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Briefing Document for NDA 20-644 Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting

Product: Serdolect®

Generic name:	Sertindole
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Table of Contents

List of Panels **5**

List of Abbreviations and Definitions of Terms **8**

Executive Summary **10**

1 Introduction **15**
1.1 Proposed Indications in NDA 20-644 for Sertindole 15
1.2 Schizophrenia and Unmet Medical Need 16
1.2.1 Clinical Features and Epidemiology 16
1.2.2 Mortality in Schizophrenia 17
1.2.3 Current Treatment of Schizophrenia 17
1.3 Regulatory History 19
1.4 Nonclinical Pharmacology, Clinical Pharmacology, and Pharmacokinetics 20
1.4.1 Compound Characteristics 20
1.4.2 Neuropharmacology – Animal and Human Characterisation 21
1.4.3 Pharmacokinetics 24
1.4.4 Metabolism 24
1.4.5 Activity of Metabolites 25
1.4.6 Drugs Affecting the Pharmacokinetics of Sertindole 25
1.4.7 Sertindole Effects on the Pharmacokinetics of Other Drugs 26
1.4.8 Sertindole Pharmacokinetics in Special Populations 26

2 Clinical Development Programme, Post-marketing Studies, and the SCoP Study .. 27
2.1 Clinical Studies 27
2.1.1 Overview 27
2.1.2 Key Patient Selection Criteria 29
2.1.3 Diagnosis 29
2.1.4 Efficacy Assessments 30
2.1.5 Demographics and Other Baseline Characteristics 30
2.1.6 Exposure and Patient Disposition 33
2.2 Post-marketing Studies 35
2.3 The SCoP Study – Study 99824 37
2.3.1 Overview 37
2.3.2 Rationale and Objective 37
2.3.3 Study Design and Methodology 38
2.3.4 Study Conduct and Periods 38
2.3.4.1 Main SCoP Study 38
2.3.4.2 The Metabolic Sub-study 39
2.3.5 Study Populations 40
2.3.5.1 Demographic Characteristics – The Main SCoP Study 40
2.3.5.2 Extent of Exposure – The Main SCoP Study 43
2.3.5.3 Demographic Characteristics and Extent of Exposure – The SCoP Metabolic Sub-study 44

3 Clinical Efficacy **46**
3.1 Overview of Key Efficacy Results 46
3.2 Short-term Efficacy 48

3.2.1 Adequate and Well-controlled Studies 48
3.2.1.1 Study M93-113 – The Landmark Study 48
3.2.1.2 Study M93-098 – The Second US Study 49
3.2.1.3 Study M92-762 50
3.2.2 Study M95-342 – The European Study 51
3.2.3 Study 97203 – The French Study 52
3.3 Long-term Efficacy 53
3.3.1 Study M93-132 – 1-year Haloperidol-referenced Study 53
3.3.2 Other Long-term Studies 57
3.4 Responder Rates and Time to Response 58
3.5 Effective Dose Range 60
3.6 Other Efficacy Measures – The Niche Study 61
3.7 Efficacy Conclusions 63

4 Effect on Suicide and Suicide Attempts 64
4.1 Suicide in Schizophrenia 64
4.2 Clinical Studies 64
4.3 Epidemiological Studies 65
4.4 The SCoP Study 65
4.4.1 Methodology Specific to Case Collection and Analyses of Effects on Suicide Attempts 65
4.4.2 Demographics for Patients with Suicide Attempts 67
4.4.3 Characteristics of Suicide Attempts 68
4.4.4 Suicide Attempt Rates According to C-CASA, MedDRA, and ISC 69
4.4.4.1 C-CASA of Suicide Events 69
4.4.4.2 MedDRA Classification of Suicide Events 72
4.4.4.3 ISC Classification of Suicidality 73
4.5 Discussion of and Conclusion on the Effect of Sertindole in Reducing the Risk of Suicide and Suicide Attempts 74

5 Safety and Tolerability 77
5.1 Most Common Adverse Events 77
5.2 Withdrawals Due to Adverse Events 77
5.3 Extrapyramidal Symptoms 78
5.3.1 EPS in the Landmark Study (Study M93-113) 78
5.3.2 EPS in the European Study (Study M95-342) and the French Study (Study 97203) 80
5.3.3 EPS-related Adverse Events in the Active-controlled Studies 80
5.4 Sedation 81
5.5 Conclusion on Tolerability and Movement Disorders 81
5.6 Laboratory Assessments 82
5.6.1 Liver Function Tests 82
5.6.2 Prolactin 83
5.7 Metabolic Parameters 84
5.7.1 Introduction 84
5.7.2 Weight, BMI, and Waist Circumference 85
5.7.3 Fasting Serum Lipids 87
5.7.4 Fasting Plasma Glucose 89
5.7.5 Blood Pressure 90
5.7.6 Metabolic Syndrome 91
5.7.7 Conclusion on Metabolic Parameters 91

5.8 Sertindole's Effect on the QT Interval 92
5.8.1 Cardiac Action Potential and Ion Channels 92
5.8.2 Nonclinical Data 92
5.8.2.1 Sertindole's Effect on the Cardiac Action Potential 93
5.8.2.2 Link between QT Prolongation and Arrhythmia 94
5.8.2.3 Early After Depolarisations or Triggered Activity 94
5.8.2.4 Transmural Dispersion 95
5.8.2.5 *In Vivo* Arrhythmia Models 96
5.8.2.6 Conclusions on Nonclinical Data 96
5.8.3 Clinical Study Data 97
5.8.3.1 ECG Reading in the Clinical Studies 97
5.8.3.2 QT Interval Results 97
5.8.3.3 Pharmacokinetic Profile and QT Interval Prolongation 99
5.8.3.4 QT_{cF} Prolongation and Poor Metabolisers of Sertindole 101
5.8.3.5 Conclusions on the Clinical ECG Data 103
5.9 Mortality 103
5.9.1 The Global Safety Database 103
5.9.2 All-cause Mortality in the Core Clinical Studies 104
5.9.3 All-cause Mortality in the Epidemiological Studies 105
5.9.4 All-cause Mortality in the SCoP Study 106
5.9.5 All-cause mortality in Post-marketing Experience 107
5.9.6 For-cause Mortality 107
5.9.6.1 Introduction 107
5.9.6.2 MedDRA Coding of Fatal Cases 108
5.9.6.3 Medical Review of Fatal Cases 109
5.9.6.4 Sudden Cardiac Death 112
5.9.7 Mortality Conclusions 113
5.10 Torsade de Pointes 114
5.11 Overdoses 115

6 Risk Minimisation Action Plan (Risk MAP) 120
6.1 Rationale 120
6.2 Patient Selection 120
6.3 ECG Recommendations 120
6.4 Education 121
6.5 Safety Surveillance Programme 123
6.6 Outlook 123

7 Conclusion 124

References 126

List of Panels

Panel 1 Sertindole Chemical Structure 21
Panel 2 Sertindole – Unique Limbic Selectivity in VTA / SNC Model After Repeated Administration to Rats for 3 Weeks 22
Panel 3 Limbic Selectivity – Ratio of SNC *Versus* VTA Inhibitory Potency for Sertindole and Other Antipsychotics 23
Panel 4 Dopamine D_2 and 5-HT_{2A} Receptor Binding Affinity – *In Vitro* and *In Vivo* Potency 23
Panel 5 Overview of Randomised, Double-blind, Controlled Clinical Studies in Patients with Schizophrenia 28
Panel 6 Overview of Open-label, Uncontrolled Clinical Studies in Patients with Schizophrenia. 29
Panel 7 Core Clinical Studies – Demographic Characteristics 31
Panel 8 Core Clinical Studies – Psychiatric History 33
Panel 9 Core Clinical Studies – Duration of Exposure 34
Panel 10 Core Clinical Studies – Patient Disposition 35
Panel 11 Active-controlled Studies – Patient Disposition 35
Panel 12 Overview of the Epidemiological Studies 36
Panel 13 Overview of the SCoP Study 37
Panel 14 The SCoP Study Design 39
Panel 15 The SCoP Study – Patient Flow 41
Panel 16 The SCoP Study – Patient Characteristics 42
Panel 17 The SCoP Study – Reason for Add-on Antipsychotic Therapy 43
Panel 18 The SCoP Study – Distribution of Dose at Weeks 12, 24, and 48 44
Panel 19 Studies M92-762, M95-342, M93-113, and M93-098 – Treatment Effect at Endpoint with 95% CI (ANOVA, LOCF, ITT) 47
Panel 20 Study M93-113 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF) 49
Panel 21 Study M93-098 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF) 50
Panel 22 Study M92-762 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF) 51
Panel 23 Study M95-342 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF) 52
Panel 24 Study 97203 – PANSS Scores at Endpoint (ANCOVA, ITT, LOCF) 53
Panel 25 Study M93-132 – Retention Rates During Maintenance Treatment (ITT) 55
Panel 26 Study M93-132 – Efficacy Variables (ANCOVA, ITT, LOCF) 56
Panel 27 Study M94-222 – CGI-S Score by Month (OC) 57
Panel 28 Study M95-339 – Change from Baseline in PANSS Scores (OC) 58
Panel 29 Study M93-113 – Responder Rates 59
Panel 30 Study M93-113 – Time to Sustained Response (≥30% Decrease from Baseline in PANSS Total Score for Each Patient) 60
Panel 31 The Niche Study – Study Design 62
Panel 32 The Niche Study – Quality of Life and Global Functioning 63
Panel 33 Suicide Rates in the Sertindole Clinical Studies and the Summary Basis of Approvals for Olanzapine and Risperidone 65
Panel 34 Suicide Rates in the ESES Study, the Sertindole Safety Survey, and the ESES Crossover Sub-study 65
Panel 35 The SCoP Study – Demographic Characteristics for Patients with Suicide Attempts (Fatal or Non-fatal) according to C-CASA (ORT+1 day Period) 68
Panel 36 The SCoP Study – Characteristics of Suicide Attempts (C-CASA ORT+1 day Period) . 68
Panel 37 Kappa Values 69

Panel 38 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to C-CASA (ORT+1 day Period) ... 70
Panel 39 The SCoP Study – Kaplan-Meier Plot of Suicide Attempts (Fatal and Non-fatal) (C-CASA, ORT+1 day Period) ... 71
Panel 40 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to MedDRA ... 72
Panel 41 The SCoP Study – Kaplan-Meier Plot of Suicide Attempts (Fatal and Non-fatal) (MedDRA, WRT+30 days Period) ... 73
Panel 42 The SCoP Study – Suicidality Rates as Classified by the ISC ... 74
Panel 43 The SCoP Study – Estimated Hazard Ratios for Suicide Attempts (Fatal plus Non-fatal) ... 75
Panel 44 Suicide and Suicide Attempts in the InterSePT Study ... 76
Panel 45 Suicide and Suicide Attempts in the SCoP Study – High-risk Patients (C-CASA, ORT+1 day Period, 2-year) ... 76
Panel 46 Placebo-controlled Studies – Adverse Events With an Incidence of 10% or More in the Sertindole Group ... 77
Panel 47 Placebo-controlled Studies – Incidence of Withdrawal Due to Adverse Events ... 78
Panel 48 Study M93-113 – Mean Changes from Baseline to Last Assessment in Movement Rating Scale Scores (ANOVA) ... 79
Panel 49 Study M93-113 – Incidence of EPS-related Adverse Events ... 80
Panel 50 Study M95-342 – Change from Baseline to Last Assessment in Movement Rating Scale Scores (ANOVA) ... 80
Panel 51 Active-controlled Studies – Incidence of EPS-related Adverse Events ... 81
Panel 52 Active-controlled Studies – Incidence of Sedation, Lethargy, and Somnolence ... 81
Panel 53 Placebo-controlled Studies – Patients With Liver Function Test Outlier Values at Last Assessment ... 83
Panel 54 Long-term Studies M92-795 and M93-061 – Mean Plasma Prolactin Concentration Up to 1 Year ... 84
Panel 55 SCoP Metabolic Sub-study – Mean Changes from Baseline in Weight, BMI, and Waist Circumference (ORT Period) ... 86
Panel 56 Short-term Placebo-Controlled Studies – Mean Changes in Weight from Baseline to Last Assessment ... 87
Panel 57 SCoP Metabolic Sub-study – Mean Changes from Baseline in Fasting Serum Lipids (ORT Period) ... 88
Panel 58 Short-term, Fixed-Dose, Placebo-Controlled Studies – Patients With Fasting Serum Lipid Outlier Values ... 89
Panel 59 SCoP Metabolic Sub-study – Mean Changes from Baseline in Fasting Plasma Glucose (ORT Period) ... 89
Panel 60 Short-term, Fixed-Dose, Placebo-Controlled Studies – Patients with Fasting Blood Glucose Outlier Values ... 90
Panel 61 The SCoP Study - Shifts in Metabolic Syndrome Status from Baseline to Last Assessment (ORT Period) ... 91
Panel 62 Concentration-response Curve for Sertindole Showing Inhibition of I_{Kr} and Late I_{Na} with IC_{50} of 12 and 51nM, Respectively ... 93
Panel 63 Effects of Astemizole and Sertindole on the Rabbit Cardiac Purkinje Fibre – Isolated Perfused Heart Model ... 94
Panel 64 Effect of Sertindole and dl-sotalol on Transmural Dispersion in an Isolated Perfused Rabbit Heart ... 95
Panel 65 Mean QT_{cF} Change from Baseline to Last Assessment ... 97
Panel 66 QT_{cF} Change from Baseline to Last Assessment by Category ... 98

Panel 67 Patients with On-drug QT_{cF} >500msec 98
Panel 68 Short-term Fixed-dose Studies – Mean Change in the QT_{cB} Interval by Dose (Original Overread) 99
Panel 69 QT_{cF} *versus* Sertindole Plasma Concentrations (Original Overread) 100
Panel 70 QT_{cF} *versus* Sertindole Plasma Concentrations in Poor and Extensive Metabolisers of Sertindole (Original Overread) 102
Panel 71 Global Safety Database – Sources, Number of Patients, and Exposure 103
Panel 72 Global Safety Database – Number of Deaths by Source 104
Panel 73 Clinical Studies – Mortality Rates 105
Panel 74 The ESES Study, the Sertindole Safety Survey, and the ESES Crossover Sub-study – All-cause Mortality Rates 106
Panel 75 The SCoP Study – Mortality Rates 106
Panel 76 Global Safety Database – Number of Deaths by MedDRA SOCs 108
Panel 77 The SCoP Study – Number of Deaths by MedDRA SOCs 109
Panel 78 Global Safety Database – Review of Fatal Cases 110
Panel 79 Fatal Case of Documented TdP 111
Panel 80 Fatal Case of Documented Arrhythmia 111
Panel 81 The SCoP Study – Classification of Sudden Cardiac Death (Criteria as Published by Ray *et al.*) 112
Panel 82 Number and Rate of Sudden Deaths in the SCoP Study and as Published by Ray *et al.* 113
Panel 83 Non-fatal Cases Reported as TdP 114
Panel 84 Global Safety Database – Overview of Overdoses 115
Panel 85 Global Safety Database – The 5 Cases With the Highest Overdose of Sertindole 116
Panel 86 Global Safety Database – Number of Deaths Associated With Overdose 116
Panel 87 Fatal Overdose With Sertindole Only – Not Associated With Cardiac Arrest or Arrhythmia 117
Panel 88 Global Safety Database – Overdoses Associated With Cardiac Arrest or Arrhythmia .. 118
Panel 89 RiskMAP – Education of Stakeholders 121

List of Abbreviations and Definitions of Terms

5-HT_2	5-hydroxytryptamine 2 receptors
ADROIT	Adverse Drug Reaction On-line Information Tracking
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotranferease
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APD	action potential duration
AST	aspartate aminotransferase
BAS	Barnes Akathisia Scale
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CAVB	chronic AV-ablation
C-CASA	the Columbia Classification Algorithm of Suicide Assessment
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	confidence interval
CME	continued medical education
DA	dopamine
DHS/S	dehydro-sertindole/sertindole concentration
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSRU	Drug Safety Research Unit
EAD	early after depolarisation
ECG	electrocardiogram
EPOS	the European Post-marketing Observational Serdolect study
EPS	extrapyramidal symptoms
ESES	Sertindole European Safety and Exposure Survey
FDA	Food and Drug Administration, United States
GAF	Global Assessment of Functioning Scale
HDL	high density lipoprotein
hERG	human ether-a-go-go gene
IDF	International Diabetes Federation
I_{KR}	rapid inward rectifying potassium channel
I_{Na}	inward rectifying sodium channel
IMC	Independent Management Committee

IND	investigational new drug
InterSePT	International Suicide Prevention Trial
ISC	Independent Safety Committee
ITT	intention to treat
LDL	low density lipoprotein
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NCEP-ATP III	National Cholesterol Education Program: Adult Treatment Panel III
NDA	New Drug Application
OC	observed cases
ORT	only randomised treatment period
PANSS	Positive and Negative Syndrome Scale
PCP	phencyclidine
PEM	Prescription Event Monitoring
PET	positron emission tomography
PK	pharmacokinetics
PYE	patient years of exposure
QT_c	QT interval on electrocardiogram reading, corrected for heart rate
QT_{cB}	QT interval on the ECG corrected by the square root of the heart rate (Bazett's correction)
QT_{cF}	QT interval on the ECG corrected by the cube root of the heart rate (Fridericia's correction)
RiskMAP	risk minimisation action plan
SANS	Scale for the Assessment of Negative Symptoms
SAS	Simpson-Angus Scale
SCoP	Sertindole Cohort Prospective (study)
SD	standard deviation
SMQ	Standard MedDRA Query
SNC	substantia nigra pars compacta
SOC	system organ class
SPC	Summary of Product Characteristics
TdP	Torsade de Pointes
VTA	ventral tegmental area
WFP	whole follow-up period
WRT	whole randomised treatment period

Executive Summary

The safety and efficacy of sertindole have been studied extensively and the studies demonstrate that:

- Sertindole is efficacious in the short-term as well as the long-term treatment of patients with schizophrenia.
- Sertindole reduces the risk of suicide and suicide attempt in patients with schizophrenia, including those at high risk of suicide.
- Sertindole is well tolerated and non-sedating, and has a placebo-level incidence of EPS.
- Sertindole's effect on the QT interval is well characterised, nonclinically and clinically, and the risk of arrhythmia is low.
- The outcome of the SCoP study, a large, simple, randomised, mortality study, confirmed that the QT prolongation observed with sertindole does not translate into a higher all-cause mortality risk in patients with schizophrenia than with standard treatment (risperidone).

Introduction

Sertindole is an efficacious, non-sedating antipsychotic for the treatment of patients suffering from schizophrenia. Sertindole has high limbic selectivity, resulting in a low propensity for extrapyramidal symptoms (EPS), and is devoid of anticholinergic and H_1 antihistamine activity.

FDA issued two approvable letters for the sertindole NDA in 1996 and 1997, but the NDA was withdrawn early in 1998. Outside the United States, sertindole was launched in most European countries from 1996 to 1998. Due to a signal of a potentially increased risk of death and cardiac death, sertindole was withdrawn from the market in 1998.

Since then, H. Lundbeck A/S has addressed the safety concerns and sertindole was re-launched in Europe in 2006. As of January 2009, sertindole was approved in 46 countries in Europe, Asia, and Latin America.

Schizophrenia is a chronic and severely debilitating disease, with symptoms leading to significant social impairment and a high rate of unemployment. Patients with schizophrenia have a two- to three-fold increase in mortality compared with the general population. Suicide is a major contributor to the mortality of patients with schizophrenia and it is the leading cause of premature death. Even a small reduction in the suicide risk will translate into a meaningful improvement in the outcome for patients with schizophrenia.

Pharmacotherapy remains the cornerstone of the management of schizophrenia, and it is therefore essential that there is a sufficient repertoire of treatment choices to increase the likelihood that a patient will receive a well-tolerated and effective treatment.

Efficacy

In short-term, double-blind, fixed-dose, placebo- and active-controlled studies, sertindole was superior to placebo in treating the positive and negative symptoms associated with acute exacerbation of schizophrenia. Responder rates and time to response with sertindole were comparable to those with haloperidol.

In a one-year, double-blind, haloperidol-controlled maintenance study, both sertindole and haloperidol showed comparable reductions in the symptoms of schizophrenia, but haloperidol-treated patients had a significantly earlier time-to-treatment failure due to hospitalisation for psychotic decompensation.

Effect on Fatal and Non-fatal Suicide and Suicide Attempts

Overall, approximately 50% of patients with schizophrenia attempt suicide during their lifetime and up to 10% die from suicide. Suicide attempt is a significant risk factor for suicide and a major reason for medical intervention and hospitalisation.

The reduction in the risk of suicides in patients with schizophrenia has been recognised by the FDA as an indication.

The suicide rate was low in the clinical studies with sertindole relative to those of two other second generation antipsychotics, risperidone and olanzapine, at the time of their respective approvals in the US. The apparently low suicide rate with sertindole was strengthened by the data from the subsequent epidemiological studies.

Therefore, in agreement with the FDA, the effect of sertindole treatment on suicide and suicide attempts was included as an endpoint in the large, simple, randomised trial of sertindole (the SCoP study) to prospectively assess the benefit of sertindole in preventing suicide attempts (fatal plus non-fatal) under normal clinical conditions of use. The endpoint of fatal plus non-fatal suicide attempts is well documented with evidence of intended self-harm, and meaningful, as even non-fatal suicide attempts still carry a significant risk of serious injury and death.

The SCoP study confirmed that patients during monotherapy with sertindole had a significantly lower risk of fatal plus non-fatal suicide attempts (hazard ratio of 0.617, p=0.0307) than patients during monotherapy with risperidone, showing a reduction of nearly 40% in the sertindole group compared to the risperidone group. This effect of sertindole was even stronger during the first year of treatment during which period the vast majority of events occurred (hazard ratio of 0.503, p=0.0058).

These results were confirmed in an analysis requested by the FDA, based on a blinded reclassification of events by experts at Columbia University according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA), which showed a hazard ratio of suicide attempts (fatal plus non-fatal) of 0.661 (p=0.0594). Again, the effect of sertindole was stronger during the first year of treatment (hazard ratio of 0.546 (p=0.0147). A similar beneficial hazard ratio (0.502, p=0.0890) was seen for the rate of completed suicide.

For patients at high risk of attempting suicide, that is, patients with a history of suicide attempts within the last 5 years before entering the SCoP study, there was a clear trend for a reduction in the risk of fatal plus non-fatal suicide attempts at one year (hazard ratio 0.567, p=0.1126).

The strength of the evidence from the analyses of this endpoint lies in both the beneficial hazard ratios observed and in the consistency of these observations in relevant subgroups and periods, which, in spite of the reduced number of events in some of these smaller samples, point in the same direction, supporting a systematic effect of sertindole.

Sertindole's ability to reduce the risk of fatal plus non-fatal suicide attempts is an important benefit in the treatment of patients with schizophrenia in general and in particular in patients with a history of suicide attempts.

Safety

Sertindole is well tolerated in short- and long-term treatment. The adverse events reported with sertindole are generally mild and manageable.

Sedation is a common adverse effect of many antipsychotics. For a disorder such as schizophrenia, which often requires chronic treatment, it is important for the patient's daily functioning that the treatment does not cause sedation. Sertindole does not sedate.

Another important aspect of the sertindole tolerability profile is that it has placebo-level EPS and akathisia, as measured using movement rating scales and adverse event reporting.

In the recent SCoP Metabolic Sub-study, patients in the sertindole group gained approximately 2.2kg over 36 weeks, which was similar to the weight gain seen in the risperidone group (2.0kg). There were no clinically relevant changes of other components of the metabolic syndrome.

Arrhythmia and Effect on the QT Interval

Sertindole prolongs the QT interval in different animal species both *in vivo* and *in vitro*. The underlying mechanism is an inhibition of the outward potassium current, I_{Kr}, and simultaneous inhibition of the late inward sodium current, I_{Na}. Thus, sertindole is a mixed ion-channel blocker with a balanced blockade of inward and outward currents. The effect on the I_{Na} mitigates the risk of arrhythmia.

In two short-term, double-blind, placebo-controlled studies, patients treated with 20mg sertindole once daily had a mean change from baseline in the QT_{cF} interval of 23msec. At that dose, an increase in QT_{cF} from normal at baseline to more than 500msec was noted in 1.4% of the patients. While QT prolongation is generally seen with the use of antipsychotics and is associated with a risk of arrhythmia, several other factors influence the extent of this risk for each compound. Therefore, the extent of QT interval prolongation alone does not predict the level of arrhythmia risk.

In the Global Safety Database for sertindole, which comprises more than 40,000 patient years, there are four reports of Torsade de Pointes during treatment with sertindole. All of these cases were in patients who had other risk factors for arrhythmia. The analysis of sudden cardiac death during treatment with sertindole and a comparison to the rates reported in the most recent literature do not indicate an increased risk for sertindole compared to other antipsychotics.

All-cause Mortality in the SCoP Study

The SCoP study was designed to determine whether the known QT interval prolongation with sertindole treatment translates into an increased all-cause mortality risk by comparing sertindole treatment to risperidone treatment in a prospective study. The primary aim of the study was to provide a reliable, real-world estimate of the mortality during treatment with sertindole compared to that during treatment with risperidone.

With nearly 10,000 patients and approximately 15,000 patient years of exposure, the SCoP study showed that the all-cause mortality with sertindole was comparable to that with risperidone. During randomised treatment only (sertindole or risperidone), the all-cause mortality rate for sertindole was 0.63 deaths per 100 patient years and not different from that for risperidone (hazard ratio of 0.980 with an upper confidence limit of 1.405). The estimated all-cause mortality ratio of sertindole to risperidone for the entire treatment period (with or without add-on antipsychotic treatment) including a 30-day safety follow-up period was 1.117 with an upper confidence limit of 1.500. Thus, the QT interval prolongation does not translate into an increase in all-cause mortality during sertindole treatment.

The outcome of the SCoP study confirmed that although a higher cardiovascular event rate is seen for patients treated with sertindole, the event rate related to arrhythmia remains very low.

The SCoP study addresses the 1997 FDA request for post-marketing surveillance data to demonstrate the safety of sertindole. Together, the SCoP study, the epidemiological studies, and the nonclinical research adequately demonstrate that although the QT interval prolongation seen during treatment with sertindole may be associated with a very small risk of arrhythmia, it does not translate into excess all-cause mortality.

RiskMAP

There are a number of contraindications, warnings, and precautionary instructions in the proposed product label that will allow the physician to judge whether sertindole is the appropriate treatment for a particular patient. Patients with an increased risk of QT interval prolongation are excluded from sertindole treatment.

A Risk Minimization Action Plan has been designed to educate the patient and all those involved in the patient's care on the appropriate use of sertindole. The programme will be monitored via passive and active safety surveillance and re-evaluated annually.

Overall Conclusion

Sertindole is an effective antipsychotic compound with a unique profile. The potential cardiac risks associated with sertindole are well characterised and can be managed. Furthermore, sertindole has a beneficial effect on reducing the risk of fatal and non-fatal suicide attempts. With this positive benefit-risk profile, sertindole offers an effective treatment modality for the treatment of schizophrenia and for reducing the risk of fatal and non-fatal suicide attempts in patients with schizophrenia.

1 Introduction

This document summarises the nonclinical and clinical data for the use of sertindole in the treatment of schizophrenia and for reducing the risk of fatal and non-fatal suicide attempts in patients with schizophrenia.

There is an unmet medical need for the treatment of schizophrenia, a chronic and severely debilitating disease. Schizophrenia is associated with increased mortality, and suicide is one of the main causes of death for patients with schizophrenia. Even a small reduction in the suicide risk will translate into a meaningful improvement in the outcome for patients with schizophrenia.

Sertindole's effect on the QT interval was identified early in the development programme. It is well characterised, nonclinically and clinically. An overview of the extensive nonclinical investigations into the mechanisms underlying the QT interval prolongation is included along with the clinical results.

For the clinical data, the main focus is on the data from the SCoP study, a large, prospective, randomised, open-label, active-controlled study comparing the safety of sertindole to that of risperidone in accordance with routine clinical practice and the country-specific package insert for both drugs (normal conditions of use). The study was designed to determine whether the known QT interval prolongation with sertindole treatment translates into an increased mortality risk by comparing sertindole treatment to risperidone treatment in a prospective study. In addition, the effect of sertindole treatment on fatal and non-fatal suicide attempts was included as an endpoint in the study, to prospectively assess the benefit of sertindole in reducing the risk of fatal and non-fatal suicide attempts under normal clinical conditions of use.

An overview is given of the proposed Risk Minimisation Action Plan (RiskMAP): The plan includes:

- identification and exclusion of patients with an increased risk of QT interval prolongation
- education of physicians, pharmacists, patients, and caregivers about on how to properly use sertindole
- an active safety surveillance programme using the monitoring of drug utilisation and outcome databases

1.1 Proposed Indications in NDA 20-644 for Sertindole

H. Lundbeck A/S is seeking approval for sertindole for the treatment of schizophrenia and for reducing the risk of fatal and non-fatal suicide attempts in patients with schizophrenia.

1.2 Schizophrenia and Unmet Medical Need

1.2.1 Clinical Features and Epidemiology

Schizophrenia is a serious, potentially fatal, debilitating, and often chronic mental disorder.

Schizophrenia is characterised by positive symptoms (for example, delusions, hallucinations) and negative symptoms (for example, blunted affect, social withdrawal, anhedonia). Patients often have cognitive symptoms (for example, disorganisation of thoughts, difficulty concentrating, impairments in memory, difficulty completing tasks) and depressive symptoms that have been associated with increased risks of psychotic relapse, suicide attempts, and completed suicides.[1] The lifetime prevalence of schizophrenia is estimated to be 0.4%.[2]

Schizophrenia most often begins in late adolescence or early adulthood and may be characterised by a lifelong course of worsening or recurrence of symptoms (relapse) and periods of symptom stability; fewer than 20% of patients with schizophrenia achieve remission of symptoms to their pre-morbid states.[3] Long term antipsychotic treatment is important for stabilisation of the patient. However, many patients discontinue drug treatment either due to insufficient efficacy with only partial symptom relief or due to side effects, and switching between compounds is frequent. Maintaining patients on treatment is one of the most important factors to reduce the risk of relapses. Patients who remain on long-term maintenance therapy with antipsychotics have 50% to 75% fewer relapses and the relapses are less severe than in patients who discontinue therapy.[4,5] Conversely, approximately 50% of patients who discontinue antipsychotic treatment have a psychotic relapse within 1 year and up to 90% of patients have relapses within 2 years of discontinuing medication.[4,6] Relapses frequently require inpatient hospitalisation and may result in increased cognitive impairments and an increase in the likelihood that the patient will become refractory to treatment.[5,7]

Schizophrenia is severely debilitating, with symptoms leading to substantial social impairment and a high rate of unemployment. Consequently, people with schizophrenia often depend on their family or social services for financial support. Others live in isolation without stable relationships or social support and many of them are homeless. They are prone to alcohol or drug abuse and are often in contact with law enforcement; large numbers of them are incarcerated.[8]

The cost of schizophrenia for society is high. A study quantifying the excess annual costs associated with patients with schizophrenia in the United States in 2002 from a societal perspective, estimated the overall cost to be $62.7 billion, with $22.7 billion excess direct health care cost, $7.6 billion excess direct non-health care costs (law enforcement, homeless shelters, and research/training related to schizophrenia), and $32.4 billion total indirect excess costs (unemployment, reduced workplace productivity, family care giving, and premature mortality from suicide).[9] The indirect excess cost due to unemployment is the largest component of overall schizophrenia excess annual costs.

1.2.2 Mortality in Schizophrenia

Schizophrenia is associated with increased mortality and a number of large cohort studies have established that patients with schizophrenia have a mortality risk that is much higher than that in the general population. Overall, patients with schizophrenia have a two- to three-fold increase in all-cause mortality compared with the general population.[10,11,12,13] In one study, all-cause mortality among patients with schizophrenia was estimated at 28 deaths per 1000 patient years and cardiovascular deaths at 8.8 deaths per 1000 patient years.[14]

The major cause for this increased mortality is the serious co-morbidity associated with schizophrenia. Suicide represents approximately one-third of all "natural deaths" in patients with schizophrenia; 10- to 34-fold increases in men and up to a 100-fold increase in women have been reported compared to that expected in the general population.[14,15,16] Also, disproportionately more patients die from diabetic and cardiovascular events. Excess cardiovascular mortality is estimated to be 1.7 to 1.8 times that of a similar non-psychiatric population.[14,16] Excess mortality becomes apparent early in the course of the disorder, that is, during the first 2 years after diagnosis and, more specifically, even during the first 3 months.[14,16]

The reduced life expectancy of people with schizophrenia is also, in part, due to unhealthy lifestyles. They tend to have poor dietary habits, live sedentary lifestyles, and have a higher prevalence of alcohol, tobacco, and substance abuse.[17,18]

1.2.3 Current Treatment of Schizophrenia

The conventional antipsychotics mediate their therapeutic effect through potent blockade of the dopamine D2 receptors in the brain.[19] Blockade of D2 receptors in the nigrostriatal system is associated with extrapyramidal symptoms (EPS). Akathisia, rigidity, and tremor associated with the parkinsonian symptoms induced by these conventional antipsychotics cause significant discomfort and often lead to discontinuation of therapy.

Other adverse effects of conventional antipsychotics include a quinidine-like effect on cardiac conduction (prolongation of the QT interval) and they may induce an increase in negative symptoms both directly, by inducing movement disorders or exacerbating or precipitating depressive symptoms, and indirectly, through the effects of anticholinergic agents required to manage these adverse effects.[20,21]

The cognitive impairment associated with schizophrenia, particularly deficits in memory and attention, may also be worsened by conventional antipsychotics and anticholinergic drugs.[22] Nevertheless, conventional antipsychotics had a dramatic effect historically in that they were the key treatments allowing community management of schizophrenia, even despite their relative modest efficacy.

The development of clozapine provided a new alternative for the treatment of psychotic disorders. Clozapine is a relatively weak D2 antagonist, with stronger affinity for other classes of dopamine receptors (for example, D4) and serotonin 5HT2 receptors.[23] This receptor profile combined with its apparent selectivity for limbic and cortical dopamine neurons is

thought to be the basis for clozapine's atypical action.[23] This is reflected in its clinical profile as a highly effective antipsychotic with low propensity for EPS adverse effects.24 Agranulocytosis is a potentially life-threatening side effect that occurs in approximately 1% of patients treated with clozapine.[23] This severe side effect limits the use of clozapine and reserves its use for patients who are refractory to treatment or treatment-intolerant. The characteristics of clozapine compared to those of conventional antipsychotics, both in terms of efficacy and in side effect profile,[25,26] provided the impetus for the development of several atypical or second generation antipsychotics that did not induce blood dyscrasia.

The term atypical antipsychotic is defined by antipsychotic efficacy combined with low(er) propensity of inducing EPS. These drugs combine D2 antagonism with even more potent antagonism of the serotonin 5HT2A receptor. [27] The high 5-HT2A:D2 receptor binding ratio is thought to contribute efficacy in negative symptoms and to reduce the induction of EPS compared with conventional antipsychotics. [28,29,30,31] However, beyond sharing a high 5-HT2A:D2 affinity ratio, the atypical or second generation antipsychotics, which include risperidone, olanzapine, quetiapine, ziprasidone, as well as sertindole, are widely diverse drugs, with diverse receptor-binding activities, elimination pathways, and side-effect profiles. Accordingly they may possess diverse activity on negative and mood symptoms as well as on cognitive performance, [32,33] and should not be perceived as necessarily substitutable.

The second generation antipsychotics seem to be of comparable efficacy to the conventional antipsychotics for positive symptoms, but may be more effective for negative symptoms. Negative symptoms and cognitive impairment are major factors for the poor functional outcome in many patients with schizophrenia.[34,35] It has been suggested that the efficacy of second generation antipsychotics in the treatment of negative symptoms comes either from antidepressive effects or, more likely, from the lower propensity of inducing EPS than conventional antipsychotics. EPS can be associated with the so-called secondary negative symptoms, which are difficult to differentiate from primary negative symptoms.

More importantly, the second generation antipsychotics are less likely than the conventional antipsychotics to cause acute EPS. However, second generation antipsychotics appear to vary in this respect, with risperidone having an incidence of dose-related EPS close to that of haloperidol. The reduction in the adverse event burden, especially the acute adverse event burden, leads to better treatment adherence, which increases the likelihood of a beneficial outcome.

A particular concern has been expressed with disproportionate numbers of patients who develop metabolic syndrome during treatment with several second generation antipsychotics, compared with the general population. "Metabolic syndrome" includes several parameters which together lead to an increased risk for cardiovascular disease. These parameters are increased waist circumference, hypertriglyceridaemia, low HDL-cholesterol, high blood pressure, and high blood glucose. The metabolic syndrome has been linked to weight gain and insulin resistance. Though weight gain has been observed to varying degrees with most second generation antipsychotics, it appears to be a particular problem with olanzapine and clozapine.[36]

Sedation is a common adverse effect of many antipsychotic medications. When patients require chronic treatment, it is important that side effects like sedation do not prevent the patient from working and functioning effectively.

Many antipsychotics, among others ziprasidone, have been associated with prolongation of the QT interval. Despite sertindole's association with prolongation of the QT interval, no increased overall mortality has been observed in the clinical trials, in the epidemiological studies, nor in a large, simple trial of sertindole under normal conditions of use (the SCoP study).

Differences in efficacy among antipsychotics are more difficult to define than differences in pharmacologic and side effect profiles. In general, second generation antipsychotics appear to have similar efficacy profiles. None of the currently available compounds is able to completely reverse the symptoms of schizophrenia and the associated impairment in a majority of patients. In fact, individual patients respond differently to different drugs and their response to the same drug may vary over time. At present, it is not possible to predict which drug will perform best for a given patient. Therefore, several drugs may have to be tried before the optimal treatment is found and, consequently, switching between drugs is common.

In summary, many patients with schizophrenia treated with second generation antipsychotics still exhibit substantially suboptimal functioning. Unmet medical needs still exist; suicide remains one of the main causes of death for patients with schizophrenia, and has been identified as a valid target for treatment. Even a small reduction in the suicide risk will translate into a meaningful improvement in the outcome for patients with schizophrenia.

Pharmacotherapy remains the cornerstone of the management of schizophrenia, and it is therefore essential that there is a sufficient number of treatment choices to increase the likelihood that an individual patient may receive a well-tolerated and effective treatment.

1.3 Regulatory History

Sertindole was discovered and developed by H. Lundbeck A/S. As of January 2009, sertindole was approved in 46 countries, including Europe and a number of countries in Asia and Latin America. Since the original marketing authorisation of sertindole in the United Kingdom in 1996, patient exposure to sertindole is now more than 40,000 patient years.

In 1998, the safety of sertindole was referred to the European Medicines Agency (EMEA) for evaluation (an Article 36 Referral) due to an apparent signal (in the United Kingdom ADROIT database) of an increased risk of sudden or cardiac death. A link between the known QT interval prolongation with sertindole and the signal was inferred. The outcome of the referral was that the Committee for Medicinal Products for Human Use (CHMP) found the benefit:risk of sertindole favourable but recommended revisions to the labelling, including additional warnings regarding the known QT interval prolongation. Further investigations of whether the QT interval prolongation with sertindole translates into an increased mortality were also a requirement. Consequently, the Sertindole Cohort Prospective (SCoP) study was

conducted and sertindole was gradually reintroduced on the market through the initiation of the study.

