produce arrhythmia at therapeutic concentrations of sertindole

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- No triggered activity or EADs
- No increased transmural dispersion of repolarization
- Vulnerable animal hearts did not produce arrhythmia at therapeutic concentrations of sertindole
- Nonclinical data support clinical safety
 - 40,000 patient years of exposure
 - 133 reports of overdose involving sertindole

General Tolerability

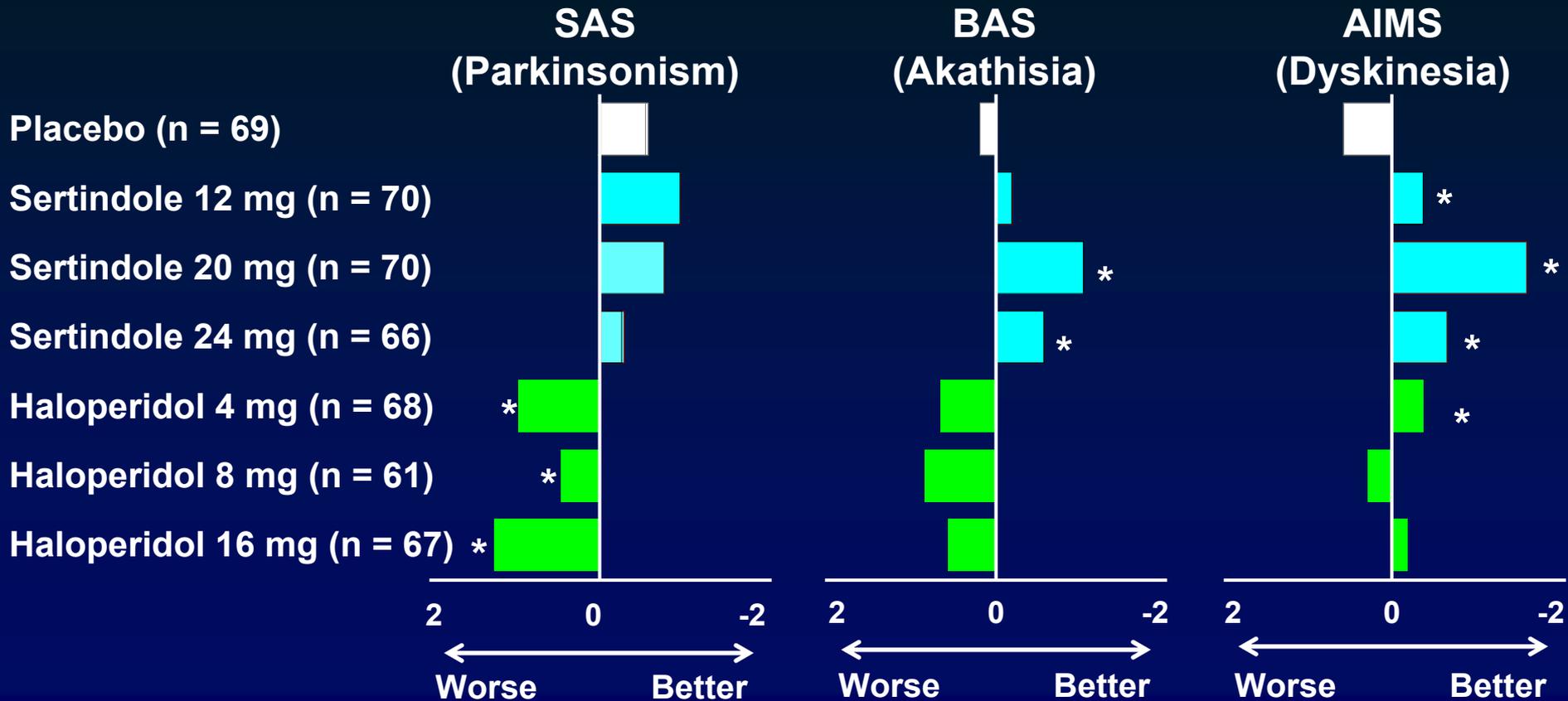
Common Adverse Events Observed with Sertindole (Incidence $\geq 10\%$)

