FDA

Psychopharmacological Drugs
Advisory Committee

15 February 2001

Briefing Document for

Ziprasidone Mesylate

FOR INTRAMUSCULAR INJECTION

AVAILABLE FOR PUBLIC DISCLOSURE

WITHOUT REDACTION

EXECUTIVE SUMMARY

Acute agitation in patients with psychosis is one of the most common psychiatric emergencies. In such situations, patients may be uncooperative or even violent, making the administration of oral medications impossible. In these emergencies, intramuscular (IM) formulations are necessary because they are easy to administer, and may be rapidly absorbed and rapidly effective. [1] Although the atypical antipsychotics have gained wide acceptance in the treatment of schizophrenia, none of the agents in this class is currently available in both an oral and intramuscular formulation. At present, conventional antipsychotics, alone or in combination with benzodiazepines, are the mainstay of treatment. However, the side effect profiles of conventional antipsychotic drugs include disturbing extrapyramidal effects and excessive or prolonged sedation. Additionally, the coexistence of a history of abuse liability represents a relative contraindication to the administration of benzodiazepines, limiting the usefulness of these agents in a large segment of the population at risk. Therefore, new agents to treat acute agitation are needed.

Studies conducted by Pfizer have previously demonstrated that ziprasidone hydrochloride, an oral atypical antipsychotic, is effective in the acute and long-term treatment of schizophrenia (see Psychopharmacological Drugs Advisory Committee Briefing Document of 19 July, 2000, enclosed).   This document presents data demonstrating that ziprasidone mesylate, formulated for intramuscular injection, is effective for the acute control and short-term management of agitation in patients with psychosis.

Intramuscular ziprasidone is effective in the acute control and short-term management of agitation in patients with psychosis

The efficacy of IM ziprasidone in the treatment of acute agitation in patients with psychosis was demonstrated in two pivotal, double-blind trials. In Study 125, 10 mg doses were administered, as required, at intervals of 2 hours, up to a maximum of 40 mg in 24 hours. In Study 126, 20 mg doses were administered, as required, at intervals of 4 hours, up to a maximum of 80 mg in 24 hours. In both studies, these doses were compared with a lower dose of ziprasidone IM, 2 mg.

Patients with a primary diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder were enrolled in these two studies. In addition to the standard ratings scales, patients were evaluated with the Behavioural Activity Rating Scale (BARS), a novel 7-point assessment scale, which was developed specifically to measure changes in the degree of agitated behavior.

Rapid improvements were measured in patients receiving either the 10 mg or the 20 mg dose, consistent with the relatively short mean T_{max} (< one hour) of IM ziprasidone. In an open-label trial conducted in agitated patients with acute psychosis (Study 306), this improvement compared favorably with the effect of intramuscular haloperidol.

IM ziprasidone demonstrates a favorable safety profile

Ziprasidone was well tolerated when given by intramuscular injection, at doses up to 80 mg per day. The most common treatment-emergent adverse events at the 10 mg and 20 mg doses of IM ziprasidone were nausea, headache, and dizziness. The vast majority of reported adverse events were mild or moderate in severity. Effects on blood pressure and heart rate were closely monitored, and do not represent a significant safety hazard.

IM ziprasidone demonstrates a low liability for movement disorders

Both the 10 mg and 20 mg doses of IM ziprasidone were associated with a low incidence of movement disorders in the two pivotal dose-response trials, and a lower incidence than haloperidol in two open-label comparative trials. The low incidence of movement disorders with IM ziprasidone was reflected in movement disorder rating scale scores as well as in the low use of anticholinergic medication.

The magnitude of QTc increase with IM ziprasidone is comparable to that described for oral ziprasidone

A substantial electrocardiogram (ECG) database from the intramuscular and oral clinical development programs permits characterization of the QTc effects of ziprasidone. The mean change in QTc with IM ziprasidone was modest and did not exceed that described following oral administration at the highest recommended total daily dose of 160 mg.   There is no evidence for increased risk of individual clinically meaningful QTc prolongation ("outliers").

Tolerability is maintained during the transition from IM to oral ziprasidone

The transition from IM to oral ziprasidone was well tolerated. There were no remarkable changes in measures of tolerability or efficacy during the transition.

In conclusion, the ziprasidone intramuscular development program provides evidence of a relatively rapid onset of a beneficial therapeutic effect following administration of well-tolerated doses. The safety of ziprasidone has been established at up to 80 mg per day. It is proposed that intramuscular ziprasidone has a favorable benefit:risk profile and will significantly contribute to the management of acute agitation in patients with psychosis.

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GLOSSARY

Abbreviation	Definition
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area Under the Curve for the interval from zero to infinity, calculated by the linear trapezoidal rule
AUC_{0-24}	Area Under the Curve for the interval from zero to 24 hours, calculated by the linear trapezoidal rule
BARS™	Behavioural Activity Rating Scale
BAS	Behavioural Assessment Scale (Same as BARS)
BID	Two Times per Day
BP	Blood Pressure
BPRS	Brief Psychiatric Rating Scale (derived from PANSS)
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
Cmax	Maximum Observed Serum Concentration
CV	Coefficient of Variation
DSM-III-R	Diagnostic and Statistical Manual (of Mental Disorders) – Third Edition, Revised
DSM-IV	Diagnostic and Statistical Manual (of Mental Disorders) – Fourth Edition
ECG	Electrocardiogram
HR	Heart Rate
IM	Intramuscular
IV	Intravenous
M9	S-methyldihydroziprasidone (metabolite)
M10	Ziprasidone sulfoxide (metabolite)
NOSIE	Nurses Observation Scale for Inpatient Evaluation
PANSS	Positive and Negative Syndrome Scale
PO	Per Os (by mouth)
QID	Four Times per Day
QTc	QT interval corrected for heart rate
RR	Time between two consecutive R waves in an ECG
SBECD	Sulphobutylether beta-cyclodextrin sodium (excipient for ziprasidone mesylate)
SD	Standard Deviation
SE	Standard Error
SGOT (AST)	Serum glutamic-oxaloacetic transaminase (Aspartate transaminase)
SGPT (ALT)	Serum glutamic-pyruvic transaminase (Alanine transaminase)
Tmax	The time of first occurrence of Cmax
$T_{1/2}$	Terminal elimination phase half-life
USPI	US Package Insert

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A. BACKGROUND

A.1 Acute Agitation in Psychosis

Acute agitation in patients with psychosis is one of the most common psychiatric emergencies. Patients with a wide variety of psychiatric illnesses may present with agitation and features of acute psychosis, although the most common underlying diagnoses lie within the schizophrenic and affective spectra of disorders.[1] Because of the uncooperative, aggressive and sometimes violent nature of these agitated patients, immediate and effective intervention is generally required to prevent patients from causing harm to themselves, their families, or to members of the medical care team. This intervention may, by necessity, be initiated in the absence of a detailed medical history or other background information. Treating physicians require swift, effective, safe, and well-tolerated therapy that allows for subsequent evaluation of the underlying illness, allows patients to participate in their treatment, and facilitates long-term management (Table 1).

Table 1.   Goals in the treatment of agitated patients with psychosis

Controlling acute agitation with outcome of reducing:	Optimizing short-, medium, and long-term treatment success by:
- Risk of self-injury - Risk of harm to others - Damaging or assaultive behavior - Time spent in the agitated state - Need for seclusion or physical restraint - Distress or pain associated with an agitated psychotic state	- Producing a calming rather than profound or prolonged sedative effect - Allowing diagnosis and conduct of further assessments of the underlying condition - Providing early treatment of the underlying psychosis - Minimizing treatment-related adverse effects - Fostering subsequent compliance with therapy and cooperation with caregivers

When treating acutely agitated patients with psychosis, the immediate aim is to gain rapid control of the agitated and disruptive behavior. At this stage, the safety of the patient, family, and medical staff is paramount. Once the acute agitation has been controlled, treatment goals shift to management of the underlying psychosis. The long-term treatment goals in schizophrenia include enhancing functional status, improving quality of life (for both patients and their families), and maintaining compliance and continued symptom control.

The etiology of acute psychotic episodes within the context of chronic schizophrenia or bipolar disorder remains to be clarified. One prominent factor is non-compliance with medication. Investigators have estimated that fewer than 50% of schizophrenic patients are even partially compliant with their antipsychotic medication.[2][3][4] The side effects associated with many of the current oral antipsychotic therapies, particularly the conventional agents, are undoubtedly relevant to this problem. Dystonic reactions are painful, and frightening to patients and families, and may occur after leaving the emergency facility. Akathisia can exacerbate agitation. These disturbing side effects, as well as other extrapyramidal symptoms and prolonged sedation, may contribute to

patient refusal to remain on medication, increasing the potential for relapse. Thus, the administration of a well-tolerated IM agent during an acute episode may be an important first step toward achieving a successful long-term treatment outcome. [2 3 5 6] As discussed more fully below, the currently available conventional IM agents often provide patients with an adverse impression of antipsychotic therapy during acute treatment, increasing the potential for patient non-compliance during oral maintenance therapy and thus the potential for further acute episodes.

A.2 Current Therapeutic Options

The currently available therapeutic options for the agitated patient suffering from acute psychosis are relatively limited. Because a rapid response is required for these crisis situations, intramuscular (IM) formulations are preferred since they are easy to administer, and may be rapidly absorbed and rapidly effective.[1] Only the conventional antipsychotics, such as haloperidol, droperodol, chlorpromazine, and fluphenazine, are commonly used in the management of patients with acute psychosis,[7] as none of the atypical antipsychotics currently have an approved IM formulation.

A continuing medical need for new IM antipsychotics exists because tolerability limits the therapeutic value of conventional IM treatments. Common adverse effects seen with conventional IM antipsychotics include movement disorders (such as extrapyramidal syndrome, akathisia, dystonia, and hypertonia), orthostatic hypotension, and sedation. Other potential adverse events include dysphoria, hepatotoxicity, seizures, and neuroleptic malignant syndrome. Of these, extrapyramidal symptoms are the most problematic, not only because they are among the most commonly experienced, but also because the susceptibility to and severity of these side effects in an individual patient are difficult to predict. This often results in the need for administration of prophylactic anticholinergic medication.

As shown in Table 2, the adverse effect profile associated with individual antipsychotics differs according to their potency.[1 8 9 10 11 12] For instance, high-potency conventional antipsychotics such as haloperidol, droperidol, and fluphenazine are associated with sedation and movement disorders. Patients experiencing movement disorders may require co-administration of anticholinergic drugs to reduce the impact of these adverse effects. [8 10 13] However, the concomitant administration of those agents carries the risk of additional side effects, such as cognitive disturbance, mood impairment, and urinary retention.[14]

The low-potency antipsychotics, such as chlorpromazine and thioridazine, can cause profound sedation and hypotension.[10 15] While in some cases, sedation/sleep may be useful for controlling agitation and the positive symptoms of schizophrenia, it can also aggravate psychosis, produce confusion, and hinder the accurate assessment of the underlying psychosis. [15]

Table 2.   Common adverse events seen with high-, medium-, and low-potency conventional antipsychotics

Potency	Adverse Effects
High	
Haloperidol, droperidol, trifluperazine, fluphenazine	▪ Movement disorders (e.g., extrapyramidal syndrome, akathisia, dystonia) ▪ Hypotension ▪ Sedation
Medium	
Loxapine	▪ Movement disorders ▪ Sedation
Low	
Thioridazine, chlorpromazine, mesoridazine	▪ Cardiovascular effects (e.g., postural hypotension, QTc prolongation, arrhythmia) ▪ Profound sedation ▪ Seizures/convulsions ▪ Injection-site pain/tissue damage ▪ Hepatic injury ▪ Neuroleptic malignant syndrome

The use of benzodiazepines (e.g., diazepam, lorazepam), whether alone or in combination with conventional antipsychotics, is also associated with distinct adverse effects. The adverse events most commonly reported when benzodiazepines are used in the treatment of acute agitation include ataxia (approximately 50% of patients), and nausea and vomiting (approximately 25% of patients).[16]   Asymptomatic tachypnea and tachycardia were frequently observed among a group of agitated patients who were heavily sedated after doses of lorazepam, regardless of route of administration.[16] Respiratory depression has also been observed in some patients given benzodiazepines (e.g., midazolam) in combination with other CNS depressants.[17] Additionally, the usefulness of these agents may be limited in many patients by the issue of abuse liability.

The disturbing side effects associated with conventional antipsychotics negatively impact patients in both the acute and maintenance phases of treatment. For this reason, there is a need to increase the armamentarium of safe and effective intramuscular agents for the treatment of acute psychosis, which are available in oral formulations as well. The existence of a single well-tolerated antipsychotic in both IM and oral formulations would permit a smooth transition from the short-term management of agitated behavior to effective, long-term treatment of the underlying disease. A new intramuscular therapeutic agent should provide rapid and effective relief of symptoms of acute agitation without producing profound or prolonged sedation, or limiting extrapyramidal or cardiovascular adverse effects.

A.3 Summary of the Ziprasidone Mesylate Clinical Development Program

A.3.1   History of Program Design

The clinical development plan for IM ziprasidone was formulated following input from several external consultants, and in consultation with the FDA Division of

Neuropharmacological Drug Products. Initial feedback from the FDA indicated that, in view of the pharmacokinetic differences between the intramuscular and oral formulations, a demonstration of efficacy would be required. Pfizer was advised to focus on "the agitation and restlessness that often characterize acutely psychotic patients," and to pursue a label claim for "psychotic agitation". Following review of the pivotal trial design, including the Behavioural Activity Rating Scale (BARS) endpoint, the FDA emphasized the requirement to demonstrate a dose-response, or between-group differences in the proposed trials.

The ziprasidone intramuscular NDA was submitted in December 1997. In December 1998, a not-approvable letter was received from FDA. "You have not submitted sufficient clinical data to support the conclusion that Zeldox IM is approvable for the 'acute control and short-term management of the agitated psychotic patient.' The deficiencies are for safety, not efficacy. We do believe that you have demonstrated, with 2 adequate and well-controlled trials, that Zeldox IM is effective for this indication. However, the approval of the IM ziprasidone formulation is inextricably linked with the approval of the oral formulation." The effect of ziprasidone on the QTc interval was identified as the specific safety issue leading to this regulatory action.

Study 054 was conducted in order to define more completely the effect of ziprasidone upon the QTc interval. The data from this trial, supported by the ongoing clinical trial safety experience with ziprasidone, were submitted to FDA and reviewed by this Advisory Committee in July 2000. In January 2001, ziprasidone was approved by FDA.

A.3.2 Proposed Indication and Dosage

The following text is proposed for the US Package Insert (USPI) for intramuscular ziprasidone:

INDICATIONS AND USAGE

Ziprasidone intramuscular is indicated for the acute control and short-term management of the agitated psychotic patient. If indicated, the patient may continue with oral ziprasidone.

DOSAGE AND ADMINISTRATION

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours, doses of 20 mg may be administered every 4 hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than 3 consecutive days has not been studied. If long term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

A.3.3 Summary of Studies

The ziprasidone intramuscular NDA summarized clinical trial data supporting the efficacy and safety of IM ziprasidone in the treatment of acute agitation in patients with psychosis and followed the NDA for oral ziprasidone which was submitted in March 1997.

Nine clinical trials were included in the NDA for IM ziprasidone: three clinical pharmacology studies involving 58 healthy volunteers and 6 Phase 2/3 trials enrolling 671 (523 ziprasidone, 142 haloperidol, 6 placebo) patients (Table 3). Of the Phase 2/3 studies, two were pivotal, randomized, double-blind trials which provided efficacy data in support of the proposed indication (Studies 126 and 125), three were open label studies that primarily investigated safety and tolerability (Studies 121, 306, and 120), and one study (Study 046) was a pharmacokinetic study conducted in patients.