The SCoP study was a large, simple trial using the restrictions in the label as entry criteria; the primary objective of the study was to compare the all-cause mortality of sertindole to that of risperidone under normal conditions of use.

In the US, Abbott Laboratories, Inc., submitted the NDA for sertindole in September 1995 for the indication "management of the manifestations of psychotic disorders" (NDA 20-644) and sertindole was discussed at an FDA Advisory Committee meeting in July 1996. The Advisory Committee voted in favour of approving sertindole.

Two approvable letters were issued to Abbott Laboratories, Inc., one in 1996 and one in 1997. During the subsequent negotiations between Abbott Laboratories, Inc., and the FDA, no agreement on labelling issues and post-marketing commitments could be reached. Abbott withdrew the NDA in January 1998. The rights of both NDA 20-644 and IND 38,373 were transferred to H. Lundbeck A/S in January 2002.

H. Lundbeck A/S has addressed the safety concerns raised by both the FDA and the European authorities. Extensive nonclinical investigations into the mechanisms underlying the QT interval prolongation have been conducted. This, in addition to the results from the SCoP study, which did not show an increase in all-cause mortality for sertindole compared with risperidone, led the CHMP to conclude that the all-cause mortality in the sertindole and risperidone groups did not differ and sertindole was re-launched in Europe in January 2006. The CHMP considers the commitment fulfilled and closure of the SCoP study was initiated in September 2007.

During the suspension of the sertindole marketing in Europe, H. Lundbeck A/S met with the FDA to present the ongoing activities. Discussions with the FDA over the potential benefit of sertindole in reducing the risk of suicide and suicide attempt resulted in H. Lundbeck A/S amending the SCoP study protocol in 2003 in order to estimate the effect of sertindole on fatal and non-fatal suicide attempts in patients with schizophrenia.

In July 2008, H. Lundbeck A/S resubmitted the sertindole NDA for the indication "treatment of schizophrenia and for reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia".

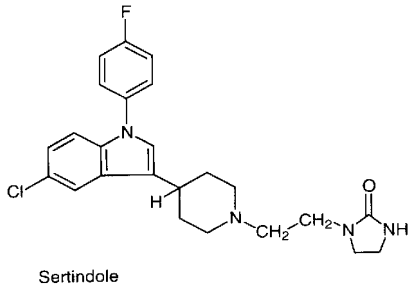
1.4 Nonclinical Pharmacology, Clinical Pharmacology, and Pharmacokinetics

1.4.1 Compound Characteristics

Sertindole is a non-sedating, second generation antipsychotic with a unique neuropharmacological profile. Sertindole is an indole derivative (Panel 1) with a high limbic selectivity.

The dosage form is coloured, film-coated tablets, which will be available in four strengths: 4mg, 12mg, 16mg, and 20mg sertindole.

Panel 1 Sertindole Chemical Structure



Sertindole

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1-H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone

1.4.2 Neuropharmacology – Animal and Human Characterisation

It has been proposed that the unique neuropharmacological profile of sertindole is derived from its selective inhibitory effect on limbic dopamine (DA) neurons and is due to balanced inhibitory effects on central DA D_2 and serotonin (5-HT_2) receptors, as well as on α_1-adrenergic receptors. The α_1-adrenoceptor antagonism of sertindole can contribute to clinical antipsychotic activity[32], but is also associated with cardiovascular (orthostatic) side effects to which, however, tolerance readily develops.

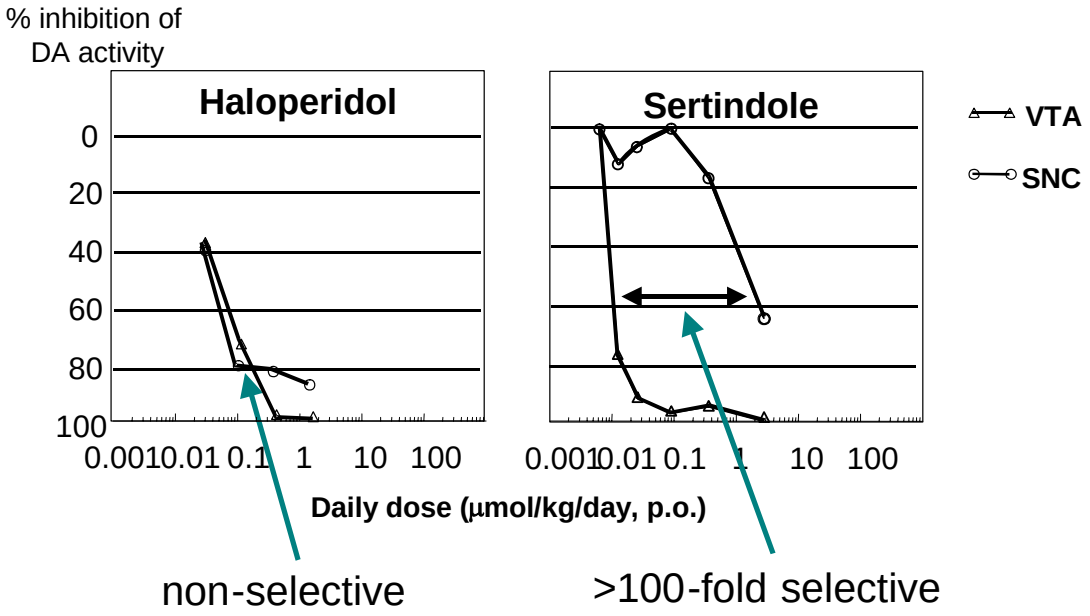
In animal studies, limbic selectivity is demonstrated after subchronic treatment with sertindole: a reduction of the number of spontaneously active DA neurons is induced in the ventral tegmental area (VTA) projecting to limbic/cortical brain regions. The selectivity ratio is more than 100 compared to inhibition of DA neurons in the substantia nigra pars compacta (SNC), projecting to the striatal motor areas (Panel 2 and Panel 3).[32]

Inhibition of SNC activity is thought to be involved in the movement side effects associated with many antipsychotic drugs. The selectivity of sertindole for VTA is consistent with its low clinical risk of EPS, its low potency to induce dystonia in non-human primates, and its lack of catalepsy-inducing effects in rats after acute dosing.[32]

Sertindole has no effect on histamine H_1 receptors, which is consistent with its lack of sedative effects related to those receptors.

Sertindole preserves cognitive function in animals, which is consistent with its weak DA D_2-blocking potency *in vivo* and absence of anticholinergic/antihistaminergic effects.[32] Furthermore, recent studies have indicated a superior pro-cognitive potential compared with other second generation antipsychotics. This was shown in an animal model of sustained cognitive impairment in the washout phase after subchronic treatment with the glutamate NMDA receptor antagonist phencyclidine (PCP). There is evidence that potent 5-HT_6 receptor antagonism and absence of anticholinergic activity is important for the unique activity of sertindole.[32,37]

Panel 2 Sertindole – Unique Limbic Selectivity in VTA / SNC Model After Repeated Administration to Rats for 3 Weeks



Arnt and Skarsfeldt, 1998[32]

The limbic selectivity of sertindole is greater than that observed with any other antipsychotic. Using the VTA / SNC model, statistically significant limbic selectivity could only be demonstrated for sertindole, clozapine, and olanzapine (Panel 3). However, the exact selectivity ratio could not be determined for the latter two drugs, since maximal tolerated doses were only slightly higher than those necessary for inhibitory activity in the limbic system, as indicated in Panel 3.

When limbic selectivity is evaluated using animal behavioural models (inhibitory activity on amphetamine-induced hyperactivity in rats versus potency to induce catalepsy in rats and dystonia in monkeys), highest selectivities were obtained for sertindole and clozapine. Intermediate selectivities were seen with quetiapine and ziprasidone, while olanzapine and risperidone showed lower selectivity, only slightly superior to the conventional antipsychotic, haloperidol.[32]

Panel 3 Limbic Selectivity – Ratio of SNC *Versus* VTA Inhibitory Potency for Sertindole and Other Antipsychotics

	Ratio ED_{50} SNC / VTA
Sertindole	110*
Clozapine	> 2.1*
Risperidone	1.5
Olanzapine	>1.0*
Quetiapine	0.76
Ziprasidone	1.0
Haloperidol	0.77

Arnt and Skarsfeldt, 1998[32]

***** $p<0.05$ Statistically significant difference between limbic and striatal activity

Sertindole and the major metabolite dehydro-sertindole have high affinities for DA D_2 and 5-HT_{2A} receptors *in vitro*, but have dominant 5-HT_{2A} antagonist effect *in vivo*. This is primarily due to a lower than expected *in vivo* DA D_2 antagonistic potency, based on predictions from relative *in vitro* affinities. This preference is larger for sertindole compared with other second generation antipsychotics (Panel 4). [32, 38, 39]

Panel 4 Dopamine D_2 and 5-HT2A Receptor Binding Affinity – *In Vitro* and *In Vivo* Potency

	SER	**DHS**	**NOR-S**	**RIS**	**CLZ**	**OLA**	**ZIP**	**QUE**
In vitro (Ki, nM)[32]								
DA D_2	0.45	0.25	2.5	0.44	36	2.1	2.8	69
5-HT_{2A}	0.20	0.29	1.9	0.39	4.0	1.9	0.25	82
Ratio D_2/5-HT_{2A}	2.3	0.86	1.3	1.1	9.0	1.1	11	0.84
In vivo[a] (ED50, mg/kg)[b]								
Pergolide antagonism (DA D_2)	1.6	1.5	>7.2	0.18	1.2	0.14	0.54	2.6
Quipazine antagonism (5-HT_{2A})	0.015	0.031	0.92	0.021	0.13	0.11	0.095	1.6
Ratio pergolide/ quipazine	107	48	>7.8	8.6	9.2	1.3	5.7	1.6

SER: sertindole; DHS: dehydro-sertindole; NOR-S: nor-sertindole; RIS: risperidone; CLZ: clozapine; OLA: olanzapine; ZIP: ziprasidone; QUE: quetiapine

a *In vivo* potencies were measured by inhibition of circling behaviour induced by the D_2 agonist pergolide in 6-hydroxy-dopamine-lesioned rats and by inhibition of head twitches induced by the 5-HT_{2A} agonist quipazine.[38,39]

b Test drug injected subcutaneously, 2 hours before test, except clozapine and quetiapine (30min).

Human positron emission tomography (PET) studies have confirmed the nonclinical pharmacology profiling.

DA D_2 occupancy in striatum was between 52% and 68% after treatment with sertindole 20mg/day for 6 to 8 weeks to patients with schizophrenia. This is in the lower range of what has been observed with other antipsychotics.[40] Striatal and extrastriatal occupancies were of similar magnitude. This confirms nonclinical work that limbic selectivity is not due to differential binding to DA receptors between brain regions, but rather to additional effects on other neurotransmitter receptors. In addition, the low maximum occupancy is consistent with the lack of EPS, which usually requires at least 80% occupancy.

In contrast, cortical 5-HT_{2A} receptor occupancy in healthy subjects was fully saturated already at the lowest recommended clinical dose of 12mg/day, given for 15 days, including dose titration, again consistent with nonclinical data.[41]

Finally, a functional imaging study investigated the effect of 8 to 12 weeks of treatment with flexible doses of sertindole (12 to 24mg/day) or haloperidol (4 to 16mg/day) on glucose metabolism in selected brain regions of patients with schizophrenic, using ^{18}F-fluoro-deoxy-glucose as the PET ligand. The effects of sertindole were clearly differentiated from those of haloperidol, substantiating the lack of motor side effects of sertindole, which were predicted by animal studies and supported by clinical studies.[42]

1.4.3 Pharmacokinetics

Sertindole is slowly absorbed (t_{max} around 10 hours) and slowly eliminated (mean terminal half-life of approximately 3 days). It has a large volume of distribution and is eliminated by oxidative metabolism. The apparent oral clearance of sertindole is approximately 40 L/h after single doses (4mg) but approximately 15 L/h at steady state (20mg/day) for most patients. Steady-state concentrations are essentially dose-proportional.

The pharmacokinetics of sertindole is not significantly different between young and elderly adults. The oral clearance of sertindole is approximately 20% lower in women than in men, but lean-mass corrected clearance is similar. No relevant race differences in pharmacokinetic studies have been identified. In population pharmacokinetic analyses it was found that the clearance of sertindole is around 20% lower in African-Americans than in Caucasians.

1.4.4 Metabolism

Sertindole is extensively metabolised by CYP2D6 and CYP3A. Two major metabolites have been identified in human plasma: dehydro-sertindole and nor-sertindole. In humans, steady-state concentrations of dehydro-sertindole and nor-sertindole are approximately 80% and 20 to 40%, of parent compound, respectively.

Both CYP2D6 and CYP3A can be inhibited by a variety of psychotropic and other drugs. CYP2D6 is polymorphic in the population. Less than 10% of Caucasians are deficient in this isozyme (poor metabolisers of CYP2D6 substrates). In CYP2D6-deficient individuals, the

clearance of sertindole is approximately 2 to 3 times slower than that in individuals who have two functioning copies of the gene. However, CYP3A and other processes are also involved, which attenuates the kinetic differences between CYP2D6 poor metabolisers and extensive metabolisers.

Dehydro-sertindole appears to be formed by both isozymes. The dehydro-sertindole/sertindole concentration ratio (DHS/S) is correlated to the sertindole clearance. Typically, poor metabolisers of sertindole have DHS/S ratio <0.6. The DHS/S ratio does not solely reflect CYP2D6 activity but includes also the contribution from CYP3A.

1.4.5 Activity of Metabolites

Both dehydro-sertindole and nor-sertindole have receptor profiles similar to sertindole, but only dehydro-sertindole has sufficient potency to possibly contribute to sertindole's therapeutic effects. Nor-sertindole displays very weak pharmacological activity *in vivo*, while dehydro-sertindole has a receptor profile and *in vitro* / *in vivo* potency similar to sertindole (Panel 4). The two metabolites are, like sertindole, blockers of the I_{Kr} (hERG) potassium channel, thus, contributing to the QT interval prolongation (section 5.8). Drug interactions with CYP2D6 and CYP3A may alter sertindole metabolism and the ratio of parent drug and metabolites. However, the nonclinical studies predict that the QT prolonging effects of sertindole are unlikely to be changed by alterations of the ratio of parent drug and metabolites. Caution is, however, advised.

1.4.6 Drugs Affecting the Pharmacokinetics of Sertindole

Major inhibitory (fluoxetine and paroxetine) and enzyme induction (carbamazepine and phenytoin) effects were discovered in the population pharmacokinetic analyses, which screened over 30 medications or medication categories. Aside from those effects, other drug interactions appear to be kinetically small and of no clinical consequences.

The primary source for obtaining this information has been population pharmacokinetic analyses from long-term clinical studies.

CYP2D6

In the long-term studies, and to a limited extent in the efficacy studies, some patients received concomitant medications known to be partially metabolised by CYP2D6. Co-administration of fluoxetine decreased the oral clearance of sertindole. This may result in 2- to 3-fold increase in sertindole concentrations. For paroxetine, similar decreases in the oral clearance of sertindole were observed. The findings and the classification of paroxetine as a very potent CYP2D6 inhibitor indicate it should be considered similar to fluoxetine. Beside this, commonly used CYP2D6 substrates are not likely to have clinically significant PK effects on sertindole clearance.

CYP3A

As CYP2D6 is the predominant isozyme involved in the metabolism of sertindole, substantial effects from mild to moderate inhibitors of CYP3A are not expected for most patients. In an interaction study where the potent CYP3A inhibitor erythromycin (250mg x 4/day) was dosed for 10 days, a single dose of sertindole was co-administered on Day 3. The overall effect was a 13% higher area under the plasma concentration curve of sertindole. Consistent with these results, the use of macrolides in a long-term study was associated with an estimated 26% decrease in sertindole oral clearance. Co-administration of calcium-channel antagonists in long-term studies resulted in an approximately 20% decrease in the oral clearance of sertindole.

Co-administration of CYP3A inducers, primarily carbamazepine, was investigated. A 2.2-fold and a 3.4-fold increase in sertindole clearance was observed in two long-term studies.

1.4.7 Sertindole Effects on the Pharmacokinetics of Other Drugs

The results from an interaction study in healthy subjects suggested that sertindole may be a modest inhibitor of the first pass metabolism of a single dose of terfenadine (CYP3A substrate).

In two other interaction studies with either the CYP3A substrate alprazolam (single dose) or digoxin (multiple doses) and sertindole, no clinically relevant interactions were identified.

1.4.8 Sertindole Pharmacokinetics in Special Populations

The pharmacokinetics of sertindole and dehydro-sertindole is not affected by renal impairment. In addition, sertindole is not removed by haemodialysis.

The clearance of sertindole after a 4mg oral dose decreased by approximately 56% in hepatically impaired patients compared to hepatically normal patients. Treatment of patients with severe hepatic impairment with sertindole is contraindicated.

2 Clinical Development Programme, Post-marketing Studies, and the SCoP Study

2.1 Clinical Studies

2.1.1 Overview

The phase II/III programme in patients with schizophrenia comprised 21 studies conducted in the US, Canada, and Europe (Panel 5 and Panel 6). The programme includes short- and long-term, double-blind and open-label studies in in- and outpatients. For the safety evaluation, data from these phase II/III studies in patients with schizophrenia were pooled (Core Clinical Studies).

During the development of sertindole, Shionogi & Co., Ltd., H. Lundbeck A/S's development partner in Japan, conducted 6 phase I studies and 7 phase II/III studies to support the registration in that region. In the Japanese phase II/III studies, a total of 372 patients were treated with sertindole, corresponding to a total exposure of 95 patient years. In these studies, the adverse event reporting was limited to events considered by the investigators as having a causal relationship to study drug. Because of these methodological differences, these data were not pooled with the data from the US, Canada, and Europe. The data from the Japanese studies are only included in the analysis of mortality.

Panel 5 Overview of Randomised, Double-blind, Controlled Clinical Studies in Patients with Schizophrenia

Study	Sertindole Dose	Number of Patients	Comparator	Number of Patients	Duration
Adequate and well-controlled studies					
M91-645[a]	Flexible dose, 4 to 20mg/day	27	Placebo	11	7 weeks
M92-762[a]	Fixed dose, 8, 12, and 20mg/day	157	Placebo	48	40 days
M93-098 [a, b] / The Second US Study	Fixed dose, 20 and 24mg/day	231	Haloperidol 16 mg Placebo	115 116	8 weeks
M93-113 [a, b] / The Landmark Study	Fixed dose, 12, 20, and 24mg/day	216	Haloperidol 4, 8, and 16mg/day Placebo	208 73	8 weeks
Other controlled studies					
M92-817 [a, b]	Fixed dose, 4 and 12mg/day	73	Haloperidol 16 mg Placebo	41 42	40 days
M91-675	Fixed dose, dose ranging (0.25, 0.5, 0.75, 1.25, 2mg/day)	9			Up to 8 weeks
M93-132[b]	Fixed dose, 24mg/day	141	Haloperidol 10 mg	141	1 year
M95-342[b]/ The European Study	Fixed dose, 8, 16, 20, and 24mg/day	492	Haloperidol 10 mg	125	56 days
M95-372[b]	Flexible dose, 12 to 24 mg/day	216	Risperidone 6-12 mg	105	84 days
96205[b]	Flexible dose, 10 to 16mg/day and 12 to 24mg/day	20	Haloperidol 5 to 8mg/day and 9 to 15mg/day	20	84 days
97203[b]/ The French Study	Flexible dose, 12 to 24mg/day	97	Risperidone 4 to 10mg/day	89	84 days
M96-424	Crossover PET 12 to 24mg/day	21	Haloperidol 4 to 16mg/day	20	8-12 weeks
96202	Single-blind, multiple dose, PET (4 to 20mg/day)	5			6-8 weeks

a Study included in pooled placebo-controlled studies; b Study included in pooled active-controlled studies

Panel 6 Overview of Open-label, Uncontrolled Clinical Studies in Patients with Schizophrenia

Study	Design	Sertindole	Number of Patients	Duration
M9l-671	Continuation of M91-645	4 to 20mg/day	5	Up to 8 weeks
M92-795	Long-term	4 to 24mg/day	668	Up to 2 years
M93-061	Long-term	4 to 24mg/day	402	Up to 1 year
M94-192	Long-term	4 to 24mg/day	37	Up to 2 years
M94-222	Long-term	4 to 24mg/day	701	Up to 4 years
M94-239	Short-term, dose-escalation, multiple-dose	4 to 24mg/day Group I: Dose escalation every 3rd day Group II: Dose escalation every 2nd day	16	Group I: 15 days Group II: 10 days
M95-339	Long-term, continuation of M95-342	8 to 24mg/day	294	Up to 3 years
98205	Long-term continuation of 97203	12 to 24mg/day	18	Up to 6 months

2.1.2 Key Patient Selection Criteria

Patients with a primary diagnosis of schizophrenia were included in the adequate and well-controlled studies.

In the short-term studies, patients aged 18 to 65 years in an acute phase (that is, with pronounced positive symptomatology) of schizophrenia were eligible for enrolment.

In the open-label safety studies, patients in a more chronic phase of schizophrenia were eligible for enrolment. Also, patients with schizoaffective or delusional disorders were eligible for enrolment in one open-label, safety study (Study M93-061).

Titration of sertindole was necessary because of the drug's α_1-adrenergic receptor antagonist activity.

In the studies conducted in the early 1990s, the concomitant use of medication with a potential effect on the QT interval or medication with an indirect effect by affecting the metabolism of sertindole was not prohibited. Thus, in the Core Clinical Studies, 41% of the patients treated with sertindole concomitantly received medication with a known potential to prolong the QT interval and more than one-third of the patients received medication potentially affecting the metabolism of sertindole.

2.1.3 Diagnosis

Schizophrenia was diagnosed using accepted diagnostic systems in use at the time the clinical studies were performed (DSM-III-R or DSM-IV).

2.1.4 Efficacy Assessments

The key clinical ratings scales to assess efficacy used in the clinical studies were:

- the Positive and Negative Syndrome Scale (PANSS): This scale consists of 30 items rated 1 to 7, with the total score consisting of the sum of the 7 items for positive symptoms, 7 items for negative symptoms, and 16 items covering general psychopathology. The PANSS positive subscale score is the sum of the 7 items for positive symptoms. The PANSS negative subscale score is the sum of the 7 items for negative symptoms. A decrease in PANSS score (total, positive, or negative) reflects improvement in the evaluated dimensions of schizophrenia.
- the Brief Psychiatric Rating Scale (BPRS): This scale consists of 18 items with the total score representing the sum of all 18 items, while the core items score is the sum of 4 items (conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content). A decrease in BPRS score reflects an improvement in the evaluated items in patients with schizophrenia.
- the Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression –Global Improvement (CGI-I) scales: The CGI-S evaluation is a single rating by the physician of the severity of illness of the patient at the time of evaluation. A decrease in CGI-S score reflects overall improvement. The CGI-I evaluation is a single rating by the physician reflecting a patient's improvement at each visit compared to baseline. A decrease in CGI-I score reflects symptomatic improvement.
- the Global Assessment of Functioning Scale (GAF): This instrument considers psychological, social, and occupational functioning on a hypothetical continuum of mental health status. An increase in GAF score reflects symptomatic improvement in patients with schizophrenia.

The PANSS total as well as the positive and negative subscales, the BPRS core items, and the CGI-S were pre-defined, primary efficacy variables in the short-term, placebo-controlled studies. The PANSS total, PANSS positive subscale, PANSS negative subscale, CGI-S, and GAF were also used as efficacy measures in the one-year maintenance study (M93-132).

2.1.5 Demographics and Other Baseline Characteristics

The demographic characteristics for each of the treatment groups in the Core Clinical Studies are summarised in Panel 7.

Panel 7 Core Clinical Studies – Demographic Characteristics

Parameter	Sertindole N = 2711	Placebo N = 290	Haloperidol N = 650	Risperidone N = 194
Age (years)				
Mean ±SD	37.9 ±10.1	38.2 ±9.1	37.9 ±10.3	37.3 ±9.0
Median	37	37.5	37	37
Range	14.0-73.0	18.0-63.0	18.0-67.0	20.0-58.0
n (%)				
<18	6 (0.2)	0	0	0
18 to 30	646 (23.8)	54 (18.6)	157 (24.2)	47 (24.2)
31 to 50	1775 (65.5)	210 (72.4)	419 (64.5)	133 (68.6)
51 to 64	257 (9.5)	26 (9.0)	68 (10.5)	14 (7.2)
65 to 75	27 (1.0)	0	6 (0.9)	0
Sex [n (%)]				
Men	1972 (72.7)	243 (83.8)	486 (74.8)	141 (72.7)
Women	739 (27.3)	47 (16.2)	164 (25.2)	53 (27.3)
Race [n (%)]				
Caucasian	2120 (78.2)	199 (68.6)	465 (71.5)	156 (80.4)
Black or African American	507 (18.7)	82 (28.3)	163 (25.1)	34 (17.5)
Other	84 (3.1)	9 (3.1)	22 (3.4)	4 (2.1)
Weight (kg)				
N	2686	288	646	188
Mean ±SD	79.1 ±17.8	79.8 ±16.8	77.8 ±17.2	78.8 ±19.9
Median	76.7	76.3	75.8	75.9
Range	38.0-176.5	48.6-129.4	43.0-154.9	43.0-153.8
BMI (kg/m^2)				
N	2664	286	640	187
Mean ±SD	26.4 ±5.7	26.4 ±5.6	26.1 ±5.3	26.6 ±6.6
Median	25.4	25.3	25.4	24.8
Range	14.4-56.1	15.9-50.2	15.6-48.4	16.8-50.6
n (%)				
<18	39 (1.4)	2 (0.7)	12 (1.8)	1 (0.5)
18 to 25	1228 (45.3)	135 (46.6)	291 (44.8)	93 (47.9)
>25 to <30	805 (29.7)	86 (29.7)	208 (32.0)	45 (23.2)
≥30	578 (21.3)	61 (21.0)	127 (19.5)	45 (23.2)

SD: standard deviation

Overall, the treatment groups were comparable with respect to demographic characteristics. The mean age was 38 years and approximately two-thirds of the patients were in the age group 31 to 50 years. The ratio of men to women was approximately 3:1. The majority of the

patients were Caucasian (69 to 80%) and one-fifth to one-fourth were Black or African American. The mean baseline body mass index (BMI) was high (26 to 27kg/m^2) and approximately 20% of the patients were obese (BMI ≥30kg/m^2).

The placebo group differed slightly from the other groups with respect to age (older patients), sex (a higher proportion of men), and race (a higher proportion of Black or African American patients). However, within the placebo-controlled studies, these characteristics were comparable in the placebo and sertindole groups.

In Panel 8, the baseline psychiatric history is presented for each of the treatment groups in the Core Clinical Studies.

Although some variations are seen, there were no major differences between the treatment groups. The patients had a mean duration of schizophrenia of 13 to 16 years. In the sertindole group, 38% of the patients had been hospitalised for their disorder at least 6 times and 26% had at least one previous suicide attempt. In the short-term, controlled studies, the patients were moderately to severely ill with mean baseline PANSS total scores of 90 to 100 points.

Panel 8 Core Clinical Studies – Psychiatric History

	Sertindole N = 2711	Placebo N = 290	Haloperidol N = 650	Risperidone N = 194
Duration of schizophrenia				
Mean ±SD (years)	15.2 ±9.4	15.7 ±8.9	15.6 ±9.0	12.8 ±8.8
Not available [n (%)]	625 (23)	3 (1)	156 (24)	8 (4)
Number of hospitalisations [n (%)]				
1 to 5	894 (33)	97 (33)	225 (35)	81 (42)
6 to 10	546 (20)	84 (29)	120 (19)	56 (29)
> 10	534 (20)	98 (34)	122 (19)	49 (25)
Not available	737 (27)	11 (4)	183 (28)	8 (4)
Number of suicide attempts [n (%)]				
0 (never)	1535 (57)	156 (54)	309 (48)	112 (58)
1 to 5	647 (24)	112 (39)	240 (37)	60 (31)
≥6	45 (2)	11 (4)	7 (1)	9 (5)
Not available	484 (18)	11 (4)	94 (14)	13 (7)
Time since last suicide attempt [n (%)]				
0 (never)	1535 (57)	156 (54)	309 (48)	112 (58)
During the past year	134 (5)	19 (7)	42 (6)	12 (6)
1 to 5 years ago	272 (10)	45 (16)	56 (9)	17 (9)
6 years or more ago	398 (15)	59 (20)	116 (18)	39 (20)
Not available	372 (14)	11 (4)	127 (20)	14 (7)

2.1.6 Exposure and Patient Disposition

The duration of exposure to sertindole, placebo, haloperidol, or risperidone in the Core Clinical Studies is summarised in Panel 9. A total of 2711 patients with schizophrenia were treated with sertindole, representing 1840 patient years of exposure (PYE). A total of 550 patients (20%) completed more than 12 months of treatment with sertindole.

Panel 9 Core Clinical Studies – Duration of Exposure

Exposure	Sertindole N = 2711	Placebo N = 290	Haloperidol N = 650	Risperidone N = 194
n (%)				
≤1 week	175 (6.5)	30 (10.3)	47 (7.2)	8 (4.1)
>1 week to 2 weeks	174 (6.4)	30 (10.3)	48 (7.4)	8 (4.1)
>2 weeks to 3 weeks	179 (6.6)	36 (12.4)	70 (10.8)	7 (3.6)
>3 weeks to 4 weeks	191 (7.0)	38 (13.1)	55 (8.5)	13 (6.7)
>4 weeks to 2 months	507 (18.7)	156 (53.8)	317 (48.8)	18 (9.3)
>2 months to 3 months	278 (10.3)		24 (3.7)	134 (69.1)
>3 months to 6 months	344 (12.7)		23 (3.5)	6 (3.1)
>6 months to 12 months	313 (11.5)		42 (6.5)	
>12 months to 24 months	261 (9.6)		24 (3.7)	
>24 months to 36 months	111 (4.1)			
>36 months	178 (6.6)			
Mean ±SD (days)	246.6 ±374.3	33.5 ±18.6	74.2 ±98.5	67.9 ±27.1
Range (days)	1-1960	1-60	1-387	1-103
Total PYE (years)	1840	27	132	36

SD: Standard deviation; PYE: Patient years of exposure

In the placebo-controlled studies, 46% of the patients in the sertindole group and 41% of the patients in the placebo group completed the study (Panel 10). In both groups, the proportion of patients who withdrew due to adverse events was low: 7% and 5% in the sertindole and placebo group, respectively. The most common reason for withdrawal was lack of efficacy; 27% in the sertindole group and 39% in the placebo group withdrew due to lack of efficacy.

In the uncontrolled, long-term studies (N = 1781), 32.5% of the patients completed the study; 15% withdrew due to adverse events and 28% withdrew due to lack of efficacy.

Panel 10 Core Clinical Studies – Patient Disposition

	Sertindole N = 704	Placebo N = 290
Number (%) of patients		
Randomised	704 (100.0)	290 (100.0)
Completed	323 (45.9)	118 (40.7)
Withdrew	381 (54.1)	172 (59.3)
Primary reason for withdrawal [n (%)]		
Adverse event	51 (7.2)	15 (5.2)
Lack of efficacy	193 (27.4)	114 (39.3)
Patient's decision	71 (10.1)	18 (6.2)
Protocol violation	7 (1.0)	2 (0.7)
Non-compliance	30 (4.3)	13 (4.5)
Lost to follow-up	18 (2.6)	6 (2.1)
Other	11 (1.6)	4 (1.4)

In the active-controlled studies, the completion rate for sertindole (53%) was comparable to those for haloperidol (49%) and risperidone (69%) (Panel 11).

Panel 11 Active-controlled Studies – Patient Disposition

	Sertindole N = 1486	Placebo N = 231	Haloperidol N = 650	Risperidone N = 194
Number (%) of patients				
Randomised	1486 (100.0)	231 (100.0)	650 (100.0)	194 (100.0)
Completed	783 (52.7)	90 (39.0)	317 (48.8)	134 (69.1)
Withdrew	703 (47.3)	141 (61.0)	333 (51.2)	60 (30.9)
Primary reason for withdrawal [n (%)]				
Adverse event	143 (9.6)	12 (5.2)	79 (12.2)	14 (7.2)
Lack of efficacy	302 (20.3)	92 (39.8)	119 (18.3)	19 (9.8)
Patient's decision	146 (9.8)	16 (6.9)	66 (10.2)	14 (7.2)
Protocol violation	22 (1.5)	2 (0.9)	14 (2.2)	4 (2.1)
Non-compliance	42 (2.8)	9 (3.9)	28 (4.3)	4 (2.1)
Lost to follow-up	26 (1.7)	6 (2.6)	19 (2.9)	2 (1.0)
Other	22 (1.5)	4 (1.7)	8 (1.2)	3 (1.5)

2.2 Post-marketing Studies

The main features of the post-marketing epidemiological studies are shown in Panel 12.

The safety of sertindole under normal conditions of use was evaluated in retrospective epidemiological studies and prospective use studies with focus on mortality and cardiac risk. The EPOS study was a prospective use study including a reference cohort of patients with schizophrenia who were not treated with sertindole; the other post-marketing studies were

retrospective. The ESES Crossover Sub-study included an internal reference group and compared the mortality, for the same cohort, during use of sertindole with the mortality during use of subsequent antipsychotic treatments. The remaining retrospective studies were uncontrolled.

The results from these epidemiological studies along with additional analyses of safety data from the clinical studies and the extensive nonclinical data formed the basis of the CHMP recommendation to allow a gradual reintroduction of sertindole through the initiation of the SCoP study.

Panel 12 Overview of the Epidemiological Studies

Study/Sponsor	Setting/Country	Design	No. of Patients/ Sertindole	Sertindole Exposure (years)
Study 97201 European Post-marketing Observational Serdolect Study (EPOS) (H. Lundbeck A/S)	Specialist In/outpatients/ Europe (10 countries)	Prospective, observational, sertindole cohort with concurrent controls	2321/ 1053	414
Prescription Event Monitoring (PEM)[43] (Drug Safety Research Unit [DSRU])	GP/UK	*Ad hoc* cohort	17,004/ 462	299
The UK Hospital Pharmacy Study (UK Psychiatric Pharmacy Group)	Hospital/UK	Retrospective, record based	841/ 184	143
Study 98604 Sertindole European Safety and Exposure Survey (ESES) (H. Lundbeck A/S)	Specialist In/outpatients/ Europe (6 countries)	Retrospective, cohort study	8608/ 8608	3,808
Nested Case Control (NCCS) ESES Amendment 3	Specialist In/outpatients/ Europe (6 countries)	Risk factors for cardiac death analysed in a matched case control	25 deaths/ 91 matched controls	Not applicable
ESES Crossover Sub-study Analysed at the Erasmus University, the Netherlands ESES Amendment 5	Mixed setting/ Belgium, the Netherlands	Retrospective, case-crossover	1112/ 1112	970
Sertindole Safety Survey ESES Amendment 6	Specialist In/outpatients/ Europe (11 countries)	Retrospective, compassionate use exposure	1439/ 1439	1,808
The Niche Study ESES Amendment 7	Specialist In/outpatients/ Europe (11 countries)	Retrospective, single-arm, crossover	370/ 370	-

The original safety signal that elicited the marketing suspension of sertindole was not confirmed in any of the epidemiological studies (section 5.9.3). Furthermore, the SCoP study

has provided a more precise estimate of the mortality and potential cardiac risk than what can be obtained in a clinical development programme.

2.3 The SCoP Study – Study 99824

2.3.1 Overview

Because the safety issues addressed by the mainly retrospective epidemiological and post-marketing studies (section 2.2) were not definitively resolved, H. Lundbeck A/S committed to conducting the SCoP study (Study 99824) as a condition for market re-introduction. The study was a large, prospective, randomised, open-label, active-controlled study comparing the safety of sertindole to that of risperidone under normal conditions of use. The main features of the SCoP study are shown in Panel 13.

Panel 13 Overview of the SCoP Study

Study	Setting/Country	Design	Total No. of Patients/ Sertindole	Total Exposure /Sertindole (years)
Study 99824 Sertindole Cohort Prospective Study (SCoP)	Specialist In-/outpatients/ Europe and Asia (38 countries)	Prospective, randomised, open-label, active-controlled	9809/ 4905	14,147 [a] /6575[a]

a Whole Randomised Treatment (WRT) period, see section 2.3.4.1

In this briefing book, the key results are presented. Details of the methodology used in the SCoP study are presented in Appendix 1.

2.3.2 Rationale and Objective

The SCoP study was designed to investigate the all-cause mortality under normal conditions of use.

Two independent committees, the Independent Management Committee (IMC) and the Independent Safety Committee (ISC) were established to oversee the study conduct and to safeguard the interest of the patients. These two committees were blinded to treatment. The study outcomes were classified by the ISC.

The endpoints of the study were:

- Primary endpoints
  - all-cause mortality (first primary endpoint)
    the primary endpoint, was chosen as it is unbiased and cannot be compromised by unblinding and thus, carries the highest degree of reliability.
  - cardiac events, including arrhythmias, requiring hospitalisation (second primary endpoint)

the purpose of this endpoint was to capture the potential risk of arrhythmias with sertindole treatment that would lead to hospitalisation but not necessarily to death.

- Secondary endpoints
  - cause-specific mortality (cardiac, suicide, and other)
  - suicide attempts (fatal and non-fatal) – added following a discussion with the FDA
  - hospitalisations (excluding hospitalisations related to the primary psychiatric disease) and including those related to suicide risk
  - duration of randomised antipsychotic treatment
  - the effect of short- and long-term treatment with sertindole or risperidone on metabolic variables in patients with schizophrenia – added following a discussion with the FDA (the SCoP Metabolic Sub-study, country-specific)

2.3.3 Study Design and Methodology

This was a multinational, multi-centre, randomised, open-label, parallel-group, active-comparator (risperidone) study.

The patients were randomised (1:1) to treatment with sertindole or risperidone within each country.

2.3.4 Study Conduct and Periods

2.3.4.1 Main SCoP Study

Patients were assessed and managed by the investigator according to usual clinical practice in line with the labelling of each drug, that is, with a minimum of interventions due to study procedures and with relatively infrequent visits. During the study, the investigator could prescribe an additional antipsychotic if necessary.

The study assessments were performed monthly during the first 3 months of treatment, and on a quarterly basis thereafter. Information on serious adverse events and non-serious cardiac adverse events were collected.

Due to the randomisation, the patients had to meet the criteria specified in the labelling for both sertindole and risperidone. The major differences between the two labels are the contraindications of clinically significant cardio-vascular disease and the mandatory ECG monitoring for sertindole.

The patients were followed up for the entire duration of the study, that is, also if the patients started add-on antipsychotic therapy or discontinued the randomised treatment; follow-up stopped only if they withdrew from the study or when the study was terminated. The accrued exposure to study drug therefore may vary from patient to patient. All efforts were made to establish the vital status of patients who were lost to follow-up.

A safety follow-up contact was scheduled for 30 days after stopping the study drug, except if the patient withdrew consent.