Adverse event	Sertindole n = 704 (%)	Placebo n = 290 (%)
Headache	28	29
Insomnia	21	21
Nasal congestion	21	8
Constipation	13	9
Dizziness	13	7

Discontinuation due to the most common adverse events < 1%

Adverse events with an incidence $\geq 10\%$ in the sertindole group in placebo-controlled studies M91-645, M92-762, M93-098, M93-113, M92-817

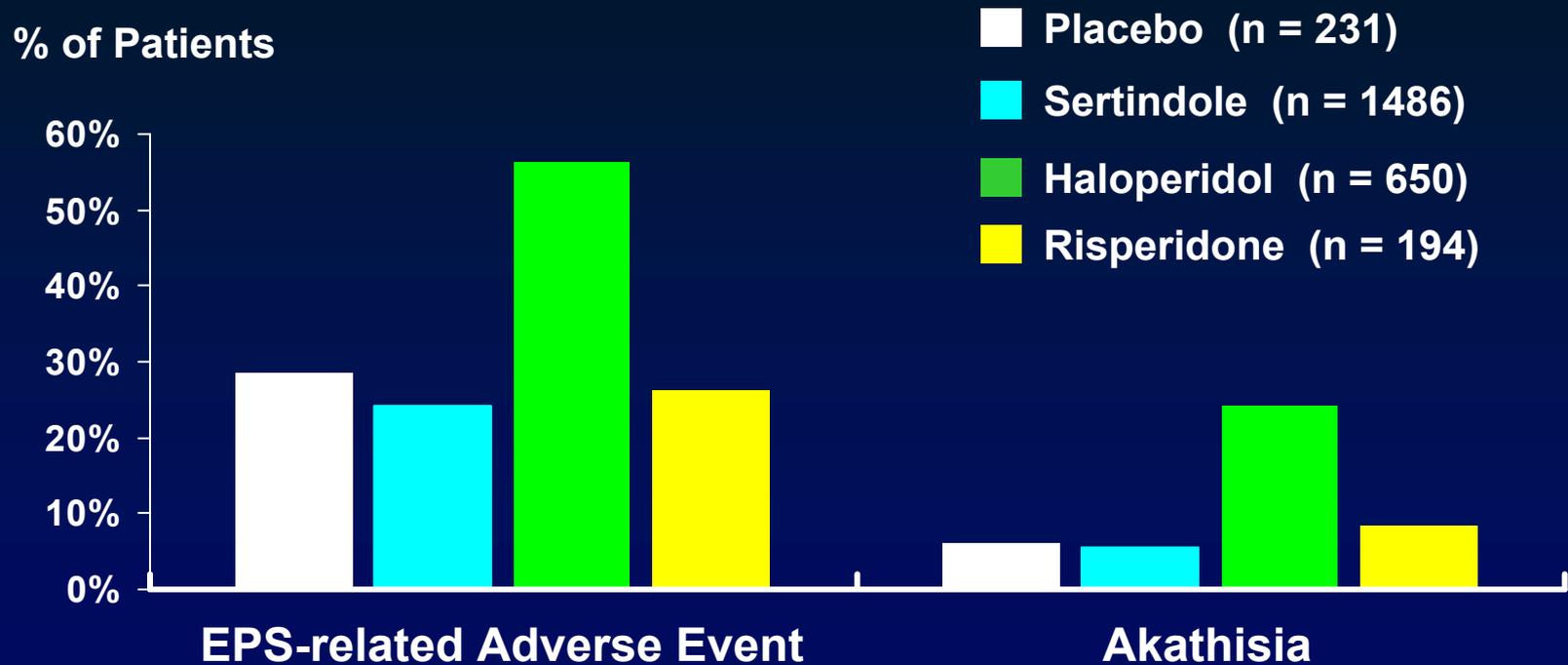
Improvement in EPS with Sertindole



* p-value ≤ 0.05 vs placebo

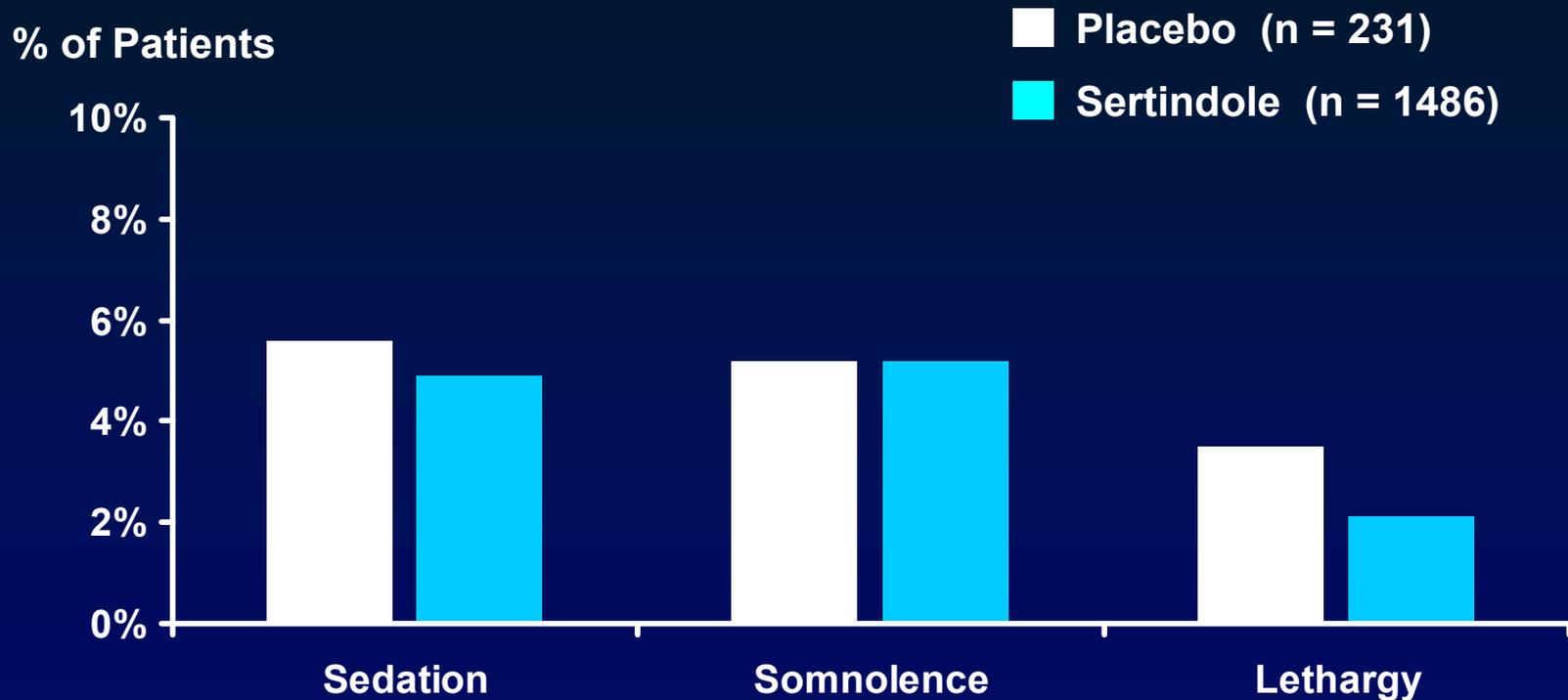
Landmark Study M93-113

Low Incidence of EPS-related Adverse Events with Sertindole



Active-controlled studies – MedDRA SMQ for extrapyramidal syndrome

Placebo-level Sedation with Sertindole



Adverse events reported – active-controlled studies

Moderate Weight Gain with Sertindole

	Sertindole n = 704	Placebo n = 290
Number of patients	584	231
Mean baseline \pm SD (kg)	80.3 \pm 16.7	79.8 \pm 16.8
Mean change \pm SD (kg)	2.9 \pm 4.3	0.2 \pm 3.9
Increase \geq7% (n%)	138 (24%)	22 (10%)

Mean change from baseline (LOCF)