Table 3.   Intramuscular ziprasidone: Summary of NDA studies

Study	Design	Duration	Treatment Groups			
Phase 1			Ziprasidone	N	Comparator	N
033† N=21	randomized, investigator-blind, fixed dose	single dose 1 day	5 mg 10 mg 20 mg	5 5 6	Placebo	5
037 N=13	randomized, open, oral/IM/IV crossover	single dose 3 dosing days/21 days total	5 mg IM 5 mg IV 20 mg PO	13 12 13	None	
038 N=24	randomized, investigator-blind, fixed dose	single dose 1 day	5 mg 10 mg 20 mg	6 6 6	Placebo	6
Phase 2/3						
046 N=25	randomized investigator-blind fixed dose	3 days	5 mg 10 mg 20 mg QID	6 7 6	Placebo	6
125 N=117	randomized double-blind fixed dose	one day	2 mg 10 mg up to QID	54 63	None	
126 N=79	randomized double-blind fixed dose	one day	2 mg 20 mg up to QID	38 41	None	
121 N=306	randomized open label fixed dose	3 days IM 4 days Oral	5 mg QID 10 mg QID 20 mg QID	69 71 66	Haloperidol Flexible dose	100
306 N=132	randomized open label flexible dose	3 days IM 4 day Oral	5 mg→20 mg up to QID	90	Haloperidol Flexible dose	42
120 N=12	randomized open label flexible dose	3 days IM 2 days Oral	2.5 mg QID to 20 mg TID IM	12	None	

†administered ziprasidone tartrate; all other trials used ziprasidone mesylate
IM = intramuscular   IV = intravenous   PO = by mouth
 QID = four times per day   TID = three times per day

The Phase 2/3 safety database for IM ziprasidone at the time of the NDA filing
comprised 671 (523 ziprasidone, 142 haloperidol, 6 placebo) patients. Results from
an additional trial that was initiated after the original submission, Study ZIP-NY-97-001,
have not been included in the general discussion of efficacy and safety of IM
ziprasidone in this briefing document because a complete regulatory report has not yet
been submitted to the Agency. However, due to the importance of electrocardiograms
(ECGs) to the discussion of ziprasidone's safety profile, available ECG data from
ZIP-NY-97-001 (53 ziprasidone, 17 haloperidol patients) have been included in the
section on cardiac safety (Section D.3). The distribution of patients in the Phase 2/3
program is shown in Figure 1.
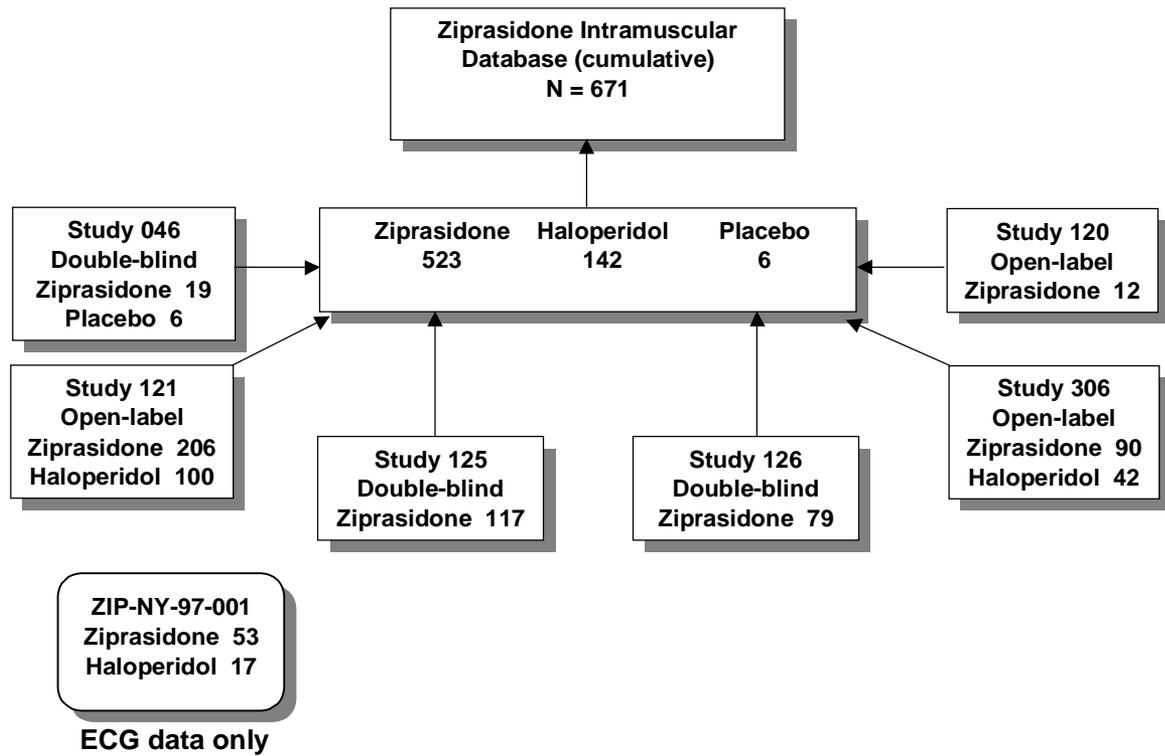
Figure 1.   Distribution of patients in IM ziprasidone Phase 2/3 clinical program

A.3.4 Demographics and Extent of Exposure

The demographics of patients in the Phase 2/3 clinical program (including Study 046) in the NDA submission are summarized in Table 4.

Table 4.   Demographic characteristics of patients in all Phase 2/3 IM ziprasidone NDA trials

		All Ziprasidone N=523	Haloperidol N=142	Placebo N=6
Gender (N)	Male	437 (83.6%)	127 (89.4%)	5 (83.3%)
	Female	86 (16.4%)	15 (10.6%)	1 (16.7%)
Age (yrs)	Mean	38.2	37.2	42.5
	Range	18-76	19-62	40-48
Race (N)	Asian	9 (1.7%)	4 (2.8%)	0
	Black	131 (25.0%)	37 (26.1%)	1 (16.7%)
	Caucasian	344 (65.8%)	92 (64.8%)	5 (83.3%)
	Other	39 (7.5%)	9 (6.3%)	0
Weight (Kg)	Male			
	Mean	80.7	80.9	93.6
	Range	42-154	46-134	81-108
	Female			
	Mean	78.1	83.1	55.8
	Range	41-113	48-130	

Table 5 summarizes the ziprasidone exposure for the 523 patients who had received IM ziprasidone and were reported in the original NDA. These data show that 160 (30.6%) patients in Phase 2/3 trials received daily doses of 40 mg or greater; and that most of those patients received ziprasidone for a full 3 days.

Table 5.   Summary of IM ziprasidone exposure

	N (%) of patients receiving IM ziprasidone	
Mean dose per day	Any duration	3 days†
Any dose	523 (100%)	250 (47.8%)
<10 mg	96 (18.4%)	3 (0.6%)
10-<20 mg	74 (14.1%)	14 (2.7%)
20-<30 mg	163 (31.2%)	80 (15.3%)
30-<40 mg	30 (5.7%)	11 (2.1%)
40-<60 mg	91 (17.4%)	75 (14.3%)
≥60 mg	69 (13.2%)	67 (12.8%)

†Includes 5 patients who received a dose of ziprasidone on the fourth calendar day.

A.3.5 Data and Analyses Included in this Document

This document summarizes the clinical pharmacology, efficacy and adverse event profile of IM ziprasidone as well as documenting effects on blood pressure and heart rate and movement disorders. The tolerability of the transition from IM to oral administration is discussed.

To address concerns surrounding the issue of QTc prolongation, ECG information from the IM database is discussed in detail. These data are supplemented by the extensive QTc database developed as part of the oral ziprasidone program. ECGs from patients in Studies 121, 125, and 126 were centrally read in a blinded manner by Global Data Exchange International (now Covance) and those from Studies 120, 046, 306 and ZIP-NY-97-001 by Premier Research Worldwide (now eResearch

Technology). The ECGs from the Phase 1 Studies 033, 037, and 038 were read locally by the individual investigators; ECGs from these studies have not been included in the QTc analyses. In Studies 037 and 038, ECGs were performed at screening only, while the single post-treatment ECG in Study 033 was not obtained on the day of dosing.

B. CLINICAL PHARMACOLOGY

- **Complete bioavailability (i.e., 100%)**

- **Rapid absorption (mean T_{max} ~ 30 - 60 minutes)**

- **Mean C_{max} of ~ 240 ng/ml following 20 mg dose**

- **Exposure increases with increasing dose**

- **Short mean $T_{1/2}$ (2-4 hours, single dose)**

- **Little to no drug accumulation observed after 3 days of multiple dosing (5, 10, and 20 mg QID)**

- **Pharmacokinetic profile of IM ziprasidone allows for rapid transition to oral therapy**

- **Ziprasidone metabolism has been well characterized**

B.1 Pharmacokinetics

B.1.1 Introduction and Overview

The clinical pharmacology of <u>oral</u> ziprasidone was fully investigated in 46 Phase 1 studies, comprising 903 subjects. A description of the receptor binding profile and oral pharmacokinetics may be found in Psychopharmacological Drugs Advisory Committee Briefing Document for the ziprasidone capsule meeting of 19 July 2000.

The pharmacokinetic characteristics of intramuscularly administered ziprasidone were investigated in three single dose studies (Studies 033, 037, and 038) conducted in healthy volunteers and one multiple dose study (Study 046) conducted in patients with schizophrenia or schizoaffective disorder. A total of 64 individuals who received ziprasidone were evaluated for pharmacokinetics in these 4 studies; the doses investigated ranged from 5 to 80 mg/day.

Three of the pharmacokinetic studies, and all of the Phase 2/3 studies with ziprasidone IM used the mesylate salt; the fourth pharmacokinetic trial (Study 033) used the tartrate salt. Ziprasidone IM is solubilized in sulphobutylether beta-cyclodextrin sodium (SBECD), a complex carbohydrate.

B.1.2 Summary of Pharmacokinetic Studies

The results of the three single dose and one multiple dose pharmacokinetic studies conducted with IM ziprasidone are summarized below.

<u>Single Dose Studies</u>

A summary of pharmacokinetic parameters determined in the single dose Studies 037, 038, and 033 in healthy volunteers is presented by study in Table 6. Studies 037 and 033 involved crossover designs and Study 038 utilized a parallel-group design. The concentration of the IM formulation used in the studies was 20 mg/ml, the same as the proposed commercial formulation.

Table 6.   **Pharmacokinetic parameters determined from single dose studies with IM ziprasidone**

Treatment Arms	# Subjects Enrolled/ Evaluated	$AUC_{0-\infty}$[a] (ng·hr/ml)	C_{max}[a] (ng/ml)	T_{max}[b] (hr)	Cl[a] (ml/min/kg)	Mean $T_{1/2}$[c] (hr)
Study 037						
Zip 5 mg IM	13/12	223 (19)	80 (32)	0.5 (60)	4.9 (13)	3.0
Zip 5 mg IV‡	12/12	217 (20)	83 (21)	1 (12)	5.0 (15)	3.1
Zip 20 mg oral capsule	13/12	514 (27)	64 (28)	8 (42)	--	3.8
Study 038						
Placebo	6/0					
Zip 5 mg IM	6/6	229 (23)	76 (7)	0.5 (38)	5.0 (28)	2.4
Zip 10 mg IM	6/6	463 (12)	156 (14)	0.7 (37)	4.7 (8)	2.2
Zip 20 mg IM	6/6	846 (29)	244 (37)	0.7 (52)	5.0 (28)	3.0
Study 033†						
Placebo	5/0					
Zip 5 mg IM	5/5	206 (20)	72 (28)	0.7 (81)	--	2.4
Zip 10 mg IM	5/5	437 (21)	133 (36)	0.7 (74)	--	3.2
Zip 20 mg IM	6/6	1057 (13)	313 (22)	0.8 (22)	--	3.4

CV = Coefficient of Variation
Cl = Clearance (i.e., the volume of serum from which the substance is eliminated per unit time)
$AUC_{0-\infty}$ = Area Under the Curve for the interval from zero to infinity, calculated by the linear trapezoidal rule
T1/2 = terminal elimination phase half-life
†tartrate salt, the other two studies used the mesylate salt; ‡1 hour IV infusion

[a] = geometric mean; [b] = arithmetic mean ; [c] = harmonic mean

Compared with a 5 mg intravenous (IV) infusion given over 1 hour, the mean bioavailability of a single 5 mg IM dose of ziprasidone in 12 healthy subjects was approximately 100% (range: 86 to 113%, Study 037). Peak serum ziprasidone concentrations (C_{max}) following the IM dose, ranged from 52 to 131 ng/ml and occurred approximately 30 minutes after dosing (range: 10 to 60 minutes). C_{max} values were similar for the IM and IV routes of administration as were the terminal elimination half-lives (approximately 3.0 hours).

Following administration of single doses of 5, 10, or 20 mg to three parallel groups of 6 healthy subjects, mean area under the curve (AUC) increased in a dose-proportional manner (Study 038). The increase in mean C_{max} was dose proportional from 5 to 10

mg but less than dose proportional from 10 to 20 mg. Peak serum ziprasidone concentrations generally occurred before 1 hour postdose (range: 20 to 90 minutes) across the range of doses tested. Individual C_{max} values at the clinically relevant doses of 10 and 20 mg ranged from 128 to 183 ng/ml, and from 144 to 359 ng/ml, respectively. Terminal elimination half-lives for IM ziprasidone were similar across the dose range of 5 mg to 20 mg.

Pharmacokinetic values reported in Study 033, which used the tartrate salt, were comparable to those observed in Study 038.

<u>Multiple Dose Study</u>

In Study 046, three parallel groups of patients with schizophrenia and schizoaffective disorder received multiple doses of IM ziprasidone, 5, 10, or 20 mg four times daily, for three days. Extensive pharmacokinetic sampling was not conducted in this study and therefore, C_{max} and T_{max}, the time to the first occurrence of C_{max}, could not be precisely characterized. Total systemic exposure, as represented by AUC_{0-24}, however, increased in a dose-related manner on both Day 1 and Day 3 (Table 7).

Table 7.   Study 046: Pharmacokinetic parameters following multiple doses of IM ziprasidone in schizophrenic patients

Treatment Arms	# Subjects Enrolled/ Evaluated	Mean Value (CV%)	
		AUC_{0-24}[a] (ng·hr/ml)	$T_{1/2}$[b] (hr)
Placebo	6/0		
Ziprasidone 5 mg IM QID	6/6		
Day 1		648 (25)	4.6
Day 3		590 (27)	8.1
Ziprasidone 10 mg IM QID	6/6		
Day 1		1363 (26)	3.9
Day 3		1116 (23)	10.4
Ziprasidone 20 mg IM QID	6/6		
Day 1		1560 (22)	3.8
Day 3		1504 (30)	ND

[a] Geometric mean.; [b]Calculated as 0.693/Kel (i.e., mean terminal elimination phase rate constant); ND = Not determined due to an insufficient time interval over which to estimate T1/2.

Based on the ratio of Day 3 to Day 1 AUC_{0-24} values, drug accumulation was low or absent in all of the dose groups. Mean serum ziprasidone concentrations observed 12 and 18 hours after the fourth IM injection on Day 3 for the 3 dose groups were low, ranging from 4 to 27 ng/ml. The mean terminal elimination half-lives were similar in all groups; these ranged from 3 to 5 hours on Day 1 and 7 to 13 hours on Day 3. The half-lives on Day 1 were comparable to those observed in the single dose IM studies (see Studies 037 and 038, above). The longer half-life values observed on Day 3 appeared related to the ability to detect an additional dispositional phase (evident with sampling at multiple timepoints during drug washout) and not to a decrease in clearance with multiple dosing. This was further supported by the absence of drug accumulation. The absence of significant drug accumulation and the observed low concentrations 12 to 18 hours after the last IM injection facilitate a rapid transition to oral therapy.

B.2 Ziprasidone Metabolism After Oral Administration

Ziprasidone is extensively metabolized in humans with less than 1% and 4% being excreted unchanged in urine and feces, respectively, following oral administration. M9 represents the major excreted metabolite, accounting for over 60% of an oral dose of ziprasidone, while the remaining material is excreted as metabolites arising via oxidation.

Available *in vitro* data suggest that there are three main pathways of ziprasidone metabolism (illustrated in Figure 2): (1) aldehyde oxidase mediated reduction, and subsequent methylation to yield M9 (S-methyldihydroziprasidone), (2) cytochrome P450 mediated S-oxidation to form M10 (ziprasidone sulfoxide) and (3) cytochrome P450 mediated N-dealkylation to form benzisothiazole piperidine (BITP). M9 and M10 are major circulating metabolites, along with BITP sulfoxide (M2) and BITP sulfone (M1).

In vitro studies using human liver microsomes and recombinant enzymes indicate that cytochrome P4503A4 (CYP3A4) is the major isozyme contributing to the oxidative pathways of ziprasidone metabolism, with some possible minor contribution from CYP1A2. The unimodal distribution and limited range (3- to 7-fold) of exposures noted in both healthy subjects and patients are consistent with a lack of CYP2D6 involvement. The involvement of CYP3A4 in ziprasidone metabolism *in vivo* is consistent with the effect of coadministration with ketoconazole (see below).

Metabolism of Ziprasidone in Humans
Proposed Metabolic Pathways to Major Circulating Metabolites
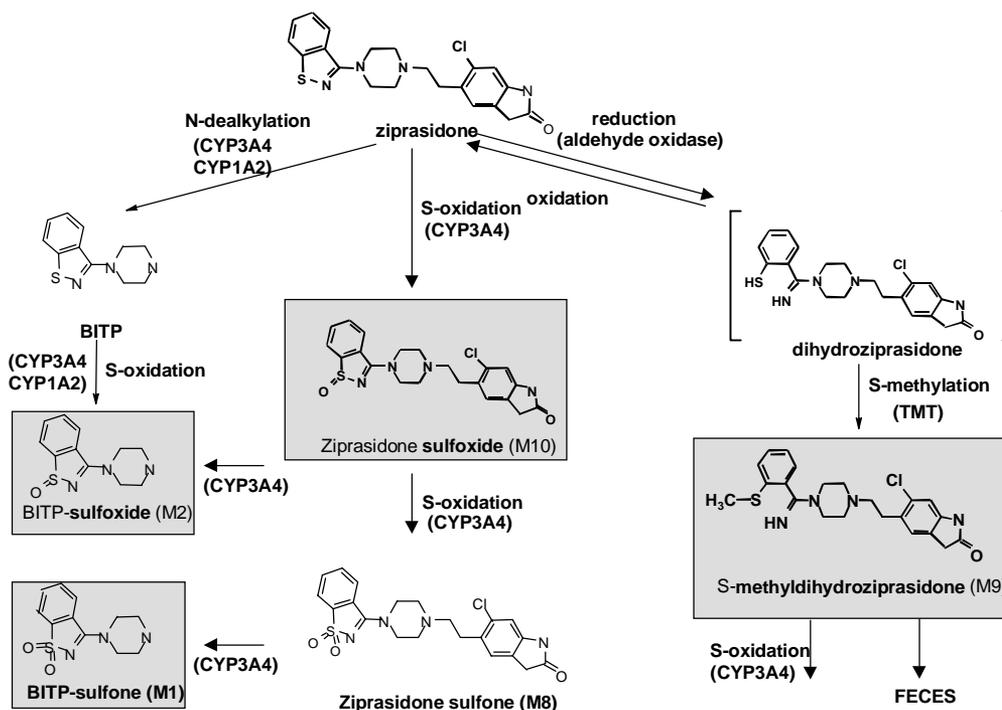
Figure 2. Proposed metabolic pathways for ziprasidone

Three of the four major circulating metabolites of ziprasidone, ziprasidone sulfoxide (M10), BITP sulfoxide (M2), and BITP sulfone (M1) each possess less than 1% of the binding affinity of ziprasidone at rat brain D_2 and 5-HT_{2A} receptors (more than 100-fold lower affinity). Accordingly, given their much lower affinity for the D_2 and 5-HT_{2A} receptors compared with ziprasidone and that the free serum concentration of these compounds achieved at the 160 mg total daily oral dose is below that of their affinity for these receptor sites, it is unlikely that these metabolites contribute to ziprasidone's antipsychotic effects. The other major metabolite of ziprasidone, M9, possesses 84- and 62-fold lower affinity than ziprasidone for these two receptor sites. Since the free concentration of M9 in serum at the highest recommended oral dose of ziprasidone (160 mg/day) at steady state falls within the range of its binding affinity for D_2 and 5-HT_{2A} receptor sites, M9 may contribute to the clinical pharmacology of ziprasidone.