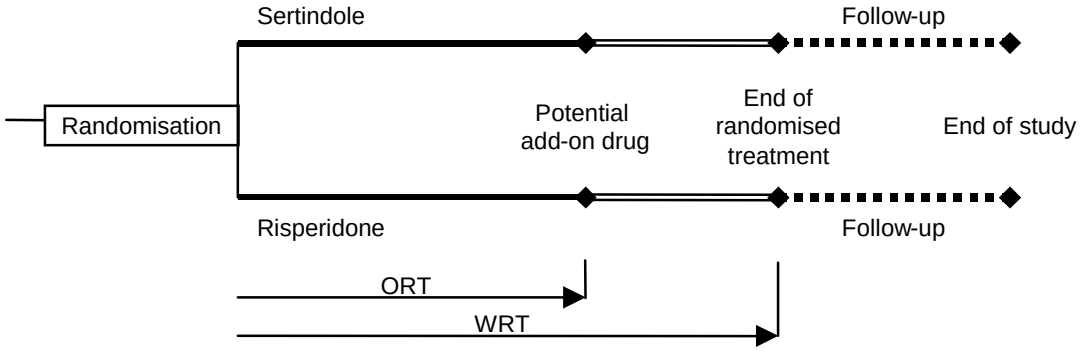
The data obtained in the study were reported for different periods of time:

- Only Randomised Treatment (ORT) period – the period in which a patient received randomised treatment as antipsychotic monotherapy. All patients started on monotherapy.
- Whole Randomised Treatment (WRT) period – The period in which a patient received randomised treatment either as monotherapy or in combination with another antipsychotic.

The primary period for reporting of the safety parameters was the WRT+30 days period, which covered the WRT period plus 30 days after discontinuation of randomised treatment.

The definition of the ORT period does not include an event if the patient took the last dose of randomised treatment the day before the event occurred or if the patient had not yet taken randomised treatment on the day of the event, so the ORT+1 day period was defined. This period is considered the most relevant in order to avoid possible confounding effects of add-on treatment, of discontinuation, and of the introduction of other treatments immediately after drug switch.

Panel 14 The SCoP Study Design



2.3.4.2 The Metabolic Sub-study

To provide data requested by the FDA, a metabolic sub-study was incorporated into the SCoP study. The effect of short- and long-term treatment with sertindole or risperidone on metabolic parameters was evaluated in a subset of patients enrolled in the SCoP study. The patient's weight, waist circumference, systolic and diastolic blood pressure, fasting serum lipid profile, fasting plasma glucose level, use of concomitant medication for the treatment of triglyceride or HDL-cholesterol abnormalities, type 2 diabetes, or hypertension, and diagnosis of type 2 diabetes were assessed at inclusion, at Weeks 8 and 12, and on a quarterly basis thereafter. Metabolic assessments were only performed during the ORT period.

The International Diabetes Federation (IDF) definition of metabolic syndrome[44] was chosen for the SCoP Metabolic Sub-study, as it is the most recent worldwide consensus definition

and because the study was conducted in countries with a preponderance of people of European origin (Europids).

The IDF definition of metabolic syndrome is similar to that in the US National Cholesterol Education Program (NCEP): Adult Treatment Panel III (NCEP-ATP III); cut-off levels for triglycerides, HDL-cholesterol, and blood pressure are identical in both definitions, whereas cut-off levels for waist circumference and fasting glucose are lower in the IDF definition.

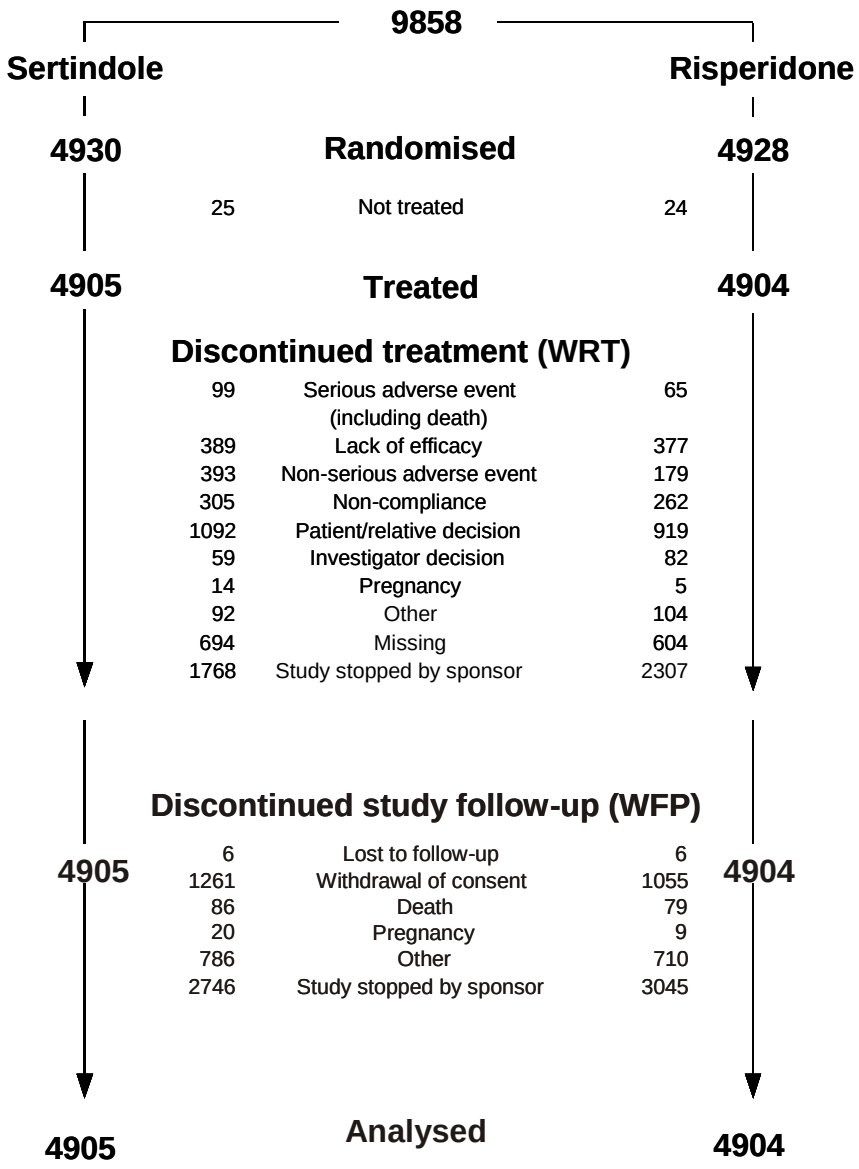
2.3.5 Study Populations

2.3.5.1 Demographic Characteristics – The Main SCoP Study

Patients with schizophrenia were recruited by psychiatrists at in- or outpatient sites in private practice, in in- or outpatient departments, or hospital settings across Europe and Asia (593 centres in 38 countries) and followed up from enrolment until the end of the study (between July 2002 and February 2008). Investigators were experienced clinicians in treating schizophrenia and did not necessarily have previous experience of clinical studies, as the study was intended to be representative of clinical routine prescription of antipsychotics.

The patient flow and patient characteristics are presented in Panel 15 and Panel 16. In total, 9809 patients were treated (4905 patients with sertindole and 4904 with risperidone). A total of 5791 of the 9809 treated patients were withdrawn from the study due to study closure. In addition, 12 patients (6 patients in each treatment group) were lost to follow-up. An additional 20 patients (9 in the sertindole group and 11 in the risperidone group) did not have contact with the investigator within the 30 days following stop of the study drug.

Panel 15 The SCoP Study – Patient Flow



Panel 16 The SCoP Study – Patient Characteristics

	Sertindole	Risperidone
Patients treated [Europe / Asia]	4905 [3545 / 1360]	4904 [3543 / 1361]
Sex (% male)	55	55
Mean age (years) [range]	38.4 [18 - 84]	38.3 [18 - 81]
Age groups (%) <35 / 35-65 / ≥65	44 / 54 / 2	44 / 54 / 2
Duration of schizophrenia (%) <5 years / 5-10 years / >10 years	30 / 26 / 42	30 / 26 / 42
Last antipsychotic treatment before study inclusion (%)		
Typical/ atypical/ both	53 / 36 / 10	53 / 37 / 10
Monotherapy/ polytherapy	77 / 23	77 / 23
Primary reason for prescription of study drug (%)		
Lack of efficacy	52.6	51.8
Adverse drug reaction	21.8	22.8
Patient's choice	19.9	20.2
Non or poor compliance	3.4	3.2
Other	2.1	1.8
Primary reason for stopping study drug (%)		
Lack of efficacy	7.7	7.9
Serious adverse event	1.3	2.0
Non-serious adverse event	3.7	8.0
Non-compliance	5.3	6.2
Patient / relative decision	18.7	22.3
Investigator decision	1.7	1.2
Pregnancy	<1	<1
Other	2.1	1.9
Not given	12.3	14.1
Sponsor study closure	47.0	36.0

The age and sex distribution and psychiatric medication history of the SCoP study population reflect that of the chronic schizophrenic population in usual clinical practice.

The demographic characteristics of both treatment groups did not differ significantly. The mean age was 38 years and men comprised a slight majority of both groups (55%). The age distribution was skewed towards a younger age for men than for women.

At baseline, approximately two-thirds of the patients in each treatment group had been diagnosed with schizophrenia for 5 years or more prior to study entry. Twelve percent of patients in each treatment group had a history of previous suicide attempts.

The reasons for enrolment into the study were similar in both treatment groups: lack of efficacy of the previous antipsychotic was the main reason (approximately 52% in both groups).

Similarly, the reasons for stopping the study drug were comparable in both treatment groups, except for "non-serious adverse events" (sertindole: 8.0%; risperidone: 3.7%), which was reported more commonly in the sertindole group. This was mainly driven by the asymptomatic ECG findings.

Except for a higher proportion of women, the demographic and psychiatric characteristics of the SCoP study population are also comparable with those of the clinical studies (Panel 7 and Panel 8). The majority in both populations were suffering from chronic schizophrenia with a duration of schizophrenia often longer than 10 years.

In summary, the SCoP study findings are applicable to a US population of patients with schizophrenia as the patient characteristics, except for gender, in the Core Clinical Studies (which were mainly conducted in the US) are similar to those in the SCoP study (which was conducted in Europe and Asia).

2.3.5.2 Extent of Exposure – The Main SCoP Study

The treatment duration of an individual patient was not limited as the study design allowed patients to continue study drug until the study was closed. Thus, many patients had treatment durations of several years (up to 63.5 months).

In the WRT period, the total exposure to study drug was 6575 years in the sertindole group and 7572 years in the risperidone group, nearly twice the planned amount in each treatment group.

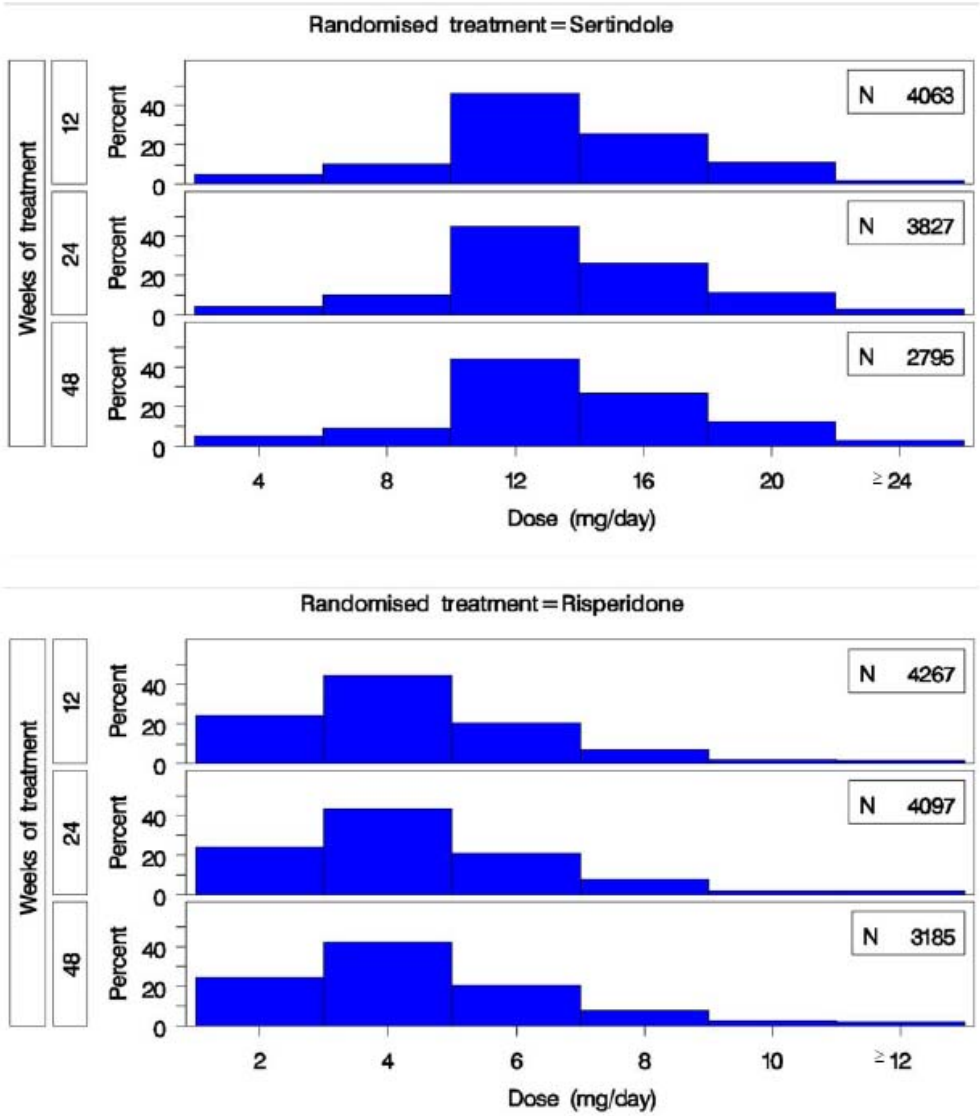
In the ORT period, the total exposure to study drug (6327 years in the sertindole group and 7218 years in the risperidone group) was only slightly smaller than that in the WRT period, as only a few patients received add-on therapy (361 in the sertindole group and 424 in the risperidone group). The reasons for add-on antipsychotic therapy are shown in Panel 17.

Panel 17 The SCoP Study – Reason for Add-on Antipsychotic Therapy

	Sertindole	Risperidone
Patients treated, n	4905	4904
Patients prescribed add-on, n (%)	361 (7.3)	424 (8.6)
Reason, n (%)		
Lack of efficacy	223 (61.7)	275 (64.8)
Other or missing	138 (38.2)	149 (35.1)

Approximately 80% of the patients in the sertindole group and 90% of the patients in the risperidone group received doses of study drug within the recommended dose range, with a preference for lower doses (12mg/day sertindole and 2 and 4mg/day risperidone). This may reflect the common clinical practice trend of using the lowest effective dose for each individual patient (Panel 18).

Panel 18 The SCoP Study – Distribution of Dose at Weeks 12, 24, and 48



2.3.5.3 Demographic Characteristics and Extent of Exposure – The SCoP Metabolic Sub-study

The SCoP Metabolic Sub-study included 131 patients in the sertindole group and 130 patients in the risperidone group in 26 centres (3 in Poland, 12 in Russia, and 11 in Ukraine).

Both in their mean age and sex distribution, the population in the Metabolic Sub-study was comparable to that of the overall population.

In each treatment group, the mean baseline weight was approximately 73kg and the mean baseline BMI was approximately 25.5kg/m^2.

In terms of their mean weight and BMI, the population in the Metabolic Sub-study was also comparable to the sertindole population in the core clinical studies, primarily conducted in the US, in which the mean weight was 79kg and the mean BMI was 26.4kg/m^2.

The total exposure to study drug was 64 PYE in the sertindole group and 76 PYE in the risperidone group (ORT period). The mean exposure was approximately 1 month longer in the risperidone group (214 days) than in the sertindole group (179 days).

3 Clinical Efficacy

3.1 Overview of Key Efficacy Results

As shown in the following summary, sertindole is effective in the treatment of schizophrenia. Also, sertindole has been shown to reduce the risk of suicide and suicide attempts in patients with schizophrenia; these results are detailed in section 4.

Three adequate and well-controlled studies (Studies M93-113, M93-098, and M92-762) established the clinical short-term efficacy of sertindole. The studies were 8-week, placebo-controlled, haloperidol-referenced studies performed in the US and Canada, using haloperidol as the active reference because it was the most widely used antipsychotic at the time:

- Study M93-113 – The Landmark Study – assessed the efficacy of three dosages of sertindole (12, 20, and 24mg/day) compared to that of three dosages of haloperidol (4, 8, and 16mg/day). Both sertindole and haloperidol were more efficacious on the PANSS total and in the treatment of the positive symptoms of schizophrenia than placebo was (20mg/day sertindole and 8mg/day haloperidol were the most effective doses). The 20mg/day sertindole also lead to a reduction in the negative symptoms of schizophrenia whereas haloperidol did not.
- Study M93-098 – The Second US Study – demonstrated that both sertindole (20 and 24mg/day) and haloperidol (16mg/day) were more efficacious on the PANSS total and positive scores than placebo was. As with Study M93-113, sertindole (24mg/day) led to significant improvements in the negative symptoms of schizophrenia whereas haloperidol did not.
- Study M92-762 investigated doses of sertindole 8, 12, and 20mg/day. The results showed that 8mg/day sertindole was a sub-effective dose whereas 12 and 20mg/day sertindole produced greater improvement than placebo as measured by the PANSS total scores.

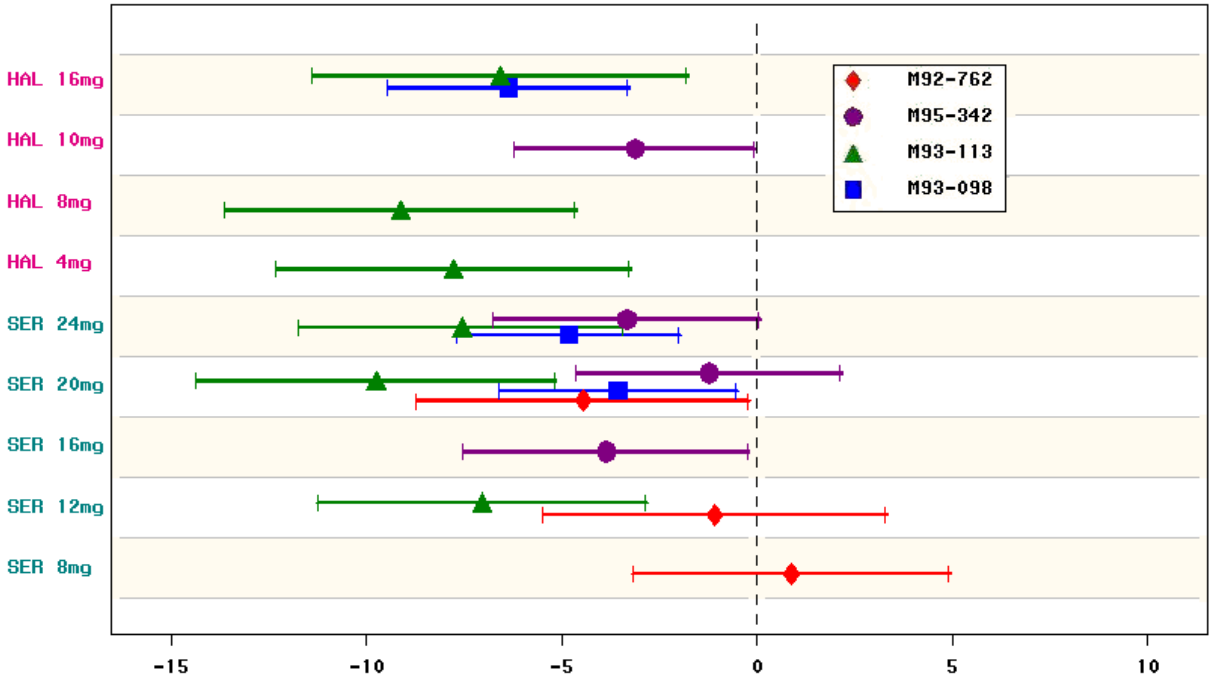
Earlier studies included Study M91-645, a double-bind, short-term, placebo-controlled, titration-to-response study that demonstrated preliminary evidence of efficacy for sertindole in the dose range 12 to 20mg/day in patients with schizophrenia. As this was a small pilot study, it will not be described in further detail but is included in the discussion of evidence for the effective dose range in section 3.5. Study M92-817, which investigated doses of 4 and 12mg/day sertindole, was discontinued following an interim analysis because of the lack of a positive dose response.

In Europe, another haloperidol-referenced, 8-week study (Study M95-342) confirmed that 16, 20, and 24mg/day sertindole was superior to 8mg/day sertindole (as seen in Study M92-762), and numerically similar to 16mg/day haloperidol.

Panel 19 shows the treatment effect with the 95% confidence interval (CI) for Studies M92-762, M95-342, M93 113, and M93-098. For Studies M92-762, M93-098, and M93-113, the treatment effect was estimated on the basis of change from baseline in PANSS total score for each dose of active treatment *versus* placebo; for Study M95-342, the treatment effect was

estimated on the basis of change from baseline in PANSS total score for each dose of active treatment *versus* the sub-effective 8mg/day sertindole dose.

Panel 19 Studies M92-762, M95-342, M93-113, and M93-098 – Treatment Effect at Endpoint with 95% CI (ANOVA, LOCF, ITT)



One of the most widely used second generation antipsychotics – risperidone – was used as an active reference in a study conducted in France (Study 97203) comparing double-blind treatment with sertindole to that of risperidone under a flexible-dose regimen (sertindole: 12 to 24mg/day; risperidone: 4 to 10mg/day). Again, sertindole showed efficacy comparable to, or better than, the comparator.

Long-term efficacy has been shown in a 1-year, double-blind, haloperidol-referenced study (Study M93-132). In this study, stable patients who had been withdrawn from their previous medications and stabilised on sertindole or haloperidol showed similar maintenance of effect and comparable improvement on the efficacy rating scales. The long-term efficacy of sertindole is further supported by results from open-label studies (Studies M94-222 and M95-339) of up to 4 years' duration.

Combined results for the three doses of sertindole or haloperidol from Study M93-113 showed that the time to onset of a sustained response was similar.

3.2 Short-term Efficacy

3.2.1 Adequate and Well-controlled Studies

3.2.1.1 Study M93-113 – The Landmark Study

Study M93-113 (the Landmark study[45]) is a placebo-controlled, dose-response study of sertindole and haloperidol in schizophrenia. The study was conducted to evaluate and compare the efficacy and safety/tolerability of three doses of sertindole with three doses of haloperidol and with placebo. For the first time, efficacy and safety/tolerability data across a range of haloperidol doses were collected, permitting an evaluation of sertindole relative to several commonly prescribed doses of haloperidol.

Patients with schizophrenia (N = 497) were randomised to receive 12, 20, or 24mg/day of sertindole; 4, 8, or 16mg/day of haloperidol; or placebo. After a 4- to 7-day washout period, the patients were titrated to the target dose over 2 weeks and maintained on that dose for a further 6 weeks. The mean PANSS total scores at baseline ranged from 92 to 100, indicating that the patients were markedly to severely ill.

Both sertindole and haloperidol were significantly more effective than placebo in reducing the patients' symptoms of schizophrenia as measured by the PANSS total score, the PANSS positive subscale score, and the CGI-I score (Panel 20). The patients in the 4mg/day and 16mg/day haloperidol groups did not show statistically significant improvements in CGI scores at the end of treatment.

The patients in the 20mg/day sertindole group had significant improvement on the PANSS negative subscale score compared with those in the placebo group.

Panel 20 Study M93-113 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment	Dose (mg/day)	N	Treatment effect[a]	95% CI	p-value
PANSS total	Sertindole	12	72	-12.3	(-21.0; -3.6)	0.007
		20	65	-18.8	(-28.0; -9.7)	0.001
		24	70	-13.1	(-21.5; -4.8)	0.003
	Haloperidol	4	68	-12.6	(-21.7; -3.5)	0.008
		8	63	-17.7	(-26.4; -9.0)	0.001
		16	68	-12.8	(-22.0; -3.5)	0.009
PANSS positive	Sertindole	12	72	-2.93	(-5.74; -0.13)	0.044
		20	65	-5.18	(-7.98; -2.38)	0.001
		24	70	-3.68	(-6.33; -1.04)	0.008
	Haloperidol	4	68	-3.02	(-5.87; -0.18)	0.041
		8	63	-6.06	(-8.46; -3.67)	0.001
		16	68	-4.17	(-6.98; -1.35)	0.005
PANSS negative	Sertindole	12	72	-2.36	(-4.84; 0.13)	0.068
		20	65	-3.90	(-6.49; -1.31)	0.004
		24	70	-1.89	(-4.30; 0.51)	0.128
	Haloperidol	4	68	-1.85	(-4.45; 0.76)	0.169
		8	63	-2.49	(-5.19; 0.21)	0.076
		16	68	-2.02	(-4.46; 0.41)	0.108
CGI-S	Sertindole	12	72	-0.47	(-0.90; -0.04)	0.036
		20	65	-0.53	(-0.97; -0.09)	0.022
		24	70	-0.62	(-1.01; -0.23)	0.003
	Haloperidol	4	68	-0.19	(-0.61; 0.23)	0.375
		8	63	-0.58	(-0.98; -0.18)	0.006
		16	68	-0.29	(-0.70; 0.12)	0.171
CGI-I	Sertindole	12	72	-0.68	(-1.23; -0.14)	0.014
		20	65	-0.84	(-1.42; -0.27)	0.004
		24	70	-0.64	(-1.20; -0.08).	0.026
	Haloperidol	4	68	-0.39	(-0.95; 0.17)	0.170
		8	63	-1.01	(-1.55; -0.46)	<0.001
		16	68	-0.65	(-1.17; -0.13)	0.014

CI: confidence interval

a The treatment effect was estimated *versus* placebo.

3.2.1.2 Study M93-098 – The Second US Study

This 8-week study evaluated the efficacy of two doses of sertindole (20 and 24mg/day) compared with haloperidol (16mg/day) and placebo in a total of 462 patients with schizophrenia. The mean PANSS total score at baseline ranged from 91 to 95, indicating that the patients were markedly to severely ill.

All active treatment groups showed significant improvements in the PANSS total score, PANSS positive subscale score, and the CGI-I score from baseline to final evaluation

compared with the placebo group.[46] On the PANSS negative subscale, one of the sertindole groups (24mg/day), but not the haloperidol group, showed significantly greater improvement than the placebo group (Panel 21).

Panel 21 Study M93-098 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment	Dose (mg/day)	N	Treatment effect[a]	95% CI	p-value
PANSS total	Sertindole	20	111	-6.69	(-12.52; -0.87)	0.025
		24	108	-9.20	(-14.93; -3.48)	0.002
	Haloperidol	16	113	-11.85	(-17.91; -5.78)	0.001
PANSS positive	Sertindole	20	111	-2.28	(-4.04; -0.52)	0.011
		24	108	-2.16	(-3.99; -0.33)	0.021
	Haloperidol	16	113	-4.67	(-6.64; -2.70)	0.001
PANSS negative	Sertindole	20	111	-0.87	(-2.71; 0.97)	0.352
		24	108	-2.22	(-4.11; -0.33)	0.021
	Haloperidol	16	113	-0.82	(-2.71; 1.07)	0.395
CGI-S	Sertindole	20	111	0.03	(-0.23; 0.29)	0.825
		24	108	-0.27	(-0.56; 0.02)	0.071
	Haloperidol	16	112	0.37	(0.11; 0.63)	0.007
CGI-I	Sertindole	20	111	-0.43	(-0.84; -0.01)	0.043
		24	108	-0.48	(-0.89; -0.07)	0.021
	Haloperidol	16	113	-0.82	(-1.21; -0.42)	<0.001

CI: confidence interval

a The treatment effect was estimated *versus* placebo.

3.2.1.3 Study M92-762

Study M92-762 was a placebo-controlled study assessing the safety and efficacy of three doses of sertindole.

Patients with schizophrenia (N = 205) were randomised to receive 8, 12, or 20mg/day sertindole or placebo. After a 4- to 7-day washout period, the patients were titrated to the target dose over 2 weeks and maintained on that dose for a further 4 weeks. The mean PANSS total scores at baseline ranged from 87 to 90, indicating that the patients were markedly ill.

The results showed that 20mg/day sertindole was effective in the treatment of the manifestations of psychoses (Panel 22). The overall improvement in PANSS total scores in the 20mg/day sertindole group was more than twice that seen in the placebo group. The patients in the 12mg/day sertindole group showed greater mean responses than those in the placebo group, although the differences for this dose group *versus* the placebo group were not

statistically significant. The response in the 8mg/day sertindole group was not distinguishable from that in the placebo group.

The patients in the 20mg/day sertindole group showed significantly greater improvement than those in the placebo group across analyses of the CGI.

Panel 22 Study M92-762 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment	Dose (mg/day)	N	Treatment effect[a]	95% CI	p-value
PANSS total	Sertindole	8	50	2.36	(-5.74; 10.46)	0.569
		12	50	-3.13	(-11.52; 5.26)	0.467
		20	51	-8.26	(-16.42; -0.10)	0.051
PANSS positive	Sertindole	8	50	0.09	(-2.36; 2.54)	0.945
		12	50	-1.28	(-3.69; 1.13)	0.300
		20	51	-1.86	(-4.21; 0.49)	0.125
PANSS negative	Sertindole	8	50	1.39	(-1.19; 3.97)	0.294
		12	50	-0.78	(-3.29; 1.73)	0.548
		20	51	-1.95	(-4.61; 0.71)	0.155
CGI-I	Sertindole	8	50	0.41	(-0.20; 1.01)	0.183
		12	51	-0.13	(-0.70; 0.45)	0.665
		20	53	-0.55	(-1.17; 0.07)	0.080

CI: confidence interval

a The treatment effect was estimated *versus* placebo.

3.2.2 Study M95-342 – The European Study

The efficacy of sertindole was further demonstrated in an 8-week haloperidol-referenced study[47] that compared three fixed doses of sertindole (16, 20, and 24mg/day) to a sub-effective sertindole dose (8mg/day) and to haloperidol (10mg/day) in 617 patients with schizophrenia. The mean PANSS total score at baseline ranged from 98 to 102, indicating that the patients were severely ill.

Patients in the 16mg/day and 24mg/day sertindole groups and the 10mg/day haloperidol group had significant symptomatic improvement on the PANSS total score compared to those in the 8mg/day sertindole group (Panel 23).

In terms of negative symptoms, a significantly greater reduction in the PANSS negative subscale was seen in the 16mg/day sertindole group than in the haloperidol group in patients who completed the 8-week study period (OC).

Panel 23 Study M95-342 – Treatment Effects at Endpoint (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment	Dose (mg/day)	N	Treatment effect[a]	95% CI	p-value
PANSS total	Sertindole	16	120	-7.85	(-14.84; -0.86)	0.029
		20	121	-3.72	(-10.18; 2.73)	0.259
		24	115	-7.28	(-13.83; -0.73)	0.031
	Haloperidol	16	123	-6.49	(-12.21; -0.76)	0.028
PANSS positive	Sertindole	16	120	-2.47	(-4.42; -0.51)	0.014
		20	121	-1.75	(-3.53; 0.04)	0.056
		24	115	-3.18	(-5.17; -1.20)	0.002
	Haloperidol	16	123	-3.22	(-5.06; -1.38)	0.001
PANSS negative	Sertindole	16	120	-1.53	(-3.51; 0.45)	0.131
		20	121	-0.76	(-2.66; 1.14)	0.433
		24	115	-0.77	(-2.62; 1.08)	0.415
	Haloperidol	16	123	-0.16	(-1.78; 1.46)	0.848
CGI-S	Sertindole	16	119	-0.43	(-0.77; -0.09)	0.012
		20	120	-0.19	(-0.51; 0.13)	0.231
		24	115	-0.33	(-0.66; -0.00)	0.049
	Haloperidol	16	123	-0.19	(-0.50; 0.12)	0.230
CGI-I	Sertindole	16	120	-0.22	(-0.62; 0.17)	0.267
		20	121	-0.11	(-0.50; 0.28)	0.586
		24	115	-0.19	(-0.59; 0.21)	0.354
	Haloperidol	16	123	-0.15	(-0.55; 0.25)	0.457

CI: confidence interval

a The treatment effect was estimated *versus* sertindole 8mg/day.

3.2.3 Study 97203 – The French Study

Sertindole has shown efficacy comparable to that of the typical antipsychotic, haloperidol, in several studies. The objective of the study was to compare the efficacy of sertindole to that of the second generation antipsychotic, risperidone, in a flexible-dose design.[48,49] At the time the study was conducted, risperidone was the most recently marketed antipsychotic in France.

Patients (N=186) with schizophrenia were randomised to sertindole or risperidone and after a placebo washout period and 2 weeks of titration to 16mg/day sertindole or 6mg/day risperidone, the investigator was free to adapt the dose according to the patient's response to treatment within the limits: 12 to 24mg/day for sertindole and 4 to 10mg/day for risperidone. The mean PANSS total score at baseline was 100 in the sertindole group and 99 in the risperidone group, indicating that the patients were severely ill.

At the end of the study, the mean modal dose was 16.2mg/day for sertindole and 6.6mg/day for risperidone. The PANSS total score improved from baseline to endpoint in both treatment groups (Panel 24).

Panel 24 Study 97203 – PANSS Scores at Endpoint (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment	Dose (mg/day)	N	Change from Baseline	Treatment Difference[a]	95% CI	p-value
PANSS total	Sertindole	12 to 24	91	-29.4	-	-	-
	Risperidone	4 to 10	85	-25.0	-4.4	(-10.66; 1.84)	0.166
PANSS positive	Sertindole	12 to 24	91	-7.8	-	-	-
	Risperidone	4 to 10	85	-7.1	-0.66	(-2.63; 1.31)	0.507
PANSS negative	Sertindole	12 to 24	91	-7.84	-	-	-
	Risperidone	4 to 10	85	-6.11	-1.73	(-3.27; -0.20)	0.028
CGI-S	Sertindole	12 to 24	91	-1.39	-	-	-
	Risperidone	4 to 10	85	-1.26	-0.13	(-0.46; 0.20)	0.442
CGI-I	Sertindole	12 to 24	91	-1.61	-	-	-
	Risperidone	4 to 10	85	-1.50	-0.11	(-0.48; 0.27)	0.571

CI: confidence interval

a Treatment difference *versus* risperidone

The analyses of the PANSS total score as well as the PANSS positive and negative subscale scores showed improvement in both treatment groups. In an ANCOVA based on the LOCF and OC data scores, sertindole-treated patients had significantly greater improvement than risperidone-treated patients on the PANSS negative subscale from baseline to endpoint. Furthermore, repeated measurements analyses showed that sertindole-treated patients had significantly greater improvements on the PANSS total as well as the positive and negative subscales.

3.3 Long-term Efficacy

3.3.1 Study M93-132 – 1-year Haloperidol-referenced Study

Study M93-132, a one-year, double-blind, positive-controlled study was conducted specifically to assess the long-term use of sertindole.

A total of 282 patients with a DSM-III-R or DSM-IV diagnosis of chronic or sub-chronic schizophrenia were randomised and had post-baseline efficacy assessments. The patients were outpatients who were stable on their prescribed antipsychotic treatment (patients treated with clozapine were excluded).

Patients were divided into two groups before randomisation: Those stable on haloperidol and those stable on all other antipsychotics (excluding clozapine). From each of those two groups, patients were randomised to sertindole or haloperidol in equal numbers before entering the transition period. During the transition period, spanning 22 days, the patients' previous antipsychotic medication was down-titrated while they were up-titrated to doses of 24mg/day for sertindole or 10mg/day for haloperidol.

Efficacy was measured as time-to-treatment failure after the end of the transition period (Day 35). Treatment failure was defined as one or more of the following:

- the patient required hospitalisation due to an exacerbation of schizophrenia
- the patient had a 20% or greater deterioration in BPRS total score from the primary baseline evaluation, or worsened by 8 or more on the sum of the four positive symptom subscale items of the BPRS (conceptual disorganisation, suspiciousness, hallucinatory behaviour, unusual thought content), or worsened by 5 or more on the sum of any two of the four positive symptom subscale items of the BPRS
- the patient discontinued treatment due to lack of efficacy or non-compliance
- the patient used antipsychotics other than double-blind study drug.

Both treatment groups showed similar improvements on the efficacy rating scales, movement rating scales, and quality of life evaluations.

Time-to-treatment failure after the start of the maintenance period was not significantly different between sertindole- and haloperidol-treated patients. Overall retention rates at selected time points are presented in Panel 25. The most frequently reported reason for treatment failure was ≥20% deterioration in BPRS total score, observed in 23 sertindole-treated patients and 34 haloperidol-treated patients.

Haloperidol-treated patients had a significantly earlier time-to-treatment failure due to hospitalisation for psychotic decompensation ($p<0.05$) and premature treatment discontinuation for non-compliance ($p<0.05$). Both treatment groups had mean decreases from baseline to the evaluation at Month 12 for PANSS total, Scale for the Assessment of Negative Symptoms (SANS) total, BPRS total, and CGI scores, indicating improvement.

The retention rates were similar in both treatment groups, which supports comparable maintenance of efficacy for sertindole and haloperidol (Panel 25).

Panel 25 Study M93-132 – Retention Rates During Maintenance Treatment (ITT)

Patient Group/ Time period	Sertindole 24mg/day N	Sertindole 24mg/day Retention Rate (95% CI)	Haloperidol 10mg/day N	Haloperidol 10mg/day Retention Rate (95% CI)
Stable on haloperidol				
Week 6	32	1.00 (1.00; 1.00)	42	1.00 (1.00; 1.00)
Week 7	29	0.94 (0.85; 1.00)	38	0.93 (0.85; 1.00)
Week 8	29	0.94 (0.85; 1.00)	36	0.88 (0.78; 0.98)
Week 10	24	0.84 (0.70; 0.97)	34	0.83 (0.72; 0.94)
Week 12	21	0.80 (0.66; 0.94)	31	0.76 (0.63; 0.89)
Month 6	20	0.80 (0.66; 0.94)	20	0.60 (0.45; 0.75)
Month 12	14	0.60 (0.41; 0.78)	16	0.54 (0.38; 0.70)
> Month 12	13	0.55 (0.36; 0.75)	14	0.47 (0.31; 0.64)
Stable on other antipsychotic (excluding clozapine)				
Week 6	62	1.00 (1.00; 1.00)	67	1.00 (1.00; 1.00)
Week 7	55	0.90 (0.83; 0.98)	57	0.89 (0.82; 0.97)
Week 8	51	0.87 (0.78; 0.95)	52	0.83 (0.74; 0.92)
Week 10	47	0.82 (0.72; 0.92)	49	0.78 (0.68; 0.88)
Week 12	42	0.76 (0.66; 0.87)	45	0.72 (0.61; 0.83)
Month 6	33	0.71 (0.59; 0.83)	35	0.60 (0.48; 0.73)
Month 12	23	0.57 (0.44; 0.71)	28	0.52 (0.39; 0.64)
> Month 12	20	0.52 (0.38; 0.66)	26	0.50 (0.37; 0.62)

N = number of patients who entered the treatment period

CI: confidence interval

The mean PANSS total score at baseline was 60 in both treatment groups, indicating that the patients were moderately ill. In spite of their stable status, patients in both treatment groups showed improvement in PANSS total scores throughout the study (Panel 26).