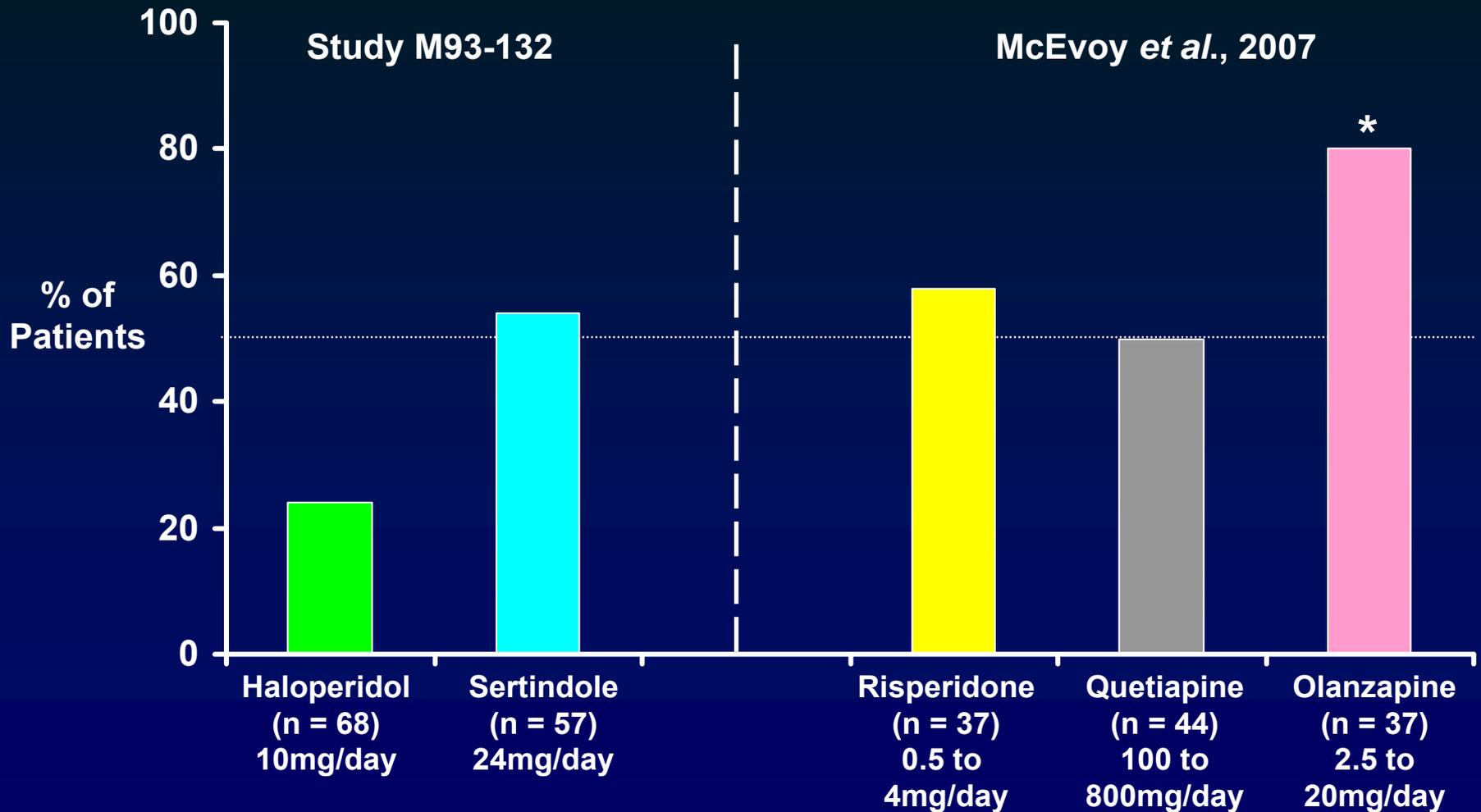
Data from short-term placebo-controlled studies: M91-645, M92-762, M92-817, M93-098, and M93-113