There are no known clinical drug interactions with aldehyde oxidase. The effect of inhibition of ziprasidone metabolism by CYP3A4 has been closely studied. The action of ketoconazole, a potent CYP3A4 inhibitor, would be expected to increase the production of M9 from ziprasidone, by blocking the alternate pathways of metabolism. M10 production and degradation are both mediated by CYP3A4, so that inhibition of that isoenzyme may have less predictable effects on M10. In a clinical trial which

examined the effect of ziprasidone upon the ECG (Study 054, see oral ziprasidone Advisory Committee Briefing Document), patients receiving the maximum recommended daily dose of ziprasidone, at steady-state, were coadministered ketoconazole. Mean ziprasidone concentration increased by 39%, M9 by 55% and M10 by 8%. There was no change in the effect of ziprasidone upon the QTc interval of the ECG.

B.3 Ziprasidone Metabolism After Intramuscular Administration

When considering the possibility of exposure to metabolites after an IM dose compared with an oral dose, pharmacokinetic principles regarding first-pass extraction must be considered (Figure 3). For compounds such as ziprasidone that are subject to extensive hepatic metabolism, oral administration will lead to potentially greater peak concentrations of metabolites.

After oral absorption, ziprasidone will travel through the portal vein to the liver, prior to reaching the systemic circulation. From human oral bioavailability and systemic clearance information, it is estimated that 30% to 40% of an oral dose of ziprasidone is converted to metabolites (such as M9 and M10) prior to entry into the systemic circulation.

After intramuscular administration, a much greater fraction of an IM dose of ziprasidone would be expected to enter the systemic circulation as unchanged drug since the liver does not have an opportunity to generate metabolites prior to systemic exposure to the parent drug and muscle tissue contains a far lower quantity of drug metabolizing enzymes. Thus, it is expected that the ratio of metabolites to ziprasidone would be less than after oral administration. Of course, circulating ziprasidone will eventually be cleared by hepatic metabolism regardless of the route of administration.

Comparison of the Effect of Oral vs. IM Administration on Metabolite Profile: Pharmacokinetic Principles

Oral

Intramuscular

GI Tract

Muscle

Biliary Secretion

Absorption into Portal Vein

Generation of Metabolites

Liver

Systemic Exposure

Release of Metabolites

Systemic Exposure

- Oral administration favors generation of metabolites due to first-pass effect.
- After IM, systemic exposure to metabolites is lower.

Figure 3. Comparison of the effect of oral versus IM administration on metabolite profile

The available clinical pharmacokinetic data supports this description of ziprasidone disposition. Concentration ratios of M9 to ziprasidone are lower after intramuscular administration than after oral administration (Table 8). The same is true for the ratio of M10 to ziprasidone.

Table 8. Ratio of M9 and M10 to parent ziprasidone after oral and IM administration

	Mean (%CV) serum concentration ratios	
Route of administration	M9:Ziprasidone	M10:Ziprasidone
Oral (N=1796)†	0.95 (131)	0.30 (126)
Intramuscular (N=130)‡	0.23 (109)	0.03 (216)

†oral Studies 054, 108E, 116B, and 601 ‡IM Studies 125 and 126

From all clinical samples for which both ziprasidone and M9 concentrations were measured, the mean M9/ziprasidone ratio was 0.23 after IM administration compared with 0.95 after oral administration. Comparable ratios for M10 to ziprasidone, were 0.03 and 0.30 for IM and oral administration, respectively. This is consistent with what would be expected from the pharmacokinetic and drug metabolism principles just described.

As also noted above, M9 may contribute to the clinical pharmacology of ziprasidone, including its effect at I$_{Kr}$ channels. The relative contributions of ziprasidone and M9 to

the effect of administered ziprasidone upon the QTc is uncertain (see Psychopharmacological Drugs Advisory Committee Briefing Document for oral ziprasidone). However, from these data it could be inferred that any contributory effects of M9 would be less after IM than after oral administration. The effect of ziprasidone IM on the QTc is further discussed in Section D.3.

B.4 Drug Interaction and Special Population Pharmacokinetics

As noted in the Psychopharmacological Drugs Advisory Committee Briefing Document for oral ziprasidone, the effect of ketoconazole (CYP3A4 inhibition) or carbamazepine (CYP3A4 induction) on the metabolism of ziprasidone following oral administration does not result in alterations of exposure to ziprasidone in excess of 40%. By avoiding first pass metabolism, the magnitude of these effects following IM administration of ziprasidone would be expected to be less.

IM ziprasidone has not been systematically studied in patients older than 65 years or in patients with hepatic or renal impairment.

B.5 Additional Clinical Pharmacology Data

A population pharmacokinetic analysis was performed on the pharmacokinetic data collected from subjects/patients participating in Studies 033, 037, 038, 046, 120, 121, 125, 126, and 306. The results showed that body size parameters (weight, height, body surface area) were correlated with clearance and volume of distribution. No statistically significant correlations were observed between pharmacokinetic parameters and age, gender, and race, and baseline clinical laboratory values (creatinine clearance, serum creatinine, AST (SGOT), ALT (SGPT), total protein, serum albumin and direct bilirubin). No relationship between concomitant benzodiazepine use and ziprasidone pharmacokinetic parameters was observed.

B.6 Conclusions

The pharmacokinetic characteristics of ziprasidone for intramuscular injection have been adequately investigated. The bioavailability of the IM formulation is 100%. After single doses, peak serum concentrations typically occur 30 to 60 minutes after dosing and the $T_{1/2}$ ranges from 2 to 4 hours. Exposure to IM ziprasidone increases in a dose-related manner and little to no accumulation is observed after 3 days of multiple dosing (5, 10, and 20 mg QID). The pharmacokinetic profile of IM ziprasidone, namely, absence of significant drug accumulation and the observed low concentrations 12 to 18 hours following the last IM injection, facilitate a rapid transition to oral therapy.

C. CLINICAL EFFICACY

- **Efficacy of IM ziprasidone in the treatment of acute agitation in patients with psychosis has been demonstrated with doses of 10 mg and 20 mg**

- **IM ziprasidone produced a rapid and dose-related response, as measured by changes in the BARS**

C.1 Summary of Efficacy Studies

C.1.1 General Characteristics of the Trials

The efficacy of ziprasidone is supported by the findings from 3 randomized parallel-group Phase 2/3 studies with IM ziprasidone.

The following two trials were pivotal, double-blind studies:

Studies 126 and 125: One-day, double-blind, randomized, fixed-dose, flexible-schedule, multicenter, parallel-group studies to compare the efficacy and tolerability of 2 mg and 20 mg (Study 126) and 2 mg and 10 mg (Study 125) IM ziprasidone in the treatment of acute agitation in patients with a psychotic disorder.

A third trial was open-label:

Study 306: A seven-day, open-label, randomized, parallel-group, flexible-dose, multicenter study comparing the safety and tolerability of IM ziprasidone or IM haloperidol for up to three days followed by treatment with oral ziprasidone hydrochloride or oral haloperidol in patients with acute non-organic psychosis.

Pivotal efficacy Studies 125 and 126 were conducted at US sites. Study 306 was conducted at sites in Germany, Italy, Northern Ireland, Spain, UK, Israel, and South Africa.

In addition to the three studies described above, Study 121, a seven-day, open-label, randomized, parallel-group, fixed-dose, multicenter study compared the safety and tolerability of IM ziprasidone or IM haloperidol for up to three days followed by treatment with oral ziprasidone hydrochloride or oral haloperidol in patients with a diagnosis of psychotic disorder. Study 121 was not conducted in patients who were experiencing agitation, but instead selected clinically stable patients who were likely to comply with the three-day fixed dosage regimen. In view of the patient population, evidence from this trial is not cited to support efficacy of IM ziprasidone in the treatment of agitation.

C.1.2 Clinical Rating Scales

The efficacy rating scales used in these studies are described briefly below:

Behavioural Activity Rating Scale (BARS):[18]   The BARS was developed for the IM ziprasidone program in response to the lack of instruments with which to assess the level of behavioral activity of patients with psychosis. It was designed to measure the degree of agitated behavior, rather than the severity of a specific diagnostic entity (e.g., schizophrenia). The validation of the BARS is presented in Appendix 1.

Briefly, the BARS describes seven levels of activity:

> 1 = difficult or unable to rouse;
> 2 = asleep but responds normally to verbal or physical contact;
> 3 = drowsy, appears sedated;
> 4 = quiet and awake (normal level of activity);
> 5 = signs of overt (physical or verbal) activity, calms down with instructions;
> 6 = extremely or continuously active, not requiring restraint;
> 7 = violent, requires restraint.

Changes in behavior were expressed as the Area Under the Curve (AUC) of the BARS score. The AUC of BARS scores represented BARS scores measured at multiple time points over a specified time interval following the first injection. A lower AUC of BARS score corresponds to a lower level of agitation.

Note that the BARS appears as the BAS (Behavioural Assessment Scale) in the IM ziprasidone protocols, clinical study reports, and summary documents. The rating scale was subsequently renamed to avoid confusion with the Barnes Akathisia Scale.

Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I):[19]   In Studies 125 and 126, the CGI scores were based on the patient's behavior, specifically the severity of agitation present since the previous rating. In Study 306, the CGI evaluation was a single rating of how mentally ill the rater felt the patient was at the time of the evaluation. For CGI-I, the patient's condition at baseline was the reference for judging improvement during the treatment period.

Positive and Negative Syndrome Scale (PANSS):[20]   This instrument was used to assess symptoms of psychosis. The PANSS Agitation Items score was the sum of the following items: anxiety, tension, hostility, and excitement.

The Brief Psychiatric Rating Scale (BPRS):[21]   Assessments were made using an anchored version of this instrument. The BPRS Agitation Items are identical to the PANSS Agitation Items.

Nurses Observation Scale for Inpatient Evaluation (NOSIE):[22]   This instrument rated patient behavior during the previous 24 hours. The NOSIE total score was the sum of the 30 rated items.

C.1.3 Diagnostic and Other Inclusion Criteria

C.1.3.1 Patient Population

As discussed above, the need for intramuscular medication is most acute in the agitated and violent patient population. However, ethical considerations preclude recruiting the most severely agitated patients to participate in these protocols, as they would typically not be able to provide informed consent. Nonetheless, patients in 3 Phase 2/3 IM ziprasidone trials demonstrated sufficient symptom levels, as measured by the BARS, BPRS, PANSS (total and agitation), or CGI-S to support therapeutic use of the IM formulation.

The target patient population and their corresponding baseline clinical rating scale scores are summarized in Table 9.

Table 9.   Baseline characteristics of patients in pivotal and supportive efficacy trials

Study No. IM Treatments	N	Patient Population	BARS	Baseline Scores (SD) of Clinical Rating Scales			
				CGI-Severity	PANSS/ BPRS† Total	PANSS/ BPRS† Agitation Items	NOSIE
Study 126							
Zip 2 mg	38	Acutely agitated with psychosis 3 of 4 PANSS Agitation Items Scores ≥3	5.00	4.7(0.8)	84.0(17.9)	14.3(2.6)	34.7(10.4)
Zip 20 mg	41		4.98	4.6(0.9)	86.7(17.9)	14.9(2.6)	35.9(11.0)
Study 125							
Zip 2 mg	54	Acutely agitated with psychosis 3 of 4 PANSS Agitation Items Scores ≥3	4.65	4.2(0.93)	89.4(18.8)	14.9(2.7)	37.6(11.2)
Zip 10 mg	63		4.79	4.4(0.85)	90.0(20.2)	15.0(3.3)	38.0(11.5)
Study 306							
Zip	90	Acutely psychotic, requiring hospitalization	NA	5.1(0.8)	45.9(10.5)	9.9(3.3)	33.6(11.4)
Hal	42		NA	4.9(1.1)	47.5(9.3)	10.5(3.5)	33.7(10.7)

†PANSS Total and Agitation Items (anxiety, tension, hostility, excitement) were assessed in Studies 125 and 126. BPRS Total/Agitation Items (same as above) were assessed in Study 306.
Zip = ziprasidone ; Hal = haloperidol   SD = Standard Deviation   NA = Not Applicable; i.e., variable was not assessed

C.1.3.2 Diagnostic Criteria

Patients were male or female aged 18 years or older with a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, schizophreniform disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, or psychotic disorder not otherwise specified, as defined in DSM-III-R (Study 306) or DSM-IV (Studies 125 and 126) (see Table 10).

Table 10.   Primary diagnoses of patients in pivotal and supportive efficacy trials

	Number (%) of Patients				
Study No.	126	125	306		Total
	Zip	Zip	Zip	Hal	
N =	79	117	90	42	328
Primary Diagnosis					
Schizophrenic Disorders	43 (54.4)	56 (47.9)	67 (74.4)	25 (59.5)	191 (58.2)
Schizophreniform Disorders	0	2 (1.7)	4 (4.4)	4 (9.5)	10 (3.0)
Schizoaffective Disorders	21 (26.6)	39 (33.3)	3 (3.3)	8 (19.0)	71 (21.6)
Delusional Disorders	0	2 (1.7)	3 (3.3)	0	5 (1.5)
Bipolar Disorder	12 (15.2)	14 (12.0)	5 (5.6)	1 (2.4)	32 (9.8)
Psychotic Disorder not otherwise specified	3 (3.8)	4 (3.4)	1 (1.1)	1 (2.4)	9 (2.7)
Brief Psychotic Disorder	0	0	7 (7.8)	3 (7.1)	10 (3.0)

Zip = Ziprasidone; Hal = Haloperidol

C.2   Pivotal Trials

C.2.1   Trial Design and Efficacy Measures

The intent of the two pivotal double-blind trials, Studies 125 and 126, was to compare the efficacy of the 10 mg and 20 mg doses of IM ziprasidone with IM ziprasidone 2 mg. Although this dose was felt likely to have some therapeutic effect, it was expected that this effect would be dose-related, permitting a valid demonstration of efficacy. A direct, blinded comparison of the two therapeutic doses within a single trial was not possible because the 10 mg and 20 mg doses require different volumes. Dilution of the 10 mg dose to match the volume required to deliver the 20 mg dose would alter the absorption characteristics of the 10 mg dose, with obvious potential clinical implications. In lieu of a direct comparison trial, two studies were designed with protocols that were identical except for dose regimen so that their results could be compared. In both studies the 2 mg dose was administered in a volume equivalent to either the 10 mg or 20 mg dose. Because these studies were intended to assess acute behavioral change rather than long-term antipsychotic effect, the duration of treatment was limited to 1 day.

In Study 125, a 2 mg or 10 mg dose of IM ziprasidone was administered initially, with successive doses administered at least 2 hours apart. A maximum of 4 doses per patient was allowed during the 24-hour treatment period (maximum total injected: 8 mg or 40 mg). In Study 126, an IM dose of 2 mg or 20 mg was administered initially with

successive doses administered at least 4 hours apart. A maximum of 4 doses per patient was allowed during the 24-hour treatment period (maximum total injected: 8 mg or 80 mg). In both studies, the investigator had the option, depending on the patient's symptoms, of administering drug less frequently than the prescribed interval or of stopping administration of drug completely after the initial dose. The therapeutic doses and the timing of drug administration in these studies were selected based on the clinical effects observed in the pilot Study 120. Patients were not allowed to use benzodiazepines during the double-blind treatment period.

The BARS was performed at screening, immediately prior to each dose, and 15, 30, 45, 60, 90, and 120 minutes after each dose, then hourly until either the next IM dose (after which the sequence was to be repeated) or until the study endpoint (six hours after administration of the last dose, or at the end of the 24-hour treatment period, whichever was later). CGI-S based on behavior was assessed at screening, baseline (within four hours prior to the first dose), at Hour 4 after the first dose and at the study endpoint. PANSS and NOSIE scores were also obtained at screening, baseline, Hour 4, and study endpoint. CGI-I scores were obtained at Hour 4 and study endpoint.

The protocol-defined primary efficacy variables were AUCs of BARS score from 0-2 hours (Study 125) or 0-4 hours (Study 126); and CGI-S at Hour 4 and at study endpoint.

The protocol-defined secondary efficacy variables comprised the following: AUCs of BARS score from 0-2 hours (Study 126) or 0-4 hours (Study 125); BARS score (assessed immediately before and at intervals after each dose); responder rate (i.e., the proportion of patients with at least a 2 point decrease in mean BARS score at 90 minutes after the first dose); time to first response; CGI-I; PANSS Total and the PANSS-derived Agitation Items score; and the NOSIE.

Primary and secondary efficacy variables with baseline values were analyzed as changes from baseline in an ANCOVA model with the baseline value as covariate and fixed effect terms for center and treatment. The BARS AUC was also analyzed in an analogous ANCOVA model using the baseline BARS score as covariate. Due to absence of a baseline value, CGI-I was analyzed in an ANOVA model with center and treatment as fixed effects. Binary outcomes (i.e., responder rates) were analyzed using a test for difference in proportions between two groups using the normal approximation to the binomial with continuity correction.

Neither trial was powered to detect significant differences in secondary endpoints.

C.2.2 Efficacy Results

C.2.2.1 Results of Clinical Ratings Scales

<u>Study 126</u>

A total of 79 patients were randomized and received at least one injection of IM ziprasidone; all patients were evaluated for efficacy (Table 11).

Table 11.   Study 126: Evaluation groups

	Ziprasidone IM		Total
	2 mg	20 mg	
Entered Study	38	41	79
Completed Study	36(94.7%)	38(92.7%)	74
Evaluated for Efficacy	38(100%)	41(100%)	79

Patients receiving the 20 mg dose of IM ziprasidone rapidly became less agitated as reflected in a decrease in the mean BARS score from 4.98 at baseline to 2.43 by 2 hours and 2.80 by 4 hours after the first IM injection. The 2 mg dose produced a smaller decrease (mean BARS score = 5.00 at baseline, 3.73 at 2 hours and 3.83 at 4 hours (Figure 4).