Panel 26 Study M93-132 – Efficacy Variables (ANCOVA, ITT, LOCF)

Efficacy Variable	Treatment (dose)	Month	N	Mean Change[a]	Treatment Difference[b]	95% CI	p-value[c]
PANSS total	Sertindole (24 mg/day)	3	91	-2.61	-	-	-
		6	91	-2.24	-	-	-
		12	91	-2.56	-	-	-
	Haloperidol (10 mg/day)	3	108	-1.86	0.23	(-3.28; 3.74)	0.897
		6	108	-1.47	0.14	(-3.51; 3.79)	0.942
		12	108	-1.08	-0.61	(-3.19; 4.41)	0.755
PANSS positive	Sertindole (24 mg/day)	3	91	-0.55	-	-	-
		6	91	-0.52	-	-	-
		12	91	-0.51	-	-	-
	Haloperidol (10 mg/day)	3	108	-0.64	0.49	(-0.61; 1.59)	0.385
		6	108	-0.55	0.34	(-0.82; 1.50)	0.569
		12	108	-0.31	0.11	(-1.09; 1.31)	0.852
PANSS negative	Sertindole (24 mg/day)	3	91	-0.84	-	-	-
		6	91	-0.74	-	-	-
		12	91	-0.87	-	-	-
	Haloperidol (10 mg/day)	3	108	-0.61	0.05	(-1.17; 1.27)	0.939
		6	108	-0.43	-0.13	(-1.46; 1.20)	0.844
		12	108	-0.44	-0.28	(-1.53; 0.97)	0.668
CGI-S	Sertindole (24 mg/day)	3	91	-0.12	-	-	-
		6	91	-0.10	-	-	-
		12	91	-0.14	-	-	-
	Haloperidol (10 mg/day)	3	108	-0.04	-0.04	(-0.22; 0.14)	0.695
		6	108	-0.05	-0.02	(-0.20; 0.16)	0.870
		12	108	-0.01	-0.14	(-0.34; 0.06)	0.156

CI: confidence interval

a Mean change from baseline

b Treatment group mean difference calculated as the score for the 24mg/day sertindole minus that for the 10mg/day haloperidol. The treatment difference was divided by two within stratum. The difference shown is the sum across strata.

c Statistically significant at the 5% level; two-tailed

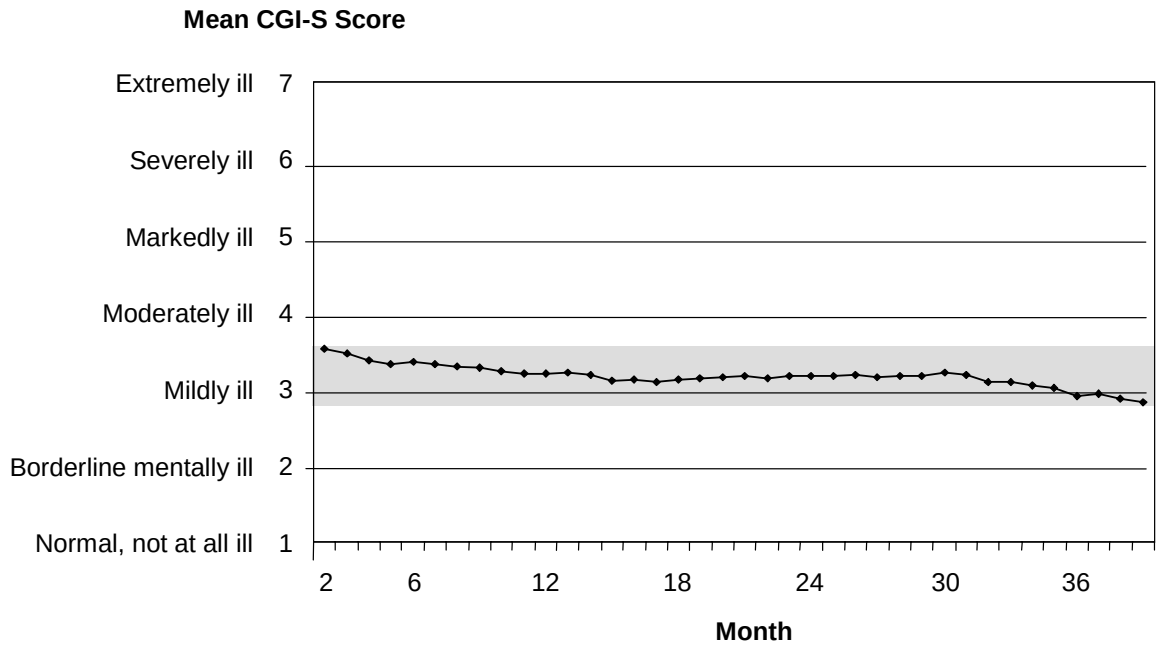
3.3.2 Other Long-term Studies

Although the main purpose of the open-label extension studies was to assess long-term safety, efficacy measures were performed in several of the studies. Overall, the efficacy scores improved during sertindole treatment compared with baseline. The symptomatic improvement occurred within the first two months of treatment and was maintained during long-term treatment.

Study M94-222 – 4-year Open-label

In the longest running study (Study M94-222), CGI-S scores were measured at regular intervals. Of the 701 patients who entered the study, 249 patients completed the full 4-year study period (Panel 27). CGI-S scores of 3 and 4 were the most prevalent in those who completed the full 4-year study period and there were no major changes in the pattern of scores, showing that sertindole's efficacy was maintained in completers during 4 years of treatment (Panel 27).

Panel 27 Study M94-222 – CGI-S Score by Month (OC)



Number of patients:
Month 1: 612 patients; Month 6: 434 patients; Month 12: 321 patients; Month 18: 254 patients; Month 24: 203 patients; Month 30: 155 patients; Month 36: 98 patients; Month 40: 7 patients

In this study, 24mg/day sertindole was the modal dose for 55% of the patients, 20mg/day was the modal dose for 22% of the patients, and 16mg/day was the modal dose for 9% of the patients.

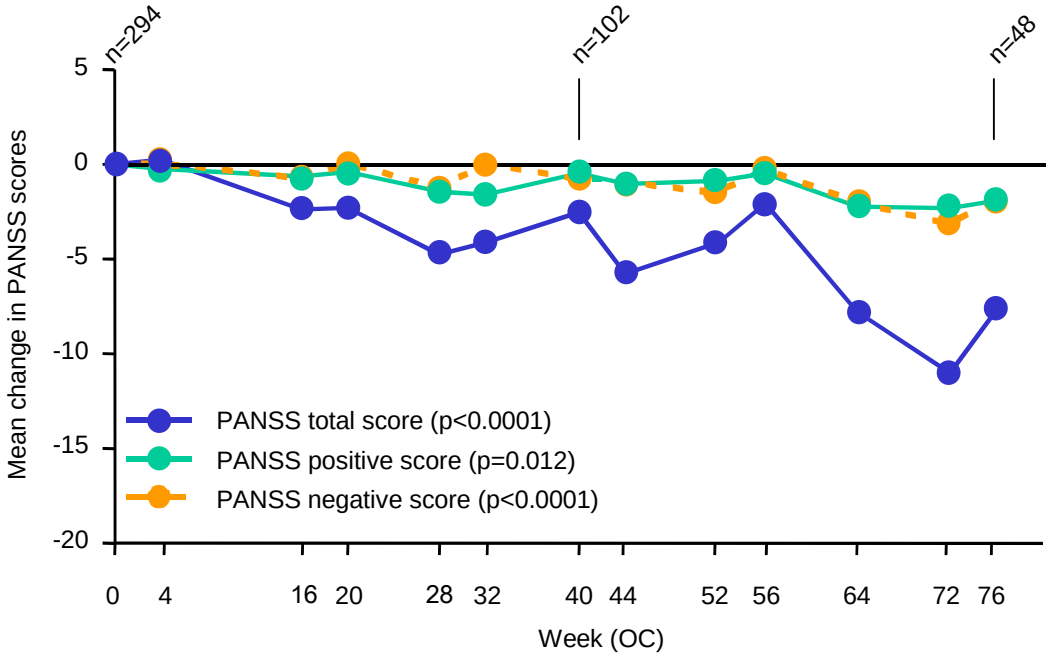
Study M95-339 – Open-label Extension of the European Study

In order to assess the long-term effects of sertindole in the treatment of schizophrenia, patients who had completed 8-week Study M95-342 were asked to participate in a long-term extension study (Study M95-339). A total of 294 patients were enrolled within 3 to 7 days of the final Study M95-342 visit; 209 patients completed the study.

The extension study was an open-label, flexible-dose (8 to 24mg/day) study in patients with schizophrenia. The study consisted of a 28-day dose-titration period, followed by a flexible-dose 6- to 18-months maintenance period, and a 3- to 5-week follow-up period. The majority of patients (56%) received a modal dose of 16mg/day sertindole.

There was a treatment-related improvement in the PANSS total score. Statistical analysis showed a significant trend for the PANSS total score to decrease over time. The same trend was seen for the PANSS positive and negative subscale scores (Panel 28) and for the general psychopathology subscale score. Furthermore, there was an overall improvement in the CGI-S score following sertindole treatment. Statistical analysis using a linear model for repeated measurements confirmed that there was improvement over time. The effective dose for most patients was 16mg/day sertindole.

Panel 28 Study M95-339 – Change from Baseline in PANSS Scores (OC)

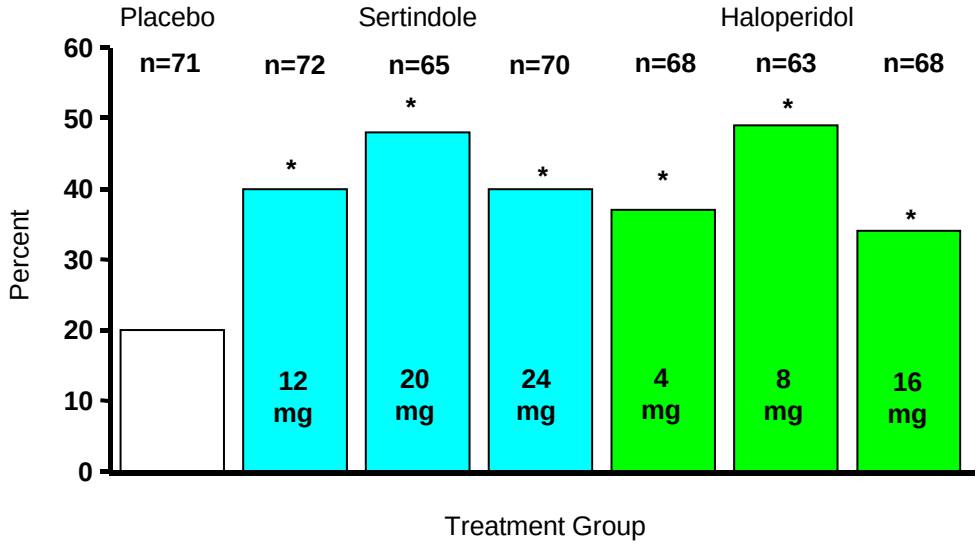


3.4 Responder Rates and Time to Response

In Study M93-113, a larger proportion of patients in the active treatment groups had improvements from baseline to the final evaluation in PANSS total score compared with the

placebo group. Each of the sertindole groups demonstrated statistically significantly higher proportions of patients who achieved ≥30% (Panel 29), ≥40%, or ≥50% improvement from baseline in PANSS total score compared with the placebo group. Similar results were seen in Study M93-098.

Panel 29 Study M93-113 – Responder Rates

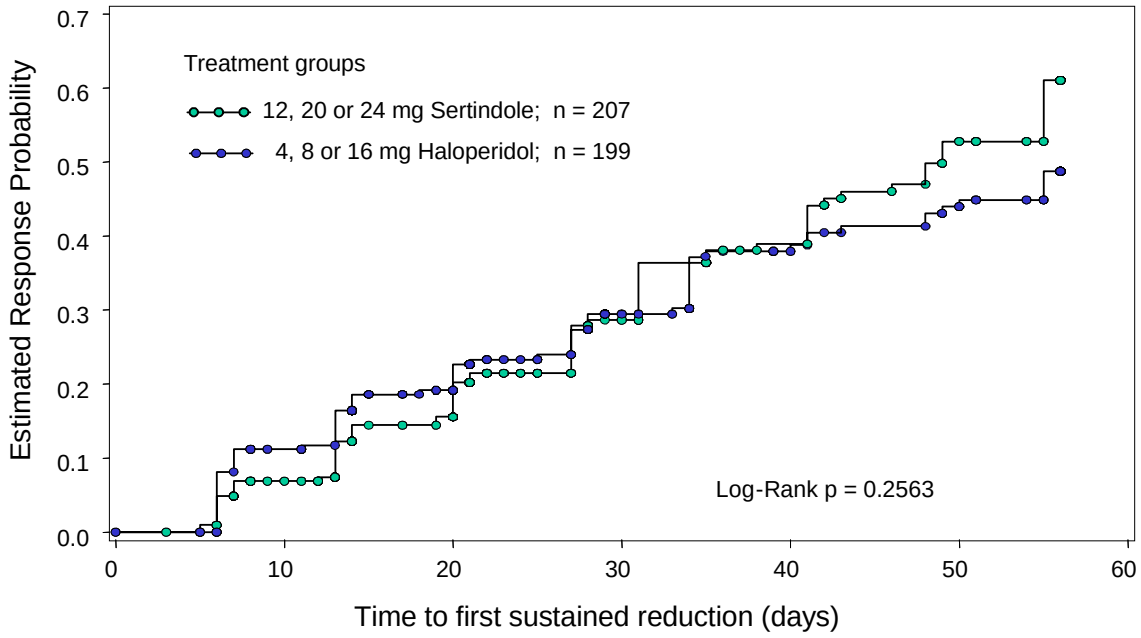


Proportion of patients in each treatment group with ≥30% reduction from baseline in PANSS total score (LOCF)
* p≤0.05 *versus* placebo (Cochran-Mantel-Haenszel)

In order to assess any possible effects of the titration period on treatment response, the time to sustained response for sertindole was compared to that of haloperidol in the large adequate and well-controlled clinical study, Study M93-113 (section 3.2.1).

The time to sustained response was defined for individual patients as the time from start of randomised treatment to the first time point at which the patient had a sustained decrease of 30% or more in PANSS total score. The time to sustained response for each treatment group is depicted in Panel 30 and shows that it was similar for sertindole and haloperidol.

Panel 30 Study M93-113 – Time to Sustained Response (≥30% Decrease from Baseline in PANSS Total Score for Each Patient)



3.5 Effective Dose Range

Patients in the placebo-controlled or dose-comparison studies were treated with fixed dosages of 8, 12, 16, 20, or 24 mg/day sertindole:

- 8mg/day sertindole was shown in Study M92-762 to be no more efficacious than placebo as measured by the PANSS total score; similar results were seen in Study M95-342.
- 12mg/day sertindole was used in Studies M93-113, M92-762, and M92-817; an analysis of pooled data from these studies showed that is was more efficacious than placebo as measured by the PANSS total scores. Based on the pooled data, the effect size of treatment with 12mg/day sertindole was estimated to 0.25.
- 16mg/day sertindole was the most efficacious dose used in Study M95-342 where it resulted in greater reductions in PANSS total score than did 20 or 24mg/day sertindole, albeit they all resulted in greater improvements than the sub-effective 8mg/day sertindole; 16 and 24mg/day sertindole were significantly better than 8mg/day sertindole.
- 20mg/day sertindole was used in Studies M93-113, M93-098, M92-762, and M95-342. Pooled data from Studies M93-113, M93-098, and M92-762 showed that the PANSS total score for patients who received 20mg/day sertindole decreased significantly more than for patients who received placebo.
- 24mg/day sertindole was used in studies M93-113, M93-098, and M95-342 and showed significantly greater reductions in PANSS total scores in all studies compared to placebo.

Sertindole was used in flexible-dose regimens in the controlled Studies M91-645, 97203, and the SCoP study:

- Study M91-645 was an early dose-ranging study of 7 weeks' duration in which patients were titrated to a clinical response and maintained on that dose to the end of the study. The mean sertindole dose at the end of the study was 16mg/day.
- In Study 97203, following the 2-week titration period to 16mg/day sertindole, investigators were free to adapt the dose according to the patient's response to treatment within the range of 12 to 24mg/day. The mean modal dose in this study was 16.2mg/day.
- In the SCoP study, patients were treated according to the labelling of their respective countries. A total of 4905 patients were treated with sertindole for up to 63.5 months (median: 360 days). Approximately 80% of the patients treated with sertindole received doses within the dose range recommended in the Summary of Product Characteristics (SPC) (12 to 20mg/day). There were more patients who received the lower doses in the recommended range (Panel 18); this may reflect the common clinical practice of using the lowest effective dose for each individual patient.

The results from fixed-dose studies show that all doses of sertindole (12, 16, 20, and 24mg/day) are efficacious and no dose shows consistently higher efficacy than the others. A dose of 8mg/day sertindole was sub-effective.

In studies where the investigators were free to adapt the dose according to the patient's clinical response, 12 and 16mg/day sertindole were the preferred doses.

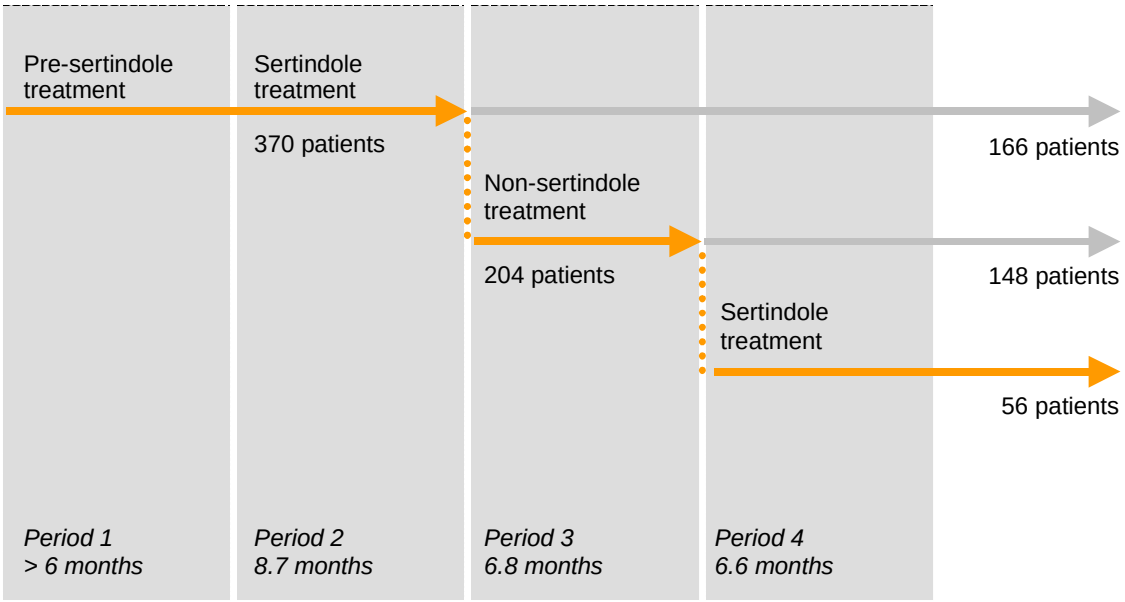
3.6 Other Efficacy Measures – The Niche Study

To assess patients for whom sertindole had proven to provide a beneficial treatment, the Niche Study was conducted under Amendment 7 to the ESES study. The study demonstrated that a group of patients will benefit more from sertindole treatment than from treatment with other antipsychotics.

The Niche Study was a retrospective data analysis from patients who had received sertindole in various other studies. The study included 4 treatment periods (Panel 31):

- Period 1 – The patients received antipsychotic treatment other than sertindole. Due to lack of efficacy, intolerance, or non-compliance, they stopped this treatment.
- Period 2 – The patients received sertindole.
- Period 3 – The patients again received antipsychotic treatment other than sertindole due to the market suspension of sertindole.
- Period 4 – The patients who did not benefit from the treatment in Period 3 again received sertindole through a compassionate use program. Thus, these patients received sertindole twice, both times after having been treated with other antipsychotics.

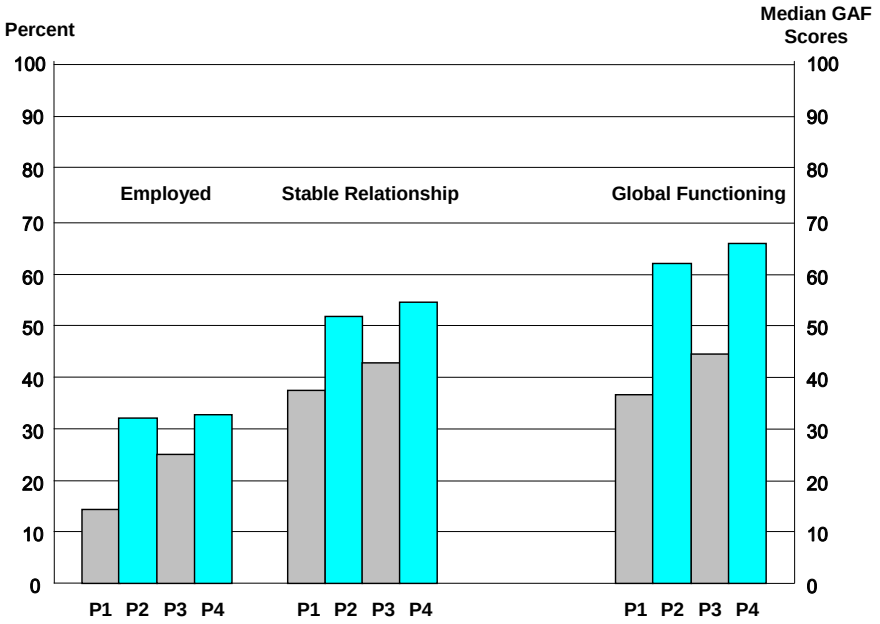
Panel 31 The Niche Study – Study Design



The patients in Period 1 were patients who had not had an adequate clinical response to at least 6 months of treatment with a second generation antipsychotic, as judged by the investigator. A shorter treatment period was allowed if the investigator was able to assess the lack of treatment response and the need for a change in treatment. Concomitant medication was allowed; only antipsychotic concomitant medication was recorded in the case report form.

The proportion of patients who were not hospitalised, who were employed, or who were in a stable relationship was greater during sertindole treatment than during other treatments. Global functioning levels (as measured by the GAF scale) were higher during sertindole treatment than during other antipsychotic treatment (Panel 32).

Panel 32 The Niche Study – Quality of Life and Global Functioning



3.7 Efficacy Conclusions

Study M93-113, unique in its design, Study M93-098, and Study M92-762 have established that sertindole is efficacious in the acute treatment of patients with schizophrenia. Together, these adequate and well-controlled studies form the core evidence for the efficacy of sertindole.

The long-term Study M93-132 show that outpatients with stable schizophrenia who were withdrawn from other antipsychotics could be stabilised and are treated effectively with sertindole over a 12-month maintenance period.

As shown in the well-controlled studies, sertindole is efficacious in doses from 12 to 20mg/day, with no additional improvement in efficacy with 24mg/day sertindole compared to 20mg/day sertindole.

The efficacy of sertindole is similar to that of other conventional and second generation antipsychotics; sertindole was comparable to haloperidol and risperidone in terms of improving the positive symptoms of schizophrenia (PANSS total and positive subscale scores).

Several clinical studies also suggested that sertindole treatment may reduce negative symptoms to a larger degree than haloperidol, and possibly even risperidone as measured by the PANSS negative subscale score.

The Niche study has demonstrated that a group of patients will have greater benefits with sertindole treatment than with other antipsychotics.

4 Effect on Suicide and Suicide Attempts

4.1 Suicide in Schizophrenia

Suicide is a major contributor to the mortality of patients with schizophrenia and it is the leading cause of premature death.[50]

Overall, approximately 50% of patients with schizophrenia attempt suicide during their lifetime and approximately 5 to 10% die from suicide.[51,52,53] Importantly, for suicide, previous suicide attempts are one of the major risk factors: 90% of people who commit suicide have made at least one prior attempt.[54]

Suicide and suicide attempts in schizophrenia may be linked to psychotic symptoms and to depressive features, and factors that may lead to treatment interruption or discontinuation and relapse. Additional risk factors for suicide are being young, male, at an early stage of illness, socially isolated, unemployed, having a recent admission to hospital with accompanying depression or suicidal ideas, a feeling of hopelessness, and frequent relapses with numerous admissions to hospital.[55]

Suicide prevention in patients with schizophrenia has been recognised by the FDA as an indication.

Studies examining the effects of typical antipsychotics on suicide and suicidal ideation have not identified a change in the incidence of suicide with their use and some have even suggested that their use may increase the risk. A complicating factor especially for typical antipsychotics is the emergence of akathisia, a state of intense inner restlessness, which may lead some patients to attempt suicide.[56]

The effect of second generation antipsychotics on suicidality in schizophrenia is also still unclear. Currently, there is only evidence for clozapine, which has been shown to reduce the risk of suicidal behaviour in patients with schizophrenia or schizoaffective disorders. In the International Suicide Prevention Trial (InterSePT), clozapine reduced the risk of suicide in patients with schizophrenia or schizo-affective disorder at high risk of suicide by preventing suicide attempts.[56] However, clozapine is associated severe side effects, including the risk of agranulocytosis at a rate of approximately 7 cases per 1000 PYE and the rate of death from clozapine due to agranulocytosis is approximately 0.2 cases per 1000 PYE.

4.2 Clinical Studies

In the clinical studies with sertindole included in the original NDA submitted in 1995, the suicide mortality rate was 0.42 per 100 PYE. Although not directly comparable, these numbers appear to be lower than those observed in the clinical studies with olanzapine and risperidone at the time of their respective marketing approvals (Panel 33).

Panel 33 Suicide Rates in the Sertindole Clinical Studies and the Summary Basis of Approvals for Olanzapine and Risperidone

	Sertindole 1995 NDA	Sertindole 2008 NDA	Olanzapine SBA	Risperidone SBA
Exposure (PYE)	476.5	1840	1122	858
Suicide mortality /100 PYE (95% CI)	0.42 (0.105 – 1.677)	0.27 (0.09 – 0.63)	0.89 (0.43 – 1.64)	1.17 (0.56 – 2.14)

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

No direct comparative results are available from the clinical studies as patients in the acute phase of illness usually are hospitalised for a large part of the controlled studies. In addition, the treatment duration of acute studies is too short to provide conclusive data. Therefore, suicide rates often stem from uncontrolled exposure.

4.3 Epidemiological Studies

The low rate of suicides seen in the clinical studies was also observed in ESES, the Sertindole Safety Survey, and the ESES Crossover Sub-study (Panel 34). In the latter study, in which the patients acted as their own controls, the suicide rate increased after patients were switched to other antipsychotic medication (post-sertindole). However, the number of events in this study was low.

Panel 34 Suicide Rates in the ESES Study, the Sertindole Safety Survey, and the ESES Crossover Sub-study

Study	Suicide Rate /100 PYE	(95% CI)
ESES (n=8608)	0.21	(0.09 – 0.41)
Sertindole Safety Survey (n=1439)	0.11	(0.01 – 0.41)
ESES Crossover Sub-study (n=1112)		
During sertindole	0.10	(0.001 – 0.57)
Post sertindole	0.71	(0.35 – 1.27)

CI: confidence interval; PYE: patient years of exposure

4.4 The SCoP Study

4.4.1 Methodology Specific to Case Collection and Analyses of Effects on Suicide Attempts

As described in sections 4.2 and 0, a lower rate of suicide was noted in the clinical trials and in the epidemiological studies with sertindole than in the clinical studies of other newer antipsychotics (as reported in the Summary Basis of Approval).

To confirm the potential benefit of sertindole in reducing the risk of suicide attempts, a composite endpoint, fatal plus non-fatal suicide attempts, was included in the SCoP study in agreement with the FDA (details of the methodology used in the SCoP study are presented in Appendix 1). This endpoint is well documented, with evidence of intended self-harm, and

meaningful, as even non-fatal suicide attempts still carry a significant risk of serious injury and death.

The SCoP study aimed at recruiting a population of patients with schizophrenia representative of the target population. Patients were included irrespective of their suicide risk. With the large sample of close to 10,000 patients, the study covered the range of risk usually seen in these patients, including also a significant proportion of patients with relatively high risk as indicated by a history of recent suicide attempts. In this respect, the SCoP study is different from clinical studies, which usually exclude patients at high risk of suicide at the time of randomisation. Due to this exclusion and their short duration, individual acute studies are usually unable to show a treatment effect on suicidality. The SCoP is also different from the InterSePT study that compared the effect of clozapine to that of olanzapine on suicidal behaviour, which recruited an enriched sample of patients at high risk of suicide.[56]

The SCoP study included information on the patients' history of suicide attempts and data on suicides and suicide attempts with or without hospitalisation. Information on these events, including an assessment concerning the intent to die, was reported by the investigators by way of serious adverse event reports, that is, within 24 hours of having knowledge of the event. Investigator training included instructions on the reporting of suicide attempts, whether fatal or non-fatal. During the study and at the time of the close-out visits at the end of the study, monitoring focussed on identifying whether there were any unreported events. The near complete follow-up provides additional reassurance that the relevant events were captured.

Event rates are presented for 3 reporting periods (ORT+1 [monotherapy+1 day], WRT+1 [monotherapy and polytherapy+1 day], and WRT+30 [monotherapy and polytherapy+30 days]). Data from the patients who received clozapine or were treated simultaneously with sertindole and risperidone before the event were excluded from the analyses.

The serious adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The Independent Safety Committee (ISC) conducted a blinded review of all events and classified the deaths into the one of the three categories *Cardiac*, *Suicide*, or *Other*; the non-fatal events were classified into one of the three categories *Cardiac*, *Suicide attempts*, or *Other*. The ISC definition used for grouping events into the category of suicide attempts was broader than the MedDRA classification, as it not only included completed suicides and suicide attempts with clearly stated intent to die, but also overdoses and self-injuries where suicidal intent was absent or unclear. Furthermore, the ISC classification (*ISC Suicide Attempts*) also included suicidal tendencies or ideations, which were not associated with an observable behaviour.

The categorisation based on the MedDRA terms *completed suicide* or *suicide attempt* included behaviours reported by the investigator as suicide or suicide attempts with intent to commit suicide. This classification was thus narrower than the ISC definition. Also, this event definition was narrower than that used in the InterSePT study, which also used hospitalisations to prevent a suicide attempt and ratings of worsening in suicidality as outcome parameters.[56]

During the review of the sertindole NDA, the FDA requested that the events in the category *ISC Suicide Attempts* be blindly reviewed by an independent expert group and classified according to the *Columbia Classification Algorithm of Suicide Assessment* (C-CASA).[54] The C-CASA uses definitions of suicidality derived from empirical findings on the phenomenology of suicidality and identified predictive and risk factors and has eight categories that distinguish suicidal events from non-suicidal events and indeterminate or potentially suicidal events (Appendix 2). The criteria for a suicide attempt include both self-injurious behaviour and suicidal intent (at least some intention to commit suicide). The inclusion of intent in the definition of suicide allows a distinction between those who self-injure in an attempt to die and those who self-injure for purely other non-suicidal reasons (for example, to manage affect). The review was performed by the expert group at Columbia University (New York), in accordance with the C-CASA.[54]

The C-CASA categories *completed suicide*, *suicide attempt*, or *preparatory act toward imminent suicidal behaviour* (categories 1, 2, and 3 [Appendix 2]; hereafter termed *C-CASA Suicide Attempts*) were included in the analysis, as requested by the FDA.

Appendix 3 presents all cases by treatment group (sertindole or risperidone), reporting period (ORT+1, WRT+1, and WRT+30), and classification (MedDRA, C-CASA, and ISC).

4.4.2 Demographics for Patients with Suicide Attempts

The demographics for patients classified according to C-CASA and with events in the ORT+1 are summarised below. A total of 36 patients in the sertindole group and 54 patients in the risperidone group had at least one suicide attempt (fatal or non-fatal) during only randomised treatment. The subgroups were similar to the overall population, except for a higher proportion of patients with a positive history of suicide attempts in the subgroup of patients with at least one suicide attempt (Panel 35).

Panel 35 The SCoP Study – Demographic Characteristics for Patients with Suicide Attempts (Fatal or Non-fatal) according to C-CASA (ORT+1 day Period)

	Sertindole (N=36)	Risperidone (N=54)	Sertindole (N=4905)	Risperidone (N=4904)
	Patients with Suicide Attempts	Patients with Suicide Attempts	All Patients	All Patients
Sex (male [%])	50	52	55	55
Mean age (years)	36	37	38	38
European region (%)	67	70	72	72
Duration of schizophrenia (%)				
<5 years	33	35	30	30
5 to 10 years	32	39	26	26
>10 years	35	26	42	42
Time since last suicide attempts (%)				
No attempts	45	57	88	88
<1 year	19	22	2	2
1 to 5 years	19	17	5	4
>5 years	17	4	5	6

4.4.3 Characteristics of Suicide Attempts

The distribution of violent and non-violent suicide attempts is shown in Panel 36. Violent attempts, which have a higher lethality than non-violent attempts, were more frequent in the risperidone group (C-CASA, ORT+1).

Panel 36 The SCoP Study – Characteristics of Suicide Attempts (C-CASA ORT+1 day Period)

	Sertindole	Risperidone
Type of Suicide Attempt	n (%)	n (%)
Total	36	54
Non-violent	23 (64)	25 (47)
Overdose	20	21
Poisoning	3	4
Violent	13 (36)	28 (53)
Cutting	1	6
Drowning	0	1
Hanging	6	12
Jumping	6	9
Unknown	0	1

4.4.4 Suicide Attempt Rates According to C-CASA, MedDRA, and ISC

This section presents the treatment effects of sertindole compared to risperidone for events classified according to C-CASA, MedDRA, and ISC for the three reporting periods (ORT+1, WRT+1, and WRT+30). A table detailing the distribution of events in the three categories is presented in Appendix 3.

The level of agreement between the C-CASA and the MedDRA classification for both the ORT+1 and the WRT+1 were *almost perfect*, with kappa values[57] of 0.88 and 0.84, respectively; for the WRT+30, the kappa value was *substantial* (kappa = 0.79) (Panel 37).

Panel 37 Kappa Values

Period	Pairwise Comparisons (95% CI) MedDRA*C-CASA	Pairwise Comparisons (95% CI) ISC*C-CASA	Pairwise Comparisons (95% CI) MedDRA*ISC
ORT+1 day	0.884 (0.81 – 0.96)	0.562 (0.44 – 0.69)	0.511 (0.39 – 0.64)
WRT+1 day	0.841 (0.75 – 0.93)	0.469 (0.33 – 0.61)	0.396 (0.27 – 0.52)
WRT+30 days	0.789 (0.68 – 0.90)	0.093 (-0.03 – 0.22)	0.065 (-0.04 – 0.17)

CI: confidence interval

Interpretation of Kappa coefficients: <0 *no agreement*; 0.0-0.2 *slight agreement*; 0.21-0.40 *fair agreement*; 0.41-0.60 *moderate agreement*; 0.61-0.80 *substantial agreement*; 0.81-1.0 *almost perfect agreement*

The level of agreement between the C-CASA and the ISC classification was weaker: *moderate* for the ORT+1 the WRT+1 (kappa = 0.56 and 0.47, respectively) and only *slight* for the WRT+30 (kappa = 0.09). This was similar to that of the agreement between the MedDRA and ISC classification.

This can be explained by the fact that the C-CASA, like the MedDRA classification, is based only on observable behaviours with a clear intent to commit or prepare for a suicide, whereas the ISC classification was broader as it also included overdoses with unclear suicidal intent as well as suicidal ideation and suicidal tendency not associated with an observable behaviour.

4.4.4.1 C-CASA of Suicide Events

The C-CASA is presented first since it can be considered to be the most relevant classification as it is based on blinded expert assessment according to objective criteria accepted as the standard by the FDA. The most relevant period for the evaluation of the effect of sertindole on suicide and suicide attempts is the ORT+1 since patients during this period received only the randomised treatment and no add-on antipsychotics. For this period, there is also no confounding due to treatment discontinuation or start of new treatments, as could be the case during the 30-day post-treatment period.

In the C-CASA there were 36 suicide attempts in the sertindole group and 54 in the risperidone group that occurred during antipsychotic monotherapy with sertindole or risperidone. The suicide attempt (fatal plus non-fatal) rates were 0.57 and 0.75 per 100 PYE in the sertindole and risperidone groups, respectively, and the hazard ratio was

0.661 (p = 0.0594) (Panel 38). This analysis therefore demonstrated a reduction in the risk of fatal plus non-fatal suicide attempts for sertindole-treated patients by one-third compared to that for risperidone-treated patients. The corresponding Kaplan-Meier plot for the C-CASA for the ORT+1 is presented in Panel 39.

Panel 38 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to C-CASA (ORT+1 day Period)

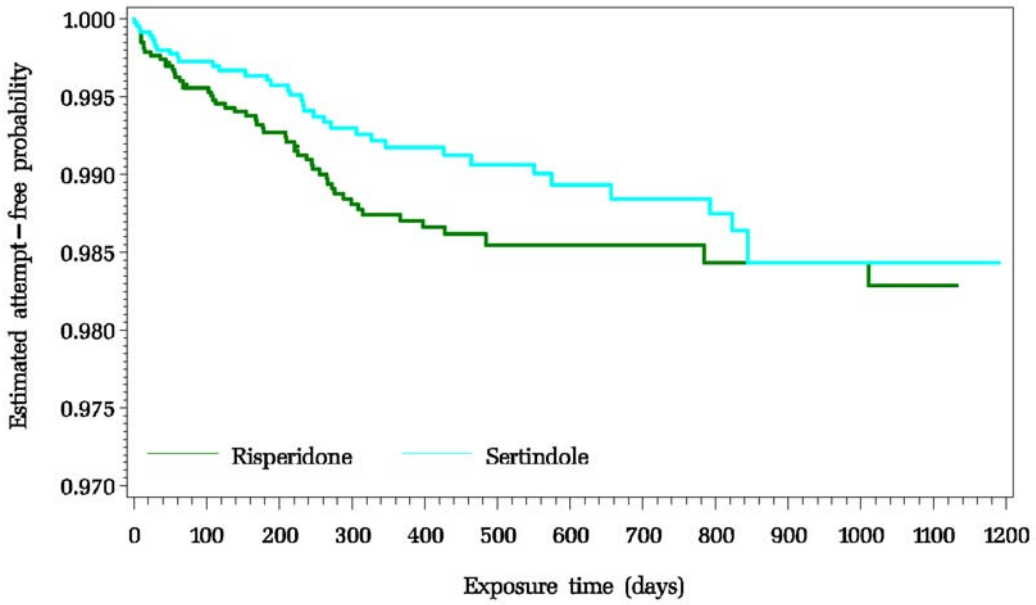
Events	Sertindole Number of Suicide Attempts (Rate per 100 PYE)	Risperidone Number of Suicide Attempts (Rate per 100 PYE)	Hazard Ratio[a]	Two-sided p-value
All patients treated (n)	4905	4904		
Suicide attempts (fatal plus non-fatal)	36 (0.57)	54 (0.75)	0.661	0.0594
Suicide attempts (fatal plus non-fatal) 1-year	27 (0.81)	47 (1.28)	0.546	0.0147
Completed suicides	9 (0.14)	19 (0.26)	0.502	0.0890
High-risk patients[b] (n)	348	335		
Suicide attempts (fatal plus non-fatal)	14 (3.25)	21 (5.15)	0.585	0.1218
Suicide attempts (fatal plus non-fatal) 1-year	13 (5.65)	20 (9.22)	0.567	0.1126

PYE: patient years of exposure

a Cox's Proportional Hazards Model

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

Panel 39 The SCoP Study – Kaplan-Meier Plot of Suicide Attempts (Fatal and Non-fatal) (C-CASA, ORT+1 day Period)



The vast majority of the suicide attempts occurred within the first year of treatment. A separate analysis of events occurring within this period with each drug was therefore conducted, as this analysis also limits possible confounding by the background events (for example, stressful life events, losses), which may increase in frequency over an extended period.

