

**FDA Psychopharmacological Drugs
Advisory Committee**

14 February 2001

**Briefing Document for
ZYPREXA[®] IntraMuscular
(olanzapine for injection)
11 January 2001**

Lilly

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Executive Summary

Olanzapine is a potent thienobenzodiazepine atypical antipsychotic agent displaying nanomolar receptor affinity in vitro at serotonin 5-HT_{2A/2B/2C}, 5-HT₃, 5-HT₆, dopamine D₁/D₂/D₃/D₄/D₅, muscarinic cholinergic (m₁-m₅), α_1 -adrenergic, and histamine H₁ receptors. Orally administered olanzapine is currently used to treat patients worldwide as a marketed product and over 5.6 million patients have been treated with olanzapine to date. Olanzapine is currently available as coated and as orally disintegrating tablets; it has been the subject of extensive preclinical, clinical and post-licensing studies. The current indications for use of oral olanzapine are the treatment of schizophrenia and the short-term treatment of acute manic episodes associated with bipolar I disorder.

Parenteral administration of antipsychotics is favored for the control of agitation where a rapid onset of action is desirable or when patients are unable to comply with oral preparations. However, the currently available intramuscular (IM) typical antipsychotics have significant safety and efficacy limitations. Atypical antipsychotics such as olanzapine may provide superior parenteral therapy for agitated patients due to improved side effect profiles. However, no IM formulations of atypical antipsychotics are available in the United States. This document summarizes the clinical program conducted to support the approval of an IM formulation of olanzapine for the rapid control of agitation.

Agitation

Agitation is a common, well-recognized behavioral syndrome that, in its severe forms, presents a psychiatric emergency mandating rapid therapeutic intervention to protect patients, caregivers and others from harm. Agitation is defined as excessive motor or verbal activity that is usually nonproductive and repetitious. Its core psychiatric symptoms include hostility, tension, excitement, uncooperativeness and poor impulse control. Although agitation may occur in association with many disorders, it is a common component and often requires treatment in three neuropsychiatric illnesses: schizophrenia, bipolar disorder, and neurodegenerative disorders. IM pharmacotherapy is clinically appropriate when the level of hostility, excitement, uncooperativeness or lack of impulse control is such that the potential exists for harm to self or others, or for the destruction of property.

The ideal IM pharmacotherapy would have the following features: a favorable safety profile including low incidences of extrapyramidal and cardiac side effects, calming effect without excessive sedation, rapid onset of action, and effective response to first dose. Two classes of drugs used parenterally that are currently employed to control agitation acutely are antipsychotics and benzodiazepines. The usefulness of these medications is limited primarily by safety concerns.

Pharmacokinetics of IM Olanzapine

The pharmacokinetics of IM olanzapine in comparison to oral administration have been extensively studied. Fundamental pharmacokinetic characteristics of olanzapine such as half-life and clearance are not significantly affected by the route of administration. Thus, the area under the curve after an IM dose is similar to that after oral administration of the same dose. The most obvious pharmacokinetic difference between IM and oral administration involves the rate of absorption after administration. The rate of absorption is more rapid after IM administration and this produces a transiently higher maximum plasma concentration of olanzapine compared with oral administration. Importantly, similar metabolite profiles were observed following IM and oral administration of olanzapine, with no new metabolites identified after IM administration.

Efficacy of IM Olanzapine

The efficacy of IM olanzapine for the control of agitation was evaluated in four randomized, double-blind, placebo- and active comparator-controlled studies in agitated patients with schizophrenia (two studies), bipolar mania (one study) and dementia associated with neurodegenerative disorders (one study). These patient populations were selected because agitation is a common clinical occurrence in these disease states which often requires pharmacological intervention. In addition, they represent a range of patient ages from young adult to the elderly, and a range of clinical conditions involving both psychotic and nonpsychotic patients with moderate to severe agitation.

Alleviation of agitation was assessed by the use of a battery of efficacy measures. The primary efficacy analysis in each of the four pivotal studies was the mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) Excited Component at 2 hours following the first IM injection. Additional efficacy measures in the studies in agitated patients with schizophrenia and bipolar mania included the Agitation-Calmness Evaluation Scale (ACES) and the Corrigan Agitated Behavior Scale. The study in agitated patients with dementia also included the ACES and the Cohen-Mansfield Agitation Inventory.