Study 126: Mean BARS scores (+/- SE) after first injection All Patients, Observed Cases

◇ 2 mg
▲ 20 mg

✶ p<0.005   ✶✶ p<0.001 vs 2 mg

Hours After First Injection
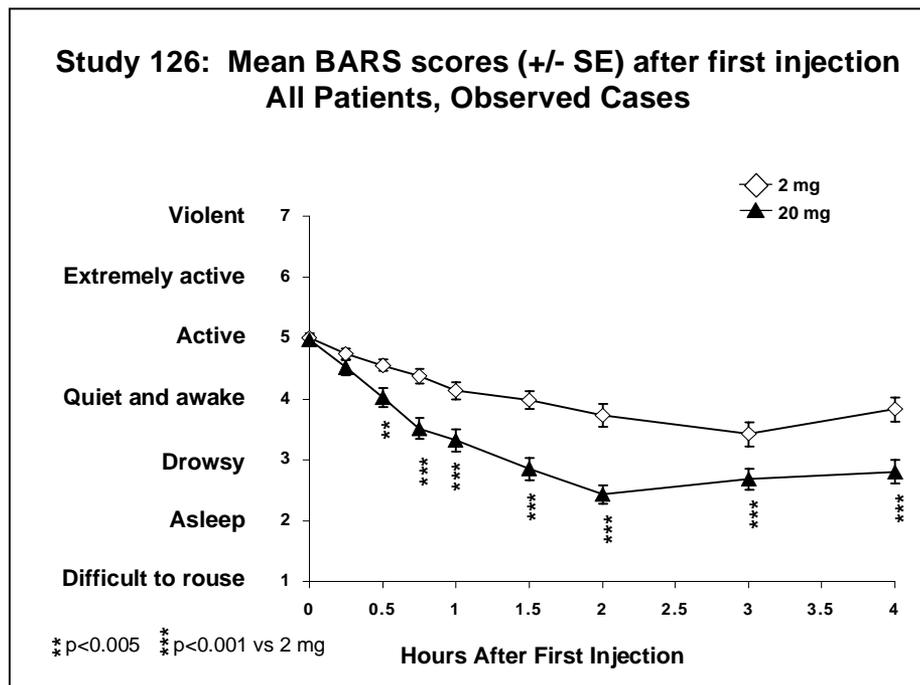
Figure 4. Study 126: Mean BARS scores from 0-4 hours after first injection of IM ziprasidone

Based on these data, the mean AUC of BARS score in the 20 mg group was significantly lower than that in the 2 mg group at both 0-2 hours and 0-4 hours after the first injection (Table 12). Overall behavior, as measured by CGI-S, was similarly improved at Hour 4 and last observation in the 20 mg group compared with the 2 mg group. The 20 mg group also showed statistically significant advantages over the 2 mg group for the secondary endpoints of BARS responder rate at 90 minutes, PANSS Agitation Items (at Hour 4) and CGI-I scores (Hour 4 and last observation). The differences between the 20 mg and the 2 mg groups in the other secondary endpoints of PANSS Total and NOSIE were not statistically significant.

In this trial, investigators were permitted to administer up to 80 mg in order to achieve effective control of agitation. However, 38 of 41 (92.7%) patients were treated with 40 mg or less.

Table 12.   Study 126: Summary of statistical outcomes for primary and secondary efficacy variables, All Patients, Observed Cases

	Mean baseline and mean change from baseline (SD) [N]		
	Zip 20 mg	Zip 2 mg	p value†
Primary Efficacy Variables			
AUC of BARS 0-4 hrs‡	12.23 (3.17) [40]	15.73 (3.06) [38]	<0.001
CGI-S			
Baseline	4.63 (0.93) [40]	4.74 (0.76) [38]	
Hour 4	-1.88 (1.45) [40]	-1.16 (1.28) [38]	0.008
Last	-1.58 (1.30) [40]	-0.92 (1.22) [38]	0.004
Secondary Efficacy Variables			
AUC of BARS 0-2 hrs‡	6.95 (1.57) [40]	8.48 (1.20) [37]	<0.001
Responder Rate at 90 min§	65.0 (26/40)	26.3 (10/38)	0.001
CGI-I			
Hour 4‡	2.15 (0.83) [40]	3.05 (1.11) [38]	<0.001
Last‡	2.38 (0.93) [40]	3.32 (1.16) [38]	<0.001
PANSS Total			
Baseline	86.65 (17.94) [40]	84.00 (17.85) [38]	
Hour 4	-17.72 (16.62) [32]	-10.09 (9.44) [35]	0.117
Last	-18.30 (14.63) [40]	-12.08 (13.57) [38]	0.074
PANSS Agitation Items			
Baseline	14.88 (2.64) [40]	14.29 (2.56) [38]	
Hour 4	-6.64 (3.93) [33]	-4.03 (3.48) [35]	0.024
Last	-5.70 (3.95) [40]	-4.03 (4.09) [38]	0.102
NOSIE			
Baseline	35.90 (10.97) [40]	34.71 (10.40) [38]	
Hour 4	-8.88 (9.92) [32]	-7.06 (8.64) [35]	0.640
Last	-4.70 (10.29) [40]	-2.29 (8.74) [38]	0.323

Zip = ziprasidone   †Zip 20 mg vs Zip 2 mg   ‡Mean (SD) values are shown   §% (n/N) are shown

Study 125

A total of 117 patients were randomized and received at least one IM injection; all patients were evaluated for efficacy (Table 13).

Table 13.   Study 125: Evaluation groups

	Ziprasidone IM		Total
	2 mg	10 mg	
Entered Study	54	63	117
Completed Study	52 (96.3%)	61 (96.8%)	113
Evaluated for Efficacy	54 (100%)	63 (100%)	117

As shown in Figure 5, mean BARS score decreased from 4.79 at baseline to 3.18 by 2 hours in the 10 mg group, and from 4.65 to 3.87 in the 2 mg group.
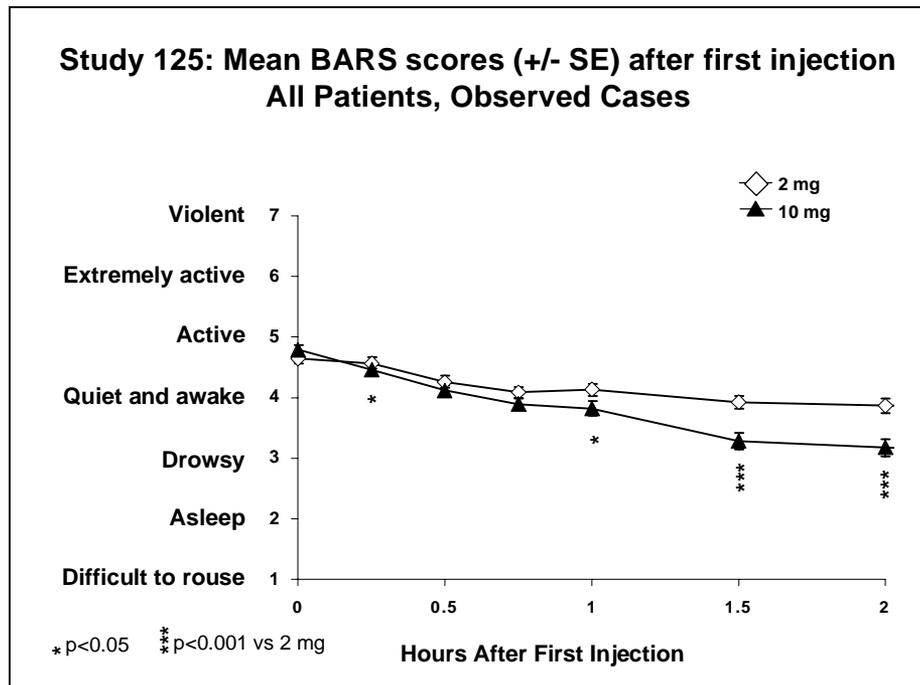

Figure 5.   Study 125: Mean BARS scores from 0-2 hours after first injection of IM ziprasidone

Based on these data, the mean AUC of BARS score in the 10 mg group was significantly lower than that in the 2 mg group at 0-2 hours and at 0-4 hours after the first injection (Table 14). The 10 mg group also showed a statistically significant advantage over the 2 mg group for the secondary efficacy parameter of BARS responder rate at 90 minutes. There were no statistically significant differences

between the 10 mg and 2 mg groups in the other primary (CGI-S) and secondary (CGI-I, PANSS Total, PANSS Agitation Items, NOSIE scores) efficacy parameters.

Table 14. Study 125: Summary of statistical outcomes for primary and secondary efficacy variables, All Patients, Observed Cases

	Mean baseline and mean change from baseline (SD) [N]		
	Zip 10 mg	Zip 2 mg	p value†
Primary Efficacy Variables			
AUC of BARS 0-2 hrs‡	7.57 (1.41) [62]	8.30 (1.18) [54]	<0.001
CGI-S			
Baseline	4.37 (0.85) [63]	4.24 (0.93) [54]	
Hour 4	-0.76 (1.07) [63]	-0.74 (1.01) [54]	0.870
Last	-0.71 (1.01) [63]	-0.50 (0.80) [54]	0.214
Secondary Efficacy Variables			
AUC of BARS 0-4 hrs‡	13.47 (3.03) [55]	15.88 (2.72) [45]	<0.001
Responder Rate at 90 min§	45.2 (28/62)	21.2 (11/52)	0.013
CGI-I			
Hour 4‡	2.78 (0.96) [63]	3.02 (0.90) [54]	0.094
Last‡	2.89 (0.99) [63]	3.09 (0.83) [54]	0.109
PANSS Total			
Baseline	90.00 (20.15) [62]	89.38 (18.84) [53]	
Hour 4	-12.68 (13.70) [57]	-13.30 (12.55) [50]	0.664
Last	-13.55 (17.29) [62]	-12.30 (15.23) [53]	0.379
PANSS Agitation Items			
Baseline	15.03 (3.25) [62]	14.93 (2.68) [54]	
Hour 4	-4.44 (4.36) [59]	-4.27 (3.77) [52]	0.475
Last	-4.02 (4.03) [62]	-3.35 (3.89) [54]	0.162
NOSIE			
Baseline	37.98 (11.54) [63]	37.63 (11.22) [54]	
Hour 4	-4.40 (7.54) [58]	-5.07 (5.89) [54]	0.679
Last	-5.41 (8.55) [63]	-4.28 (8.03) [54]	0.349

Zip = ziprasidone   †Zip 10 mg vs Zip 2 mg   ‡Mean (SD) values are shown   §% (n/N) are shown

C.2.2.2 Onset of Response

The speed with which agitation is controlled is important since agitated patients with disruptive behavior may be a danger to themselves and to others. The data presented below suggest that IM ziprasidone produces rapid (i.e., within 30 minutes) and dose-related improvement in agitated behavior, based on changes in BARS scores.

A rapid onset of effect is apparent in the mean reduction in BARS score, with a statistically significant difference noted as early as 15 minutes (the first timepoint) in Study 125 and 30 minutes in Study 126 (Figure 6).
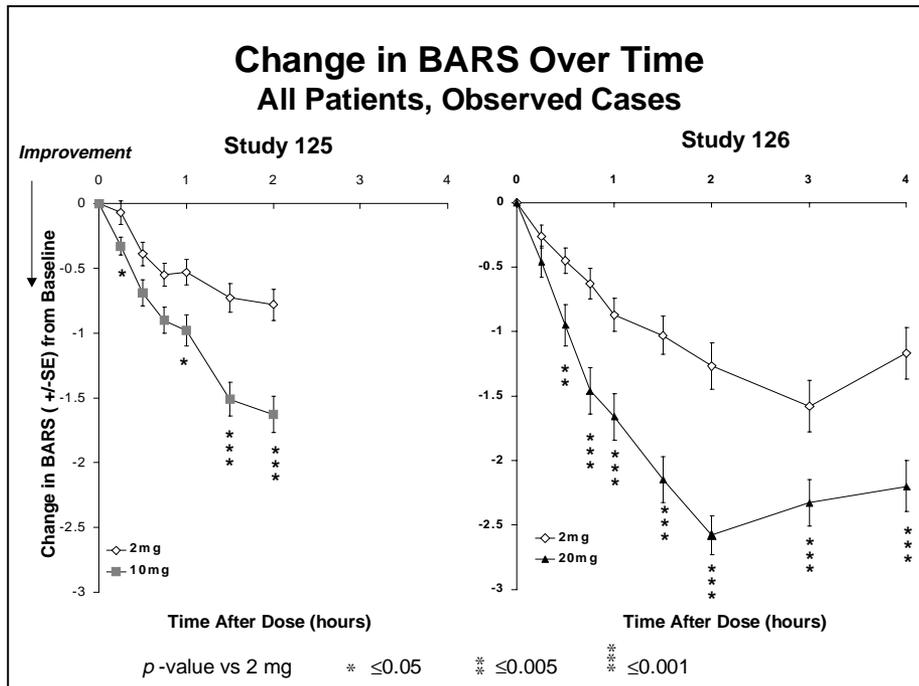
Figure 6.   Studies 125 and 126: Change in BARS score over time

A decrease of at least 2 points on the BARS (e.g. a change from "overt activity, calms with instruction," to "drowsy, appears sedated") was prospectively defined as a robust and clinically meaningful improvement (response). Statistically significant differences in the proportion of responders favoring the therapeutic dose groups compared with the 2 mg group were seen as early as 30 minutes in Study 125 (10 mg) and 45 minutes in Study 126 (20 mg) (Figure 7).
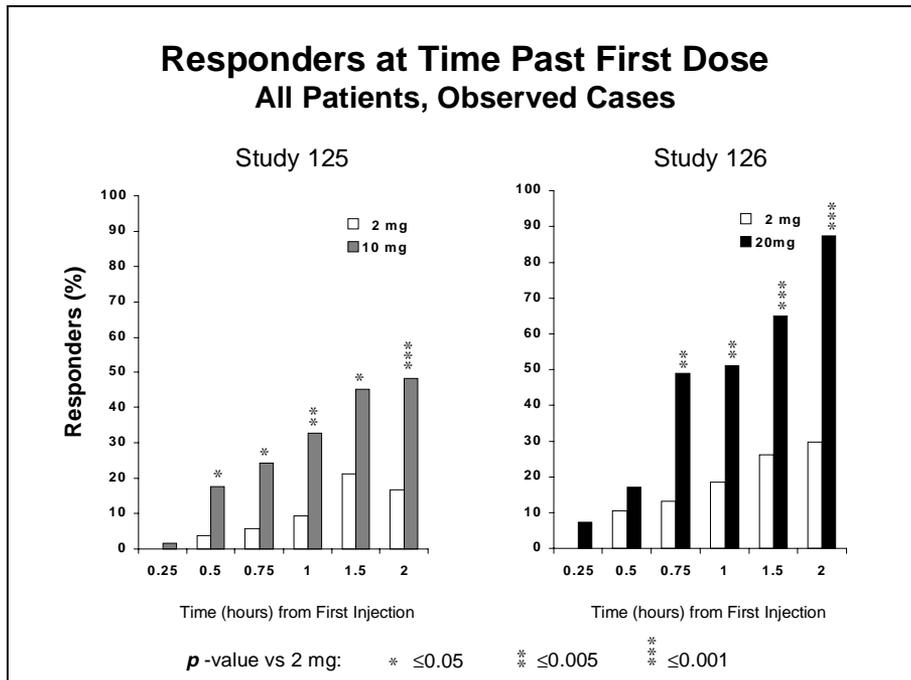
Figure 7. Studies 125 and 126: Observed percentages of responders at specific timepoints past first dose

To provide another view of onset of treatment effect, a Kaplan-Meier "survival-type" analysis was applied to time-to-first-response data (Figure 8). In this analysis, patients given a 10 mg or 20 mg dose reached the response criterion (change of 2 points in BARS from baseline) in significantly less time than those given the 2 mg dose in their respective studies. Fifty percent of patients responded within 1 hour of receiving a 20 mg dose and within 2 hours of receiving a 10 mg dose. For comparison, the 2 mg group reached a 50% rate of response at 6 to 8 hours after (in some cases, multiple) dosing.
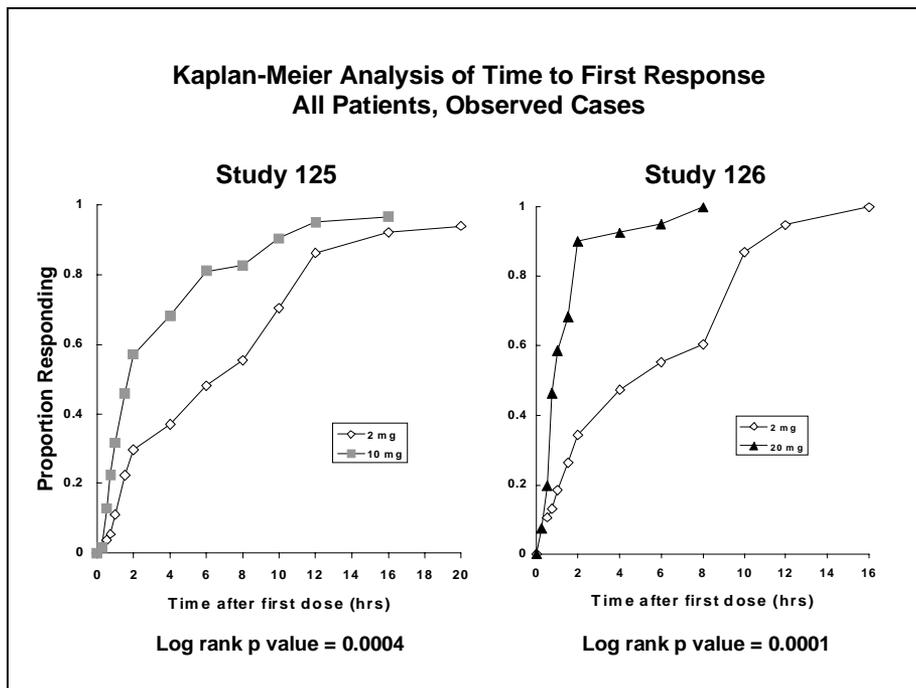
Figure 8. Studies 125 and 126: Kaplan-Meier "survival-type" analysis of time to first response

The timing of these improvements in behavioral symptoms coincides with the rapid absorption of ziprasidone following IM injection, with peak drug exposure occurring approximately 30 minutes (range 10 to 90 minutes) after dosing.