The Cox analyses with a fixed follow-up period of 1 year of treatment showed similar results to that for the entire treatment period, though with a stronger and more beneficial treatment effect of sertindole compared to risperidone (estimated hazard ratio of 0.546, p = 0.0147), showing a reduction of 45% in the risk of suicide attempts within the first year of treatment with sertindole compared to the first year of treatment with risperidone.

Patients with a history of suicide attempts are particularly at risk of attempting suicide and indeed of committing suicide. A substantial number of patients in the study had attempted suicide one or more times prior to entry in the study. The analysis of the subgroup of patients who had a previous suicide attempt within the last 5 years before entering the study (high-risk patients) showed a tendency for these patients to benefit more from sertindole treatment than from risperidone treatment (hazard ratio of 0.585, p=0.1218) (Panel 38).

The numbers of completed suicides according to the C-CASA during treatment with sertindole or risperidone (ORT+1) were 9 and 19, respectively, resulting in suicide rates of 0.14 and 0.26, respectively, per 100 PYE (Panel 38). The events coded as *completed suicide* in MedDRA were the same events classified as completed suicide in the C-CASA.

The results for the C-CASA for the periods WRT+1 and WRT+30 are summarised in Appendix 3.

4.4.4.2 MedDRA Classification of Suicide Events

The results of the MedDRA classification, which was based on a code of *completed suicide* or *suicide attempt*, are in line with those of the C-CASA and are summarised in Panel 40.

According to the MedDRA classification, a total of 34 patients in the sertindole group and 54 patients in the risperidone group had at least one suicide attempt (fatal or non-fatal) during the ORT+1. The corresponding rates of suicide attempts were 0.54 and 0.75 per 100 PYE in the sertindole and risperidone groups, respectively, and the estimated hazard ratio was 0.617 (p = 0.0307), showing a 38% reduction in the risk of suicide attempt for sertindole-treated patients compared to that for risperidone-treated patients (Panel 40). The Cox's regression analysis is adjusted for age, sex, duration of schizophrenia, time since last suicide attempt, and time since start of study. In the SCoP study report, the primary period of reporting for this endpoint was the WRT+30 and the Kaplan-Meier plot for this period is thus presented in Panel 41.

Again, a fixed follow-up period of 1 year of treatment showed similar results to that for the entire treatment period, though with a stronger and more beneficial treatment effect of sertindole compared to risperidone (estimated hazard ratio of 0.503, p = 0.0058), showing a reduction of nearly 50% in the risk of suicide attempts within the first year of treatment with sertindole compared to the first year of treatment with risperidone.

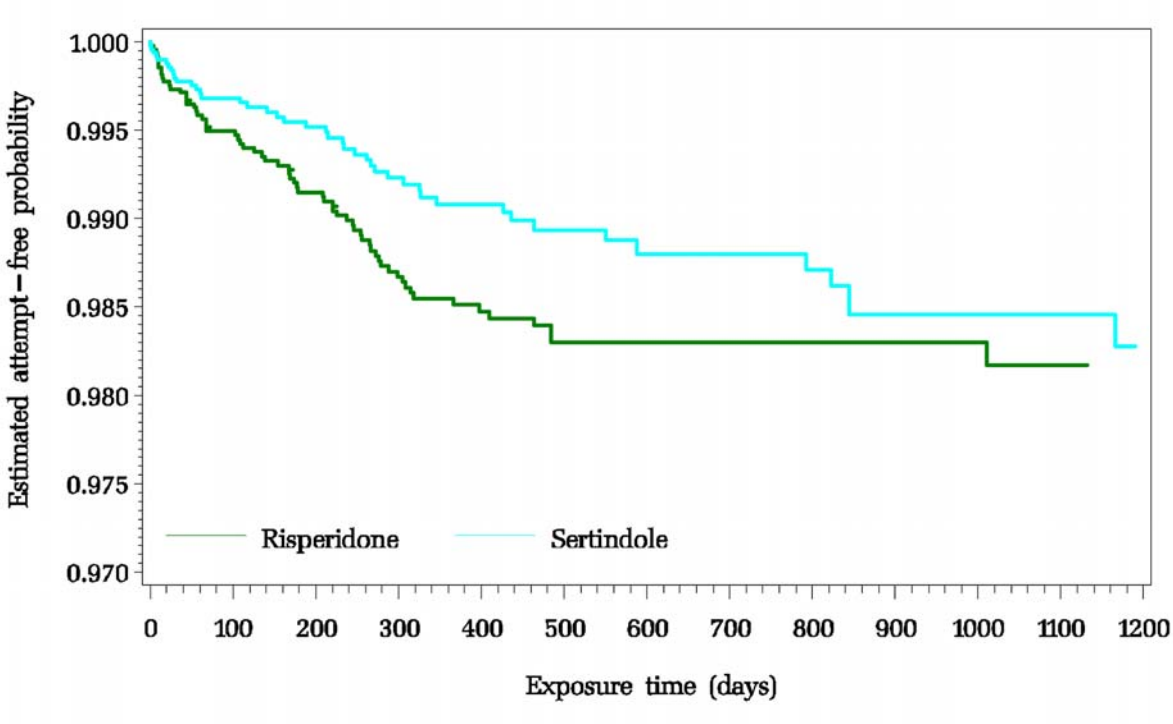
Panel 40 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to MedDRA

Events	Period	Sertindole Number of Suicide Attempts (Rate per 100 PYE)	Risperidone Number of Suicide Attempts (Rate per 100 PYE)	Hazard Ratio[a]	Two-sided p-value
Suicide attempts (fatal plus non-fatal)	ORT+1	34 (0.54)	54 (0.75)	0.617	0.0307
Suicide attempts (fatal plus non-fatal) 1-year	ORT+1	26 (0.78)	49 (1.34)	0.503	0.0058
Completed suicides	ORT+1	9 (0.14)	19 (0.26)	0.502	0.0890
Suicide attempts (fatal plus non-fatal)	WRT+1	36 (0.55)	55 (0.73)	0.660	0.0568
Suicide attempts (fatal plus non-fatal)	WRT+30	42 (0.61)	61 (0.77)	0.697	0.0768

PYE: patient years of exposure; ORT: only randomised treatment; WRT: whole randomised treatment

a Cox's Proportional Hazards Model

Panel 41 The SCoP Study – Kaplan-Meier Plot of Suicide Attempts (Fatal and Non-fatal) (MedDRA, WRT+30 days Period)



4.4.4.3 ISC Classification of Suicidality

The broader ISC classification, which included events without clear suicidal intent and suicidal ideations as well as suicidal tendencies, did not allow a clear differentiation between the two treatments. The results are presented in Panel 42.

Panel 42 The SCoP Study – Suicidality Rates as Classified by the ISC

Events	Period	Sertindole Number of Suicide Attempts (Rate per 100 PYE)	Risperidone Number of Suicide Attempts (Rate per 100 PYE)	Hazard Ratio[a]	Two-sided p-value
Suicide attempts (fatal plus non-fatal)	ORT+1	55 (0.87)	63 (0.88)	0.896	0.5564
Suicide attempts (fatal plus non-fatal) 1-year	ORT+1	44 (1.32)	53 (1.45)	0.829	0.3649
Suicide attempts (fatal plus non-fatal)	WRT+1	61 (0.93)	63 (0.84)	1.005	0.9789
Suicide attempts (fatal plus non-fatal)	WRT+30	67 (0.97)	71 (0.90)	0.978	0.8953

PYE: patient years of exposure; ORT: only randomised treatment; WRT: whole randomised treatment
a Cox's Proportional Hazards Model

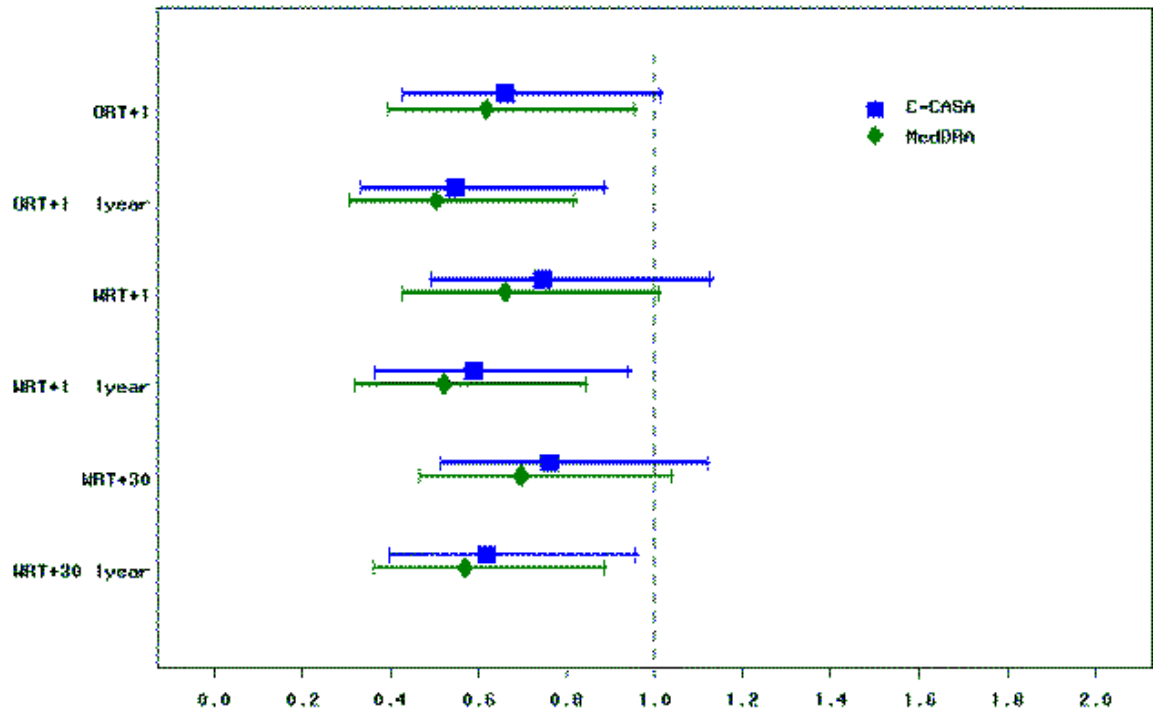
4.5 Discussion of and Conclusion on the Effect of Sertindole in Reducing the Risk of Suicide and Suicide Attempts

The early signal that sertindole presented an advantage in preventing suicides in the clinical studies, which was supported by the epidemiological studies, has been confirmed in a large, simple trial of sertindole under normal conditions of use. Patients in the sertindole group had a lower risk of fatal plus non-fatal suicide attempts than patients in the risperidone group and there was a trend towards a beneficial effect of sertindole on the rate of completed suicide.

When the events were reviewed (blinded) and classified by the expert group at Columbia University according to the C-CASA, there was substantial difference between sertindole and risperidone in preventing suicide attempts (fatal plus non-fatal) as well as in preventing completed suicides. These findings were in line with the results based on the MedDRA classification, while the ISC classification, using the broader definition of suicide attempt that included events without clear suicidal intent and suicidal ideations as well as suicidal tendencies, did not differentiate between the two treatments.

The SCoP study results, based on a representative sample of patients with schizophrenia recruited from a large variety of settings, including private practices, outpatient departments, and psychiatric hospitals, consistently show a benefit for sertindole with regards to a reduced risk of fatal plus non-fatal suicide attempts (Panel 43).

Panel 43 The SCoP Study – Estimated Hazard Ratios for Suicide Attempts (Fatal plus Non-fatal)



The sample was not specifically selected for risk of suicide and is representative of a clinical population at various stages of the illness. With the very large number of participants, the study included a significant proportion of patients at risk of a suicide attempt and thus permits a reliable estimate of the sertindole treatment effect on prevention of suicide attempts.

In the InterSePT study, which, in contrast, selected patients at high risk of suicide, the numbers of suicide attempts (fatal and non-fatal) were similar to those reported in the SCoP study, namely 34 in the clozapine group and 55 in the olanzapine group. These results showed a beneficial effect of clozapine in this group relative to olanzapine (hazard ratio of 0.76, p = 0.030; Panel 44).[56] The corresponding suicide attempt rates were 4.6 per 100 PYE in the clozapine group and 7.0 per 100 PYE in the olanzapine group. Suicide attempt rates of nearly the same order of magnitude were seen in the SCoP study after 2 years of treatment for the high risk subgroup of patients with a history of at least one suicide attempt within the last 5 years before entering the study: 4.1 suicide attempts per 100 PYE in the sertindole group and 6.1 suicide attempts per 100 PYE in the risperidone group. This high-risk group also showed a benefit from sertindole treatment (C-CASA, ORT+1, 2-year; Panel 45).

Both in the InterSePT study, which selected patients on the basis of their suicide risk, as well as in the high risk subpopulation in SCoP study, the numbers of suicides that occurred during the first 2 years of treatment were low.

Panel 44 Suicide and Suicide Attempts in the InterSePT Study

Events	Clozapine (N=490) Number of Events (Rate per 100 PYE)	Olanzapine (N=490) Number of Events (Rate per 100 PYE)	Hazard Ratio[a]	Two-sided p-value
Suicide attempts	34 (4.6)	55 (7.0)	0.76	0.030
Completed suicides	5 (0.67)	3 (0.38)	>1	-

PYE: patient years of exposure

a Cox's Proportional Hazards Model

Panel 45 Suicide and Suicide Attempts in the SCoP Study – High-risk Patients (C-CASA, ORT+1 day Period, 2-year)

Events	Sertindole (N=348) Number of Events (Rate per 100 PYE)	Risperidone (N=335) Number of Events (Rate per 100 PYE)	Hazard Ratio[a]	Two-sided p-value
Suicide attempts (fatal and non-fatal)	14 (4.05)	20 (6.08)	0.614	0.1643
Completed suicides	4 (1.14)	5 (1.46)	0.701	0.5984

PYE: patient years of exposure

a Cox's Proportional Hazards Model

In conclusion, sertindole reduces the risk of fatal plus non-fatal suicide attempts, which is an important benefit in the treatment of patients with schizophrenia in general and in particular in patients with a history of suicide attempts.

5 Safety and Tolerability

5.1 Most Common Adverse Events

Panel 46 shows the incidence of any adverse event and of the most common adverse events (10% or more in the sertindole group) for the placebo-controlled studies.

Panel 46 Placebo-controlled Studies – Adverse Events With an Incidence of 10% or More in the Sertindole Group

	Sertindole N = 704	Placebo N = 290
Patients (%) with		
Any adverse event	618 (88)	249 (86)
Headache	197 (28)	84 (29)
Nasal congestion	149 (21)	23 (8)
Insomnia	147 (21)	61 (21)
Constipation	93 (13)	27 (9)
Dizziness	88 (12.5)	20 (7)

The overall incidence of adverse events in the sertindole group was comparable to that in the placebo group (88% and 86%, respectively). The incidence of adverse events was slightly lower in the 4mg/day and 8mg/day sertindole groups (82% and 85%, respectively), and similar in the 12, 20, and 24mg/day sertindole groups (89%) (Panel 47).

The adverse events in the sertindole group with an incidence of 5% or more and at least twice that in the placebo group were (sertindole *versus* placebo): nasal congestion (21% *versus* 8%), dry mouth (9% *versus* 4%), and ejaculation failure (decreased ejaculatory volume) (9% *versus* 1% of men). A dose response was seen for nasal congestion and dry mouth. The incidence of ejaculation failure did not show a clear dose response in the 12, 20, and 24mg/day groups (10.5%, 12%, and 10%, respectively).

5.2 Withdrawals Due to Adverse Events

In the placebo-controlled studies, the overall incidence of withdrawal from study due to adverse events was low in the sertindole group and similar to that in the placebo group (7% and 5%, respectively) (Panel 47). There was a tendency to a dose response with the highest incidence of withdrawals in the 20mg/day sertindole group.

Panel 47 Placebo-controlled Studies – Incidence of Withdrawal Due to Adverse Events

	N	Any adverse event n (%)	Withdrawals due to Adverse event(s) n (%)
Sertindole	704	618 (88)	49 (7)
4mg	39	32 (82)	1 (3)
8mg	52	44 (85)	2 (4)
12mg	161	144 (89)	9 (6)
20mg	239	213 (89)	24 (10)
24mg	186	164 (88)	11 (6)
Flexible	27	21 (78)	2 (7)
Placebo	290	249 (86)	14 (5)

The withdrawals due to adverse events were distributed across many different diagnoses without a clear pattern and no single adverse event contributed to withdrawal in more than 1% of the patients.

5.3 Extrapyramidal Symptoms

As expected from the neuropharmacological profile, the clinical studies showed that the occurrence of EPS for sertindole was low and at the level for placebo. This finding was seen in the movement rating scale scores and in the adverse event pattern.

5.3.1 EPS in the Landmark Study (Study M93-113)

The Landmark study (Study M93-113) evaluated and compared three doses of sertindole with three doses of haloperidol and with placebo over 8 weeks. The sample size was based on the ability to detect a significant difference between sertindole and haloperidol in the proportion of patients with EPS.

Three movement rating scales were used to assess the occurrence of EPS: the Simpson-Angus Scale[58] (SAS), which measures parkinsonian symptoms; the Barnes Akathisia Rating Scale[59] (BAS), which measures akathisia; and the Abnormal Involuntary Movement Scale[60] (AIMS), which measures dyskinesia.

The study demonstrated that the level of EPS associated with sertindole was similar to that in the placebo group as measured by the SAS, BAS, and AIMS and the incidence of EPS-related adverse events.

The mean changes from baseline to last assessment for each of the movement rating scales are shown in Panel 48.

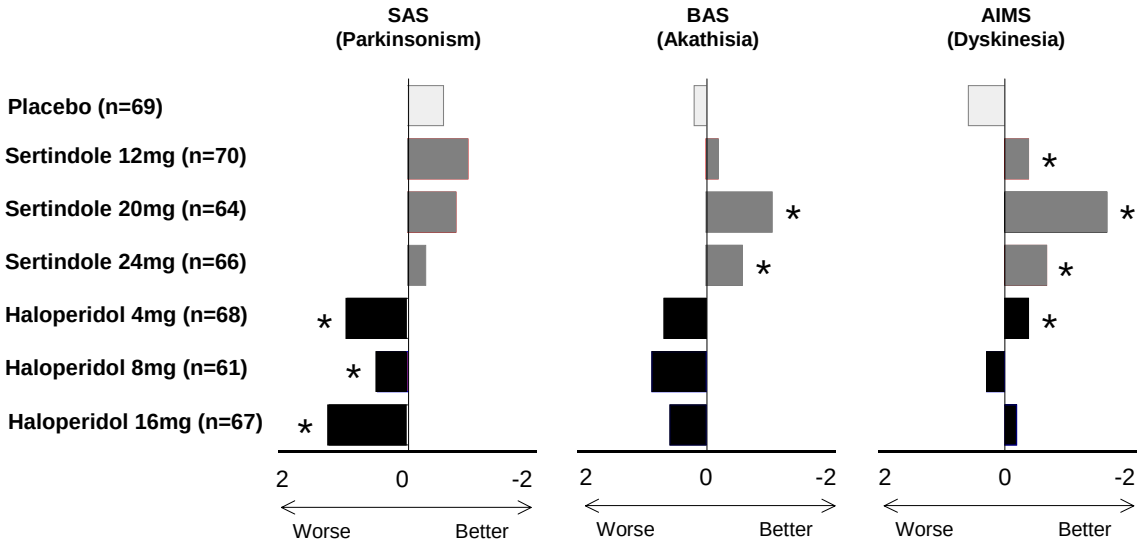
For the SAS total scores, no statistically significant differences between any sertindole group and the placebo group were detected for mean changes from baseline to last assessment, while

there were statistically significant deteriorations for each of the haloperidol groups *versus* placebo.

For the BAS scores, statistically significant improvements were seen for the 20 and 24mg/day sertindole groups compared with placebo.

Finally, for the AIMS scores, statistically significant improvements were seen for each sertindole group and the 4mg/day haloperidol group compared with placebo.

Panel 48 Study M93-113 – Mean Changes from Baseline to Last Assessment in Movement Rating Scale Scores (ANOVA)



* p ≤0.05 *versus* placebo

The level of EPS with sertindole, as measured by the incidence of EPS-related adverse events (Panel 49), was similar to that of placebo.

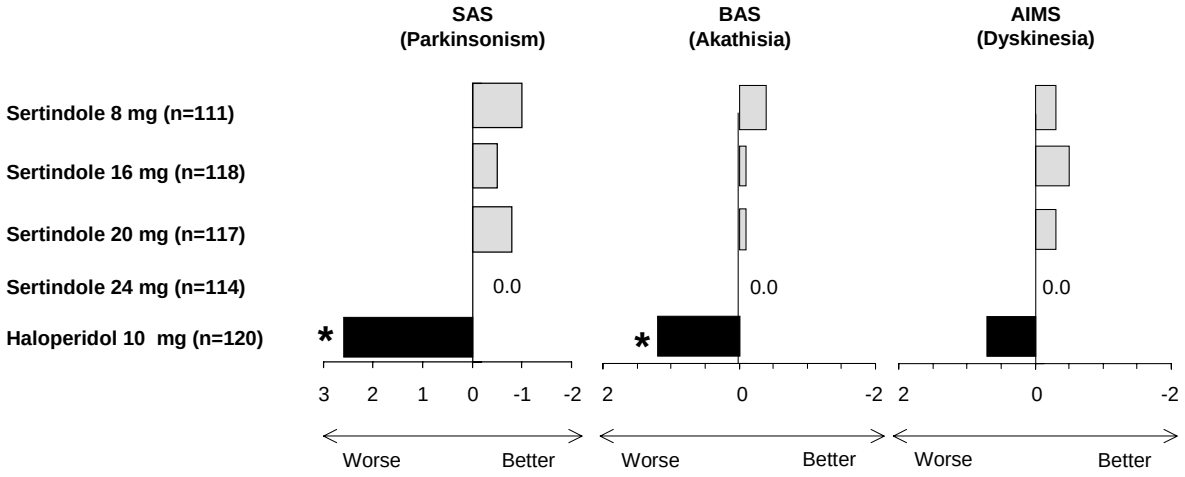
Panel 49 Study M93-113 – Incidence of EPS-related Adverse Events

	Sertindole 12mg/day N=76	Sertindole 20mg/day N=68	Sertindole 24m g/day N=72	Placebo N=73	Haloperidol 4mg/day N=71	Haloperidol 8mg/day N=67	Haloperidol 16mg/day N=70
Any EPS-related Adverse Event	26 (34%)	13 (19%)	22 (31%)	26 (36%)	35 (49%)	36 (54%)	44 (63%)

5.3.2 EPS in the European Study (Study M95-342) and the French Study (Study 97203)

In the 8-week European study, the scores on the three movement rating scales (BAS, SAS, and AIMS) either improved, or no change was seen, during treatment with sertindole (Panel 50). There were no significant differences in the scores between the 8 to 24mg/day sertindole treatment groups. In the haloperidol group, the mean BAS and SAS scores both deteriorated statistically significantly, while the mean AIMS score deteriorated numerically.[61]

Panel 50 Study M95-342 – Change from Baseline to Last Assessment in Movement Rating Scale Scores (ANOVA)



p ≤0.05 *versus* all sertindole doses

In the 12-week French study (Study 97203), 14% of patients on sertindole (N=97; flexible dose 12 to 24mg/day) had EPS-related adverse events compared to 24% of those on risperidone (N=89; flexible dose 4 to 10mg/day).

5.3.3 EPS-related Adverse Events in the Active-controlled Studies

The placebo-level EPS as measured using the SAS, BAS, and AIMS was confirmed by the adverse event pattern in the pooled active-controlled studies (Panel 51). The selection of the

EPS-related adverse events is based on the Standardised MedDRA Query (SMQ) on EPS, a reproducible search that captures all adverse events potentially related to EPS.

Panel 51 Active-controlled Studies – Incidence of EPS-related Adverse Events

	Sertindole N=1486	Placebo N=231	Haloperidol N=650	Risperidone N=194
Any EPS-related Adverse Event (MedDRA SMQ)	359 (24.2%)	66 (28.6%)	365 (56.2%)	51 (26.3)
Akathisia	83 (5.6%)	14 (6.1%)	158 (24.3%)	16 (8.2%)

Akathisia is part of the EPS syndrome and is of special interest as it is very unpleasant for the patients and confers a high risk of non-compliance; in addition, it may be related to an increased risk of suicidal behaviour. Sertindole was not associated with more akathisia than was placebo.

5.4 Sedation

Sertindole is non-sedating, a characteristic that is in agreement with its low affinity for the histamine H_1 receptors. Panel 52 shows that there were no differences in the incidences of lethargy, somnolence, or sedation between the placebo and sertindole groups in the active-controlled studies.

Panel 52 Active-controlled Studies – Incidence of Sedation, Lethargy, and Somnolence

MedDRA Preferred Term	Sertindole N=1486	Placebo N=231	Haloperidol N=650	Risperidone N=194
Sedation	73 (4.9%)	13 (5.6%)	44 (6.8%)	11 (5.7%)
Lethargy	31 (2.1%)	8 (3.5%)	23 (3.5%)	4 (2.1%)
Somnolence	77 (5.2%)	12 (5.2%)	53 (8.2%)	9 (4.6%)

The overall incidence of sedation for sertindole in the Core Clinical Studies (N=2711), including long-term exposure, was 8.0%.

5.5 Conclusion on Tolerability and Movement Disorders

Sertindole is well tolerated by patients. The overall incidence of withdrawal from the clinical studies due to adverse events was low in the sertindole group and similar to that in the placebo group (7% and 5%, respectively).

Sertindole patients demonstrate a higher frequency of ejaculation failure than reported for patients receiving placebo. This finding is also commonly observed with other antipsychotics

and related to the α_1-adrenoceptor antagonism causing absent contraction of the seminal vesicle, ampulla and ductus deferens. The effect is usually temporary and the ejaculatory function is restored. With proper counselling this is considered a manageable problem in the clinic.

Sertindole has a favourable side effect profile on issues very important to patients, such as EPS, akathisia, and sedation. The low incidence of movement disorder adverse events is in line with nonclinical experimental data showing selective dopaminergic inhibition of neurons in the ventral tegmental area over the substantia nigra pars compacta. The placebo-level incidence of EPS with sertindole has been demonstrated both by movement disorder rating scales and by low reporting of adverse events. It is a consistent finding in multiple clinical studies and significantly different from the EPS side-effect profile of haloperidol over a large range of sertindole dosages.

5.6 Laboratory Assessments

5.6.1 Liver Function Tests

Liver function tests (alanine aminotranferease [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [T-bilirubin]) were measured throughout the sertindole clinical studies.

In the patients treated with sertindole, liver function values at last assessment that were outliers occurred mostly in patients with values above normal at baseline, and less than 1% of the patients with normal values at baseline had outlier values at last assessment.

The incidence of patients with normal results or results above the upper limit of normal at baseline and outlier results at last assessment for the liver function tests is presented in Panel 53.

Panel 53 Placebo-controlled Studies – Patients With Liver Function Test Outlier Values at Last Assessment

Parameter/ Baseline status	Sertindole N	Sertindole Patients with Outlier Value n (%)	Placebo N	Placebo Patients with Outlier Value n (%)
ALT				
>ULN	137	12 (8.8)	66	5 (7.6)
Normal	545	3 (0.6)	209	0
AST				
>ULN	78	4 (5.1)	30	0
Normal	604	0	245	0
ALP				
>ULN	32	0	14	0
Normal	649	0	261	0
T-bilirubin				
>ULN	8	1 (12.5)	5	0
Normal	673	0	270	0

Upper limit of normal (ULN): ALT (36U/L); AST (33U/L); ALP (130U/L); T-bilirubin (21µmol/L)
Outlier criteria: ALT (≥3xULN); AST (≥3xULN); ALP (≥3xULN); T-bilirubin (≥34.2µmol/L)

As of 11 July 2008 (the cut-off date NDA 120-days safety update), the Global Safety Database included a total of 30 reports related to hepatic disorders.

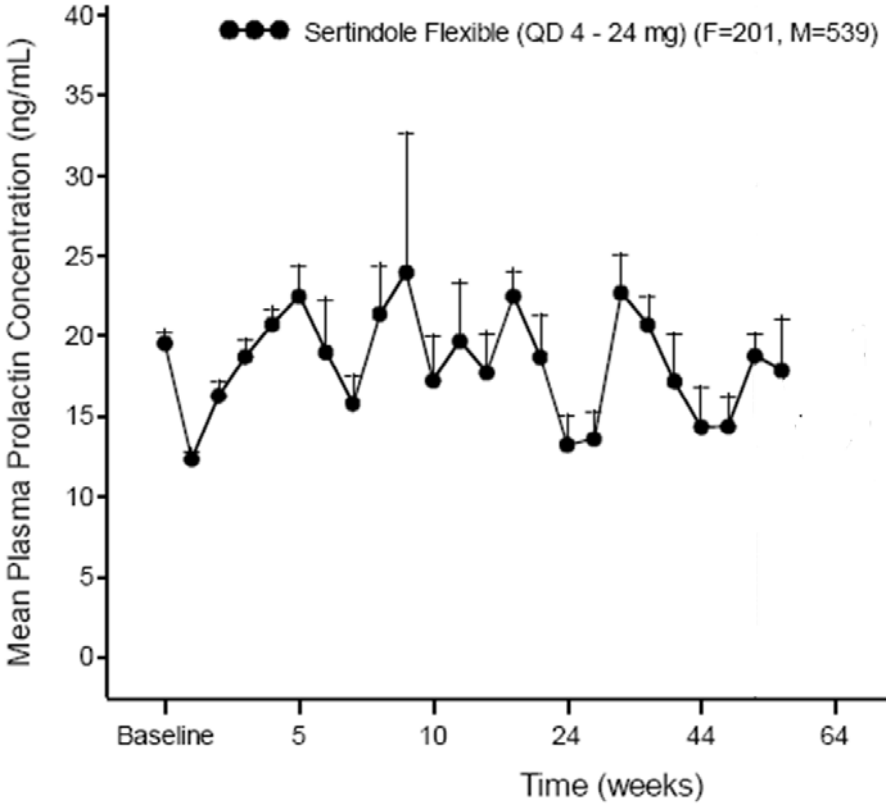
The reports cover a variety of events, the majority (18 reports) being related to various forms of abnormal liver function tests. There were no common trends in the cases and no reports of liver failure. Concomitant medication, polypharmacy, alcohol use, and underlying liver disease are confounding most cases and there are no cases of permanent liver damage.

5.6.2 Prolactin

Most antipsychotics block D_2 receptors, resulting in hyperprolactinaemia. The symptoms vary from galactorrhea to gynecomastia and altered libido. For some antipsychotics, high serum prolactin levels in humans increase the risk of osteopenia and bone demineralisation without specific interventions to improve bone density.[62]

Mean plasma prolactin concentrations following both acute, single-dose sertindole administration in healthy subjects or chronic treatment of patients with schizophrenia were mainly within the normal range and only sporadically above the upper limit of normal. Panel 54 shows the prolactin levels over time from two long-term studies and it is seen that the levels did not increase.

Panel 54 Long-term Studies M92-795 and M93-061 – Mean Plasma Prolactin Concentration Up to 1 Year



Normal range (prolactin): 1.1 – 20.5ng/mL (M); 1.8 – 26.5ng/mL (F).
Data from 740 patients with baseline serum prolactin measurements.
Week 4: N=394; Week 16: N=251; Week 36: N=143; Week 52: N=128

In the Global Safety Database, a total of 23 reported events (22 in women and 1 in a man) of increased prolactin level-related reactions have been identified. The reports comprise cases with elevation in plasma prolactin associated with galactorrhoea and amenorrhoea in women. The male patient developed a benign painless glandular swelling on the right aerola that resolved completely during continued treatment with sertindole.

5.7 Metabolic Parameters

5.7.1 Introduction

The prevalence of obesity among patients with schizophrenia is higher than that in the general population.[63] Multiple factors may contribute to obesity in patients with schizophrenia, including sedentary lifestyle, poverty, unhealthy eating habits, and impaired ability to participate in medical care. Treatment with antipsychotics further increases the risk of excess body weight in these patients and during the last decade there has been an increasing awareness that treatment with the second generation antipsychotics may induce weight gain,

impaired glucose tolerance, and hyperlipidaemia. Weight gain is a health concern for all patients, including patients with schizophrenia, and serves as an additional reason for non-adherence with pharmacologic treatment.

In this section, the data on weight, total cholesterol, triglycerides, and glucose obtained in the Core Clinical Studies are presented. The fasting serum lipid and glucose data were identified as fasting based on the laboratory tests specified in the protocol. In the 1990s, when these studies were conducted, metabolic syndrome was not recognised as a distinct medical problem and the metabolic effects of the second generation antipsychotics were not well known. However, the SCoP study was amended to further investigate the effect of short- and long-term treatment with sertindole or risperidone on metabolic variables in patients with schizophrenia (the SCoP Metabolic Sub-study). The study duration was not pre-specified (section 2.3.4); data are presented for Weeks 12, 24, and 36, and last assessment. After Week 36, there were too few patients for meaningful analysis.

5.7.2 Weight, BMI, and Waist Circumference

The results from the SCoP Metabolic Sub-study demonstrated moderate increases in mean weight, BMI, and waist circumference during treatment with either sertindole or risperidone; after 12 weeks, the increase in weight was 1.3 kg and 1.1 kg, respectively, and after 36 weeks it was 2.2 kg (4.8 lbs) and 2.0 kg (4.4 lbs), respectively (Panel 55).

In both treatment groups, similar proportions of patients (sertindole: 17% *versus* risperidone: 16%) had weight increases ≥7% from baseline to last assessment (up to 60 weeks).

Panel 55 SCoP Metabolic Sub-study – Mean Changes from Baseline in Weight, BMI, and Waist Circumference (ORT Period)

Variable	Time Point	Sertindole N	Sertindole Mean (±SD)	Risperidone N	Risperidone Mean (±SD)
Weight (kg)	Baseline	107	71.7 (±13.1)	116	73.4 (±13.8)
	ΔWeek 12	92	1.3 (±3.1)	108	1.1 (±2.6)
	ΔWeek 24	78	1.6 (±3.7)	97	1.4 (±3.1)
	ΔWeek 36	54	2.2 (±4.0)	63	2.0 (±3.7)
	ΔLast Assessment	107	1.8 (±3.5)	116	1.7 (±3.4)
BMI (kg/m^2)	Baseline	107	24.7 (±3.8)	116	25.6 (±4.5)
	ΔWeek 12	92	0.5 (±1.09)	108	0.4 (±0.9)
	ΔWeek 24	78	0.6 (±1.3)	97	0.5 (±1.1)
	ΔWeek 36	54	0.7 (±1.4)	63	0.7 (±1.3)
	ΔLast Assessment	107	0.6 (±1.2)	116	0.6 (±1.2)
Waist Circumference (cm)	Baseline	107	84.8 (±13.2)	116	85.8 (±13.8)
	ΔWeek 12	93	1.1 (±4.1)	108	1.1 (±3.6)
	ΔWeek 24	78	1.0 (±5.1)	78	1.6 (±3.8)
	ΔWeek 36	54	1.5 (±6.0)	63	2.0 (±3.9)
	ΔLast Assessment	107	1.4 (±4.8)	116	1.6 (±3.9)

SD: Standard deviation

In the Core Clinical Studies (Panel 7), which were mainly conducted in the US in the 1990s, the mean BMI at baseline was high (26 to 27kg/m^2) and approximately 20% of the patients were obese (BMI ≥30kg/m^2). In the placebo-controlled studies, the mean weight change from baseline to last assessment was 2.9kg in the sertindole group and 0.2kg in the placebo group. The proportion of patients with a weight increase ≥7% was 24% in the sertindole group and 10% in placebo group (Panel 56).

Panel 56 Short-term Placebo-Controlled Studies – Mean Changes in Weight from Baseline to Last Assessment

	Sertindole N = 704	**Placebo N = 290**
Number of patients	584	231
Mean baseline ± SD (kg)	80.3 ± 16.7	79.8 ± 16.8
Mean change ± SD (kg)	2.9 ± 4.3	0.2 ± 3.9
Increase ≥7% (n [%])	138 (24)	22 (10)

Data from Studies M91-645, M92-762, M92-817, M93-098, and M93-113
SD: Standard deviation

Comparable long-term data are available from the controlled clinical Study M93-132, in which data from the 24mg/day sertindole group and the 10mg/day haloperidol group is available for up to 1 year. In this study, the mean weight change after 6 to 12 months of treatment was 6kg in the sertindole group (N=56) and 0.7kg in the haloperidol group (N=63). The proportion of patients with a weight increase ≥7% was 54% in the sertindole group and 24% in the haloperidol group. At last assessment (LOCF analysis), the corresponding numbers were 4.6kg and 38% for sertindole (N=88) and -0.3kg and 13% for haloperidol (N=103). For patients treated with sertindole in the Core Clinical Studies, including the long-term data from controlled and uncontrolled (open-label) studies, the mean weight increase was 6.8kg in the period of 6 to 12 months of treatment. At last assessment (LOCF analysis; mean exposure 247 days), the mean weight increase was 4.3kg (9.5lbs) and 34% had a weight increase ≥7%.

5.7.3 Fasting Serum Lipids

In the SCoP Metabolic Sub-study, the mean changes from baseline to each assessment in triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol were small in both treatment groups (Panel 57).

In the sertindole group, the number (%) of patients with serum triglycerides ≥2.2mmol/L (200mg/dL) was 12 patients (12%) at last assessment *versus* 5 patients (6%) at baseline. Similarly, the number (%) of patients with serum total cholesterol ≥6.2mmol/L (240mg/dL) was 15 patients (14%) at last assessment *versus* 9 patients (10%) at baseline.

Panel 57 SCoP Metabolic Sub-study – Mean Changes from Baseline in Fasting Serum Lipids (ORT Period)

Variable	Time Point	Sertindole N	Sertindole Mean (±SD)	Risperidone N	Risperidone Mean (±SD)
Triglycerides (mmol/L)	Baseline	89	1.25 (±0.5)	103	1.52 (±1.0)
	ΔWeek 12	71	0.00 (±0.7)	93	-0.15 (±0.9)
	ΔWeek 36	33	-0.05 (±0.6)	47	-0.04 (±0.9)
	ΔLast Assessment	89	0.03 (±0.6)	103	-0.04 (±0.7)
Total cholesterol (mmol/L)	Baseline	89	4.8 (±1.2)	103	5.0 (±1.3)
	ΔWeek 12	71	0.11 (±1.2)	93	-0.12 (±1.1)
	ΔWeek 36	33	0.13 (±1.3)	47	-0.06 (±1.3)
	ΔLast Assessment	89	0.05 (±1.2)	103	-0.09 (±1.2)
HDL-cholesterol (mmol/L)	Baseline	89	1.28 (±0.4)	103	1.26 (±0.3)
	ΔWeek 12	71	0.10 (±0.4)	93	0.01 (±0.3)
	ΔWeek 36	33	0.12 (±0.4)	47	0.0 (±0.4)
	ΔLast Assessment	89	0.06 (±0.4)	103	0.02 (±0.3)
LDL-cholesterol (mmol/L)	Baseline	89	3.0 (±1.0)	100	3.1 (±1.1)
	ΔWeek 12	71	0.00 (±1.0)	89	-0.08 (±0.9)
	ΔWeek 36	33	0.03 (±1.1)	44	-0.02 (±1.2)
	ΔLast Assessment	89	-0.03 (±1.0)	100	-0.10 (±1.0)

SD: standard deviation

Small differences in fasting lipids between the sertindole and placebo groups were noted in the short-term, fixed-dose, placebo-controlled studies (Panel 58). In these studies, 29% and 47% of the patients treated with sertindole had outlier results for cholesterol (>240mg/dL) and triglycerides (≥200mg/dL), respectively. For the patients who received placebo, 25% and 36% had an outlier value for cholesterol and triglycerides, respectively. The majority of the outlier values in both groups were observed in patients who had outlier values at baseline. Only 7% and 5% of the patients treated with sertindole or placebo, respectively, had a normal baseline value and an outlier value for serum cholesterol during the study. Similarly for triglycerides, 13% of the patients treated with sertindole and 9% of the patients who received placebo had normal baseline values and an outlier value at last assessment.