The results of the four pivotal studies support the efficacy of IM olanzapine in controlling agitation across different patient populations. In all four pivotal studies, the primary efficacy analysis, mean change from baseline to endpoint in the PANSS Excited Component at 2 hours following the first IM injection, showed that IM olanzapine was superior to placebo. This finding occurred in all IM olanzapine dose arms (2.5, 5, 7.5, and 10 mg/injection). The additional efficacy measures of agitation yielded similar results. In the pivotal studies where the Corrigan Agitated Behavior Scale and the ACES were used (agitation in schizophrenia dose ranging, agitation in schizophrenia, and agitation in bipolar mania), the mean change from baseline to endpoint at 2 hours following the first IM injection for both scales showed that IM olanzapine was superior to placebo. In the pivotal study of agitation in dementia where the ACES and Cohen-Mansfield Agitation Inventory were used, both scales again showed that IM olanzapine

was superior to placebo at 2 hours following the first IM injection within at least one of the IM olanzapine dose arms studied.

The majority of IM olanzapine treated patients required only one injection to control their agitation with a very small number of patients needing three injections. This was similar to the active comparator assigned patients but significantly different compared to IM placebo treated patients where more injections were given.

The onset of action of IM olanzapine and its active comparators was investigated across the four studies at various time points ranging from 15 minutes to 2 hours following the first IM injection. In each study, IM olanzapine demonstrated superior reduction in agitation on the PANSS Excited Component at the earliest time point measured compared with IM placebo within at least one of the IM olanzapine dose arms studied. In the two schizophrenia studies and in the bipolar mania study, IM olanzapine was also superior to IM haloperidol and to IM lorazepam at the earliest time point measured in at least one of the dose arms studied. These data support the rapid onset of IM olanzapine for the control of agitation across patient populations.

An assessment of the individual items of the PANSS Excited Component was conducted and demonstrated that IM olanzapine was significantly efficacious compared with IM placebo on the majority of the items (poor impulse control, tension, hostility, uncooperativeness, and excitement) across the four pivotal studies.

Safety of IM Olanzapine

The IM olanzapine clinical trial safety data establish IM olanzapine as a safe and well tolerated therapy for the control of agitation. In the IM olanzapine clinical studies, the incidence of adverse events leading to discontinuation and serious adverse events was relatively low. Further, no treatment-emergent adverse events occurred at a statistically significantly greater incidence in IM olanzapine-treated patients compared with IM placebo-treated patients, or compared with IM haloperidol- or IM lorazepam-treated patients. The assessment of laboratory analytes and ECGs revealed no clinically significant changes associated with IM olanzapine. Notably, the analyses of ECG data in all four pivotal studies revealed no significant QTc interval prolongations associated with IM olanzapine at any dose when compared with IM placebo. The lack of the QTc abnormalities in the agitation in dementia study is particularly relevant due to the advanced age and presence of co-morbid medical conditions in this patient population. In the assessment of vital signs in these controlled clinical study databases, IM olanzapine was not associated with any effects except for mild and transient decrements in blood pressure and heart rate that were not clinically significant. IM olanzapine did not produce excessive or undesirable sedation.

For extrapyramidal symptoms, IM olanzapine exhibited a favorable profile compared with IM haloperidol. In the IM olanzapine clinical studies, the incidence of treatment-emergent extrapyramidal symptoms in IM olanzapine-treated patients was comparable to

IM placebo-treated patients whereas IM haloperidol-treated patients experienced a significant higher incidence of extrapyramidal symptoms compared with IM placebo-treated patients. In addition, IM olanzapine was significantly superior to IM haloperidol and comparable to IM placebo for assessments of akathisia using the Barnes Akathisia scale and parkinsonism using the Simpson-Angus scale. There were no cases of acute dystonia associated with IM olanzapine whereas 6.6% of patients treated with IM haloperidol experienced this adverse event.

Dosing

Dosing recommendations can be made based on the IM olanzapine efficacy, safety, and pharmacokinetic data. The dose ranging study in agitated patients with schizophrenia explored the relationship between a range of IM olanzapine doses (2.5, 5, 7.5, and 10 mg/injections) and treatment response. A statistically significant dose response relationship was shown to exist with the optimal dose being 10 mg based on the linear dose response and a similar safety profile across all IM olanzapine doses. The efficacy of a 10-mg dose was confirmed by the second study in agitated patients with schizophrenia and in the study in agitated patients with bipolar mania. Further, the magnitude of effect of the 10-mg dose was similar in agitated patients with schizophrenia or bipolar mania. Therefore, 10 mg is the recommended dose in these patient populations. In agitated patients with dementia, a dose range of 2.5 to 5 mg demonstrated efficacy in controlling agitation. Thus, the recommended dose in patients with dementia is 2.5 mg based on similar efficacy across both doses and clinical practice in this patient population supporting conservative dosing.