C.3 Supportive Efficacy Trials

C.3.1 Rationale for Open-label Study Design

Because of differences in the appearance, viscosity, and volume between the IM ziprasidone formulation and that of potential comparators, a flexible-dose, double-blind study using a standard comparator agent would require dosage selection, preparation and administration to be carried out by investigator staff distinct and separate from those assessing efficacy. The patient could be blinded from drug name, but not from other potential identifying characteristics of the administered agent. Alternatively, comparison of fixed doses of ziprasidone and haloperidol, matched for volume, was acceptable to most US investigators only if prophylactic administration of anticholinergic medication was permitted, to reduce the risk of dystonia. This coadministration of anticholinergic medication again presented a significant risk to patient and investigator blinding. In view of these considerations, an open-label comparison of ziprasidone and haloperidol was conducted.

C.3.1.1 Study 306

Study 306 was a seven-day, open-label, flexible-dose, parallel-group study in patients requiring hospitalization for acute psychosis. The duration of IM treatment was dependent on the severity of symptoms and the clinical judgement of the investigator, up to a maximum of 3 days. Subsequently, patients were transferred to oral therapy with the same medication, for a total treatment duration of 7 days. Seventy percent of patients received IM treatment for two days or less. Mean daily doses on Days 1 and 2 were 23 mg and 28 mg for ziprasidone, and 8 mg and 10 mg for haloperidol, respectively. Efficacy assessments included BPRS, CGI-S, CGI-I, and NOSIE. None of these variables was prospectively defined as primary in the protocol

One hundred thirty-two patients received at least one IM injection of open-label treatment in this study; all patients were evaluated for efficacy (Table 15).

Table 15.   Study 306: Evaluation groups

	Ziprasidone	Haloperidol	Total
Entered Study	90	42	132
Completed Study	82	34	116
Evaluated for Efficacy	90	42	132

Both treatment groups demonstrated improvement in all efficacy measures during both IM and oral drug administration. The ziprasidone group demonstrated significantly greater improvement than the haloperidol group in BPRS Total and Agitation items, and CGI-S (Table 16). Differences between treatment groups in CGI-I and NOSIE scores were not statistically significant.

Table 16. Study 306: Summary of outcomes for efficacy variables, All Patients, Observed Cases

	Mean baseline and mean change from baseline (SD) [N]		p value†
	Ziprasidone	Haloperidol	
BPRS Total			
Baseline	45.87 (10.51) [86]	47.49 (9.31) [41]	
Last IM	-6.24 (8.30) [83]	-3.18 (6.55) [40]	0.023
Last Observation	-8.76 (11.62) [86]	-5.83 (9.50) [41]	0.087
BPRS Agitation Items			
Baseline	9.91 (3.30) [86]	10.49 (3.46) [41]	
Last IM	-1.93 (3.41) [83]	-0.80 (2.81) [40]	0.015
Last Observation	-2.09 (4.41) [86]	-1.59 (3.61) [41]	0.190
CGI-S			
Baseline	5.07 (0.80) [90]	4.93 (1.07) [42]	
Last IM	-0.49 (0.68) [87]	-0.15 (0.53) [41]	0.002
Last Observation	-0.89 (1.23) [90]	-0.38 (1.17) [42]	0.025
CGI-I			
Last IM‡	3.38 (0.98) [87]	3.49 (0.81) [41]	0.473
Last Observation‡	3.07 (1.33) [90]	3.14 (1.00) [42]	0.539
NOSIE			
Baseline	33.58 (11.41) [90]	33.73 (10.67) [41]	
Last IM	-2.01 (8.50) [88]	-1.38 (9.55) [40]	0.583
Last Observation	-3.46 (9.13) [90]	-4.00 (8.14) [41]	0.734

†ziprasidone vs haloperidol   ‡Mean (SD) values are shown

A total daily ziprasidone dose of up to 80 mg was permitted, however 81/90 (90%) patients received a maximum daily dose of no more than 40 mg.

C.4 Conclusions

IM ziprasidone, at doses of 10 mg and 20 mg, is effective in the treatment of acute agitation in patients with psychosis. Data from two double-blind, parallel-group trials demonstrate that both the 10 mg and 20 mg doses produce a statistically significant improvement in agitation, as scored on the BARS at 2 and 4 hours after the first injection. Statistically significant improvements in CGI-S and the PANSS Agitation Items score are additionally seen after the 20 mg dose. A rapid onset of effect is apparent in the reduction in mean BARS score, following administration of the first dose of 10 mg or 20 mg.

Study 306, a one-week, open-label, haloperidol comparative study, which utilized IM ziprasidone followed by oral dosing, supports the efficacy of IM ziprasidone. This study demonstrated at least comparable improvement in scores in the ziprasidone and haloperidol groups.

D. CLINICAL SAFETY

D.1 Discontinuations and Adverse Events

- **Well tolerated in adults**

- **Discontinuations due to adverse events low**

- **Most common treatment-emergent adverse events at 10 mg and 20 mg doses: nausea, headache, and dizziness**

- **Low incidence of movement disorder adverse events (akathisia, extrapyramidal syndrome, dystonia, hypertonia)**

D.1.1 Introduction and Overview

This section examines the safety and tolerability of intramuscular ziprasidone. In Studies 125 and 126, patients were randomized to a fixed dose of ziprasidone for one day, although the number of doses and the dosing interval could vary. In Study 121, the amount, frequency and timing of ziprasidone dosing was fixed, for three days of treatment. The flexible-dose Study 306 will be considered separately, as each patient in that trial could have received a number of different doses, depending upon their clinical condition.

The design characteristics of the fixed-ziprasidone-dose trials are summarized below:

Study	Duration IM Dosing	Treatment groups	Dosing regimen
125	1 day	2 mg, 10 mg, fixed dose ziprasidone	maximum of 4 doses within 24 hours, successive doses at least 2 hours apart
126	1 day	2 mg, 20 mg, fixed dose ziprasidone	maximum of 4 doses within 24 hours, successive doses at least 4 hours apart
121	3 days	5 mg, 10 mg, 20 mg, fixed dose ziprasidone	QID; 5 mg and 10 mg doses at least 2 hours apart 20 mg doses at least 4 hours apart
		Haloperidol up to 10 mg	2 to 4 times daily

In this section, the data from the 2 mg groups in Studies 125 and 126 have been pooled while the data from the 10 mg and 20 mg groups represent their individual respective studies. Fixed-ziprasidone-dose Study 121 is presented separately. In this study, fixed doses were administered IM four times daily for three days. Thus, patients receiving the 20 mg dose QID would have received 80 mg daily. The majority of haloperidol-treated patients received two doses daily, and the mean total daily dose of IM haloperidol was 11 mg.

Study 306 compared flexible dosage regimens of ziprasidone and haloperidol, in the treatment of patients hospitalized with acute psychosis. Over the first two days of dosing, the average daily doses of ziprasidone were 23 mg and 28 mg, respectively; the average daily doses of haloperidol were 8 mg and 10 mg, respectively.

Studies 121 and 306 included oral continuation treatment; safety data are presented for the IM portion of the trial, except where otherwise noted.

D.1.2 Discontinuations

In the one-day, fixed-ziprasidone-dose Studies 125 and 126, 2 of 63 (3.2%) patients in the 10 mg group and none of the 41 patients in the 20 mg group were discontinued from the study due to treatment-emergent adverse events. There was no apparent relationship between dose of ziprasidone and the rate of discontinuation due to adverse events.

Table 17.   Studies 125 and 126: Discontinuations from study by randomized dose

	N(%) of patients who were discontinued from study		
	Zip 2 mg N=92	Zip 10 mg N=63	Zip 20 mg N=41
Adverse Event	2 (2.2)	2 (3.2)	0
Insufficient Clinical Response	1 (1.1)	0	0
Other	1 (1.1)	0	3 (7.3)
Overall rate of Discontinuation	4 (4.3)	2 (3.2)	3 (7.3)

The "other" category includes patients who were discontinued for a protocol violation/deviation (1 patient) or because they withdrew consent (3 patients)

In the 3-day, fixed-dose Study 121, 1 of the 71 (1.4%) patients in the 10 mg ziprasidone group and 4 of 66 (6.1%) patients in the 20 mg ziprasidone group were discontinued during the IM portion of the study due to treatment-emergent adverse events compared with 1 of 100 (1.0%) patients receiving haloperidol (Table 18).

Table 18.   Study 121: Discontinuations during the IM portion of study by randomized dose

	N(%) of patients who were discontinued			
	Zip 5 mg N=69	Zip 10 mg N=71	Zip 20 mg N=66	Haloperidol N=100
Adverse Event	0	1 (1.4)	4 (6.1)	1 (1.0)
Insufficient Clinical Response	0	0	0	0
Other	5 (7.2)	8 (11.3)	4 (6.1)	6 (6.0)
Overall rate of Discontinuation	5 (7.2)	9 (12.7)	8 (12.1)	7 (7.0)

The "other" category includes patients who defaulted (19 patients), or were discontinued for a protocol violation/deviation (1 patient), because they did not meet randomization criteria (2 patients), or for other reasons (1 patient)

In Study 306, one patient in the ziprasidone group was discontinued due to a treatment-emergent adverse event during the IM portion of the study (Table 19).

Table 19.   Study 306: Discontinuations during the IM portion of study

	N(%) of patients who were discontinued	
	Ziprasidone N=90	Haloperidol N=42
Adverse Event	1 (1.1)	0
Insufficient Clinical Response	0	0
Other	1 (1.1)	1 (2.4)
Overall rate of Discontinuation	2 (2.2)	1 (2.4)

The reason for discontinuation of the 2 patients in the "other" category was "patient defaulted".

The adverse events leading to discontinuation during the IM portion of the Phase 2/3 trials are summarized in Table 20 below.

Table 20.   Phase 2/3 IM ziprasidone studies: Patients who were discontinued for adverse events during the IM portion of study

Treatment	Randomized Dose	Onset Day	Adverse Event
Zip 2 mg			
125 07950071	2 mg	1	Hypertension, Agitation, Psychosis
126 06380121	2 mg	2	Priapism
Zip >2 mg			
121 05200559	20 mg	3	Suicide Gesture
121 05650217	20 mg	1	Tachycardia
121 05890101	10 mg	1	Akathisia, Psychosis, Somnolence
121 06630203	20 mg	2	Respiratory Tract Infection
121 07590150	20 mg	1	Migraine
125 06530077	10 mg	1	Diarrhea, Nausea, Akathisia
125 07950130	10 mg	2	Agitation, Personality Disorder
306 03540106	Flexible	2	Hypertension
Haloperidol			
121 07570024	Flexible	2	Dystonia, Extrapyramidal Syndrome

Phase 2/3 trials included Studies 046, 120, 121, 125, 126, 306)

D.1.3 Incidence of Treatment-Emergent Adverse Events

The adverse experience data reported below include all spontaneously reported, treatment-emergent adverse events, whether attributed to drug or not. Special rating instruments were also used to assess the occurrence of extrapyramidal signs and symptoms (see Section D.4).

<u>Fixed-ziprasidone-dose studies</u>

Incidences of individual treatment-emergent adverse events experienced by ≥5% of patients in any dose group in the fixed-ziprasidone-dose Studies 125 and 126 are shown in Table 21.

Table 21.   Studies 125 and 126: Incidence of treatment-emergent adverse events (≥5% in any group)

	Number (%) of patients with treatment-emergent adverse events		
	Zip 2 mg N=92	Zip 10 mg N=63	Zip 20 mg N=41
Headache	3 (3.3)	8 (12.7)	2 (4.9)
Nausea	4 (4.3)	5 (7.9)	5 (12.2)
Dizziness	3 (3.3)	2 (3.2)	4 (9.8)
Somnolence	7 (7.6)	5 (7.9)	8 (19.5)
Injection site pain	8 (8.7)	4 (6.3)	3 (7.3)

The most common adverse events among patients receiving 10 mg or 20 mg doses were somnolence, headache, nausea, and dizziness. Across the ziprasidone dose groups, the incidence of injection site pain ranged from 6.3% to 8.7%, with no clear relationship to dose. The vast majority of treatment-emergent adverse events were mild or moderate in severity. One severe adverse event was reported in a patient receiving the 10 mg dose (agitation). For Studies 125 and 126, four severe adverse events (priapism, hypertension, agitation, psychosis) were reported in patients receiving the 2 mg dose.

Table 22 shows the incidence of treatment-emergent adverse events during the IM portion of Study 121.

Table 22. Study 121: Incidence of treatment-emergent adverse events (≥5% in any treatment group) during the IM portion of the study

	Number (%) of patients with treatment-emergent adverse events			
	Zip 5 mg N=69	Zip 10 mg N=71	Zip 20 mg N=66	Haloperidol N=100
Headache	12 (17.4)	10 (14.1)	13 (19.7)	8 (8.0)
Nausea	9 (13.0)	14 (19.7)	12 (18.2)	3 (3.0)
Dizziness	11 (15.9)	14 (19.7)	10 (15.2)	0
Insomnia	7 (10.1)	11 (15.5)	14 (21.2)	12 (12.0)
Anxiety	11 (15.9)	10 (14.1)	11 (16.7)	13 (13.0)
Somnolence	5 (7.2)	7 (9.9)	4 (6.1)	8 (8.0)
Injection site pain	4 (5.8)	7 (9.9)	11 (16.7)	2 (2.0)
Vomiting	6 (8.7)	8 (11.3)	8 (12.1)	5 (5.0)
Tachycardia	2 (2.9)	8 (11.3)	5 (7.6)	6 (6.0)
Agitation	6 (8.7)	5 (7.0)	6 (9.1)	9 (9.0)
Dyspepsia	6 (8.7)	6 (8.5)	3 (4.5)	5 (5.0)
Constipation	0	3 (4.2)	6 (9.1)	0
Hypertension	3 (4.3)	5 (7.0)	4 (6.1)	1 (1.0)
Asthenia	2 (2.9)	2 (2.8)	4 (6.1)	0
Increased Salivation	0	2 (2.8)	4 (6.1)	3 (3.0)
Tremor	2 (2.9)	4 (5.6)	2 (3.0)	3 (3.0)
Abnormal Vision	0	5 (7.0)	2 (3.0)	1 (1.0)
Dystonia	5 (7.2)	2 (2.8)	2 (3.0)	10 (10.0)
Extrapyramidal Syndrome	0	1 (1.4)	3 (4.5)	15 (15.0)
Hypertonia	1 (1.4)	1 (1.4)	2 (3.0)	11 (11.0)
Akathisia	4 (5.8)	4 (5.6)	8 (12.1)	21 (21.0)

The most common adverse events among patients receiving 10 mg or 20 mg doses of IM ziprasidone were headache, nausea, dizziness, insomnia, and anxiety.   Injection site pain was also more commonly observed in the ziprasidone groups than in the haloperidol group. Haloperidol-treated patients had a higher incidence of movement disorder adverse events including extrapyramidal syndrome, dystonia, akathisia, and hypertonia.

The vast majority of treatment-emergent adverse events reported in the ziprasidone and haloperidol groups were mild or moderate in severity. One severe treatment-emergent adverse event was reported in the 10 mg group (somnolence), one in the 20 mg group (migraine), and two (nausea, vomiting) in the 5 mg dose group. Two severe treatment-emergent adverse events were reported in patients receiving haloperidol (tachycardia; dystonia).

Study 306

The adverse event profile emergent during the IM portion of the flexible-dose haloperidol-comparator Study 306 is shown below (Table 23).

Table 23.   Study 306: Incidence of treatment-emergent adverse events (≥5% in either treatment group) during IM portion of study

	Number (%) of patients with treatment-emergent adverse event	
	Ziprasidone N=90	Haloperidol N=42
Hypertension	6 (6.7)	0
Dystonia	1 (1.1)	3 (7.1)
Extrapyramidal Syndrome	0	9 (21.4)
Hypertonia	0	3 (7.1)

Hypertension was the most commonly reported adverse event among ziprasidone-treated patients while incidences of extrapyramidal syndrome, dystonia, and hypertonia were more common in patients receiving haloperidol. Four of the 6 cases of hypertension in the ziprasidone-treated group were mild in severity and only one patient was discontinued due to the event. Three of the hypertension cases were from one center.

The vast majority of the treatment-emergent adverse events in ziprasidone- and haloperidol-treated patients were mild or moderate. Five severe treatment-emergent adverse events were reported in the ziprasidone group (hypertension, postural hypotension, dystonia, psychosis, laryngismus) and one in the haloperidol group (increased salivation).

Injection site pain

Within the context of treatment-emergent adverse events, the incidence of pain at the site of the injection merits additional discussion. In Studies 125 and 126, the incidence of injection site pain was 6.3% and 7.3% in the 10 mg and 20 mg ziprasidone groups. In Study 121, the incidence of injection site pain was 5.8%, 9.9% and 16.7% in the 5 mg, 10 mg and 20 mg groups, respectively, compared with 2.0% in patients receiving haloperidol. Injection site pain was described as mild in the majority (23/29, 79%) of cases. Most of the patients in Study 121 who experienced this adverse event complained of slight local discomfort (soreness/burning/stinging/mild pain/tenderness) of short duration (minutes) and no patients were discontinued from the study due to this adverse event.

There were no reports of injection site pain as an adverse event in Study 306.