Panel 58 Short-term, Fixed-Dose, Placebo-Controlled Studies – Patients With Fasting Serum Lipid Outlier Values

Parameter	Sertindole N	Sertindole n (%)	Placebo N	Placebo n (%)
Cholesterol	574	164 (28.6)	224	55 (24.6)
Triglycerides	574	271 (47.2)	224	81 (36.2)
Patients with outlier values at last assessment but not at baseline				
Cholesterol	574	41 (7.1)	224	12 (5.4)
Triglycerides	574	77 (13.4)	224	19 (8.5)

Outlier Criteria: Cholesterol ≥ 240mg/dL; Triglycerides ≥200mg/dL
Data from Studies M93-113, M93-098, and M92-762

5.7.4 Fasting Plasma Glucose

For the SCoP Metabolic Sub-study, the baseline values and mean changes from baseline in fasting plasma glucose are summarised in Panel 59.

In both treatment groups, the mean changes from baseline in plasma glucose were small. No patients were diagnosed with type 2 diabetes.

Panel 59 SCoP Metabolic Sub-study – Mean Changes from Baseline in Fasting Plasma Glucose (ORT Period)

Variable	Time Point	Sertindole N	Sertindole Mean (±SD)	Risperidone N	Risperidone Mean (±SD)
Plasma glucose (mmol/L)	Baseline	85	5.2 (±0.7)	102	5.4 (±0.9)
	ΔWeek 12	69	0.16 (±1.1)	90	-0.04 (±1.0)
	ΔWeek 36	31	0.08 (±0.6)	47	-0.08 (±1.1)
	ΔLast Assessment	85	0.12 (±0.6)	102	-0.04 (±1.1)

SD: Standard deviation

The number of and proportion of patients with fasting glucose outlier values are presented in Panel 60 for the short-term, fixed-dose, placebo-controlled studies. In the placebo-controlled studies, 28% of the patients in the sertindole group had a plasma glucose value ≥126mg/dL whereas 19% of the 224 patients in the placebo group had a plasma glucose value ≥126mg/dL. Patients with outlier values at last assessment but not at baseline represented 8% and 4% of the patients in the sertindole and placebo groups, respectively.

Panel 60 Short-term, Fixed-Dose, Placebo-Controlled Studies – Patients with Fasting Blood Glucose Outlier Values

Parameter	Sertindole N	Sertindole n (%)	Placebo N	Placebo n (%)
Blood Glucose	574	162 (28.2)	224	42 (18.8)
Patients with outlier values at last assessment but not at baseline Blood Glucose	574	45 (7.8)	224	9 (4.0)

Outlier Criteria: blood glucose ≥ 126mg/dL
Data from Studies M93-113, M93-098, and M92-762

Controlled long-term data on blood glucose are available from the controlled Study M93-132, where 24mg sertindole *versus* 10mg haloperidol was studied in patients for up to 1 year. In this study, at baseline, 33% of the 138 patients treated with sertindole and 26% of the 137 patients treated with haloperidol had impaired fasting blood glucose or diabetes mellitus based upon their baseline fasting blood glucose values; in the sertindole group, 12% of the patients met the criteria for diabetes (fasting blood glucose >126mg/dL) while 7% of the patients in the haloperidol group met this criterion. Among the patients in the sertindole group with normal baseline blood glucose values, 26 patients (28%) had an impaired fasting blood glucose value and 4 patients (4%) met the criteria for diabetes at last assessment. In the haloperidol group of patients with normal baseline glucose values, 22 patients (22%) had impaired fasting blood glucose and 3 patients (3%) met the criterion for diabetes.

5.7.5 Blood Pressure

Titration

Nonclinical data has shown that sertindole, like other antipsychotic drugs, is a blocker of the α_1-adrenoceptor.[64]

In the first study of sertindole in healthy subjects, the side effects of dizziness, postural hypotension, and syncope, which are all mediated by α_1-adrenergic antagonism, were reported after a single-dose of 8mg sertindole. To minimise the possibility of these side effects, a series of studies were undertaken to optimise the titration regimen. Based on the results of these titration studies, escalation of sertindole doses faster than increases by 4mg every two to three days is not recommended.

The titration regimen for sertindole is well studied and well tolerated by patients in short- and long-term clinical studies. In the placebo-controlled studies, only 2% of the patients withdrew due to adverse events in the titration period with a similar incidence in the sertindole and the placebo groups.

Maintenance Treatment

In the SCoP Metabolic Sub-study, the mean changes from baseline to Weeks 12, 24, and 36 in systolic and diastolic blood pressure were small (at most 2 mmHg) in both treatment groups. Four patients in the sertindole group and 1 patient in the risperidone group had *hypertension* reported as an adverse event in this study.

5.7.6 Metabolic Syndrome

Increase in weight and waist circumference, serum lipids, plasma glucose, and blood pressure are each considered as individual risk factors for heart disease. However, in combination they constitute the criteria for the metabolic syndrome, a diagnosis that is used to estimate the risk for cardio-vascular disease.

In the SCoP Metabolic Sub-study, the effect of sertindole and risperidone on metabolic parameters was further evaluated using the International Diabetes Federation (IDF) definition of metabolic syndrome[44] (details of the methodology used in the SCoP study are presented in Appendix 1). The shifts in metabolic status from baseline to last assessment are shown in (Panel 61). The majority of patients in each treatment group (80% in the sertindole group and 69% in the risperidone group) did not have metabolic syndrome either at baseline or at last assessment. At last assessment, the proportions of patients with shifts from normal to abnormal metabolic status were comparable between the two treatment groups (7% in the sertindole group and 10.5% in the risperidone group).

Panel 61 The SCoP Study - Shifts in Metabolic Syndrome Status from Baseline to Last Assessment (ORT Period)

	Sertindole N=98	Risperidone N=105
Normal to normal	78 (80%)	72 (69%)
Normal to abnormal	7 (7%)	11 (10.5%)
Abnormal to normal	5 (5%)	9 (9%)
Abnormal to abnormal	8 (8%)	13 (12%)

Mean exposure: sertindole 179 days; risperidone 214 days

5.7.7 Conclusion on Metabolic Parameters

Treatment with sertindole is associated with moderate weight gain. The weight gain was higher in the Core Clinical Studies than in the more recent SCoP Metabolic Sub-study, where the mean increase in weight was 2.2kg over 36 weeks.

In the Core Clinical Studies, a large number of patients entered the studies with metabolic parameters above normal range. Among the patients with normal baseline values, there was a shift towards abnormal values in 7 to 13% in patients on sertindole treatment as compared to 4 to 9% of patients on placebo.

In the SCoP Metabolic Sub-study, designed to evaluate these parameters, no clinically relevant mean changes in blood pressure, serum lipids, or plasma glucose were observed. In total, the risk for cardiovascular disease, as evaluated by the criteria for metabolic syndrome, is manageable for sertindole and comparable to that for risperidone.

5.8 Sertindole's Effect on the QT Interval

5.8.1 Cardiac Action Potential and Ion Channels

The surface ECG is a reflection of the sum of all cardiac action potentials activated during the contraction of the heart. The length of the plateau phase of the cardiac action potential is defined by the ability of the muscle cell to repolarise and determines the length of the QT interval as measured on the ECG.

Following the contraction of the heart, each cardiac muscle cell needs to repolarise within a very narrow time window in order to fit into the overall functional structure of the normal heart. If this repolarisation is too fast or too slow, the heart muscle will destabilise and the risk of arrhythmia arises. In case of extreme slowing of the repolarisation, the QT interval is prolonged; this may be acquired QT interval prolongation, due to external factors, or congenital (long QT syndrome).

The action potential of the cardiac muscle cell is dependent on a very delicate balance of outward and inward ion currents. The general rule is that the cell is depolarised by sodium inflow into the cell, followed by repolarisation by potassium outflow from the cell. This in- and outward transport passes through different ion channels present in the cell membrane.

One of the most discussed ion currents is the rapid delayed rectifier potassium current (I_{Kr}), passing through the hERG channel. The I_{Kr} current plays a crucial role for the plateau phase of the action potential that determines the duration of the QT interval. The hERG channel and, thereby, the I_{Kr} current can be blocked by various compounds, including a variety of drugs, leading to acquired or drug-induced QT interval prolongation.

The risk associated with QT interval prolongation is not only dependent on the I_{Kr} blockade and subsequent duration of the QT interval but also on the effect on other ion channels. A selective I_{Kr} blockade is perceived as being associated with the highest risk of arrhythmia, while multi-channel blockade may mitigate the risk. Especially simultaneous blockade of the late sodium channel will counteract the effect of the I_{Kr} blockade and limit the magnitude of QT interval prolongation and the risk of arrhythmia.

5.8.2 Nonclinical Data

The effect of sertindole on the QT interval was identified early during clinical development. This finding initiated considerable nonclinical research into the underlying mechanisms as well as extensive ECG monitoring during the clinical studies. In general, QT interval prolongation raises a concern based on the perceived link between QT interval prolongation and enhanced proarrhythmic effects that might lead to Torsade de Pointes (TdP).

5.8.2.1 Sertindole's Effect on the Cardiac Action Potential

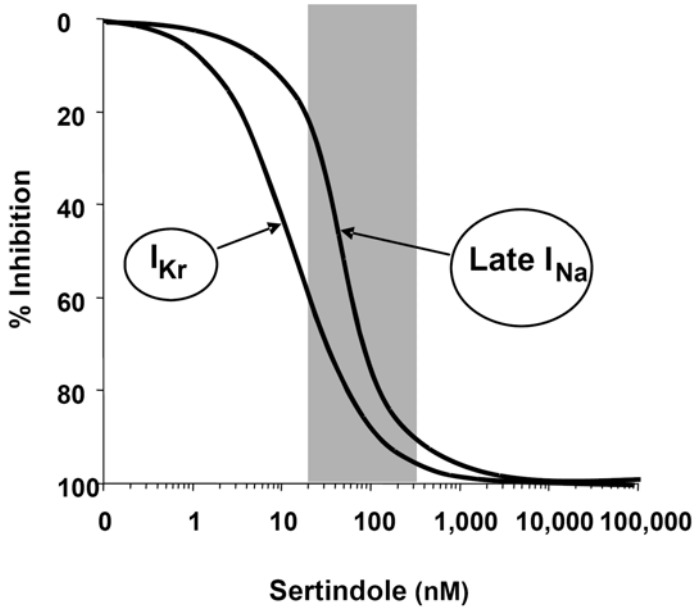
The mechanism by which sertindole induces QT interval prolongation is by inhibition of the I_{Kr} current. This inhibition is, however, counteracted by inhibition of the late sodium inward current (late I_{Na}), mitigating the risk of arrhythmia.

Sertindole blocks the I_{Kr} current with an IC_{50} of 12 to 64nM, depending on assay conditions.[65,66] The active metabolite of sertindole, dehydro-sertindole, displays a similar level of inhibition of the I_{Kr} when compared to its parent compound. The potency of the I_{Kr} inhibition by nor-sertindole, a metabolite of lesser pharmacological activity, is about 10-fold less than that by the parent compound.

Sertindole also inhibits the late I_{Na} as measured in canine ventricular mid-myocardial cells (IC_{50}=51nM) (Panel 62).

The effect on I_{Kr} and late I_{Na} occurs in the therapeutic range and is expected to influence cardiac repolarisation following sertindole administration to humans.

Panel 62 Concentration-response Curve for Sertindole Showing Inhibition of I_{Kr} and Late I_{Na} with IC_{50} of 12 and 51nM, Respectively



Effect of sertindole on I_{Kr} and late I_{Na} in dog mid-myocardial cells. The shaded area represents plasma concentration measurements from Study M93-061, which included long-term, open-label dosages of sertindole (4 to 24mg/day). In this study, 90% of the concentrations were ≤140ng/ml (~320 nM).

5.8.2.2 Link between QT Prolongation and Arrhythmia

The link between QT interval prolongation and risk of arrhythmia is not fully understood. However, it is recognised that two conditions must be met in order for the myocardium to initiate and sustain arrhythmia:

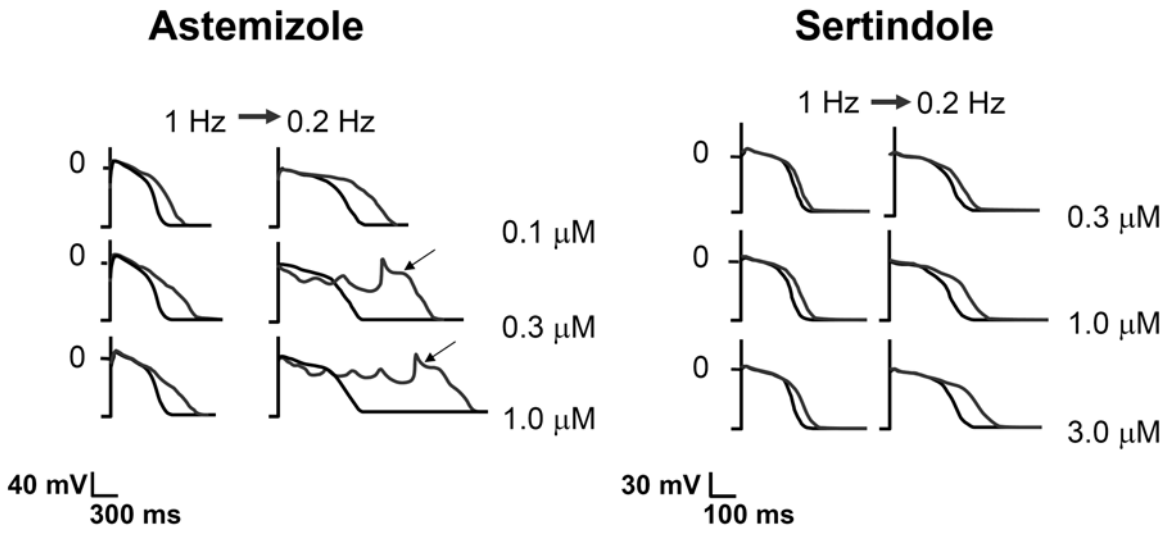
- Instability of the action potential (phase III) and occurrence of early after depolarisations (EADs) is the event that may trigger an arrhythmia.
- Increased transmural dispersion is a prerequisite for an arrhythmia to be sustained.

Both of these mechanisms have been investigated with sertindole in experimental animal models.

5.8.2.3 Early After Depolarisations or Triggered Activity

In Panel 63, an example of EADs and action potential (phase III) instability is shown following exposure to the drug astemizole (positive control). Following low frequency stimulation, astemizole caused reverse use dependency and EADs (left panel). The comparative experiment with sertindole (right panel) shows clear absence of EADs and other proarrhythmic activity. Neither of the two sertindole metabolites, dehydro-sertindole or nor-sertindole, caused EADs in this animal model of proarrhythmia.

Panel 63 Effects of Astemizole and Sertindole on the Rabbit Cardiac Purkinje Fibre – Isolated Perfused Heart Model



A low frequency challenge induces reverse use dependency and EADs with astemizole (arrows) but not with sertindole. 1Hz equals 60 beats per minute and 0.2Hz equals 12 beats per minute.

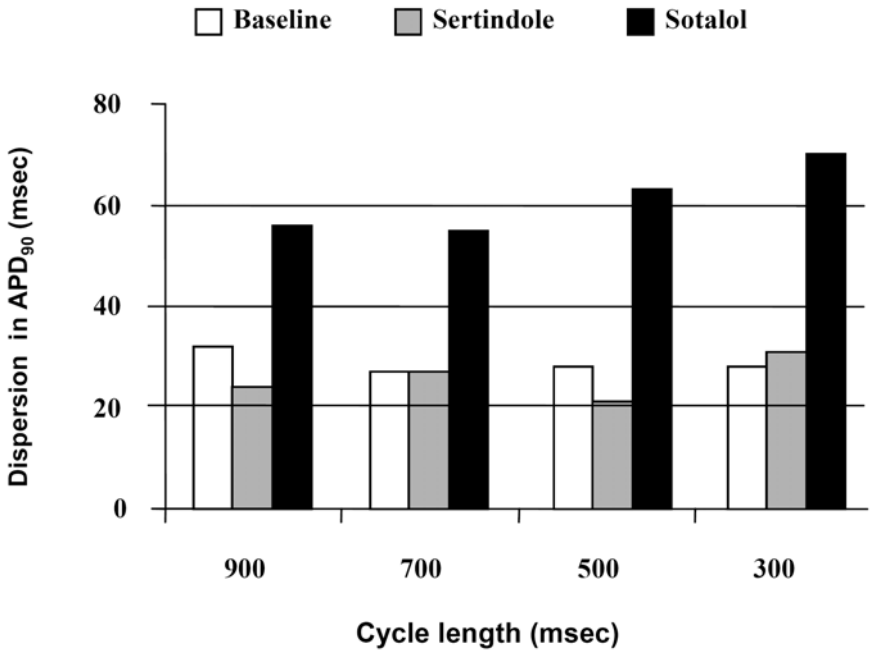
5.8.2.4 Transmural Dispersion

Increased transmural dispersion makes the heart vulnerable to a sustained arrhythmia. This was studied in an animal model, where sertindole was tested in concentrations of 0.5µM to 1.5µM.[67] This concentration range is considerably above the 100nM to 300nM seen with clinical doses.

The study was designed to show the risk of arrhythmia at a QT interval prolongation of similar magnitude to that observed with the drug dl-sotalol. Both sertindole (1.5µM) and d-sotalol (10µM) maximally increased the QT interval by approximately 17% in this model.

However, unlike dl-sotalol, sertindole did not increase the transmural dispersion compared to baseline (Panel 64). For sertindole, the QT interval prolongation is homogenous across the cardiac wall and the myocardium remains stable.

Panel 64 Effect of Sertindole and dl-sotalol on Transmural Dispersion in an Isolated Perfused Rabbit Heart



Recordings of transmural dispersion over a range of different cardiac rates in AV-node ablated perfused rabbit hearts. Dispersion is measured by the difference in action potential recordings (APD90) between endocardial and epicardial electrodes. White bars indicate baseline recordings, grey bars 1µM of sertindole and black bars 10µM of the positive control, dl-sotalol. Only dl-sotalol causes an increase in transmural dispersion compared to baseline. Cycle lengths of 300, 500, 700, and 900msec represent hearts rates of 200, 120, 85 and 67 beats per minute.

5.8.2.5 *In Vivo* Arrhythmia Models

Testing in Healthy Animals

The toxicological and safety pharmacological testing of sertindole in conscious and anaesthetised dogs included both oral (for up to 1 year) and intravenous dosing (for up to 14 days). The maximum exposure was 2- to 20-fold higher than the human therapeutic levels. No cardiac events were observed in the 149 Beagle dogs receiving sertindole.

Testing in Animals with Chronic AV-ablated Hearts

The effect of sertindole has also been investigated in a study in chronic AV-ablated (CAVB) dogs.[68] Chronic AV-ablation leads to bi-ventricular eccentric cardiac hypertrophy that together with electrical remodelling, pacing at an idioventricular rhythm and absence of sinus node activity makes these hearts extremely vulnerable to TdP. Furthermore, only dogs shown to produce TdP upon challenge with dofetilide (positive control) were included in the study. The CAVB dog is recognised as a sensitive model for assessing the potential for TdP in patients with numerous underlying risk factors.

In this model, arrhythmia occurred only after supra-therapeutic intravenous doses of sertindole at time points corresponding to the highest peak plasma concentrations (minutes after dosing) and only in 3 of 5 CAVB dogs. No arrhythmia occurred in these vulnerable hearts at concentrations mimicking therapeutic ranges.

Thus, in this model particularly sensitive to TdP, arrhythmias were not seen at clinically relevant therapeutic concentrations but after rapid intravenous administration of sertindole at supra-therapeutic concentrations only. Additionally, in this model, TdP only occurred when underlying cardiac disease and idioventricular pacing (non-sinus rhythm) were present.

5.8.2.6 Conclusions on Nonclinical Data

Sertindole prolongs the QT interval in different animal species both *in vivo* and *in vitro*. The underlying mechanism is an inhibition of the outward potassium current, I_{Kr}, and simultaneous inhibition of the late inward sodium current, I_{Na}. Thus, sertindole is a mixed ion-channel blocker with a balanced blockade of inward and outward currents.

The counteracting inward and outward currents result in a low torsadogenic potential for sertindole as demonstrated in a number of experimental models:

- Sertindole is not associated with events associated with proarrhythmia; that is, reverse use-dependence, action potential (phase III) instability, EADs, or transmural dispersion.
- Only a combination of a diseased heart known to be extremely vulnerable to TdPs and very high concentrations following rapid intravenous dosing of sertindole induced ventricular arrhythmias in the chronic AV-node ablated dog model.

It can be concluded from the nonclinical data that, for sertindole, the magnitude of the QT interval prolongation appears not to translate into a proportional increase in the risk of arrhythmia.

5.8.3 Clinical Study Data

5.8.3.1 ECG Reading in the Clinical Studies

The ECGs from the sertindole Core Clinical Studies were initially read and reported by the investigators while the studies were being conducted. For the original NDA submission, the ECGs from 17 of the 21 Core Clinical Studies were overread at the University of Indiana.

The ECG reading methodology used by the University of Indiana in the late 1990s differed somewhat from current standards. As requested by the FDA, a subset of the ECGs (nearly 2000 ECGs) was re-read in 2007.

The re-read performed in 2007 included ECGs from all patients treated with placebo or 20mg sertindole in Studies M93-098 and M93-113 and all ECGs where a QT/QT_c interval originally was measured to be ≥500ms during sertindole treatment.

The results in the following section are based on this re-read, unless otherwise stated.

5.8.3.2 QT Interval Results

Change in the QT_{cF} Interval

The QT_{cF} mean change from baseline to last assessment for patients treated with placebo or 20mg/day sertindole in Studies M93-098 and M93-113 are presented in Panel 65.

Panel 65 Mean QT_{cF} Change from Baseline to Last Assessment

Study Drug	N	Mean ± SD (msec)	Median (msec)	Range (msec)
Baseline to Last Assessment				
Placebo	137	-6.2 ± 24.7	-5.0	-135.0 – 57.0
Sertindole 20mg/day	140	23.2 ± 30.2	26.0	-84.0 – 126.0

Table includes patients with baseline and at least one post-baseline ECG.

As expected, the QT_{cF} mean change was higher in the sertindole group than that in the placebo group. The mean change from baseline in QT_{cF} was 23msec.

In Panel 66, the corresponding QT_{cF} change by category is presented.

Panel 66 QT_{cF} Change from Baseline to Last Assessment by Category

QT_{cF} Change Category	Sertindole 20mg/day (N=140) n (%)	Placebo (N=137) n (%)
Baseline to Last Assessment		
<30msec	77 (55.0)	132 (96.4)
≥30 to <60msec	49 (35.0)	5 (3.6)
≥60msec	14 (10.0)	0

Table includes patients with baseline and at least one post-baseline ECG.

A greater proportion of patients treated with 20mg/day sertindole had a change in QT_{cF} ≥30msec to <60msec from baseline to last assessment (49 patients [35.0%]) than did patients treated with placebo (5 patients [3.6%]. Also the proportion of patients with a change from baseline to last assessment ≥60msec was higher for patients treated with 20mg/day sertindole (14 patients [10.0%]) than for patients treated with placebo (none).

The proportions of patients with QT_{cF} >500msec at any time during treatment with either placebo or 20mg/day sertindole in Studies M93-098 and M93-113 are presented in Panel 67. At the 20mg/day dose, 1.4% of patients had an increase in QT_{cF} above the 500msec threshold.

Panel 67 Patients with On-drug QT_{cF} >500msec

Type of Read	Placebo N	Placebo QT_{cF} >500 msec n (%)	Sertindole 20mg/day N	Sertindole 20mg/day QT_{cF} >500 msec n (%)
Standard Read	137	0	140	2 (1.4)

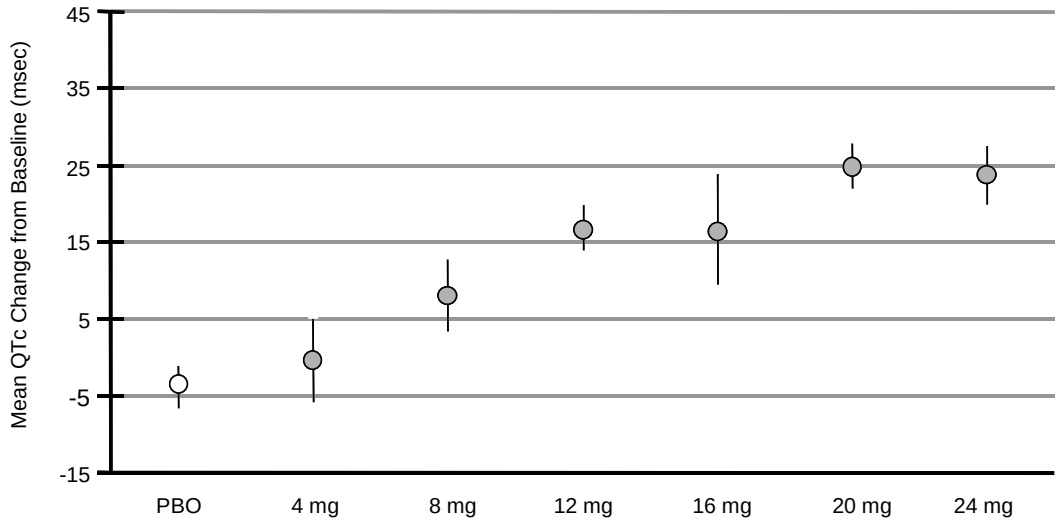
N = number of patients with a post-baseline ECG

n = number of patients with an ECG with a QT_c >500msec

From the original reading of the ECG recordings, it was demonstrated that the QT/QT_c interval change from baseline is dose dependent. These readings are based on Bazett's correction factor and mean values are therefore slightly higher than for the re-readings using Fridericia's correction factor in accordance with current standards.

In agreement with the nonclinical data, the mean QT_c interval prolongation appears to level off, with increasing concentration/dose, as seen for the dosages between 12 and 24mg/day (Panel 68).

Panel 68 Short-term Fixed-dose Studies – Mean Change in the QT_{cB} Interval by Dose (Original Overread)



Data source: patients with a baseline and at least one post-treatment QTc value in studies M92-762, M92-817, M93-098, M93-113, and M95-342. N=1001.

These findings are consistent with those observed in a European study conducted in France (Study 97203). The French study used standard and well-defined ECG procedures (average of 3 readings, maximum QT, any lead) for assessing digitised ECGs that were prospectively and centrally read by cardiac experts. In this study, sertindole doses in the range of 12 to 24mg/day were compared to risperidone doses in the range of 4 to 10mg/day. The mean daily dose of sertindole was 16.2mg and the mean ΔQT_{cF} at last assessment was 20.2msec (±25.5msec) for sertindole in this study.

5.8.3.3 Pharmacokinetic Profile and QT Interval Prolongation

The pharmacokinetic profile of sertindole is different from that of several other newer antipsychotics; these have faster absorption and shorter half-lives which lead to greater fluctuations in drug plasma concentrations than those for sertindole. QT measurements are therefore considered to be relatively insensitive to the time since last dose for patients treated with sertindole.

Given the long half-life (3 days) and slow absorption of sertindole and the fact that it is dosed daily, it follows that the plasma concentration of sertindole at steady state would be largely independent of time since last dose. Therefore, the ECG measurements taken after patients had reached their maintenance dose during the clinical studies can be considered representative of sertindole's maximum effect on the QT interval.

The relationship between sertindole plasma concentration and QT_{cF} are presented in Panel 69. The plot includes data from six clinical studies. A total of 1139 patients contributed with

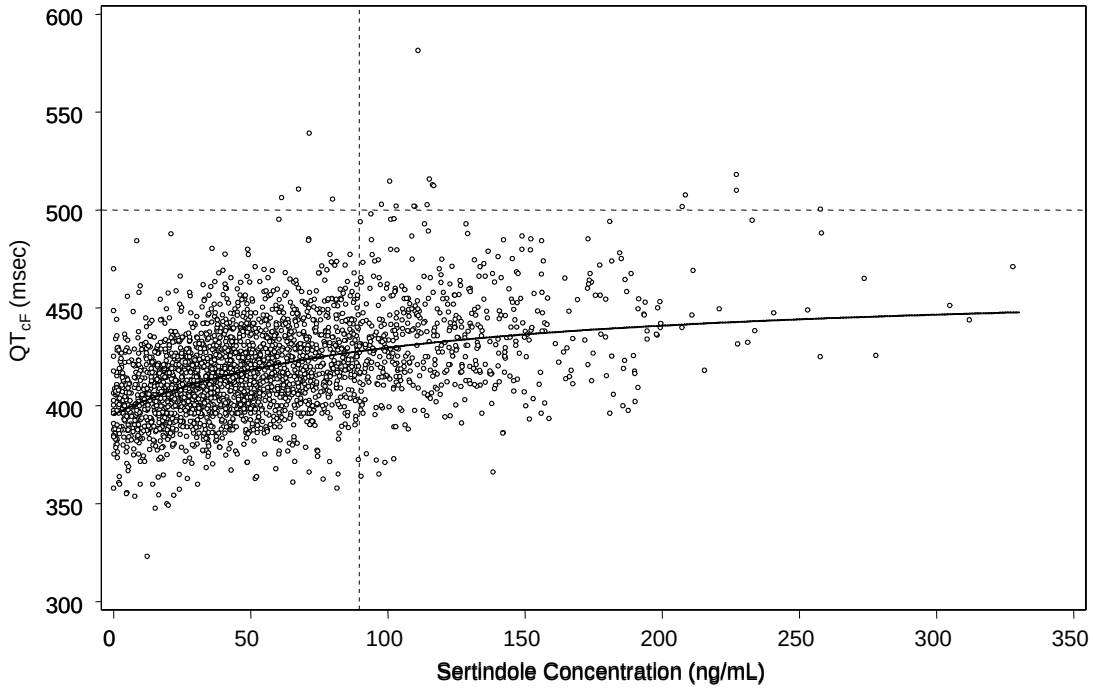
2770 sertindole plasma concentrations with corresponding ECG recordings; that is, each patient may contribute with more than one point. The ECGs were recorded on the same date (after at least 21 days of treatment) as the plasma samples were taken and 1296 of the 2770 sertindole plasma concentrations were measured within 1 hour of the QT_{cF} measurement. The mean sertindole concentration was 133nM (±100nM).

There were 19 samples from 16 patients with QT_{cF} values greater than or equal to 500msec. The sertindole plasma concentrations in these patients ranged from 138 to 585nM. The daily doses in these patients ranged from 16mg to 28mg.

Panel 69 QT_{cF} *versus* Sertindole Plasma Concentrations (Original Overread)

QT_{cF} *versus* sertindole plasma concentrations in short- and long-term studies

Observed Cases (at least 21 days of treatment)



Note: Patients may be represented in more than one study.
Data source: NLMIXED, SAS, Studies M91-645, M92-762, M93-098, M93-113, M93-061, M92-795: 2770 observations from 1139 patients.

The vertical line shows a typical mean pre-dose steady-state plasma concentration of sertindole following dosing with 20mg/day (Study M93-061). The line through the data is predicted from an E_{max} model. The Fridericia correction of QT was applied.
Conversion factor for sertindole concentration: 1ng/mL = 2.268nM

The population average shown in Panel 69 was calculated using an E_{max} model, with random intercept and including baseline QT_c.

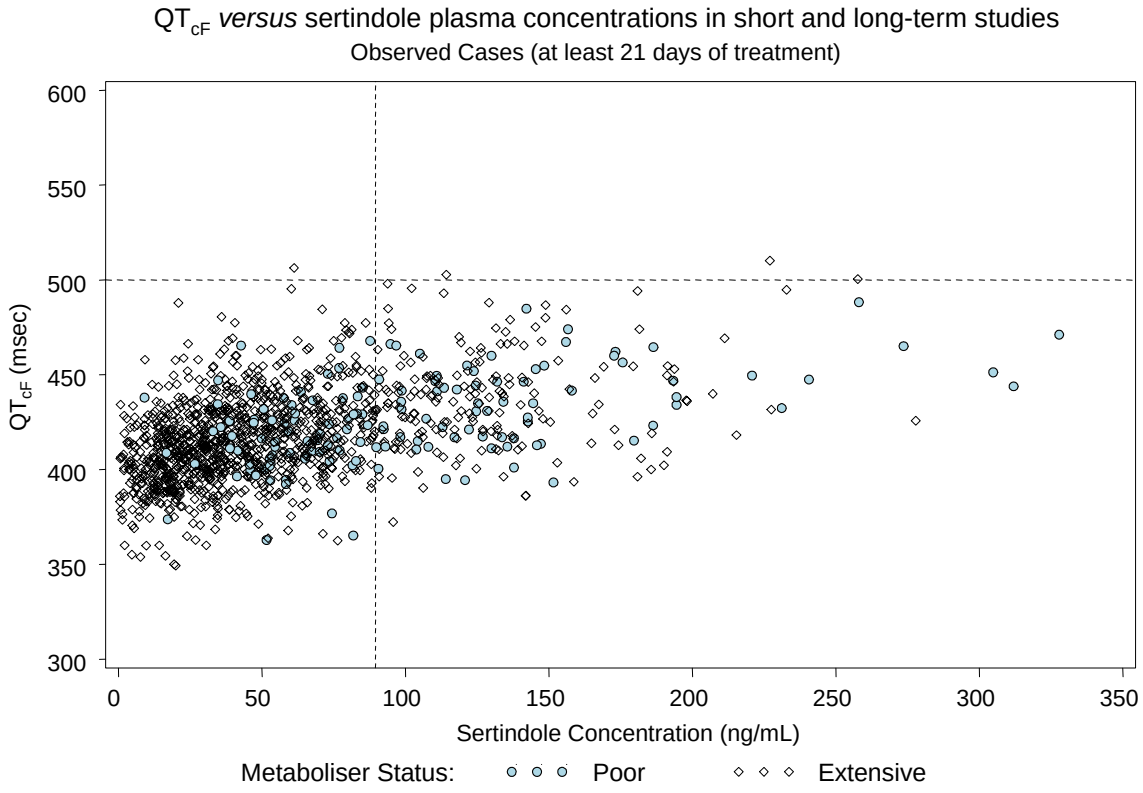
As is indicated from the fitted curves, QT_{cF} increases in a curvilinear fashion relative to sertindole plasma concentration. Thus, the increase in QT_{cF} will as a consequence of the

curvilinear relationship taper off with increasing sertindole concentrations. However, it is important to stress, that QT_{cF} values in individual patients cannot be accurately predicted based on plasma concentrations of sertindole, because of intra-individual variation in the QT interval, thus, therapeutic monitoring of sertindole would not be of value in predicting QT prolongation.

5.8.3.4 QT_{cF} Prolongation and Poor Metabolisers of Sertindole

Sertindole is extensively metabolised by the CYP2D6 and CYP3A isozymes of the cytochrome P450 system. One of the metabolites (dehydro-sertindole, DHS) appears to be formed by both isozymes. The dehydro-sertindole/sertindole concentration ratio (DHS/S) is correlated with sertindole clearance. The DHS/S ratio does not solely reflect CYP2D6 activity but includes also the contribution from CYP3A. Panel 70 shows the degree of QT_{cF} prolongation in poor and extensive metabolisers of sertindole, respectively.

Panel 70 QT_{cF} *versus* Sertindole Plasma Concentrations in Poor and Extensive Metabolisers of Sertindole (Original Overread)



Note: Patients may be represented in more than one study.
Data source: Studies M91-645, M92-762, M93-098, M93-113, M93-061, M92-795: 1312 observations from 584 patients.

The vertical line shows a typical mean pre-dose steady state plasma concentration of sertindole following dosing with 20mg/day (Study M93-061). The Fridericia correction of QT was applied.
Poor metabolisers of sertindole (DHS/S ratio ≤0.4) are shown as filled circles, extensive (DHS/S ratio >0.4) as open diamonds.
DHS was measured in 1312 samples containing matched observations of sertindole, metabolite, and QT_{cF} values. Of these, 1166 samples were from 499 patients classified as extensive metabolisers and 146 samples from 85 patients classified as poor metabolisers of sertindole.
Conversion factor for sertindole concentration: 1ng/mL = 2.268nM

The poor metabolisers of sertindole were in this context defined as patients having a DHS/S plasma concentration ratio of ≤0.4, ensuring that these patients have a high ratio of sertindole *versus* DHS concentrations. Even though the poor metabolisers in general have higher sertindole concentrations, the variability is similar to that of the extensive metabolisers and there are no apparent differences between the two groups.

This observation may be attributed to the fact that sertindole and its metabolites have similar cardiac electrophysiological properties and, thus, may contribute similarly to the effect on the QT_{cF} interval.

5.8.3.5 Conclusions on the Clinical ECG Data

In the clinical studies, treatment with sertindole was associated with a prolongation of the QT interval. The effect is dose and concentration dependent with a tendency to a plateau with higher dosages or high concentrations. The mean increase in the QT_{cF} interval is 23msec at the 20mg/day dose. At this dose, 10% of the patients had a change in the QT_{cF} interval larger than 60msec and 1.4% or the patients had a QT_{cF} interval above 500msec.

Poor metabolisers, defined by a high sertindole plasma concentration in relation to its major metabolite, did not have a different variability in the length of QT_c interval than did extensive metabolisers of sertindole. This may be because the sertindole metabolites, in particular dehydro-sertindole, have electrophysiological properties similar to those of the parent compound.

5.9 Mortality

5.9.1 The Global Safety Database

As of 11 July 2008, the safety experience with sertindole comprises more than 40,000 PYE from four different sources of data (Panel 71).

Panel 71 Global Safety Database – Sources, Number of Patients, and Exposure

Source	Number of patients[a]	Patient Years of Exposure[a]
Clinical Studies ((Core Clinical Studies, phase I studies, the Japanese studies, and ongoing studies)	3390	1983
Epidemiological Studies (the ESES and EPOS studies)	9672	4222
The SCoP study	4905	6978[b]
Post-marketing surveillance	-	27,450

a The number of patients and exposure are for sertindole only

b WRT+30 days Period

It is important to distinguish between the different sources of safety data because they differ with respect to intensity of follow-up and availability of information about the patients, ranging from the very intense monitoring of patients in a clinical study environment to the, at least in some cases, more sparse information received in the post-marketing spontaneous reports. The SCoP study represents a special category. In this large study, that was conducted under normal conditions, only very few patients were lost to follow-up (Panel 15).

The clinical study data in the Global Safety Database include data from the Core Clinical Studies, as well as data from the phase I studies, the Japanese Studies, and the ongoing Studies 11286, 11723A, 12009A, and 99823 (Named Patient Use).

The number of deaths reported to the Global Safety Database by source is presented in Panel 72.