SD: standard deviation

Moderate Mean Changes in Weight, BMI and Waist Circumference – Up to 12 Months

Variable	Time point	Sertindole n = 107	Risperidone n = 116
Weight (kg)	Baseline	71.7	73.4
	Δ Last assessment	1.8	1.7
BMI (kg/m²)	Baseline	24.7	25.6
	Δ Last assessment	0.6	0.6
Waist (cm)	Baseline	84.8	85.8
	Δ Last assessment	1.4	1.6

Weight Increase $\geq 7\%$ after 12 Months Comparable to Risperidone



* p-value <0.05 vs quetiapine or risperidone

Small Mean Changes in Blood Lipids and Glucose – Up to 12 Months

Variable (mmol/L)	Time point	Sertindole ^a	Risperidone ^b
Triglycerides	Baseline	1.25	1.52
	Δ Last assessment	0.03	-0.04
Total cholesterol	Baseline	4.8	5.0
	Δ Last assessment	0.05	-0.09
HDL	Baseline	1.28	1.26
	Δ Last assessment	0.06	0.02
LDL	Baseline	3.0	3.1
	Δ Last assessment	-0.03	-0.10
Plasma glucose	Baseline	5.2	5.4
	Δ Last assessment	0.12	-0.04

^a n = 89, except for plasma glucose where n = 85

^b n = 100 to 103 depending on the variable

Sertindole is Well Tolerated

- Placebo-level
 - sedation
 - EPS, including akathisia
- Moderate weight gain
- No clinically relevant changes in other metabolic parameters

Overall Safety Conclusion

- Sertindole prolongs the QT interval
 - mean increase 23 msec at 20 mg/day
- Very few cases of arrhythmia
 - all confounded by medical history or concomitant treatment
- The overdose experience supports a low risk of cardiac events
- All-cause mortality similar to other antipsychotics
 - similar mortality for sertindole and risperidone in a large simple trial
- Sertindole is well tolerated

Concluding Remarks and Benefit / Risk Assessment

Anders Gersel Pedersen, MD, dr. med. sci.
Senior Medical Officer
Head of Drug Development
H. Lundbeck A/S

Sertindole is Effective and Offers Unique Benefits

- Efficacy is well established
- Clinical trials document placebo-level sedation and EPS
- Reduction of suicide attempts consistently demonstrated in
 - clinical trials
 - epidemiological studies
 - SCoP study
- 25% to 40% reduction of suicide attempts both in general and in high-risk populations

Benefit of Reduction in Suicide Attempts for Sertindole Comparable to Clozapine

Study	Suicide attempts			Suicide			Overall mortality		
	n	Hazard ratio	p-value	n	Hazard ratio	p-value	n	Hazard ratio	p-value
InterSePT^a CLZ / OLZ n = 956	34/55	~0.62	0.03	5/3	~1.7	0.73	12/8	~1.5	0.50
SCoP^b SER / RIS n = 9,809	32/51	0.61	0.03	8/17	0.50	0.10	34/40	0.91	1.43

^aMeltzer *et al.*, 2003

^bC-CASA ORT +1, 2 years

Risk has been Extensively Investigated

- Sertindole prolongs the QT interval
- Clinical and epidemiological studies and analysis of overdose experience show a low risk of cardiac events
- All-cause mortality is similar to other antipsychotics
 - no difference in all-cause mortality between sertindole and risperidone in a large naturalistic safety study (SCoP)
 - findings supported re-introduction in the European Union
- As a precaution, risk management program will be developed with FDA

Proposed Risk Management Plan for Sertindole

- Reduce risk by ensuring appropriate patient selection and use
- Prominent black-box warning in labeling regarding cardiovascular risk
- Extensive education for prescribers, pharmacists and patients / caregivers
- Active safety surveillance with regular re-evaluation and improvements

Positive Benefit / Risk Profile

- Effective antipsychotic agent with a favorable clinical profile
- Reduction in suicide attempts is a substantial public health benefit
 - 50% of people with schizophrenia attempt suicide
- Arrhythmic events are rare and do not translate into increased all-cause mortality
- Positive benefit / risk profile can be further enhanced by risk management program

Serdolect[®] (Sertindole) Tablets for Treatment of Schizophrenia

United States Food and Drug
Psychopharmacologic Drugs Advisory Committee
April 7, 2009