In Study 121, ziprasidone was administered four times daily by protocol; thus, 86% to 99% of ziprasidone-treated patients received 4 injections on each of 3 days of dosing. As haloperidol was given in a flexible-dose regimen, only 8% to 12% of haloperidol-

treated patients received 4 injections each day while the majority received 2 injections daily.

D.1.4 Conclusions – Safety and Tolerability

Ziprasidone given intramuscularly at 10 mg and 20 mg for up to 3 days is a well-tolerated treatment for acute agitation in patients with psychosis. Daily doses in excess of 40 mg were permitted, by protocol, in Studies 126 and 306, both conducted in acutely psychotic patients. In these studies, 93% of patients did not require a total daily dose greater than 40 mg on any treatment day. The safety and tolerability of daily doses up to 80 mg have been demonstrated in Study 121.

D.2 Blood Pressure and Heart Rate

- **Occurrences of clinically significant changes in blood pressure were isolated and transient and were not considered significant safety concerns**

- **Incidence of tachycardia reported as a treatment-emergent adverse event was comparable to haloperidol**

- **Only 2 discontinuations due to blood pressure-related events; one patient was discontinued due to tachycardia**

D.2.1 Introduction and Overview

Because ziprasidone acts as an antagonist at the α1-adrenoreceptor, blood pressure and heart rate were monitored closely in clinical trials. The effect of IM ziprasidone on vital signs is examined below, by reference to the fixed-ziprasidone-dose Study 121, which by design ensured assessment of the effects of repeated doses of ziprasidone at the shortest recommended intervals, up to 80 mg per day for three consecutive days; and to the flexible-dose Study 306 (see Section C.1.1 for study design details). Both of these trials included a haloperidol control group.

Blood pressure (BP) and heart rate (HR) were measured prior to each intramuscular dose, and 30 and 60 minutes after each dose. In Study 121, therefore, more vital sign measurements were obtained from each patient treated with ziprasidone (mean: 31/patient) than from each patient treated with haloperidol (mean: 18/patient).

D.2.2 Blood Pressure

In Study 121, the median changes in systolic and diastolic blood pressure in the ziprasidone groups ranged between –1 and 5 mm Hg compared with –1 to 4 mm Hg for haloperidol (Table 24).

Table 24. Study 121: Median changes from baseline in systolic/diastolic blood pressure

	Standing Systolic (mm Hg)			Standing Diastolic (mm Hg)		
	N	Median Baseline	Median Change	N	Median Baseline	Median Change
Ziprasidone QID:						
5 mg	65	120	3	65	80	1
10 mg	70	121	-1	70	80	0
20 mg	62	121	4	62	79	5
Haloperidol (flexible)	92	122	0	92	80	-1
	Sitting Systolic (mm Hg)			Sitting Diastolic (mm Hg)		
	N	Median Baseline	Median Change	N	Median Baseline	Median Change
Ziprasidone QID:						
5 mg	67	120	3	67	78	2
10 mg	70	119	1	70	78	0
20 mg	63	122	0	63	78	1
Haloperidol (flexible)	94	120	4	94	80	1

In Study 306, the median change in blood pressure in the ziprasidone group was -1 mm Hg for standing systolic blood pressure and 0 for all others compared with 0 in all cases for haloperidol.

Hypotension

In Study 121, the incidences of hypotension reported as a treatment-emergent adverse event were 1.4% in the 5 mg group, 4.2% in the 10 mg group and 0% in the 20 mg group; the incidences of postural hypotension were 1.4%, 4.2%, and 4.5% in the 5 mg, 10 mg, and 20 mg groups, respectively. In flexible-dose Study 306, the incidences of hypotension and postural hypotension in the ziprasidone group were each 1.1%. No patients given IM haloperidol reported these adverse events in either Study 121 or Study 306.

There were no patients who were discontinued from ziprasidone treatment due to hypotension or postural hypotension.

In Study 121, there was no consistent relationship between dose and the proportion of patients with clinically significant decreases from baseline in systolic (criterion = BP<90 mm Hg and decrease ≥20 mm Hg) or diastolic (criterion = BP<50 mm Hg and decrease ≥15 mm Hg) blood pressure (Table 25).

Table 25. Study 121: Proportion of patients with clinically significant decreases in systolic/diastolic blood pressure

| | Standing Blood Pressure | | Sitting Blood Pressure | |
	Systolic	Diastolic	Systolic	Diastolic
	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients
Ziprasidone QID:				
5 mg	5/65 (7.7)	2/65 (3.1)	3/67 (4.5)	1/67 (1.5)
10 mg	12/70 (17.1)	1/70 (1.4)	5/70 (7.1)	2/70 (2.9)
20 mg	7/62 (11.3)	3/62 (4.8)	1/63 (1.6)	2/63 (3.2)
Haloperidol (flexible)	8/92 (8.7)	3/92 (3.3)	3/94 (3.2)	3/94 (3.2)

Systolic blood pressure criterion: BP<90 mm Hg and decrease ≥20 mm Hg; diastolic blood pressure criterion: BP<50 mm Hg and decrease ≥15 mm Hg
n = number of patients showing a clinically significant decrease in systolic/diastolic blood pressure; N = Total number of patients

In Study 306, the proportion of patients with clinically significant decreases in blood pressure was low (range: 0% to 3.5%) in both treatment groups (Table 26).

Table 26. Study 306: Proportion of patients with clinically significant decreases in systolic/diastolic blood pressure

| | Standing Blood Pressure | | Sitting Blood Pressure | |
	Systolic	Diastolic	Systolic	Diastolic
	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients
Ziprasidone	2/84 (2.4)	1/84 (1.2)	3/85 (3.5)	0/85 (0.0)
Haloperidol	0/39 (0.0)	0/39 (0.0)	1/39 (2.6)	0/39 (0.0)

Systolic blood pressure criterion: BP<90 mm Hg and decrease ≥20 mm Hg; diastolic blood pressure criterion: BP<50 mm Hg and decrease ≥15 mm Hg
n = number of patients showing a clinically significant decrease in systolic/diastolic blood pressure; N = Total number of patients

These data suggest that hypotension occurs infrequently in patients given IM ziprasidone. The proposed labeling does acknowledge that hypotension can occur in patients and that caution should be exercised.

Hypertension

In Study 121, the incidence of hypertension reported as a treatment-emergent adverse event in the 5 mg, 10 mg and 20 mg IM ziprasidone groups was 4.3%, 7.0% and 6.1%, respectively, compared with 1.0% for patients receiving haloperidol. In Study 306, the incidence of hypertension was 6.7% among patients receiving ziprasidone compared with 0% in the haloperidol group. There was no consistent relationship between ziprasidone dose and incidence of hypertension. Two patients were discontinued due to the adverse event of hypertension.

In fixed-ziprasidone-dose Study 121, the proportion of patients with clinically significant increases in blood pressure from baseline (systolic criterion: BP >180 mm Hg and increase ≥20 mm Hg: diastolic criterion: BP >105 mm Hg and increase ≥15 mm Hg) was generally comparable in ziprasidone and haloperidol-treated patients (Table 27). The one exception appears to be standing diastolic blood pressure in the 20 mg ziprasidone group, in which ten of 62 patients experienced an increase from baseline. In these individuals, the increases were generally isolated and transient, and none required discontinuation of treatment. Additionally, there was no consistent temporal relationship between blood pressure increase and dose.

Table 27.   Study 121: Proportion of patients with clinically significant increases in systolic/diastolic blood pressure

	Standing Blood Pressure		Sitting Blood Pressure	
	Systolic	Diastolic	Systolic	Diastolic
	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients
Ziprasidone QID:				
5 mg	1/65 (1.5)	6/65 (9.2)	1/67 (1.5)	6/67 (9.0)
10 mg	2/70 (2.9)	6/70 (8.6)	1/70 (1.4)	5/70 (7.1)
20 mg	0/62 (0.0)	10/62 (16.1)	0/63 (0.0)	4/63 (6.3)
Haloperidol (flexible)	3/92 (3.3)	3/92 (3.3)	0/94 (0.0)	5/94 (5.3)

Systolic blood pressure criterion = BP >180 mm Hg and increase ≥20 mm Hg: diastolic blood pressure criterion: BP >105 mm Hg and increase ≥15 mm Hg
n = number of patients showing a clinically significant increase in systolic/diastolic blood pressure; N = Total number of patients

Table 28 displays the proportion of patients with clinically significant increases in blood pressure in Study 306. With the exception, again, of standing diastolic blood pressure in which 7 of 84 patients experienced an increase, there appeared to be no excess incidence of clinically significant elevations in the ziprasidone group compared with the haloperidol group.

Table 28.   Study 306: Proportion of patients with clinically significant increases in systolic/diastolic blood pressure

	Standing Blood Pressure		Sitting Blood Pressure	
	Systolic	Diastolic	Systolic	Diastolic
	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients	n/N (%) Patients
Ziprasidone	1/84 (1.2)	7/84 (8.3)	1/85 (1.2)	4/85 (4.7)
Haloperidol	0/39 (0.0)	1/39 (2.6)	1/39 (2.6)	2/39 (5.1)

Systolic blood pressure criterion: BP >180 mm Hg and increase ≥20 mm Hg: diastolic criterion: BP >105 mm Hg and increase ≥15 mm Hg
n = number of patients showing a clinically significant increase in systolic/diastolic blood pressure; N = Total number of patients

D.2.3 Heart Rate

Table 29 displays the median change in heart rate, from baseline to final observation in Study 121. A range of 1 to 7 beats/minute was noted in the ziprasidone groups, with the greatest median change being the 7 beats/minute increase in standing heart rate seen in the 10 mg QID group.

Table 29. Study 121: Median changes from baseline in heart rate

	Standing Heart Rate (Beats/Min)			Sitting Heart Rate (Beats/Min)		
	N	Median Baseline	Median Change	N	Median Baseline	Median Change
Ziprasidone QID						
5 mg	65	88	4	67	80	4
10 mg	70	88	7	70	84	2
20 mg	62	88	1	63	84	4
Haloperidol (flexible)	92	86	4	94	78	1

In Study 306, the median changes from baseline in standing/sitting heart rate ranged from -2 to 0 beats/minute in both the ziprasidone and haloperidol groups.

Tachycardia

Tachycardia was reported as a treatment-emergent adverse event in the 5 mg, 10 mg, and 20 mg dose groups at incidences of 2.9%, 11.3% and 7.6%, respectively, compared with 6.0% for haloperidol. The incidence of tachycardia in the ziprasidone group in Study 306 was 2.2% compared with 0% for haloperidol. One patient in the 20 mg group in Study 121 was discontinued due to tachycardia.

In fixed-ziprasidone-dose Study 121, the 10 mg and/or 20 mg ziprasidone groups had a higher incidence of clinically significant increases from baseline in standing/sitting heart rate (criterion: HR>120 beats/minute and increase $\geq$15 beats/minute) than the haloperidol group (Table 30).

Table 30. Study 121: Proportion of patients with clinically significant increases in heart rate

	Standing Heart Rate n/N (%) patients	Sitting Heart Rate n/N (%) patients
Ziprasidone QID:		
5 mg	11/65 (16.9)	6/67 (9.0)
10 mg	22/70 (31.4)	6/70 (8.6)
20 mg	21/62 (33.9)	8/63 (12.7)
Haloperidol (flexible)	15/92 (16.3)	9/94 (9.6)

Criterion for clinically significant increases in heart rate: HR>120 beats/min and increase $\geq$15 beats/min
n = number of patients/ showing clinically significant change in heart rate; N = Total number of patients

In Study 306, the incidences of clinically significant increases in standing (ziprasidone, 5/84, 6.0% vs. haloperidol, 2/39, 5.1%) and sitting (1/85, 1.2% vs. 1/39, 2.6%) heart rate were comparable in the two treatment groups.

D.2.4 Conclusions – Blood Pressure and Heart Rate

The pharmacology of ziprasidone does suggest a potential for the drug to cause hypotension and tachycardia, but does not provide a potential mechanism for hypertension. In some instances (e.g., standing diastolic blood pressure, tachycardia), the observed rates of abnormal changes appear higher in the ziprasidone group than in the haloperidol group. This, however, could in part represent an artifact of the sampling difference rather than evidence of a meaningful increase in risk, i.e., by trial design, the patients receiving ziprasidone had a greater mean number of vital sign measurements than patients receiving haloperidol. Such a sampling bias could inflate the estimate of risk attributable to ziprasidone relative to haloperidol.

In summary, therefore, the effect of ziprasidone IM on blood pressure and heart rate does not appear to represent a clinically meaningful hazard. This conclusion is supported by a database of over 5000 appropriately timed measurements, at doses up to 80 mg daily.

D.3 QTc and Cardiac Safety

- **Mean QTc change from baseline to last for all IM ziprasidone doses ≥5 mg was 0.1 msec**

- **QTc changes associated with oral ziprasidone dosing have been well characterized**

- **QTc changes following IM ziprasidone dosing are within the range of those experienced during oral dosing**

QTc values presented in this section were calculated using a heart rate correction formula that was based upon the QT-RR relationship observed in ECG data obtained at baseline from patients with ECG data in the ziprasidone oral and intramuscular databases, respectively. These are referred to as the "Baseline" corrections for oral and intramuscular QTc values.

D.3.1 Effects of IM Ziprasidone on the ECG Mean and Categorical QTc

QTc mean changes from baseline to last assessment on IM dosing in fixed-ziprasidone-dose and flexible-dose studies with IM ziprasidone are shown in Table 31. These QTc data are derived from ECGs recorded at random times relative to IM dosing during the clinical trials. Mean QTc change for all IM ziprasidone doses ≥5 mg was 0.1 msec compared with a mean change of 0.6 msec for IM haloperidol. No

relationship between QTc change and ziprasidone dose was observed across doses of 2 mg to 20 mg in fixed-ziprasidone-dose trials.

Table 31. Phase 2/3 IM ziprasidone trials: Change in QTc from baseline to Last Observation

Treatment Group	N	Baseline QTc (msec)			Final QTc (msec)			Mean change
		mean	median	Range	mean	median	range	
<u>All Trials</u>								
Ziprasidone ≥5 mg	445	405.2	406.9	335.0 – 465.1	405.3	405.3	334.8 – 494.8	0.1
Haloperidol	137	405.5	404.2	335.0 – 465.1	406.1	405.2	348.7 – 454.3	0.6
<u>Fixed-Ziprasidone-Dose Trials*</u>								
Ziprasidone								
2 mg	91	413.2	414.4	377.5 – 460.0	413.3	413.0	362.6 – 452.1	0.1
5 mg	74	410.4	410.6	349.9 – 455.5	410.7	409.4	357.1 – 494.8	0.3
10 mg	138	412.7	413.0	353.2 – 465.1	411.4	411.5	372.3 – 445.1	-1.3
20 mg	109	410.7	413.8	364.5 – 454.3	411.5	411.9	361.3 – 466.2	0.8
All Zip ≥5 mg	321	411.5	413.0	349.9 – 465.1	411.2	411.5	357.1 – 494.8	-0.2
Haloperidol	95	411.1	410.3	368.2 – 465.1	411.1	411.0	349.9 – 454.3	-0.1
<u>Flexible-Dose Trials**</u>								
Ziprasidone	124	389.0	388.5	335.0 – 433.6	390.0	388.7	334.8 – 437.9	1.0
Haloperidol	42	392.8	393.1	335.0 – 437.6	395.0	394.3	348.7 – 436.2	2.3

* Studies 046, 121, 125, 126; ** Studies 001, 120, 306
Includes measurements made within 1 day of last IM dose
QTc calculated using Baseline correction (QTc = QT/RR$^{0.40}$)

Table 32 shows the categorization of maximum QTc values and QTc increases from baseline in the IM ziprasidone trials (ziprasidone doses ≥5 mg only). There were no QTc values >500 msec with IM ziprasidone. QTc values ≥450 msec were infrequent (1.1% with ziprasidone compared with 1.3% with haloperidol).

Table 32.   Phase 2/3 IM ziprasidone trials: Incidence of categorical QTc increases

	Ziprasidone		Haloperidol	
N*	476		149	
Incidence	n	%	n	%
QTc ≥450 msec	5	1.1	2	1.3
QTc ≥480 msec	1	0.2	0	0
QTc ≥500 msec	0	0	0	0
N**	445		137	
Increase from Baseline:	n	%	n	%
≥30 msec	34	7.6	13	9.5
≥60 msec	1	0.2	2	1.5
≥75 msec	1	0.2	0	0
≥15%	2	0.4	2	1.5
≥25%	0	0	0	0

Includes only ziprasidone patients with doses ≥5 mg.
*N = all patients with post baseline ECG; **N = patients with both baseline and post-baseline ECG,
Studies 001, 046, 120, 121, 125, 126, 306;
Includes measurements made within 1 day of last IM dose
QTc calculated using Baseline Correction (QTc = $QT/RR^{0.40}$)

D.3.2 Effects of Oral Ziprasidone on the QTc

The effect of ziprasidone on the QTc has been carefully studied in the oral clinical development program, and is described in the oral ziprasidone Advisory Committee Briefing Document. This program includes Study 054, an open-label, randomized, parallel-group study which examined the effect of ziprasidone on the QTc in patients receiving the maximum recommended dose (160 mg/day), before and during the coadministration of ketoconazole, a potent CYP3A4 inhibitor. As noted in the oral ziprasidone Advisory Committee Briefing Document, the effect of ziprasidone on the QTc was not affected by coadministration of ketoconazole (15.9 msec vs. 16.6 msec), which was associated with an increase in mean serum ziprasidone concentration of approximately 40%. The highest serum ziprasidone concentration recorded in these patients was 380 ng/ml.