Panel 72 Global Safety Database – Number of Deaths by Source

Source	Number of Deaths during Treatment with Sertindole	Number of Deaths in the 30-day Period after Stop of Sertindole	Total
Clinical Studies	19	16	35
Core Clinical Studies	15	12	27
Phase I studies	1	0	1
Japanese studies	1	1	2
Ongoing studies	2	3	5
Epidemiological Studies	46	8	54
ESES (Study 98604, including amendments)	40	5	45
EPOS (Study 97201)	6	3	9
The SCoP study (sertindole group)	46[a]	18	64
Post-marketing spontaneous reports	32	6	38
Total number of deaths	143	48	191

a Number of deaths in the WRT+1 day period. Number of deaths in the ORT+1 day period: 40.

The Global Safety Database includes a total of 41 reports on deaths that occurred more than 30 days after stop of sertindole: 10 in the Core Clinical Studies, 2 in the EPOS study, 28 in the SCoP study (sertindole treatment group), and 1 from spontaneous reporting.

5.9.2 All-cause Mortality in the Core Clinical Studies

In the Core Clinical Studies, a total of 15 patients died during or within 1 day after stop of sertindole treatment and with a total exposure of 1840 PYE, this corresponds to a mortality rate of 0.82 deaths per 100 PYE. A total of 27 patients died during treatment with sertindole or within 30 days thereafter, corresponding to a mortality rate for sertindole of 1.47 per 100 PYE.

When comparing the mortality rates from the clinical development programmes of other second generation antipsychotics (Panel 73), no excess all-cause mortality is found for sertindole, despite the fact that concurrent cardiovascular disease was not an exclusion criterion in the sertindole clinical studies as it was in the olanzapine and risperidone studies. The comparison is made between the NDA dossier data (Summary Basis of Approval), as comparative data within a development programme is not possible due to the very limited exposure and few events in the blinded comparative periods.

Panel 73 Clinical Studies – Mortality Rates

Compound[a]	All-cause Mortality Rate Deaths per 100 PYE	95% Confidence Interval
Sertindole	0.82	0.5 – 1.3
Sertindole[b]	1.47	1.0 – 2.1
Risperidone	1.86	1.1 – 3.0
Olanzapine	1.87	1.2 – 2.9
Aripiprazole	0.90	-
Ziprazidone	1.62	-
Quetiapine	1.09	-

PYE: patient years of exposure

a Competitor data from respective Summary Basis of Approval

b Reporting period: Treatment +30 days

As clinical studies are conducted under circumstances, which are not comparable to treatment in real life, there will always be a risk that the mortality will be underestimated compared to that observed under more normal conditions of use.

H. Lundbeck A/S initiated a series of epidemiological studies in order to investigate mortality outside of a clinical study setting. The results from these studies confirmed the low all-cause mortality seen in the Core Clinical Studies.

5.9.3 All-cause Mortality in the Epidemiological Studies

Data from the largest retrospective cohort study, the ESES study and its amendments (the Sertindole Safety Survey and the ESES Crossover Sub-study), including a total of more than 10,000 patients, is presented in Panel 74. The mortality rates in these retrospective cohort studies are less than half of those reported for the general schizophrenic population.

This low mortality seen in ESES could in theory reflect selection bias. During the clinical studies, patients with cardiovascular disease were not excluded. Therefore, in contrast to other development programmes where this was the case, an increase in mortality was not seen when the sertindole was marketed and patients from the broader population were exposed to the drug. This limitation of the use of the sertindole to patients without cardiovascular disease and subsequent possible reduction in mortality as seen in ESES is in fact the intention with the labelling.

In one particular study, the ESES Crossover Sub-study, this selection bias was eliminated as patients served as their own controls. In this study, patients on sertindole also had a lower mortality as compared to when they were switched to other treatments. Given the uncertainty as to the circumstances of the switch, one should, however, be careful of drawing too strong conclusions, other than the large amount of data from real life use of sertindole support a low mortality.

Panel 74 The ESES Study, the Sertindole Safety Survey, and the ESES Crossover Sub-study – All-cause Mortality Rates

Event	ESES Study	Sertindole Safety Survey	ESES Crossover Sub-study
No. of patients	8608	1439	1112
Patient years of exposure (PYE)	3808	1808	970
No. of deaths	29[a]	9[a]	7
All-cause mortality rates/ 100 PYE (95% CI)	0.76 (0.51– 1.10)	0.51 (0.23 – 0.97)	0.72 (0.29 – 1.49)

CI: confidence interval

The number of deaths is different from the number in Panel 72 due to different reporting periods

a Reporting period: Treatment +5 days

5.9.4 All-cause Mortality in the SCoP Study

The results from the large, simple trial, the SCoP study, represent a reliable estimate of the all-cause mortality under normal conditions of use. Details of the methodology used in the SCoP study are presented in Appendix 1.

The primary endpoint was all-cause mortality. During randomised treatment (sertindole or risperidone; ORT+1), the all-cause mortality rate for sertindole was 0.63 deaths per 100 PYE and not different from that for risperidone (hazard ratio 0.980 with an upper confidence limit of 1.405).

In Panel 75, the number of deaths during treatment with sertindole and risperidone, respectively, is presented for the period exclusively on randomised treatment (ORT+1) as well as for the entire treatment period (including any add-on antipsychotic treatment) and 30 days thereafter.

Panel 75 The SCoP Study – Mortality Rates

Source	Sertindole N=4905	Risperidone N=4904
ORT+1 day Period		
Fatal events n (%)	40 (0.82%)	44 (0.90%)
Exposure (years)	6327	7218
Mortality (deaths per 100 PYE)	0.63	0.61
Hazard ratio (sertindole *versus* risperidone)	0.980[a]	
90% confidence interval	0.684 – 1.405	
WRT+30 days Period		
Fatal events n (%)	64 (1.30%)	61 (1.24%)
Exposure (years)	6978	7975
Mortality (deaths per 100 PYE)	0.92	0.76
Hazard ratio (sertindole *versus* risperidone)	1.117[a]	
90% confidence interval	0.831 – 1.500	

a adjusted for age, sex, time since last suicide attempt, previous polytherapeutic treatment, and study accrual time

The estimated all-cause mortality ratio of sertindole to risperidone for the WRT+30 was 1.117 with an upper confidence limit of 1.500.

Thus, the hypothesis of an excess all-cause mortality (defined as the upper limit of the 90% confidence interval of the hazard ratio >1.5) for sertindole *versus* risperidone, under normal conditions of clinical use, was rejected.

When interpreting these results, it should be taken into consideration that patients with significant cardiac disease or prolonged QT interval were not eligible for inclusion in the study, a contraindication that is not part of the risperidone labelling.

5.9.5 All-cause mortality in Post-marketing Experience

As of 11 July 2008, the Global Safety Database for sertindole comprises more than 40,000 PYE, of which more than two-thirds represent post-marketing exposure. There are 38 spontaneous reports of fatal events during treatment with sertindole or within 30 days thereafter, corresponding to an overall mortality rate of 0.14 deaths per 100 PYE.

5.9.6 For-cause Mortality

5.9.6.1 Introduction

The concern for sertindole, as well as for several other antipsychotics, is the translation of QT prolongation into an increased risk for arrhythmias and eventually into an increased mortality. Therefore, the clinical outcome of interest is death by arrhythmia.

To thoroughly evaluate the causes of death, three different methodologies have been used in the analysis of for-cause mortality in the Global Safety Database for sertindole.

All of these three analyses are complementary to each other and none of them should be considered superior. They do not represent a continuum or flow but are three different approaches with the purpose of evaluating the cause of death during or after treatment with sertindole.

MedDRA Coding of Fatal Cases

At reporting, fatal cases are coded using the hierarchical MedDRA dictionary. In general, the cause of death as given by the reporter is translated into the corresponding MedDRA term categorised into one of 27 SOCs or main categories. The SOC *Cardiac disorders* is of interest since the outcome of interest is death by arrhythmia. In addition, the SOC *General disorders and administration site conditions*, which includes sudden deaths and deaths without any specified cause, is also of interest.

Medical Review of all individual fatal cases

The medical review of all fatal cases was performed with the aim of identifying deaths caused by cardiac arrhythmia. No two cases in a safety database are identical and the review was performed as a case-by-case evaluation using no systematic algorithm. As the purpose was to identify arrhythmia-related deaths, efforts were made to propose a precise diagnosis for cardiac-related cases. The outcome of the review is not a clarification of the MedDRA coding and will therefore only to some extent reflect this classification.

Sudden Cardiac Death

Finally, a comparison of the incidence of Sudden Cardiac Death in the Global Safety Database with that for users of antipsychotics in general was performed. The background for this comparison was a recent publication by Ray *et al*., who investigated the rate of Sudden Cardiac Death among users of antipsychotics in a retrospective cohort study of Medicaid enrolees in Tennessee comprising more than 90,000 users of antipsychotics and more than 186,000 non-users.[69] The endpoint was defined as *sudden cardiac death occurring in the community* based on a set of strict criteria in order to eliminate background noise.[70] This definition serves as an epidemiological tool in the investigation and is not an attempt to propose a new set of criteria for defining Sudden Cardiac Death.

5.9.6.2 MedDRA Coding of Fatal Cases

The primary concern for sertindole is an increased risk for cardiac death associated to QT prolongation. Therefore the MedDRA coding in the Global Safety Database as given by the reporter has been searched in order to identify events coded to either of the SOCs *Cardiac Disorders* or *General Disorders and Administration Site Conditions* - the latter being the category where deaths without any specified cause are assigned to.

The number of deaths reported in these two SOCs from the clinical studies, the epidemiological studies, and from spontaneous reporting, is shown in Panel 76.

Panel 76 Global Safety Database – Number of Deaths by MedDRA SOCs

Source	Cardiac Disorders	General Disorders and Administration Site Conditions	Other SOCs
Clinical Studies	4	10	21
Epidemiological studies	9	20	25
Post-marketing spontaneous reports	3	20	15

SOC: System Organ Class
Reporting period: Treatment +30 days

The number of deaths in the SOC *General disorders and administration site conditions* from spontaneous reporting to some extent is a reflection of the limited information available in these cases.

For the SCoP study, the numbers of deaths in these two SOCs for sertindole and risperidone, respectively, are shown in Panel 77.

Panel 77 The SCoP Study – Number of Deaths by MedDRA SOCs

Treatment Group	Cardiac Disorders	General disorders and administration site conditions	Other SOCs
Sertindole	17	11	36
Risperidone	8	6	47

SOC: System Organ Class
Reporting period: WRT+30 days

In the SCoP study, the proportion of the deaths in the two SOCs is lower for risperidone than for sertindole. One of the explanations for this may be ascertainment bias. The SCoP study was an open-label study conducted due to a cardiac safety concern for sertindole and with mandatory ECG monitoring only for sertindole-treated patients; risperidone patients were only to have an ECG at inclusion.

As a part of the safety surveillance of the SCoP study (Appendix 1), all fatal and non-fatal serious adverse events were blindly reviewed on an ongoing basis by the ISC to secure the safety of the patients and evaluate the need for intervention in the study conduct. The review was based on a conservative approach, that is, a case was considered cardiac unless another cause of death could be documented. The review did not give rise to interference with the study conduct.

For all sources of data, it must be taken into consideration that the SOC *Cardiac Disorders* covers a variety of cardiac diagnoses and only very few documented arrhythmias.

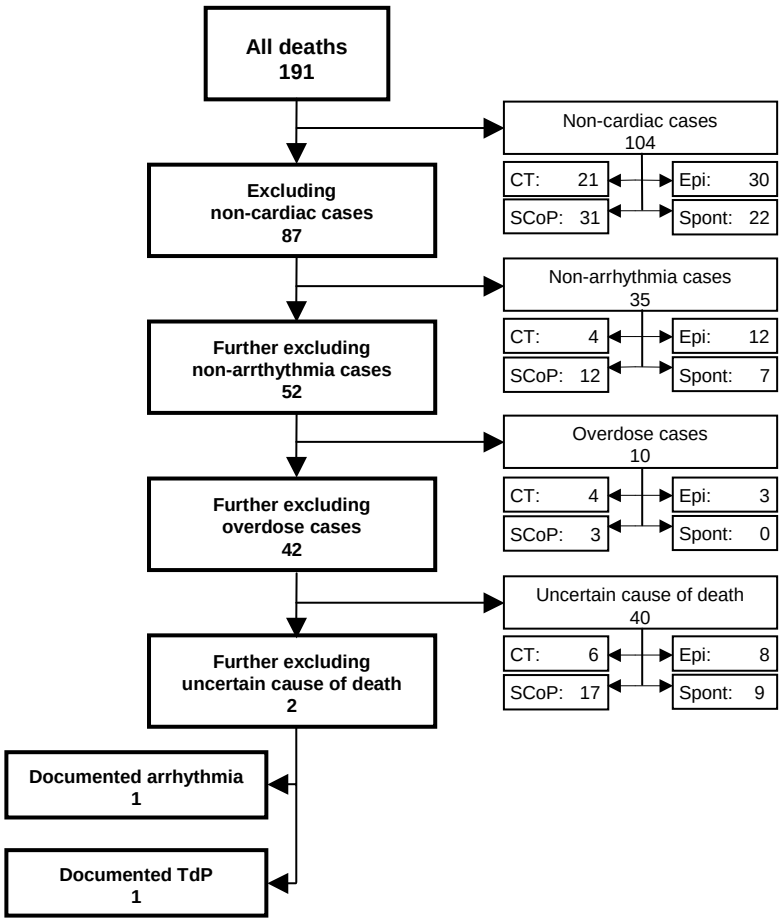
5.9.6.3 Medical Review of Fatal Cases

In order to quantify whether QT prolongation resulted in an increase in mortality, deaths by arrhythmia was examined as an outcome in all fatal cases in the Global Safety Database. Pharmacovigilance can not be done based on queries in the safety database alone - it always requires a medical review and classification of relevant cases in order to analyse any issue thoroughly.

Therefore, all fatal cases in the Global Safety Database reported during treatment with sertindole or within 30 days thereafter were reviewed and classified with the purpose to conclude if the cause of death was non-cardiac, non-arrhythmic cardiac or a documented cardiac arrhythmia.

As seen in Panel 78, the classification was done in several steps. First, obviously non-cardiac deaths were excluded, then non-arrhythmic cardiac deaths, then overdoses, cases of unknown cause, and finally documented arrhythmias (non-Torsade de Pointes (TdP)).

Panel 78 Global Safety Database – Review of Fatal Cases



CT: clinical studies; Epi: epidemiological studies; SCoP: the SCoP study; Spont: spontaneous reports

The review comprised all 191 fatal cases that occurred during treatment with sertindole or within 30 days thereafter in the Global Safety Database.

Non-cardiac cases were cases where an obvious non-cardiac cause of death was identified, for example, suicides by traumatic measures, accidents, or cases where a definite non-cardiac cause of death was demonstrated by autopsy.

The non-arrhythmic cardiac cases were mainly cases where an acute myocardial infarction or ischaemic heart disease had been identified as the cause of death, in some cases from an autopsy, in others from clinical observations.

As the aim was to review events occurring during treatment with therapeutic dosages, cases related to overdoses were excluded during the process and are discussed separately in section 5.11.

The cases of uncertain cause of death are cases where the patients were found dead or where investigations, observations, or medical history do not support any specific explanation. Also cases with limited or no information available are categorised here. For these cases an exact cause of death cannot be identified.

In 40 (21%) of the cases, the cause of death remains unknown - in most cases due to limited information about the circumstances of the event.

From the review it can be seen that the incidence of fatal documented TdP and arrhythmia during treatment with therapeutic dosages of sertindole is very low.

One documented TdP in a patient with several confounding factors was identified (Panel 79).

Panel 79 Fatal Case of Documented TdP

Case ID (Source)	Age/ Sex	QT_c	Narrative
1013530 (The SCoP study)	79/F	563 msec	This case concerns a 79-year-old woman with a medical history of hypertension, ischaemic heart disease and myocardial damage from this. The patient had a syncope in relation to an ECG recording. This ECG recording showed a QTc interval of 563msec and TdP. The patient recovered spontaneously but was hospitalised later on the same day. Sertindole was discontinued and the patient was treated with xylocaine and amiodarone due to additional arrhythmic events, and with furosemide due to signs of heart failure A Holter monitoring performed 2 days after admission showed increased QTc interval without ventricular arrhythmia and only with ventricular extrasystoles. Following this, the patient was taken off cardiac monitoring but stayed hospitalised. Four days after discontinuation of sertindole, she was found dead. Two days before she died, treatment with perazine was initiated due to psychiatric symptoms. It is unclear what role the heart condition, amiodarone, furosemide, perazine, or sertindole played in her death.

An additional 1 fatal case is considered a documented arrhythmia (Panel 80). The case was not reported or described as an arrhythmia, but as cardio-version was performed, the presence of arrhythmia is likely.

Panel 80 Fatal Case of Documented Arrhythmia

Case ID (Source)	Age/ Sex	QT_c	Narrative
0990027 (Epidemiological studies)	69/F	-	This case concerns a 69-year-old woman who was reported to have a “heart-attack” accompanied by nausea and collapse. The patient had been treated with sertindole for 6 months prior to the event. Cardio-version was performed but there is no information about the specific arrhythmia and there is generally very sparse information on this case. Verapamil, digoxin, and haloperidol were reported as concomitant medication, all drugs associated with risk for arrhythmia.

5.9.6.4 Sudden Cardiac Death

As described in section 5.9.6.1, the purpose of this analysis was to compare the rate of Sudden Cardiac Death for sertindole to that of other antipsychotics. The comparison was done using results recently published by Ray *et al*.[69] based on a database comprising more than 90,000 users of antipsychotics and more than 186,000 non-users was analysed. The definition applied in this analysis was not an attempt to revise the definition of Sudden Cardiac Death but to provide a suitable tool for analysing large amounts of real life data.

The criteria excluded deaths later than 30 days after treatment discontinuation, cases with an obvious non-cardiac or non-arrhythmic cause, overdoses, hospitalised patients, cases with limited or no information, patients dying later than 48 hours after the event, and patients younger than 30 years or older than 74 years of age.

The SCoP data resembles the Medicaid data due to the natural conditions of use and the very complete follow-up. As the reporting period (WRT+30) in the SCoP study already excluded cases later than 30 days after stop of treatment, this criteria is not part of the sequential exclusion. Applying all other criteria used by Ray *et al* on all 64 fatal cases for sertindole-treated patients in the SCoP study, 12 cases were classified as a *sudden cardiac death occurring in the community*. The criteria were applied sequentially in the order presented in Panel 81. Therefore, a case may meet several of the exclusion criteria but would be excluded at the first instance.

Panel 81 The SCoP Study – Classification of Sudden Cardiac Death (Criteria as Published by Ray *et al*.)

	Number of deaths n (%)
Total number of deaths	64
Deaths excluded - sequentially:	
Obvious non-cardiac cause	30 (46.9)
Non-arrhythmic cardiac cause	12 (18.8)
Extrinsic factor (for example, overdose)	4 (6.3)
Hospitalisation	1 (1.6)
Death later than 48 hours after event	0
No information about vital status 24 hours prior to death	2 (3.1)
Little information provided	1 (1.6)
Age > 74 years	0
Age < 30 years	2 (3.1)
Sudden Cardiac Death Occurring in the Community	12 (18.8)

Reporting period: WRT+30 days
Criteria by Ray *et al* (2001 and 2009)[69,70]

The corresponding rate of Sudden Cardiac Death in the SCoP study is 0.17 events per 100 PYE and comparable to or lower than those observed in the Medicaid database (Panel 82).

Panel 82 Number and Rate of Sudden Deaths in the SCoP Study and as Published by Ray *et al*.

	Patient Years of Exposure	Number of Sudden Deaths	Rate Events per 100 PYE
The SCoP study	6978	12	0.17
Any typical agent[a]	86,736	255	0.29
Any atypical agent[a]	79,589	223	0.28

Reporting period for the SCoP study: WRT+30 days

a Ray *et al*. (2009)[69]

The low rate of Sudden Cardiac Death seen in the SCoP study compared to the results published by Ray *et al*. [69] is likely to be explained by demographic differences between the two populations and the active screening and exclusion for cardiac disease in the SCoP study. However, due to the amount of exposure, the very complete follow-up, and the conditions under which the patients were treated, the SCoP population remains representative of patients treated with sertindole under normal conditions of use and the outcome is a reliable estimate compared to a real world scenario.

5.9.7 Mortality Conclusions

The data in the Global Safety Database covering the clinical and epidemiological studies as well as spontaneous reports from dawn to 11 July 2008 consistently show an all-cause mortality not different from those observed for other second generation antipsychotics.

The SCoP study showed that the all-cause mortality with sertindole was comparable to that with risperidone. During the ORT+1, the all-cause mortality rate for sertindole was 0.63 deaths per 100 PYE and not different from that for risperidone (hazard ratio of 0.980 with an upper confidence limit of 1.405). The estimated all-cause mortality ratio of sertindole to risperidone for the WRT+30 was 1.117 with an upper confidence limit of 1.500. Thus, the QT interval prolongation does not translate into an increase in all-cause mortality during sertindole treatment.

Reports of documented arrhythmias in relation to fatal cases are very few and only one case, with several confounding factors, is a documented episode of TdP.

The analysis of Sudden Cardiac Death during treatment with sertindole and a comparison to the rates reported in the most recent literature do not indicate an increased risk for sertindole compared to other antipsychotics.

The evaluation of the fatal cases employed three different, complementary approaches, all of which gave rise to the same conclusion.

5.10 Torsade de Pointes

In the Global Safety Database for sertindole, there are a total of 4 cases reported as TdP during treatment with sertindole: 1 in relation to a fatal case and 3 non-fatal cases. For details on the fatal case, see Panel 79 in section 5.9.6.3. The 3 non-fatal cases are described in Panel 83.

Panel 83 Non-fatal Cases Reported as TdP

Case ID (Source)	Age/ Sex	QT_c	Narrative
1016275 (The SCoP study)	43/F	-	This case concerns a 43-year-old woman who 18 months after treatment start was brought to the emergency room due to palpitations and shortness of breath. The ECG was normal but the patient was admitted for observation. During admission, the ECGs showed a mixture of ventricular pacing, short runs of ventricular extrasystoles and a single episode of a 3-beats polymorphic non-sustained ventricular tachycardia, compatible with, but not diagnostic for, TdP. The patient was treated with a temporary pacemaker and recovered completely. At time of admission, the patient had low serum potassium (3.4mmol/L). Prior to the event, the patient had been treated with an unknown antibiotic and with a traditional Chinese cough medicine, both of which may have contributed to the event.
0980776 (Spontaneous report)	40/F	600msec	This case concerns a 40-year-old woman who 7 weeks after treatment start had syncope and was hospitalised. Cardiac monitoring was normal and the patient was transferred to the psychiatric ward where a subsequent ECG showed a QTc value of 600msec and TdP. The patient was treated medically but due to more episodes of TdP, cardioversion was required. Treatment with sertindole was discontinued in relation to the event and the patient recovered. The patient had a medical history of "palpitations and cardiac irregularity". The patient was followed after treatment discontinuation and several ECGs recorded in that period showed extreme bradycardia with a heart rate as low as 37 beats per minute. Ajmaline is listed as concomitant medication. Ajmaline is known to cause a variety of cardiac conduction disturbances including sinus arrest, bradycardia, and in rare cases TdP and, thus, may have contributed to the event.
0981022 (Spontaneous report)	31/F	573msec 617msec	This spontaneous case concerns a 31-year-old woman who was treated with sertindole for 4 months when she suddenly became unconscious. Resuscitation was performed and the patient was transferred to hospital. At admission, the patient had serum potassium at 3.2mmol/L. The next day, two episodes of TdP was observed. No treatment was reported. The patient recovered completely. Several ECGs were recorded for this patient. The ECGs from the week prior to the event showed QTc intervals up to 573 to 617msec. All ECGs prior to this showed QTc intervals within normal ranges. The patient had a medical history of collapse. The patient's sister died suddenly and unexpected 2 to 3 years prior to the event. The patient was treated with fluoxetine prior to the event. Arrhythmias and TdP have been reported in relation to treatment with fluoxetine.

Conclusion

In total, there were 4 cases of reported TdP. All cases were confounded by risk factors in the medical history and concomitant treatment, some with compounds known to carry the risk for ventricular arrhythmia.

5.11 Overdoses

In the Global Safety Database for sertindole, there are a total of 218 patients for whom an overdose was reported. A total of 133 cases involved sertindole: 91 cases of overdose with sertindole only and 42 cases of mixed overdose with sertindole. (Panel 84).

Panel 84 Global Safety Database – Overview of Overdoses

Source	Number of Patients With Overdose	Overdose of 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
The SCoP study[a]	67	18	11	38
Spontaneous Reports[b]	29	19	9	1

a Includes all events in patients randomised to sertindole, irrespective of study period and whether the patient was still on sertindole treatment

b Number of reports

For the 91 overdoses with sertindole only, a total of 47 patients had one or more adverse event reported in relation to the overdose. The most frequently reported events were: *Electrocardiogram QT prolonged* (25% of patients), *Suicide attempt* (15% of patients, including one report of *Suicidal ideation*) and *Somnolence* (7% of patients). No other adverse event was reported with a frequency greater than 5% of patients.

The highest overdose reported is a non-fatal case of where the patient took 2560mg sertindole. For details on the 5 cases involving the highest overdoses of sertindole, see Panel 85.

Panel 85 Global Safety Database – The 5 Cases With the Highest Overdose of Sertindole

Case ID (Source)	Age/ Sex	Sertindole dose	QT_c	Narrative
Non-fatal				
1027877 (The SCoP study)	28/F	2560mg	-	Overdose of 2560mg sertindole and an unknown quantity of insecticide in an attempted suicide. The patient vomited and was hospitalised and further treated with gastric lavage. No associated symptoms reported. The patient recovered and was discharged the next day.
0950493 (Clinical studies)	26/M	840mg	-	Overdose of 840mg sertindole and 37.5mg lorazepam in an attempted suicide. The patient was hospitalised and made a full recovery. No associated symptoms or treatment were reported.
0970115 (Clinical studies)	34/M	720mg	520msec	Mixed overdose of sertindole (720mg) and lorazepam (30mg) in a suicide attempt. ECG showed AV-block, QT prolongation and ventricular tachycardia. ECG. The patient recovered without intervention.
0970292 (Sponta-neous report)	34/M	672mg	509msec	Overdose of 672mg sertindole, 120mg citalopram, and 1L alcohol in an attempted suicide. The patient was hospitalised with the following symptoms: dyspnoea, somnolence, and chest pain. ECG recording showed QTc at 509msec. The patient made a full recovery.
Fatal				
0960013 (Clinical studies)	22/M	660mg	-	Overdose of 660mg sertindole, 125mg lorazepam, and alcohol. The patient was hospitalised the next day but did not present any symptoms. The patient died 6 hours after admission. Post mortem blood samples showed sertindole concentration 8-10 times that expected at 24mg daily dose. No other information was provided.

A total of 3 deaths were reported in association with an overdose of sertindole only (Panel 86).

Panel 86 Global Safety Database – Number of Deaths Associated With Overdose

Source	Number of Patients with Overdose	Deaths Associated with Overdose of Sertindole Only	Deaths Associated with Mixed Overdose, including Sertindole	Deaths Associated with Overdose, not including Sertindole	Deaths Associated with Overdose Total
All sources	218	3	4	6	13
Clinical studies	83	0	2	1	3
Epidemiological studies	39	2	0	0	2
The SCoP study[a]	67	1	1	5	7
Spontaneous Reports[b]	29	0	1	0	1

a Includes all events irrespective of study period and whether the patient was still on sertindole treatment

b Number of reports

Two of the three cases were associated with arrhythmia (Cases 1026897 and 0981575) and are detailed in Panel 88.

The third fatal case of overdose with sertindole only is described in Panel 87.

Panel 87 Fatal Overdose With Sertindole Only – Not Associated With Cardiac Arrest or Arrhythmia

Case ID (Source)	Age/ Sex	QT_c	Narrative
0980685 (Spontaneous report)	33/F	-	This case concerns a 33-year-old woman who had been treated with sertindole for 1 year. The patient collapsed in front of the nursing staff and resuscitation was unsuccessful. Suicide was suspected. Autopsy was without findings, except for plasma levels of sertindole approximately 7 times the therapeutic level (990µg/L). Due to this information, the case is considered an overdose (unknown dose). Concomitant medication: chlorprothixene and diazepam.

There were 8 cases of overdose associated with cardiac arrest or arrhythmia; details are presented in Panel 88.

Panel 88 Global Safety Database – Overdoses Associated With Cardiac Arrest or Arrhythmia

Case ID (Source)	Age/ Sex	Overdose	QT_c	Narrative
Fatal				
0200614 (Sponta-neous report)	43/F	Sertindole Sertraline	632msec (OD) 609msec (day of death)	The patient was hospitalised due to a mixed overdose including 448 mg sertindole in a suicide attempt from which she recovered. Nine days later she attempted suicide by strangulating. A further 3 days later the patient became unconscious during a medical examination. QT interval prolongation and VF was observed on arrival of the resuscitation team. Resuscitation was unsuccessful. Autopsy without any conclusion. Post mortem toxicology screen was negative. The patient had a medical history of suicide attempt by overdosing with sertindole. From the description of the case, the most likely cause of death is suicide by overdose of unknown drug or substance.
0981575 (Clinical Studies)	31/F	Sertindole	-	Overdose of 120 tablets of sertindole in an attempted suicide. Resuscitation at hospital was unsuccessful and the patient died. There was no autopsy or blood sampling to confirm death and implications of other concomitant drugs.
1026897 (The SCoP study)	35/M	Sertindole	500msec	Overdose of sertindole (360mg) in a suicide attempt. ECG showed prolonged QT interval. During detoxification the patient was found unconscious and not breathing. Resuscitation was unsuccessful. No autopsy performed. The patient had a medical history of previous suicide attempts.
Non-fatal				
0970115 (Clinical Studies)	34/M	Sertindole Lorazepam	520msec	See Panel 85
0970233 (Clinical Studies)	36/F	Sertindole Haloperidol Lorazepam	527msec	Mixed overdose of sertindole (576mg), haloperidol (288mg) and lorazepam (236mg) in a suicide attempt. On admission: QT interval prolongation, extrasystoles and short runs of VF. The patient was treated with IV electrolytes and lidocaine and made complete recovery. The patient had a medical history of previous suicide attempt.
0981017 (Sponta-neous report)	33/F	Sertindole Fluvoxamine	540msec	Overdose of 480mg sertindole in an attempted suicide. The patient was hospitalised and the ECGs showed TdP. The patient was treated with hemodialysis and temporary pacing. The patient recovered. The patient had a medical history of previous suicide attempts.
0981493 (Sponta-neous report)	-/F	Sertindole Thioridazine Flunitraze-pam	580msec	3-4 months after discontinuation of sertindole the patient was reported to have taken an overdose of sertindole (48mg) and thioridazine (unknown amount) in a suicide attempt. The patient presented with TdP. She received IV electrolytes and was reported to make a complete recovery.
0981344 (Sponta-neous report)	38/F	Sertindole	480msec	Overdose of sertindole (240mg). The patient was hospitalised and ventricular fibrillation during detoxification was reported. No further information is available. The patient recovered.

Overdose Conclusion

A total of 133 cases of overdose involving sertindole have been reported:

- 91 cases of overdose with sertindole only, of which 3 were fatal.
- 42 cases of mixed overdose with sertindole, 4 of which were fatal.

The highest overdose reported was a non-fatal case where the patient had taken 2560mg sertindole.

A total of 8 of the 133 cases of overdose with sertindole were associated with cardiac arrest or arrhythmia: 3 were overdoses with sertindole only and 5 were mixed overdoses.

Like other antipsychotics, multiple targets are influenced in overdoses with sertindole. The resulting symptoms affect multiple autonomic functions, including the central nervous system, gastrointestinal system, and not least the autonomic functions of the cardiovascular and respiratory system. For many of the cases with sertindole overdose, patients who were hospitalised when intoxicated recovered. However, as is common with any drug overdose, the time between the intoxication and the initiation of life support determines the outcome, primarily due to generalised depressive actions on the cardiovascular and respiratory functions.

6 Risk Minimisation Action Plan (Risk MAP)

6.1 Rationale

Sertindole has the potential to prolong the QT interval. The potential safety consequences of a prolonged QT interval are a cause for concern for any drug with this pharmacodynamic property.

The rationale behind this RiskMAP is to provide instructions for the safe use of sertindole, primarily by identifying and excluding patients with an increased risk of QT interval prolongation.

An important element of this is to carefully educate prescribers, pharmacists, patients, and caregivers on how to properly use sertindole.

Finally, in addition to general pharmacovigilance activities, H. Lundbeck A/S will monitor the use of sertindole through drug utilisation and outcome databases, to identify any potential safety issues.

6.2 Patient Selection

The proposed sertindole labelling specifies that patients at risk are to be excluded from treatment. Specifically, the patients to be excluded are those who have:

- clinically significant cardiovascular disease, such as congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia
- congenital long QT syndrome or known acquired QT interval prolongation
- severe hepatic impairment
- known uncorrected hypokalaemia or hypomagnesaemia. This may occur in patients with diarrhoea or those taking diuretics

Sertindole treatment should be avoided in patients who are taking other medications known to significantly prolong the QT interval. Sertindole should be used with caution in patients who are taking medications that inhibit sertindole metabolism (for example, potent CYP2D6 and moderate CYP3A inhibitors).

6.3 ECG Recommendations

When sertindole is prescribed for patients with schizophrenia, the labelling recommends that ECGs be performed.

Following treatment initiation, it is recommended that an ECG should be obtained 3 to 4 weeks after treatment start, that is, when the maintenance dose has been reached.

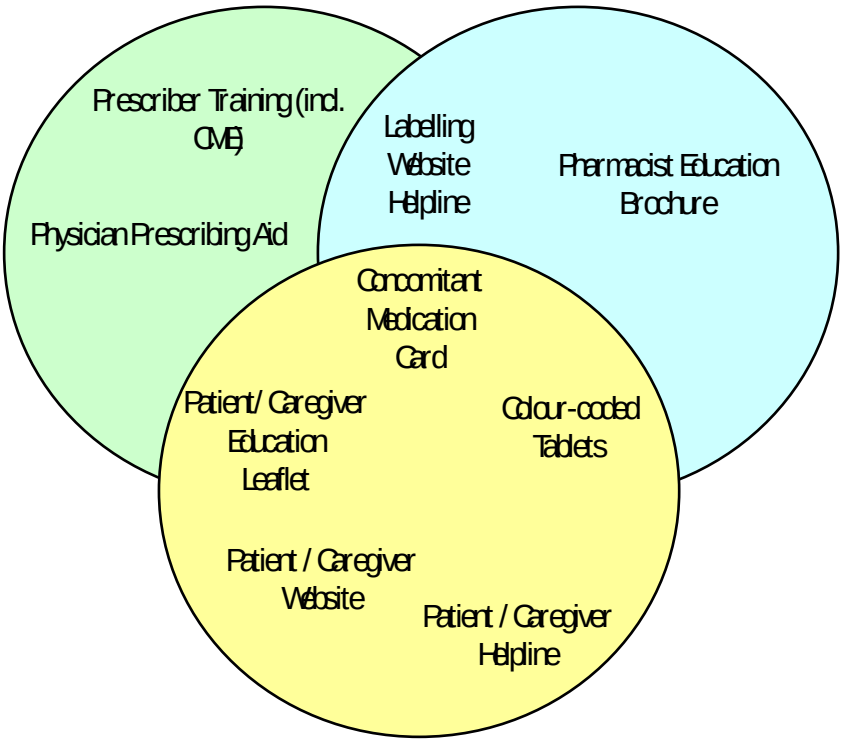
Also, if there is an increase in dose or if additional medications that prolong the QT interval or that may increase the sertindole concentration (potent CYP2D6 inhibitors, moderate CYP3A inhibitors) are prescribed, additional ECGs are recommended.

Furthermore, it is recommended that sertindole be discontinued in patients who have persistent QT_c measurements above 500msec.

6.4 Education

The Serdolect® RiskMAP is designed to offer repetitive educational opportunities to reinforce the important safety messages. This ensures that physicians, pharmacists, patients, and caregivers receive consistent information about the appropriate use of sertindole on multiple occasions, and will be more effective in conveying the safety information than just the product labelling by itself (Panel 89).

Panel 89 RiskMAP – Education of Stakeholders



The programme objective is to promote compliance with the labelling using different tools delivered through several channels.

Prescribers

Individual training of prescribers will emphasize the importance of identifying patients at risk and of monitoring patients during treatment. In addition, the training will focus on how to educate patients (and their caregivers) who will be treated with sertindole. Training will also include continued medical education (CME) accredited courses.

In addition to training, prescribers will receive written materials and access to other educational resources including:

- the product labelling
- the Physician Prescribing Aid
- the Serdolect® toll-free helpline
- the Health Professional section of the Serdolect® website

When prescribing sertindole to a patient, the prescribing physician will hand out and discuss the following materials with the patient (and/or caregiver, as appropriate):

- the Concomitant Medication Card
- the Patient/Caregiver Education Leaflet

The Concomitant Medication Card is also intended to be used in consultations with other doctors who may prescribe concomitant medications with the potential for interactions with sertindole.

Pharmacists

Pharmacists will have access to many of the same tools as the prescribers:

- the product labelling
- the Pharmacist Education Brochure
- the Serdolect® toll-free helpline
- the Health Professional section of the Serdolect® website

Pharmacists will discuss the instructions on the Concomitant Medication Card with the patient (and/or caregiver, as appropriate), also when dispensing other prescription medication (that may have the potential for unwanted interactions) to the patient, and use it in consultations with other doctors that may prescribe concomitant medication.

To decrease the potential of dispensing and dosing errors, both for pharmacists and patients/caregivers, sertindole tablets are colour-coded according to dosage strengths.

Patients (and/or Caregivers)

The following educational tools will be available to the patient (and caregiver):

- the Patient/Caregiver Education Leaflet
- the Concomitant Medication Card

- a customised Patient/Caregiver Website
- the Serdolect® toll-free helpline

The patient/caregiver is encouraged to discuss the instructions on the Concomitant Medication Card with the pharmacist, when any prescription (for sertindole or other prescription or Over-the-counter medication (OTC)) gets filled at the pharmacy.

Multiple Educational Opportunities

The Serdolect® RiskMAP is designed to offer repetitive educational opportunities to reinforce the important safety messages. This ensures that physicians, pharmacists, patients, and caregivers receive consistent information about the appropriate use of sertindole on multiple occasions, and will be more effective in conveying the safety information than just the product labelling by itself.

6.5 Safety Surveillance Programme

The passive safety surveillance with spontaneous reporting and literature surveillance comply with the FDA MedWatch programme. In addition, an active safety surveillance programme will be established using the monitoring of drug utilisation databases, such as the Medicaid database. This active programme will evaluate prescription patterns and will be used to identify potential safety issues and relate these to the number of patients exposed to sertindole to assess the magnitude of a potential issue. Data will originate from the use of sertindole both in hospitals and in primary care settings.

6.6 Outlook

When designing the RiskMAP for sertindole, H. Lundbeck A/S created a programme for the patient and all those involved in the patient's care, to properly educate them on the appropriate use of sertindole. Prescriber training, written materials for physicians, pharmacists, and patients, toll-free helplines, and web-based information sources will provide the important safety messages that can be understood and followed. The programme will be monitored via passive and active safety surveillance and re-evaluated annually.

7 Conclusion

Schizophrenia is a serious, potentially fatal, debilitating, and mostly chronic mental disorder. It is estimated that approximately 2 to 3 million Americans suffer from this condition, which is associated with a significant burden of illness. This burden includes both the high suicide potential in patients with schizophrenia as well as the costs to society associated with this condition.

Sertindole is an efficacious, non-sedating, second generation antipsychotic with a unique neuropharmacological profile.

The clinical experience with sertindole is extensive with more than 40,000 patient years, which far exceeds that of most other NDAs.

Sertindole's efficacy is comparable to that of other first and second generation antipsychotics. Sertindole provides clinically significant symptomatic relief to patients with schizophrenia in short- and long-term treatment. The efficacy is due to improvements in both the positive and negative symptoms. Responder rates and the onset of effect were similar to that for haloperidol.

Sertindole provides an additional therapeutic benefit by reducing the risk of suicide attempts (both fatal and non-fatal) by up to 50%. Clinical trials, epidemiological studies, and a large naturalistic clinical study (the SCoP study) consistently show that sertindole is associated with a lower rate of suicide than other antipsychotics, also in a direct comparative setting in patients with a high risk of suicide.

Sertindole is well tolerated. The overall safety profile of sertindole is well characterised and understood. The placebo-level incidence of EPS, akathisia, and sedation provide further benefits, especially in long-term use.

Like many other second generation antipsychotics, sertindole prolongs the QT interval in a dose-dependent manner; however, the SCoP study confirmed that the QT interval prolongation observed with sertindole does not translate into a higher mortality risk in patients with schizophrenia than with standard treatment (risperidone).

Patients with an increased risk of QT interval prolongation should be excluded from sertindole treatment. To help prescribing physicians to identify vulnerable patients, there are contraindications, warnings, and precautionary instructions in the proposed product labelling. In addition, a Risk Minimization Action Plan provides instructions for the patient and all those involved in the patient's care regarding the safe and appropriate use of sertindole.

In summary, sertindole is an effective antipsychotic compound with a unique profile. The potential cardiac risks associated with sertindole are well characterised and can be managed. Furthermore, sertindole has a beneficial effect on reducing the risk of fatal and non-fatal suicide attempts. With this positive benefit-risk profile, sertindole offers an effective

treatment modality for the treatment of schizophrenia and for reducing the risk of fatal and non-fatal suicide attempts in patients with schizophrenia.

References

[1] Keck PE, Jr., Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. *J Clin Psychiatry* 2000; 61 (Suppl 3): 4-9.

[2] Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; 2: e141.

[3] Freedman R. Schizophrenia. *N Engl J Med* 2003; 349: 1738-1749.

[4] Dossenbach M, rango-Davila C, Silva IH, Landa E, Aguilar J, Caro O, et al. Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine, or haloperidol: 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *J Clin Psychiatry* 2005; 66: 1021-1030.

[5] Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003; 160: 1209-1222.

[6] DeQuardo JR. Pharmacologic treatment of first-episode schizophrenia: early intervention is key to outcome. *J Clin Psychiatry* 1998; 59 (Suppl 19): 9-17.

[7] Ohmori T, Ito K, Abekawa T, Koyama T. Psychotic relapse and maintenance therapy in paranoid schizophrenia: a 15 year follow up. *Eur Arch Psychiatry Clin Neurosci* 1999; 249: 73-78.

[8] Ill-Equipped: U.S. Prisons and Offenders with Mental Illness published by Human Rights Watch, 350 Fifth Avenue, New York.

[9] Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. *J Clin Psychiatry* 2005; 66: 1122-1129.

[10] Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000; 177: 212-217.

[11] Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000; 45: 21-28.

[12] Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. *Br J Psychiatry* 2001; 179: 498-502.

[13] Heila H, Haukka J, Suvisaari J, Lonnqvist J. Mortality among patients with schizophrenia and reduced psychiatric hospital care. *Psychol Med* 2005; 35: 725-732.

[14] Allebeck P. Schizophrenia: a life-shortening disease. *Schizophr Bull* 1989; 15: 81-89.

[15] Baxter DN. The mortality experience of individuals on the Salford Psychiatric Case Register. I. All-cause mortality. *Br J Psychiatry* 1996; 168: 772-779.

[16] Mortensen PB, Juel K. Mortality and causes of death in schizophrenic patients in Denmark. *Acta Psychiatr Scand* 1990; 81: 372-377.

[17] Sacks FM. Metabolic syndrome: epidemiology and consequences. *J Clin Psychiatry* 2004; 65 (Suppl 18): 3-12.

[18] Batel P. Addiction and schizophrenia. *Eur Psychiatry* 2000; 15: 115-122.

[19] Pickar D. Prospects for pharmacotherapy of schizophrenia. *Lancet* 1995; 345: 557-562.

[20] DeQuardo JR, Tandon R. Do atypical antipsychotic medications favorably alter the long-term course of schizophrenia? *J Psychiatr Res* 1998; 32: 229-242.

[21] Möller HJ, Muller H, Borison RL, Schooler NR, Chouinard G. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. *Eur Arch Psychiatry Clin Neurosci* 1995; 245: 45-49.

[22] Gallhofer B, Bauer U, Lis S, Krieger S, Gruppe H. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *Eur Neuropsychopharmacol* 1996; 6 (Suppl 2): S13-S20.

[23] Janicak PG, Davis JM, Preskorn SH, Ayd FJ. Principles and practice of psychopharmacotherapy. Baltimore, MD: Williams and Wilkins; 1993. 81-86 and 93-118.

[24] Kerwin RW. The new atypical antipsychotics. A lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; 164: 141-148.

[25] Lieberman JA. Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry* 1998; 59 (Suppl 3): 38-43.

[26] Fleischhacker WW. Clozapine: a comparison with other novel antipsychotics. *J Clin Psychiatry* 1999; 60 (Suppl 12): 30-34.

[27] Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology* 1996; 124: 2-34.

[28] Meltzer HY. The mechanism of action of novel antipsychotic drugs. *Schizophr Bull* 1991; 17: 263-287.

[29] Altar CA, Wasley AM, Neale RF, Stone GA. Typical and atypical antipsychotic occupancy of D2 and S2 receptors: an autoradiographic analysis in rat brain. *Brain Res Bull* 1986; 16: 517-525.

[30] Bersani G, Grispini A, Marini S, Pasini A, Valducci M, Ciani N. Neuroleptic-induced extrapyramidal side effects: clinical perspectives with ritanserin (R 55667), a new selective 5-HT2 receptor blocking agent. *Curr Ther Res* 1986; 40: 492-499.

[31] Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. *Psychopharmacol Bull* 1989; 25: 390-392.

[32] Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacology* 1998; 18: 63-101.

[33] Zorn SH, Lebel LA, Schmidt AW. Pharmacological and neurochemical studies with the new antipsychotic ziprasidone. In: Palomo T, Beninger RJ, Archer T, eds. Interactive monoaminergic disorders. Madrid: Editorial Sintesis 1999; 377-393.

[34] Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; 153: 321-330.

[35] Kane JM. What are the therapeutic needs in schizophrenia and how are they satisfied by new antipsychotics? *Int Clin Psychopharmacol* 1997; 12 (Suppl 2): S3-S6.

[36] Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry* 2007; 68 (Suppl 4): 8-13.

[37] Rodefer JS, Nguyen TN, Karlsson JJ, Arnt J. Reversal of subchronic PCP-induced deficits in attentional set shifting in rats by sertindole and a 5-HT(6) receptor antagonist: comparison among antipsychotics. *Neuropsychopharmacology* 2008; 33: 2657-2666.

[38] Sanchez C, Arnt J. In-vivo assessment of 5-HT2A and 5-HT2C antagonistic properties of newer antipsychotics. *Behav Pharmacol* 2000; 11: 291-298.

[39] Sanchez C, Arnt J, Dragsted N, Hyttel J, Lembøl HL, Meier E, Perregaard J, Skarsfeldt, T. Neurochemical and in vivo pharmacological profile of sertindole, a limbic-selective neuroleptic compound. *Drug Development Research* 1991; 22: 239-250.

[40] Nyberg S, Olsson H, Nilsson U, Maehlum E, Halldin C, Farde L. Low striatal and extra-striatal D2 receptor occupancy during treatment with the atypical antipsychotic sertindole. *Psychopharmacology* 2002; 162: 37-41.

[41] Petit-Taboue MC, Landeau B, Barre L, Onfroy MC, Noel MH, Baron JC. Parametric PET imaging of 5HT2A receptor distribution with 18F-setoperone in the normal human neocortex. *J Nucl Med* 1999; 40: 25-32.

[42] Buchsbaum M, Gupta A, Haznedar M, Hazlett E, Chu KW, Goldstein K, Goodman C, Newmark R, Torosjan y, Bark N, Wolkin A. FDG-PET and MRI imaging of the effect of sertindole in the striatum of schizophrenia. *Int J Neuropsychopharmacology* 2006; 9 (Suppl 1): S160.

[43] Wilton LV, Heeley EL, Pickering RM, Shakir SA. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. *J Psychopharmacol* 2001; 15: 120-126.

[44] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469-480.

[45] Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. *Am J Psychiatry* 1997; 154: 782-791.

[46] Kane JM. Sertindole: a review of clinical efficacy. *Int Clin Psychopharmacol* 1998; 13 (Suppl 3): S59-S63.

[47] Hale A, Azorin J-M, Kasper S, Maier W, Syvalahti E, van der Burght M, et al. Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *Int J Psych Clin Pract* 2000; 4: 55–62.

[48] Azorin JM, Strub N, Loft H. A double-blind, controlled study of sertindole versus risperidone in the treatment of moderate-to-severe schizophrenia. *Int Clin Psychopharmacol* 2006; 21: 49-56.

[49] Hale A. Sertindole: a clinical efficacy profile. *Int J Psych Clin Pract* 2002; 6 (Suppl 1): S21-S26.

[50] Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. *Am J Psychiatry* 1990; 147: 602-607.

[51] Fenton WS. Depression, suicide, and suicide prevention in schizophrenia. *Suicide Life Threat Behav* 2000; 30: 34-49.

[52] Siris SG. Suicide and schizophrenia. *J Psychopharmacol* 2001 Jun; 15(2): 127-35.

[53] Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 2005; 62: 247-253.

[54] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; 164: 1035-1043.

[55] Pompili M, Amador XF, Girardi P, Harkavy-Friedman J, Harrow M, Kaplan K, *et al*. Suicide risk in schizophrenia: learning from the past to change the future. *Ann Gen Psychiatry* 2007; 6: 10.

[56] Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, *et al*. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 200; 60: 82-91.

[57] Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33: 159-174.

[58] Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; 212 (Suppl): 11-19.

[59] Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; 154: 672-676.

[60] Guy W. ECDEU assessment manual for psychopharmacology, revised 1976. US Department of Health, Education, and Welfare 1976; 534-537.

[61] Hale A, Azorin J-M, Kasper S, Maier W, Syvalahti E, van der Burght M, et al. Sertindole is associated with a low level of extrapyramidal symptoms in schizophrenic patients: Results of a phase III trial. *Int J Psych Clin Pract* 2000; 4: 47-54.

[62] Meaney AM, O'Keane V. Bone mineral density changes over a year in young females with schizophrenia: Relationship to medication and endocrine variables. *Schizophrenia Research* 2007; 93: 136-143.

[63] Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 1999; 60: 215-220.

[64] Nourian Z, Mow T, Muftic D, Burek S, Pedersen ML, Matz J, et al. Orthostatic hypotensive effect of antipsychotic drugs in Wistar rats by in vivo and in vitro studies of alpha1-adrenoceptor function. *Psychopharmacology* 2008; 199: 15-27.

[65] Crumb WJ, Ekins S, Sarazan RD, Wikel JH, Wrighton SA, Carlson C, Beasley CM. Effects of Antipsychotic Drugs on I_{to}, I_{Na}, I_{sus}, I_{K1}, and hERG: QT Prolongation, Structure Activity Relationship, and Network Analysis. *Pharmaceutical Research* 2006; 23: 1133-1143.

[66] Rampe D, Murawsky MK, Grau J, Lewis EW. The antipsychotic agent sertindole is a high affinity antagonist of the human cardiac potassium channel HERG. *J Pharmacol Exp Ther* 1998; 286: 788-793.

[67] Eckardt L, Breithardt G, Haverkamp W. Electrophysiologic Characterization of the Antipsychotic Drug Sertindole in a Rabbit Heart Model of Torsade de Pointes: Low Torsadogenic Potential Despite QT Prolongation. *Journal of Pharmacology and Experimental Therapeutics* 2002; 300: 64-71.

[68] Thomsen MB, Volders PG, Stengl M, Spatjens RL, Beekman JD, Bischoff U, et al. Electrophysiological safety of sertindole in dogs with normal and remodeled hearts. *J Pharmacol Exp Ther* 2003 Nov; 307: 776-784.

[69] Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. *N Engl J Med* 2009; 360: 225-235.

[70] Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; 58: 1161-1167.

Appendix 1

The SCoP Study

1 Rationale and Objective

The SCoP study (Study 99824) was designed in collaboration with the CHMP to investigate whether the known QT interval prolongation observed in sertindole-treated patients would translate into increased all-cause mortality in comparison to a well-known antipsychotic (risperidone) when used under normal conditions of use.

It was recognised that the epidemiological studies showed a low mortality risk.[1] However, it was questioned whether there was patient selection bias that could partially account for this. The most appropriate design for addressing this question in the real world is a naturalistic prospective study (large, simple trial) that reflects usual clinical practice, that is, with a minimum of interventions due to study procedures and with relatively infrequent visits. The strength of the SCoP study lies in the fact that it was conceptualised and conducted as a simple, open-label study to evaluate mortality under normal conditions of use. To obtain a valid conclusion, information on the vital status of all the patients is necessary (ideally without missing data and without loss to follow-up).

To counterbalance bias related to the study being an open-label trial, two independent committees, the Independent Management Committee (IMC) and the Independent Safety Committee (ISC), were established to oversee the study conduct and to safeguard the interests of the patients. These two committees were blinded to treatment. The IMC included an epidemiologist, a cardiologist, a psychiatrist, a pharmacovigilance expert, and a statistician, none of whom were affiliated with H. Lundbeck A/S. The ISC included experts from the same disciplines as the IMC as well as an internist, none of whom were affiliated with H. Lundbeck A/S. The membership of the two committees was mutually exclusive. The IMC monitored the development of the protocol, procedures, progress, and analysis of the study and the ISC made a blinded evaluation and classification of serious adverse events (deaths and other events) as cardiac, suicide, or other.

The purpose of the study was to compare the safety of sertindole with that of risperidone under normal conditions of use. Risperidone was selected as the comparator drug because it was available throughout most of the world for the treatment of acute and chronic schizophrenic psychoses, it had the longest marketing experience of any atypical antipsychotic, was one of the most extensively used antipsychotics world-wide, and because it was not subject to any major regulatory safety concern.

The endpoints in the SCoP study were:

- Primary endpoints:
  - all-cause mortality (first primary endpoint) – the primary endpoint was chosen as it is unbiased and cannot be compromised by unblinding and thus carries the highest degree of reliability

  - cardiac events, including arrhythmias, requiring hospitalisation (second primary endpoint) – the purpose of this endpoint was to capture the potential risk of arrhythmias with sertindole treatment that would lead to hospitalisation but not necessarily to death
- Secondary endpoints:
  - cause-specific mortality (cardiac, suicide, and other)
  - suicide attempts (fatal and non-fatal) – added following a discussion with the FDA
  - hospitalisations (excluding hospitalisations related to the primary psychiatric disease) and including those related to suicide risk
  - duration of randomised antipsychotic treatment
  - the effect of short- and long-term treatment with sertindole or risperidone on metabolic variables in patients with schizophrenia – added following a discussion with the FDA (the SCoP Metabolic Sub-study, country-specific)

2 Study Design and Methodology

The rationale, design, and methodology of the SCoP study have been described in Peuskens *et al*., 2008.[2] To maximise the external validity of the results, treatment occurred under normal conditions of use, that is, in accordance with routine clinical practice and the respective national Summary of Product Characteristics (SPC) for sertindole and risperidone, which provided conditions for prescribing the drug. Patients with schizophrenia were recruited by psychiatrists at in- or outpatient clinics in private practice, in in- or outpatient departments, or in hospital settings across Europe and Asia (593 centres in 38 countries) and followed up from enrolment until the end of the study (between July 2002 and February 2008). The investigators were experienced in treating patients with schizophrenia and did not necessarily have previous experience in conducting clinical trials, as the study was intended to be representative of routine clinical practice.

To ensure that the study population was representative of patients with schizophrenia, only a limited number of selection criteria were imposed. Patients who were at least 18 years of age, had a clinical indication for a single new antipsychotic, and met the criteria set out in the national or European (in countries where sertindole was not marketed) SPC could be considered for inclusion. Patients who were last treated with sertindole or risperidone, had contraindications to either drug, or had no history of antipsychotic drug use, were excluded.

This was a multinational, multi-centre, randomised, partially-blinded, parallel-group, active-comparator (risperidone) study. The patients were randomised (1:1) to treatment with sertindole or risperidone. The study was open-label for the patients and their physicians. The study outcome parameters were classified blindly by the ISC.

3 Study Conduct

3.1 Main SCoP Study

Patients were assessed and managed by the investigator according to usual clinical practice, that is, with a minimum of interventions due to study procedures and with relatively infrequent visits. The study assessments were performed monthly during the first 3 months of treatment, and on a quarterly basis thereafter. At each visit, the patient's vital status was recorded, as were any non-serious cardiac adverse events that had occurred since the last visit. Also, information related to the patient's current treatment (dose of study drug, type of any add-on antipsychotic, and reasons for add-on or withdrawal) was recorded. Information on serious adverse events (SAEs) and hospitalisations were collected on an ongoing basis. Sertindole-treated patients were to have ECGs taken in accordance with the SPC for sertindole.

The initial and maintenance dosages as well as dose titration were set by the investigator, in accordance with the SPC of each study drug. During the trial, the investigator could prescribe an additional antipsychotic if necessary. The decision to stop the study drug and to switch to an alternative antipsychotic treatment was left to the investigator.

The patients were followed up for the entire duration of the study, that is, also if the patients started add-on antipsychotic therapy or discontinued the study drug and until they withdrew from the study or the study was terminated. The accrued exposure to study drug thus varied from patient to patient.

A safety follow-up visit was scheduled for 30 days after stopping the study drug, except if the patient withdrew consent. Thirty days after the stop of study drug was an appropriate observation period to follow the conventional period of reporting adverse events in clinical trials.

All efforts were made to establish the vital status of patients who were lost to follow-up: the investigator or his delegate tried to contact the patient by telephone, or contacted the patient's relatives or caregivers, general practitioner, or social worker; if possible, the investigator requested psychiatric nurses to visit the patient at home; when applicable and legal, the investigator or his delegate made a request to the national death registry or searched for information regarding the patient's use of other health-care services in medical administrative databases.

Reporting of Adverse Events

Adverse events were collected by the investigator and coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA). The ISC reviewed blinded case reports and used case definitions to classify events. During the study, cardiac events were classified as definite or putative. If there was doubt as to the exact cause of death, especially if information was lacking, the case was conservatively classified as putative cardiac by default. Vascular deaths (for example, non-cardiac thrombosis, embolus) were not considered cardiac

deaths. At completion of the study, all events that had been classified as cardiac (definitive or putative) were reviewed to confirm the classification based on available information.

Event classification was ascertained based on death certificates, hospitalisation data, and post-mortem examination, as applicable.

For all cases where suicide, suicide attempt, intentional overdose, poisoning, or self injury was suspected, the investigator was asked to confirm whether it was a suicide / suicide attempt, if not stated clearly in the SAE report. A suicide attempt reported by the investigator required the conjunction of an observable suicidal act and intent to commit suicide. Completed suicide was determined by the ISC on the basis of the death certificate, post-mortem examination if applicable, and other information from investigators. The ISC working procedures specified that an episode of serious self-harm or intentional overdose or poisoning was considered suicidal behaviour, even if the patient expressed no overt suicidal intention, and regardless of the investigator's assessment. Thus, the ISC could consider that events such as suicidal ideation and suicidal tendency, as well as self-injuries and overdoses, represented suicidal behaviour, even if not confirmed as suicide attempts by the investigator.

3.2 The Metabolic Sub-study

The effect of short- and long-term treatment with sertindole or risperidone on metabolic variables was evaluated in a subset of patients enrolled in the SCoP study (261 patients in Poland, Russia, and Ukraine). The patient's weight, waist circumference, blood pressure, fasting serum lipid profile, fasting plasma glucose level, use of concomitant medication for the treatment of triglyceride or HDL-cholesterol abnormalities, type 2 diabetes, or hypertension, and diagnosis of type 2 diabetes were assessed at inclusion, at Weeks 8 and 12, and on a quarterly basis thereafter.

4 Statistical Methodology and Analysis

4.1 Sample Size Calculation

The sample size was based on assumptions of a mortality rate in schizophrenia of 2 deaths per 100 patient years of exposure (PYE); under this assumption, a total of 7600 PYE were required to ensure 80% power at the 5% significance level of rejecting the null hypothesis of excess mortality.

As the actual mortality rate in the study was only about half the anticipated rate of 2 deaths per 100 PYE, the duration of the study increased markedly. It was decided (and agreed with the CHMP) to close the study as of 20 September 2007, as the pre-defined interim analyses showed that the mortality rates were similar and had stabilised over time and that continuing the study would not add new information.

4.2 Analysis Set

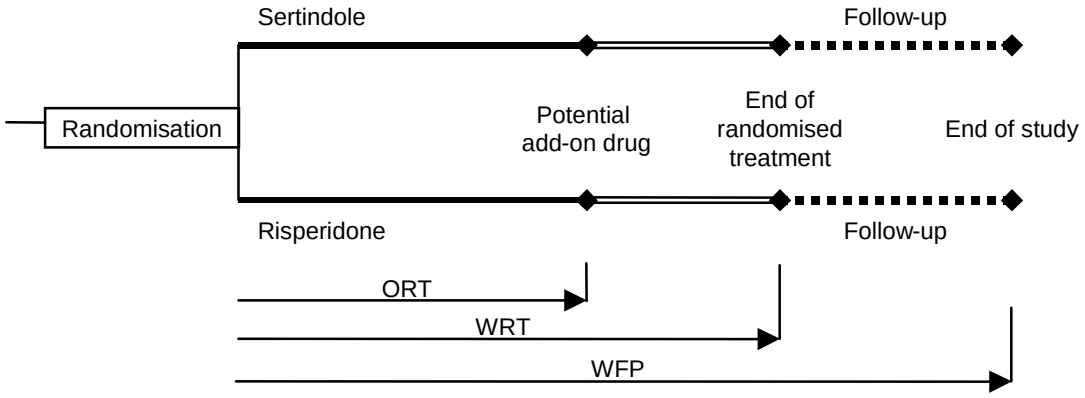
The primary analysis set was the all-patients-treated set, which comprised all randomised patients who took at least one dose of study drug.

4.3 Study Periods

The data obtained in the study were reported for different periods of time (Table 1):

- Only Randomised Treatment (ORT) Period – the period in which a patient received randomised treatment as monotherapy. All patients started on monotherapy.
- Whole Randomised Treatment (WRT) Period – the period in which a patient received randomised treatment either as monotherapy or in combination with another antipsychotic.
- Whole Follow-up (WFP) Period – the period from the start of randomised treatment until the patient withdrew from the study or the study was stopped.

Table 1 The SCoP Study Design



The primary period of reporting for the safety parameters was the WRT+30 days period, which covered the WRT period plus 30 days after discontinuation of randomised treatment.

The definition of the ORT period does not include an event if the patient took the last dose of randomised treatment the day before the event occurred or if the patient had not yet taken randomised treatment on the day of the event, so the ORT+1 day period was defined. This period is considered the most relevant in order to avoid possible confounding effects of add-on treatment, of discontinuation, and of the introduction of other treatments immediately after drug switch.

4.4 Analysis of the First Primary Endpoint

The all-cause mortality ratio (MR) of the hazard in sertindole-treated patients compared to the hazard in risperidone-treated patients was obtained using Cox's Proportional Hazards model and adjusting for age and sex, as per the protocol. The MR was also estimated using a model,

where, in addition to age and sex, all variables of prognostic information (time since last suicide attempt, last previous antipsychotic treatment [mono- or poly-therapy], and year since start of enrolment) were included. Variables of prognostic information were identified by backward elimination: initially, all baseline variables were included in the model; the least significant variable that did not meet a significance level of 0.1 for staying in the model was then removed; once a variable was removed from the model, it remained removed. The resulting model was then examined for the new least significant variable that did not meet the significance level, which was then removed. This procedure was repeated until all variables in the model met the specified significance level. Mortality ratios (MRs) were estimated both for the time until the CHMP cut-off and for the time period including the study closure period.

If the upper limit of the one-sided 95% CI for the estimated all-cause mortality ratio was less than the pre-specified equivalence limit of 1.5, the null hypothesis of an excess mortality in sertindole-treated patients was rejected. The null hypotheses were MR ≥1.5 with an alternative hypothesis of MR ≤1. The test was constructed so as to have probability 0.05 of concluding that MR ≤1, if the true MR was 1.5.

The study closure procedures may have introduced a bias due to potential changes in the clinical practice. Therefore, the analysis of the first primary endpoint (all-cause mortality) was based on all deaths that occurred until the time it was decided to close the SCoP study. However, the analysis of the first primary endpoint was repeated based on all deaths, including those that occurred in the study closure period. Both analyses were based on accumulated exposure from the WRT+30 days period.

4.5 Analysis of the Second Primary Endpoint

The statistical analysis of the second primary endpoint (cardiac events including arrhythmia that required hospitalisation) was not performed due to the limited number of events.

4.6 Analysis of Secondary Endpoint – Suicide Attempts (Fatal and Non-fatal)

The analysis of suicidal behaviour was based on all suicide attempts (fatal and non-fatal) and the accumulated exposure from the WRT+30 days period.

The suicide attempt rates were compared between treatment groups using the Cox's Proportional Hazards model with variables for treatment group, age, sex, duration of schizophrenia, and time since last suicide attempt, and including terms for any of the remaining baseline variables that held significant prognostic information. In this model, the suicide attempt ratio of the hazard in the sertindole group compared to that in the risperidone group was estimated and the null hypothesis of no difference (suicide attempt ratio = 1) was tested against the one-sided alternative of less suicide attempts in sertindole-treated patients (suicide attempt ratio ≤1). The p-value was derived as the tail probability to the left of the associated regression parameter estimate divided by its standard error using the standardised normal distribution. As specified in the statistical analysis plan, the analysis of suicide attempts (fatal plus non-fatal) was performed for events as reported by the investigator and

coded in MedDRA (*completed suicide* and *suicide attempt*) as well as for events as classified by the ISC.

4.7 Analyses in the SCoP Metabolic Sub-study

The effect of sertindole or risperidone on metabolic parameters was evaluated based on: incidence of patients with metabolic syndrome and of patients who met each individual criterion defining the metabolic syndrome; change from baseline in weight/BMI, waist circumference, systolic and diastolic blood pressure, fasting serum lipid profile, fasting plasma glucose; incidence of patients who had potentially clinically significant (PCS) weight changes or serum lipid values.

The International Diabetes Federation (IDF) definition of metabolic syndrome[3] was chosen for the SCoP Metabolic Sub-study, as it is the most recent worldwide consensus definition and because the study was conducted in countries with a preponderance of people of European origin (Europids).

According to the IDF criteria, a person is considered to have metabolic syndrome if:

- he/she has central obesity (a waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women), *and*
- he/she has two (or more) of the following:
  - elevated serum triglycerides (TG) – TG ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
  - low serum HDL-cholesterol – HDL-cholesterol <40 mg/dL (1.03 mmol/L) for men and <50 mg/dL (1.29 mmol/L) for women or specific treatment for this lipid abnormality
  - elevated blood pressure (BP) – systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension
  - elevated fasting plasma glucose (FPG) – FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed Type 2 diabetes

The IDF definition of metabolic syndrome is similar to that in the US National Cholesterol Education Program (NCEP): Adult Treatment Panel III (NCEP-ATP III); cut-off levels for triglycerides, HDL-cholesterol, and blood pressure are identical in both definitions, whereas cut-off levels for waist circumference and fasting glucose are lower in the IDF definition.

In the analysis of the fasting serum lipid profile, the PCS thresholds corresponded to those set out by the NCEP-ATP III for clinically abnormal values (as distinct from the metabolic syndrome thresholds) and were as follows (the NCEP-ATP III values have been converted to SI units):

- triglycerides ≥2.2mmol/L (200mg/dL)
- total cholesterol ≥6.216mmol/L (240mg/dL)
- HDL-cholesterol <1.036mmol/L (40mg/dL)
- LDL-cholesterol ≥4.144mmol/L (160mg/dL)

Weight increases or decreases of ≥7% from baseline were defined as PCS.

Metabolic assessments were only performed during the ORT period.

References

[1] Moore N. Higher cardiovascular mortality with sertindole in ADROIT: a signal not confirmed. *Int J Psych Clin Pract* 2002; 6 (Suppl. 1): S3-S9.

[2] Peuskens J, Tanghøj P, Mittoux A. The Sertindole Cohort Prospective (SCoP) study: Rationale, design, and methodology. *Pharmacoepidemiol Drug Safety* 2008; 17: 425-433.

[3] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469-480.

Appendix 2

Table 1 C-CASA Categories[a]

Code	Category	Definition
Suicidal events		
1	Completed suicide	A self-injurious behaviour 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 behaviour, 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 behaviour or circumstance. A suicide attempt may or may not result in actual injury.
3	Preparatory act toward imminent suicidal behaviour	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.
4	Suicidal ideation	Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behaviour.
Indeterminate or potentially suicidal events		
5	Self-injurious behaviour, suicidal intent unknown	Self-injurious behaviour where associated intent to die is unknown and cannot be inferred. The injury or potential for injury is clear, but why the individual engaged in that behaviour is unclear.
6 (fatal); 7 (non-fatal)	Not enough information	Insufficient information to determine whether the event involved deliberate suicidal behaviour or ideation. There is reason to suspect the possibility of suicidality but not enough to be confident that the event was not something other, such as an accident or psychiatric symptom. An injury sustained on a place on the body consistent with deliberate self-harm or suicidal behaviour (for example, wrists), without any information as to how the injury was received, would warrant placement in this category.
Non-suicidal events		
	Self-injurious behaviour, no suicidal intent	Self-injurious behaviour associated with no intent to die. The behaviour is intended purely for other reasons, either to relieve distress (often referred to as "self-mutilation," for example, superficial cuts or scratches, hitting/banging, or burns) or to effect change in others or the environment
	Other, no deliberate self-harm	No evidence of any suicidality or deliberate self-injurious behaviour associated with the event. The event is characterised as an accidental injury, psychiatric or behavioural symptoms only, or medical symptoms or procedure only

Blue: events included in the analysis

a Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; 164: 1035-1043.

Appendix 3

Table 1 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to C-CASA (WRT+1 and WRT+30)

Events	Number of Suicide Attempts (Rate per 100 PYE) Sertindole	Number of Suicide Attempts (Rate per 100 PYE) Risperidone	Hazard Ratio[a]	Two-sided p-value
WRT+1	4905	4904		
Suicide attempts (fatal plus non-fatal)	40 (0.61)	55 (0.73)	0.745	0.1644
Suicide attempts (fatal plus non-fatal) 1-year	29 (0.85)	48 (1.28)	0.589	0.0278
WRT+30				
Suicide attempts (fatal plus non-fatal)	46 (0.67)	62 (0.79)	0.761	0.1676
Suicide attempts (fatal plus non-fatal) 1-year	34 (0.95)	55 (1.42)	0.619	0.0318

PYE: patient years of exposure

a Cox's Proportional Hazards Model

Table 2 The SCoP Study – Classifications of All Suicide and Suicide Attempts in Each Reporting Period: Sertindole Group

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
Monotherapy							
1013798	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1013622	Hospitalisation because of suicide thoughts	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1018694	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1023317	Overdose	Intentional overdose	Overdose	Fatal	Suicide	6	
1028056	Autointoxication by ingesting 15 tablets amisulpride	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	
1023727	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1019693	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1011215	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1018243	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1013761	Overdose	Intentional overdose	Overdose	Non-fatal	Other	9	
1022552	Suicide attempt	Suicide attempt	Jumping/ falling	Non-fatal	Suicide attempt	2	
1015435	Overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	9	
1024501	Drug abuse	Drug abuser	Overdose	Non-fatal	Suicide attempt	9	
1020167	Suicidal ideation	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1015790	Attempted overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	3	
1025236	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1027851	Suicide attempt	Suicide attempt	Jumping/ falling	Non-fatal	Suicide attempt	3	
1008561	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1011693	Suicide attempt with medication	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1017137	Completed suicide defenestration	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1017178	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1015343	Suicide	Completed suicide	Overdose	Fatal	Suicide	1	
1012959	Suicide	Completed suicide	Overdose	Fatal	Suicide	1	
1020462	Suicidal ideation	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1020464	Suicidal ideation	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1021163	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1026760	Overdose to relief symptoms of anxiety and depression	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1013726	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1020722	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1027015	Intentional overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	9	
1027072	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1019393	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1012973	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1014943	Sertindole poisoning	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	
1026320	Overdose of sertindole	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1013313	Overdose	Overdose	Overdose	Non-fatal	Suicide attempt	9	
1027877	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1030341	Overdose due to demanding auditory hallucinations	Intentional overdose	Overdose	Non-fatal	Suicide attempt	9	
1018529	Self inflicted stab wound	Intentional self-injury	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1017798	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1010888	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1009656	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1014084	Attempt of suicide (chemical intoxication – not by drugs)	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1016877	Death - suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1024338	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1021104	Overdose to combat insomnia	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1012309	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1010767	Suicidal thoughts and tendencies	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1016780	Overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1028916	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1016159	QTc prolongation	Electrocardiogram QT prolonged	Overdose	Non-fatal	Suicide attempt	8	
1017831	Overdose intentional	Intentional overdose	Overdose	Non-fatal	Suicide attempt	9	
1026679	Overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1027931	Drug overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	
1023473	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1017983	Overdose	Overdose	Overdose	Non-fatal	Suicide attempt	8	
1013087	Suicide attempt	Suicide attempt	Jumping/ falling	Non-fatal	Suicide attempt	2	
1022842	Demonstrative incomplete suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1017683	Suicide attempt	Suicide attempt		Non-fatal	Suicide attempt	-	
Polytherapy							
1011977	Burning of feet	Thermal burn	Burning	Non-fatal	Other	5	Dominal
1008094	Suicidal tendency	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	Fluspirilen
1010985	Suicidal tendency	Suicidal ideation	Other self injury	Non-fatal	Suicide attempt	2	Amisulpride
1028059	Hospitalisation due to self inflicted stab wound	Self mutilation	Cutting/ stabbing	Non-fatal	Suicide attempt	5	Olanzapine

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1013889	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Haloperidol
1025238	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	Promazin
1027797	Suicide behaviour	Suicidal behaviour	Cutting/ stabbing	Non-fatal	Suicide attempt	2	Promazin
1011267	Unintended overdose	Accidental overdose	Overdose	Non-fatal	Suicide attempt	8	Olanzapine
1030356	Overdose of unknown medication	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	Levomepro-mazine
1017285	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Risperidone
Within 30 days after stopping randomised treatment							
1010216	Suicide by drowning	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1008129	Suicide	Completed suicide	Gunshut	Fatal	Suicide	1	
1013359	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Amisulpride
1024898	Jump from 9th floor	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1030354	Suicide attempt	Suicide attempt		Non-fatal	Suicide attempt	2	Levomepro-mazine
1015163	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1018149	Completed suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	

Table 3 The SCoP Study – Classifications of All Suicide and Suicide Attempts in Each Reporting Period: Risperidone Group

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
Monotherapy							
1014517	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1015062	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1027310	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1027121	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1016160	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1017073	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1010350	Suicidal attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1020566	Fell down from the 1st floor by accident	Intentional self-injury	Jumping/ falling	Non-fatal	Suicide attempt	9	
1016974	Overdose	Overdose	Overdose	Non-fatal	Suicide attempt	9	
1010536	Suicidal attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1016464	Suicidal attempt	Suicide attempt	Drowning	Non-fatal	Suicide attempt	2	
1011583	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1017161	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1027332	Intentional overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1027315	Intensional overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1027338	Drug intoxication	Intentional overdose	Overdose	Non-fatal	Suicide attempt	8	
1011699	Intentional self-harm by sharp object	Intentional self-injury	Cutting/ stabbing	Non-fatal	Suicide attempt	5	
1012259	Strangulation suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1011830	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1012131	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1009921	Abuse	Intentional overdose	Overdose	Non-fatal	Other	8	

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1019494	Overdose	Multiple drug overdose intentional	Overdose	Non-fatal	Suicide attempt	8	
1009262	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1008506	Suicide by hanging	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1015276	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1011995	Imminent suicidal risk	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1012977	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	9	
1011789	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1020706	Overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	
1016924	Overdose	Intentional overdose	Overdose	Non-fatal	Suicide attempt	2	
1011856	Suicidal attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1024605	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1018056	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1013452	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1028104	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1016363	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1017502	Suicide	Completed suicide		Fatal	Suicide	1	
1016085	Suicidal ideation	Suicidal ideation	Suicidal ideation/ tendency	Non-fatal	Suicide attempt	4	
1016786	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1028240	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1017631	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1018526	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1013652	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1016347	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1016583	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1012064	Attempted Suicide	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1015201	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1021069	Suicide attempt, ingestion of insecticide	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1027393	Suicide attempt	Suicide attempt	Other self injury	Non-fatal	Suicide attempt	5	
1016814	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1018864	Suicide attempt	Suicide attempt	Jumping/ falling	Non-fatal	Suicide attempt	2	
1017928	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1016685	Suicide by hanging	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1016132	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1030316	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1023318	Suicide resulting in death	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1012327	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1011558	Suicide attempt	Suicide attempt	Poisoning	Non-fatal	Suicide attempt	2	
1027312	Suicide	Completed suicide	Overdose	Fatal	Death, cardiac	1	
1027655	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1010101	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	
1014116	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1020079	Completed Suicide	Completed suicide	Cutting/ stabbing	Fatal	Suicide	1	
1021473	Incomplete Suicidal attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1020142	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1024444	Incomplete Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	
1022388	Suicide attempt	Suicide attempt	Jumping/ falling	Non-fatal	Suicide attempt	2	
1026352	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	

Case ID	Reported Term	MedDRA Term	Method	Outcome	ISC Classification	C-CASA Code	Pre-event Add-on or Switch
1025756	Completed Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
Polytherapy							
1022315	Suicidal attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Flupentixol
Within 30 days after stopping randomised treatment							
1007920	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	Sertindole
1030806	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Sertindole
1030800	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Other	2	Sertindole,
1010195	Drug intoxication	Intentional overdose	Overdose	Fatal	Suicide	8	
1011772	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Chlorprotixen
1008105	Suicide	Completed suicide	Hanging/ strangulation	Fatal	Suicide	1	Olanzapine
1015646	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Aripiprazole
1018986	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	
1012284	Suicide	Completed suicide	Jumping/ falling	Fatal	Suicide	1	
1019864	Suicide attempt	Suicide attempt	Hanging/ strangulation	Non-fatal	Suicide attempt	2	Clozapine
1018974	Incised wound of forearms	Intentional self-injury	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1013758	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	Clozapine
1022582	Suicide attempt	Suicide attempt	Cutting/ stabbing	Non-fatal	Suicide attempt	2	
1025690	Suicide attempt	Suicide attempt	Overdose	Non-fatal	Suicide attempt	2	