The overall oral ziprasidone Phase 2/3 clinical trial database (including Study 054) includes 9994 serum ziprasidone concentrations, measured in 3014 patients. Of these, 2435 serum ziprasidone concentrations, from 1359 individuals, were measured within one hour of an electrocardiogram. A plot of QTc change vs. serum ziprasidone concentration is presented in Figure 9. Twelve of 2435 serum ziprasidone concentrations exceeded 380 ng/ml, the maximum observed in Study 054. Serum ziprasidone concentrations for the nine patients with serum concentrations >400ng/ml are noted on the right hand side of the graph. The change in QTc for each of these individuals is indicated by the position of each notation on the vertical axis. The change in QTc in the patient with the highest recorded serum ziprasidone concentration (955 ng/ml) was 2 msec. There were no QTc values in excess of 500 msec among these 12 patients.
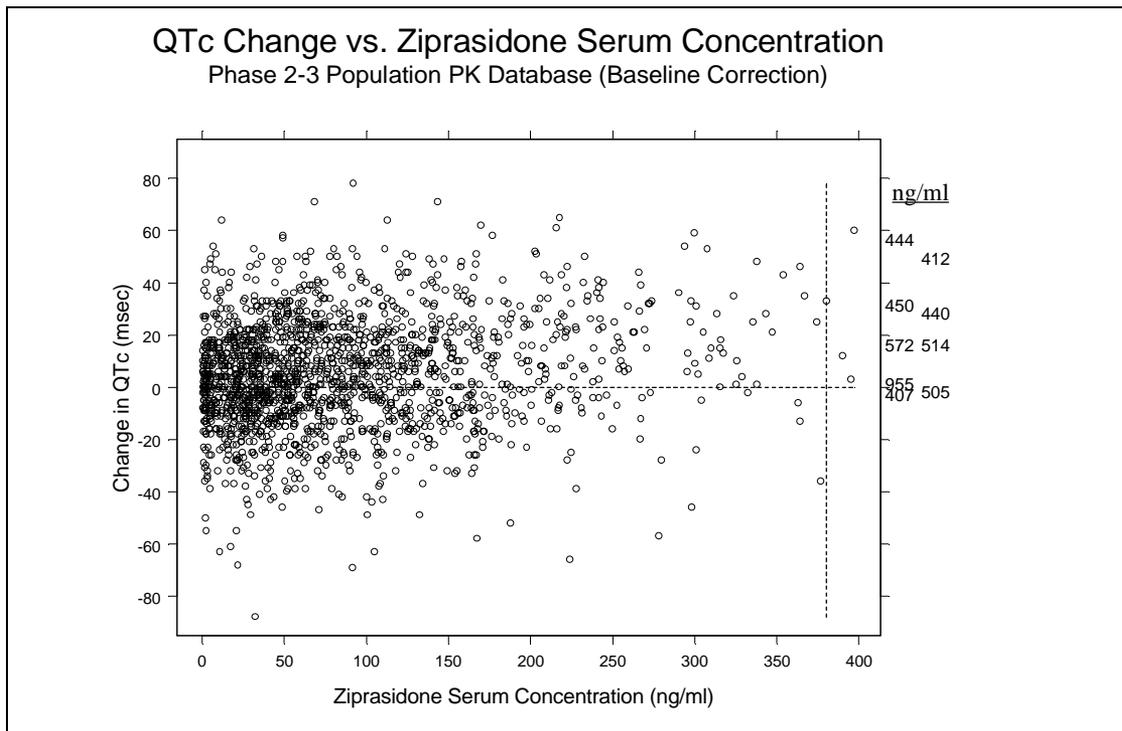
**Figure 9.   QTc change vs. ziprasidone serum concentration, Phase 2/3 population
pharmacokinetic database**

D.3.3 Effects of IM Ziprasidone on the QTc

Table 31 and Table 32 summarize the findings of the full ziprasidone IM ECG
database, and include tracings obtained at variable intervals after dosing. As noted in
Section B.1.2, following intramuscular administration of ziprasidone, serum
concentration increases with increasing dose, and C_{max} is generally attained within the
first hour after dosing. Following C_{max}, exposure falls quickly, with values decreasing
by approximately one order of magnitude by 8 hours postdose. This pattern is
illustrated in Figure 10 which shows mean ziprasidone serum concentrations following
single IM doses of 10 mg and 20 mg in the Phase 1 Study 038 (see Section B.1.2).
For comparison, the figure also displays the mean concentration – time relationship for
an oral dose of 80 mg, administered at steady-state (80 mg BID).
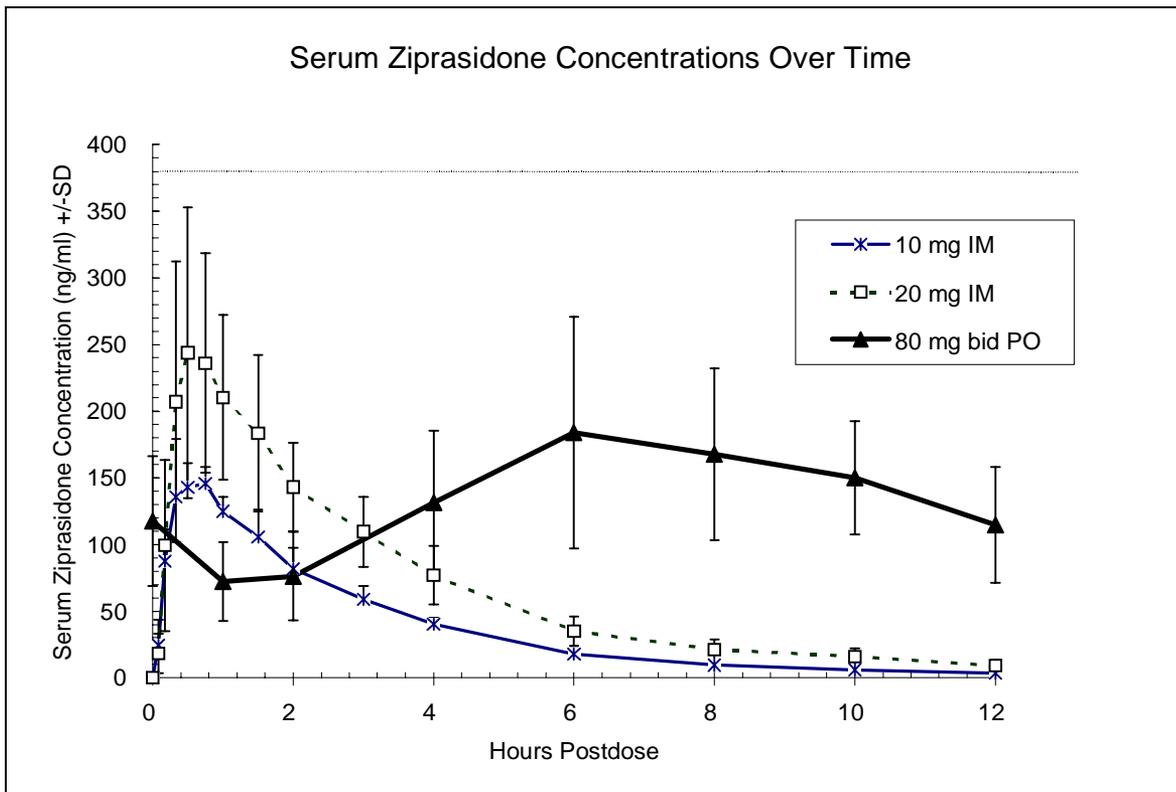
Figure 10. Mean serum ziprasidone concentrations, single dose IM administration and steady-state oral exposure

In the IM ziprasidone clinical program, a total of 2136 ziprasidone serum samples were collected from 425 individuals administered IM doses while participating in 9 clinical trials (see Table 3). Among these, 1362 samples (Table 33) were collected within 6 hours of a dose $\geq$ 5 mg and these are shown in Figure 11. It can be seen that ziprasidone concentrations following IM administration lie within the range that has been experienced in the capsule development program (Figure 10).   As expected, the highest ziprasidone concentrations are observed within the first 2 hours post-dose.

Table 33.   Serum samples collected in the IM ziprasidone clinical program

Ziprasidone	All Times		Within 6 hours of prior dose	
	N – Samples	N – Individuals*	N - Samples	N – Individuals*
All doses	2136	425	1375	298
5 mg	752	104	533	104
10 mg	740	202	503	149
20 mg	589	123	326	88

*Individuals could contribute samples to more than one dose group; consequently the number of individuals for individual doses will not sum to the number of individuals for "All doses".

Of the 2136 ziprasidone IM serum samples there were 7 samples from 5 individuals that exceeded 380 ng/ml (mean: 401 ± 21 ng/ml; range: 386 – 432 ng/ml).
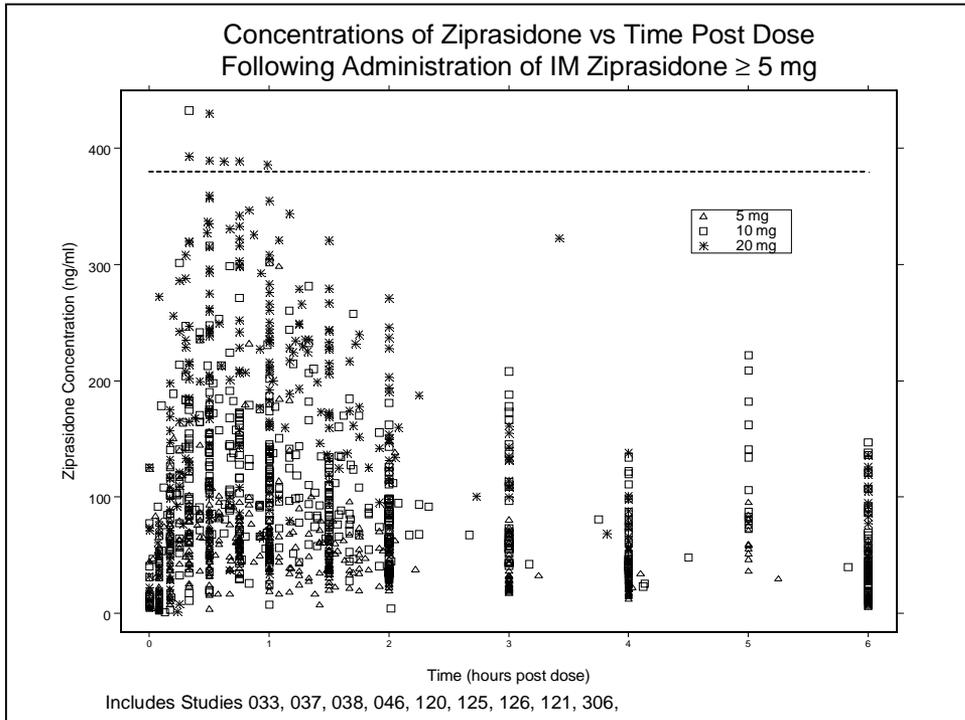
Figure 11.   Ziprasidone serum concentrations within 6 hours following IM dosing (≥5 mg)

Figure 12 shows the QTc values measured within 6 hours of IM dosing, including 86 measures for individuals who received ziprasidone and 24 measures for individuals who received haloperidol. The QTc changes observed with ziprasidone were similar to those observed with haloperidol. Table 34 summarizes the QTc changes observed for these ziprasidone and haloperidol-treated patients within various intervals after dosing.
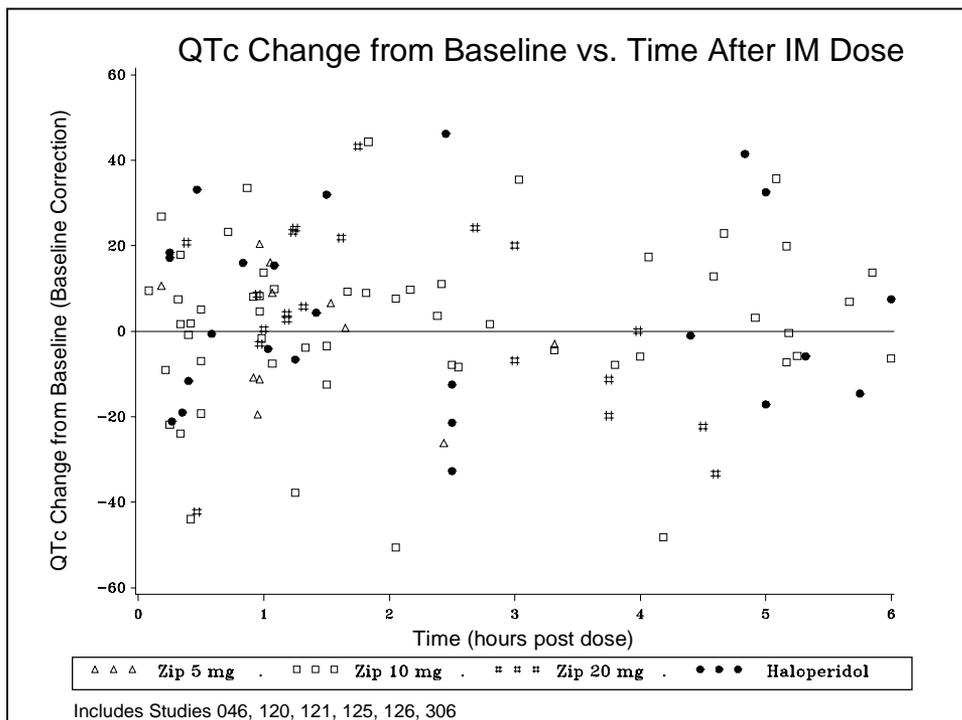
Figure 12.   QTc change from baseline within 6 hours following IM dosing (≥5 mg)

Table 34.   Mean QTc changes for periods 0-2, 2-4, and 4-6 hours after IM dosing

		Mean QTc Change for Time Post-Dose (N†)					
		0-2 hours		2-4 hours		4-6 hours	
	N	Mean Δ (95%CI)	N	Mean Δ (95%CI)	N	Mean Δ (95%CI)	
Ziprasidone							
5 mg	9	2.4 (-8.0, 12.9)	2	-14.6 (NA‡)	0		
10 mg	30	1.4 (-5.8, 8.5)	12	-1.3 (-14.0, 11.3)	13	4.9 (-7.5, 17.3)	
20 mg	12	9.1 (-4.2, 22.4)	6	1.1 (-17.4, 19.5)	2	-27.8 (NA‡)	
All Ziprasidone ≥5 mg	51	3.4 (-1.9, 8.6)	20	-2.0 (-10.6, 6.7)	15	0.6 (-11.8, 12.9)	
Haloperidol	13	5.6 (-5.2, 16.4)	4	-5.1 (-61.1, 50.9)	7	6.1 (-15.0, 27.2)	

Includes Studies 046, 120, 121, 125, 126, 306
† N = Number of data points
‡ not presented due to small sample size

The mean QTc change during the first two hours following administration of a 20 mg dose of ziprasidone IM was 9.1 msec (95% CI: -4.2 msec to 22.4 msec), compared to 5.6 msec (95% CI: -5.2 msec to 16.4 msec) during the first 2 hours following intramuscular dosing with haloperidol.

D.3.4 Conclusions – QTc and Cardiac Safety

In summary, the extensive oral capsule ECG database, including 2435 concentration – QTc datapoints, permits a characterization of the relationship between ziprasidone concentration and QTc change. Ziprasidone concentrations observed in intramuscular clinical trials lie within the range observed in the oral program. Direct examination of QTc changes observed near the time of C_{max} following IM administration suggests that the pharmacodynamic QTc profile for IM ziprasidone does not differ meaningfully from that following oral administration.

D.4 Movement Disorders

- **The burden of movement disorders, as assessed by the incidence of spontaneously reported adverse events, Simpson-Angus and Barnes Akathisia rating scales, or concomitant use of anticholinergic medication, was low in patients receiving up to 20 mg QID IM ziprasidone and contrasted clearly with that observed in haloperidol-treated patients**

D.4.1 Introduction and Overview

For patients and their families, movement disorders such as akathisia, dystonia, hypertonia, parkinsonian rigidity, and akinesia, are among the most distressing adverse events associated with conventional antipsychotics. Spontaneously reported adverse events are reported above (see Section D.1.3). In addition, objective assessment scales were used to evaluate the movement disorder liability of IM ziprasidone in the fixed-ziprasidone-dose Study 121 and flexible-dose Study 306. A comparison is made with flexible-dose IM haloperidol. Results from the two specific assessment scales are reported in this section:

Simpson-Angus Rating Scale:[23] a 10-item evaluation for parkinsonian symptoms; scores ranged from 0 to 4 with the higher numbers indicating a greater severity of symptoms.

Barnes Akathisia Scale:[24] a scale used to assess the presence of akathisia. The outcome variables included objective, subjective awareness, and subjective distress scores rated on a scale from 0 (normal/absent) to 3 (severe), and the global assessment of akathisia score rated on a scale from 0 (absent) to 5 (severe akathisia).

The Simpson-Angus and Barnes Akathisia scales were performed prior to treatment, at intervals during the treatment period, and at last observation.

Concomitant use of the anticholinergic, benztropine, was also used as an indirect measure of movement disorders in patients receiving ziprasidone or haloperidol.

D.4.2 Results of Movement Disorder Assessments

D.4.2.1 Study 121

The mean change from baseline to the assessment following the last IM dose in Simpson-Angus score for the 5 mg, 10 mg, and 20 mg doses of ziprasidone were -0.45, -0.11, and –0.18, respectively. Among haloperidol-treated patients, the mean change from baseline was +0.15 (Figure 13). This suggests that IM ziprasidone has a low movement disorder burden compared with haloperidol, even at ziprasidone doses up to 80 mg daily. The corresponding mean changes in Barnes Akathisia scores ranged from –0.09 to 0.02 for ziprasidone compared with +0.19 for haloperidol.
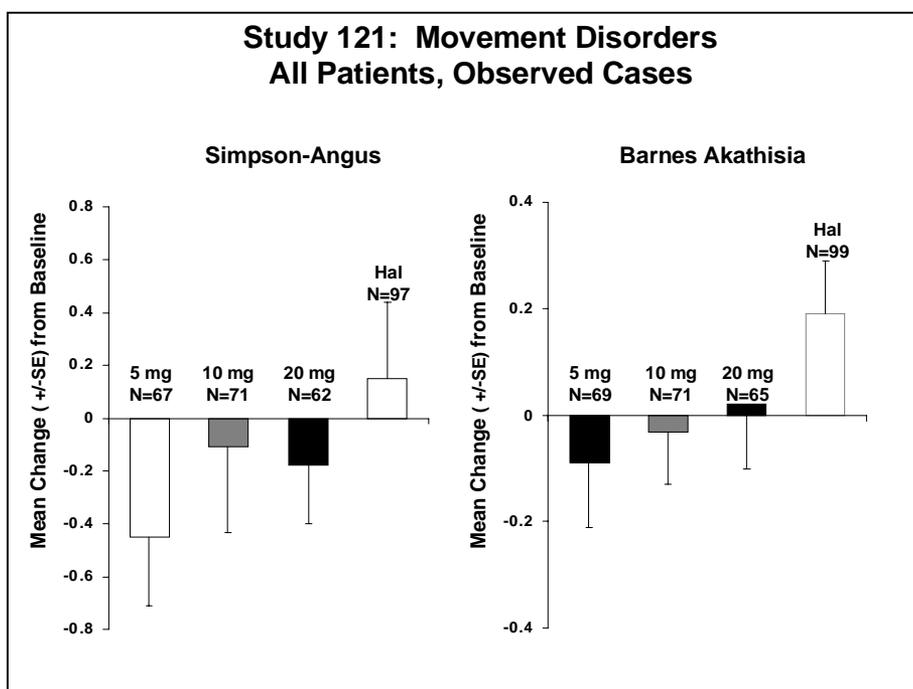
Figure 13. Study 121: Mean change from baseline to last IM in Simpson-Angus and Barnes Akathisia scores

D.4.2.2 Study 306

The mean changes from baseline to measurement following the last IM dose in the Simpson-Angus and Barnes Akathisia scales for Study 306 are shown in Figure 14. These results again show a mean decrease from baseline in movement disorder scores in patients receiving IM ziprasidone compared with the mean increase observed in patients receiving IM haloperidol.
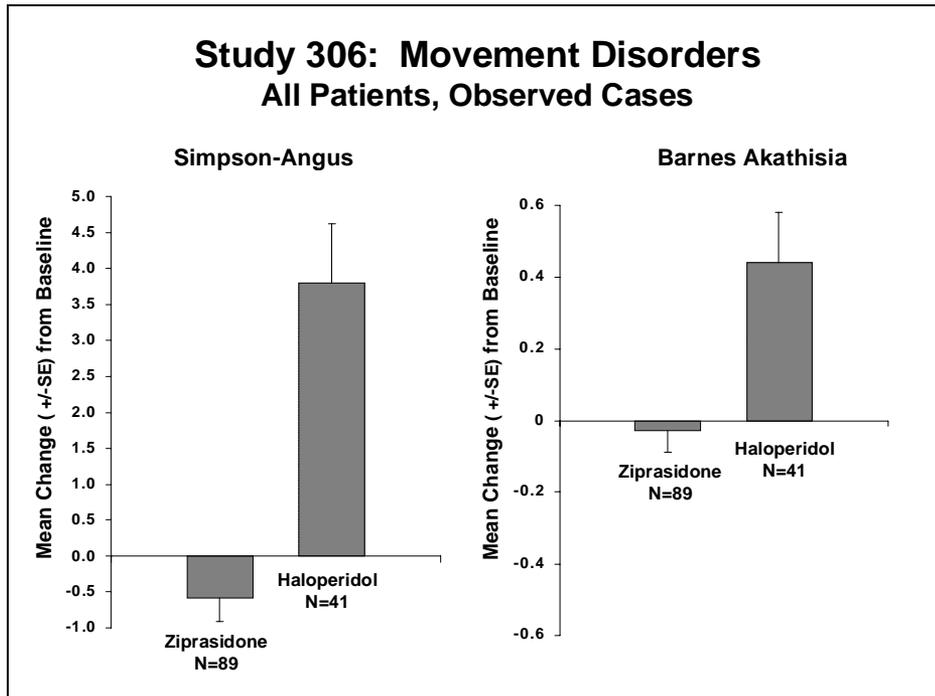
Figure 14.   Study 306: Mean change from baseline to last IM in Simpson-Angus and Barnes Akathisia scores

D.4.2.3 Use of Anticholinergics

The low incidence of movement disorders with ziprasidone IM was also reflected in the reduced requirement for concomitant anticholinergic medication compared with haloperidol. The use of the anticholinergic, benztropine, in Studies 126 and 125 was modest (11 of 92 patients receiving 2 mg, 6 of 63 patients receiving 10 mg, and 3 of 41 receiving 20 mg also received an anticholinergic).

In the 7-day Study 121, a smaller proportion of ziprasidone-treated patients than haloperidol-treated patients used benztropine during both the IM and oral portions of the study (Figure 15).
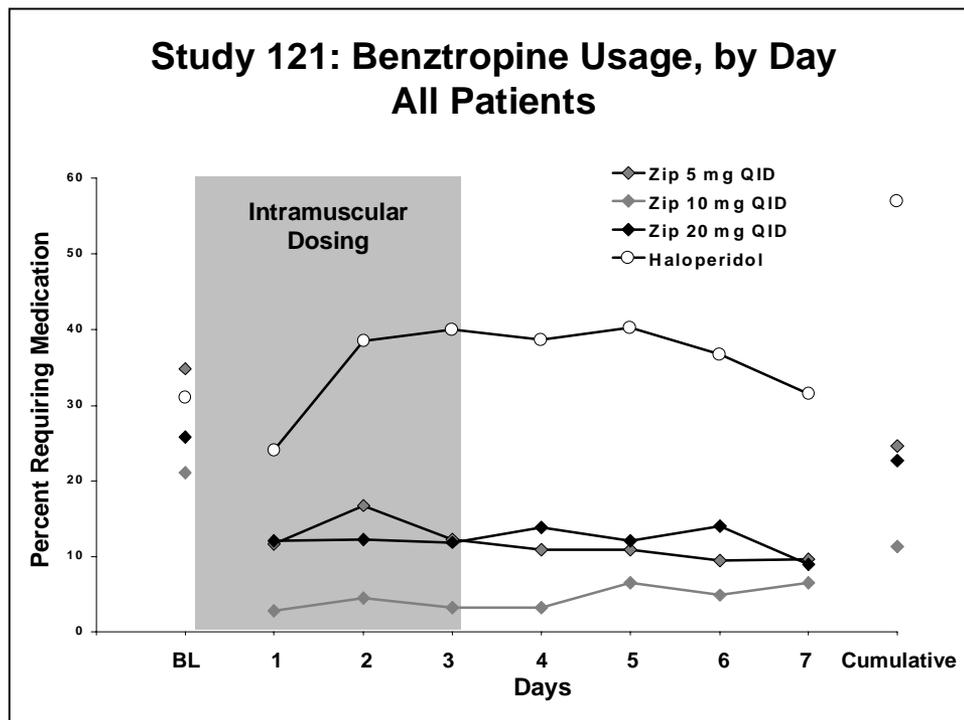
**Figure 15.   Study 121: Percent of patients requiring benztropine for movement
disorders during IM and oral dosing with ziprasidone**

Similarly, in Study 306, 14.4% of patients in the ziprasidone group received an
anticholinergic at least once during the study compared with 47.6% of patients in the
haloperidol group.

D.4.3 Conclusions – Movement Disorders

In the fixed-ziprasidone-dose Study 121 and flexible-dose Study 306, ziprasidone was
clearly associated with a lower movement disorder burden than haloperidol. The
burden of movement disorders remained lower than that of haloperidol at all doses
tested, including the 80 mg total daily IM dose of ziprasidone.

D.5 Conclusions

Ziprasidone given intramuscularly at 10 mg and 20 mg for up to 3 days is a well-
tolerated treatment for acute agitation in patients with psychosis. In open-label (Study
306) and double-blind (Study 126) clinical trials, more than 90% of agitated patients
were treated with a maximum daily dose $\leq$40 mg. Safety and tolerability of daily doses
up to 80 mg was demonstrated.

A database of over 5000 appropriately timed measurements, at doses up to 80 mg daily for three days, suggests that the effect of IM ziprasidone on blood pressure and heart rate does not represent a significant safety hazard.

Ziprasidone concentrations observed in intramuscular clinical trials lie within the range observed in the oral program. QTc changes observed near the time of C_{max} following IM administration suggests that the effect of IM ziprasidone on the QTc is not meaningfully different from that following oral administration. No QTc values >500 msec have been observed with IM ziprasidone.

Intramuscular ziprasidone was consistently associated with a lower movement disorder burden than haloperidol at all IM ziprasidone doses investigated.

E. ORAL TRANSITION

- **The pattern of safety-related discontinuations and adverse events observed during the transition from IM to oral ziprasidone suggests that the switch in formulations was well tolerated**

- **The improvement in clinical ratings scales observed during IM treatment was sustained through the transition to oral therapy**

E.1 Introduction and Overview

The transition from IM to oral ziprasidone was examined in Studies 121 and 306, both of which used haloperidol as an active comparator. In both of these trials, the initial daily dose of oral ziprasidone was, by protocol, twice the total IM dose from the previous day.

The following section describes the tolerability of the transition from IM to oral ziprasidone. Efficacy data were also examined to determine whether the improvement observed during IM treatment was sustained during the transition to oral therapy.

E.2 Tolerability

Data from Studies 121 and 306 demonstrated that the transition from IM to oral ziprasidone was well tolerated. Specifically, there was no remarkable change in the pattern of safety-related discontinuations during the transition (Table 35). Four safety-related discontinuations were reported in ziprasidone-treated patients during oral treatment (3 for adverse events considered related to study drug (laryngospasm; orthostatic hypotension; akathisia) and one for an adverse event not related to study drug (intermittent urinary tract infection).

Overall, comparable proportions of ziprasidone- and haloperidol-treated patients were discontinued prematurely in these two studies. A smaller proportion of ziprasidone-treated patients than haloperidol-treated patients (3.7% vs. 7.5%) was discontinued for all reasons during the oral phase.

Table 35. Studies 121 and 306: Discontinuation from study relative to the transition from IM to oral study drug

	DCs (%) on IM	Day of Oral Treatment						Total DCs (%) on Oral
		1	2	3	4	5	6	
Dose Group: Ziprasidone N=296								**N=272**
Lack of Efficacy	0	-	1	-	-	-	-	1(0.4)
Adverse Event	6(2.0)	2	2	-	-	-	-	4(1.5)
Patient Defaulted	14(4.7)	-	2	-	1	-	-	3(1.1)
Other	4(1.4)	-	-	1	-	-	1	2(0.7)
Total	24(8.1)	2	5	1	1	-	1	10(3.7)
Dose Group: Haloperidol N=142								**N=134**
Lack of Efficacy	0	-	1	-	1	1	-	3(2.2)
Adverse Event	1(0.7)	1	-	-	-	-	-	1(0.7)
Patient Defaulted	7(4.9)	1	4	-	-	-	-	5(3.7)
Other	0	1	-	-	-	-	-	1(0.7)
Total	8(5.6)	3	5	-	1	1	-	10(7.5)

DCs = number of patients who were discontinued from study drug
The "patient defaulted" category includes patients who withdrew consent or were lost to follow-up. The "other" category includes patients who were discontinued for other reasons, a protocol violation/deviation, or those who did not meet the randomization criteria.

Table 36 shows the number (%) of patients with newly emergent (i.e. during the oral treatment period) adverse events (threshold: ≥2% in either treatment group) during the IM and oral periods of Studies 121 and 306. The incidences of akathisia and extrapyramidal syndrome were lower in ziprasidone-treated patients than haloperidol-treated patients during both the IM and oral phases of the studies. There is no evidence to suggest an increase in the incidence of adverse events, or a significant change in the nature of adverse events, in association with the transition from IM to oral ziprasidone therapy.

Table 36.   Studies 121 and 306: Incidence of treatment-emergent adverse events (≥2% in either group) during IM and oral portions of study

	Number (%) of Patients with Treatment-Emergent Adverse Events Studies 121 and 306 combined			
	Ziprasidone		Haloperidol	
	IM	Oral	IM	Oral
N =	296	272	142	134
Body as a Whole				
Injection Site Pain	22 (7.4)	0	2 (1.4)	1 (0.8)
Asthenia	10 (3.4)	4 (1.5)	0	0
Headache	37 (12.5)	22 (8.1)	8 (5.6)	6 (4.5)
Cardiovascular				
Hypertension	18 (6.1)	3 (1.1)	1 (0.7)	0
Postural Hypotension	8 (2.7)	0	0	1 (0.8)
Tachycardia	17 (5.7)	1 (0.4)	6 (4.2)	1 (0.8)
Digestive				
Constipation	9 (3.0)	4 (1.5)	0	0
Dry Mouth	8 (2.7)	2 (0.7)	3 (2.1)	1 (0.8)
Dyspepsia	15 (5.1)	7 (2.6)	5 (3.5)	3 (2.2)
Increased Salivation	6 (2.0)	0	4 (2.8)	1 (0.8)
Nausea	37 (12.5)	10 (3.7)	4 (2.8)	3 (2.2)
Vomiting	25 (8.4)	10 (3.7)	5 (3.5)	4 (3.0)
Nervous				
Agitation	17 (5.7)	7 (2.6)	9 (6.3)	3 (2.2)
Akathisia	18 (6.1)	4 (1.5)	21 (14.8)	10 (7.5)
Anxiety	32 (10.8)	9 (3.3)	13 (9.2)	8 (6.0)
Dizziness	38 (12.8)	7 (2.6)	0	1 (0.8)
Dystonia	10 (3.4)	8 (2.9)	13 (9.2)	5 (3.7)
Extrapyramidal Syndrome	4 (1.4)	2 (0.7)	24 (16.9)	15 (11.2)
Hypertonia	4 (1.4)	3 (1.1)	14 (9.9)	5 (3.7)
Insomnia	33 (11.2)	7 (2.6)	12 (8.4)	6 (4.5)
Somnolence	16 (5.4)	3 (1.1)	8 (5.6)	3 (2.2)
Tremor	9 (3.0)	7 (2.6)	4 (2.8)	6 (4.5)
Respiratory				
Respiratory tract Infection	6 (2.0)	3 (1.1)	1 (0.7)	1 (0.8)
Skin & Appendages				
Sweating	2 (0.7)	0	3 (2.1)	2 (1.5)
Special Senses				
Abnormal Vision	7 (2.4)	1 (0.4)	1 (0.7)	0

E.3 Efficacy

Studies 121 and 306 were short-term studies designed to examine the tolerability of ziprasidone IM over a treatment period of up to three days. In both trials, measures of disease severity were captured at the end of the intramuscular treatment period and again during oral dosing. As shown in Table 37, the improvement in BPRS Total Score, CGI-S, CGI-I, and NOSIE scores evident in ziprasidone-treated patients after the last IM dose was sustained after the transition to oral dosing.

Table 37. Studies 121 and 306: Mean change from baseline in efficacy scores to last observation on IM and oral study drug

	Baseline And Mean Change (SD) From Baseline To Last IM and Last Oral Scores For Patients Having at Least One Observation on Oral Ziprasidone					
	Ziprasidone			Haloperidol		
	Baseline	Last IM	Last Oral	Baseline	Last IM	Last Oral
Study 121						
BPRS Total	36.5(12.2)	-5.6(7.6)	-6.2(8.2)	38.0(13.8)	-6.3(10.5)	-7.5(10.5)
CGI-S	3.7(1.2)	-0.2(0.6)	-0.3(0.8)	3.8(1.0)	-0.3(0.7)	-0.4 (0.8)
CGI-I†	NA	3.6(0.9)	3.3(1.0)	NA	3.7(0.9)	3.5(0.9)
NOSIE	28.8(11.4)	-3.3(8.9)	-4.1(10.1)	29.6(11.1)	-4.6(10.1)	-4.5(10.2)
Study 306						
BPRS Total	45.4(10.4)	-6.4(8.2)	-9.0(11.7)	47.6 (9.0)	-3.9(6.2)	-7.2(9.2)
CGI-S	5.0 (0.8)	-0.5(0.7)	-0.9(1.3)	5.0 (1.1)	-0.2(0.6)	-0.4(1.2)
CGI-I†	NA	3.4(1.0)	3.0(1.4)	NA	3.4(0.8)	3.0(1.0)
NOSIE	33.2(11.2)	-1.9(8.5)	-3.5(9.2)	33.0(11.0)	-1.3(9.0)	-4.0(7.3)

†CGI-I relative to baseline; mean(SD) values are shown   NA = Not Applicable

E.4 Conclusions

These data indicate that the transition from IM to oral ziprasidone was successful because (1) it was well tolerated as measured by the pattern of safety-related discontinuations and the emergence of adverse events; and (2) the improvement in efficacy variables observed during IM treatment was sustained or increased through oral treatment.

F. OVERALL SUMMARY AND CONCLUSIONS

In patients with psychosis, agitation is a distressing condition that puts the patient and others at immediate risk of harm. In this acute setting, rapid and effective control of symptoms is required to minimize potential harm and allow for the initiation of long-term management of the underlying psychosis.

Intramuscular ziprasidone has been shown to be an effective treatment for the acute control of agitation in patients with psychosis. A favorable therapeutic effect was apparent after administration of doses of 10 mg or 20 mg, with some evidence for dose-response. Consistent with the pharmacokinetics of intramuscular ziprasidone, the onset of this effect was relatively rapid, as judged by the reduction in BARS scores.

Safety data support the use of the IM formulation for up to 3 days and a switch to the oral capsule formulation of ziprasidone at a dose of up to 80 mg twice daily.

Movement disorders such as extrapyramidal syndrome, akathisia, dystonia, and hypertonia were seen less frequently with IM ziprasidone than with IM haloperidol in Phase 2/3 studies.

In summary, despite clear clinical need, only a handful of traditional antipsychotics are currently available as intramuscular formulations for the treatment of acute psychosis, including for patients who are agitated and aggressive. Intramuscular ziprasidone represents a significant step forward in the management of acutely agitated patients with psychosis, allowing a patient to continue on oral atypical antipsychotic treatment following successful treatment of the agitated state.

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