Conclusion

In summary, a clinical development program was conducted evaluating the efficacy and safety of IM olanzapine for the rapid control of agitation in four randomized, double-blind, placebo- and active-comparator controlled studies in agitated patients with schizophrenia, bipolar mania, or dementia. IM olanzapine was safe and well tolerated, and positive efficacy results were achieved in each of the four studies. These data provide a body of evidence supporting the conclusion that IM olanzapine is a safe and effective therapy for agitated patients, thus supporting the following indication statement:

ZYPREXA IntraMuscular [IM olanzapine] is indicated for the rapid control of agitation.

The efficacy of ZYPREXA IntraMuscular for the control of agitation was established in 4 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia, Bipolar I Disorder (manic or mixed episodes), or dementia.

1. Introduction

1.1. Phenomenology of Agitation

Agitation is a common, well-recognized behavioral syndrome that, in its severe forms, poses a psychiatric emergency mandating rapid therapeutic intervention to protect patients, caregivers and others from harm. Its phenomenology is remarkably similar across disease states and its clinical description has been well characterized. Agitation comprises both motor and verbal components. The Diagnostic and Statistical Manual 4th Edition (DSM IV) defines psychomotor agitation as “*excessive motor activity...that is usually nonproductive and repetitious*” (American Psychiatric Association 1994). Examples of motor manifestations of agitation are hyperactivity, assaultiveness, physical destructiveness and threatening gestures. Other authors describe verbal forms of agitation as excessive verbal or vocal expression which include vocal outbursts, threatening language, verbal abuse and excessive verbalizations of distress (Cohen-Mansfield and Billing 1986; Lantz and Marin 1996; Mintzer and Brawman-Mintzer 1996; Fugate et al. 1996; Lindenmayer 2000). An extensive review of the agitation literature revealed a constellation of core psychiatric symptoms that were common across diverse disease states which included hostility, excitement, tension, uncooperativeness and poor impulse control. Appendix 1 is a list of clinical studies identified during the literature review.

Agitation has not been viewed historically as a unique diagnostic entity or indicative of any one disorder. Rather, it is a group of psychiatric symptoms that commonly occur across a number of disease states. Agitation is precipitated in the context of diverse psychopathological events such as the arousal and fear occurring in reaction to a threatening hallucinatory voice in schizophrenia or the disorienting impact of cognitive decline in neurodegenerative diseases. The neurochemical mechanisms that mediate agitation have not been fully elucidated and therefore it is not possible to determine if agitation associated with diverse disease states share a common neurochemical pathophysiology. However, despite the diversity in disease states in which agitation occurs, the core features of agitation are relatively homogenous, readily recognizable by clinicians, able to be reliably measured, and, as discussed below, demonstrate a relatively consistent temporal and quantitative response to specific pharmacological agents.

1.2. Agitation and Neuropsychiatric Illnesses

Although agitation may occur in association with many disorders, it is a common component and often requires treatment in three neuropsychiatric illnesses: schizophrenia, bipolar disorder and dementia associated with neurodegenerative disorders. In schizophrenia, agitation often arises as a secondary result of exacerbation in psychotic symptoms. Auditory hallucinations and paranoid delusions may be so unsettling, frightening, or threatening that patients become agitated. Violence to self or

others, and erratic or disruptive behavior may ensue in response to misinterpretation of the environment.

In bipolar mania, grandiose and occasionally paranoid delusions may similarly lead to a misinterpretation of the patient's environment such that the intentions of others are misconstrued. Hostility, excitement, uncooperativeness and lack of impulse control may also be present in manic patients as part of the core features of mania in the absence of psychosis.

Patients with dementia associated with neurodegenerative decline may develop psychopathology and/or behavioral disturbances in addition to their characteristic cognitive impairment. Agitation is commonly observed in elderly patients with dementia, and leads to substantial difficulty in the care of this patient population (Taft 1989). Agitation often is the precipitant that forces institutional care of patients who otherwise would be cared for at home or other community based outpatient programs. There is substantial empirical evidence that in patients with dementia, psychotic symptoms and agitated behaviors may co-exist and commonly respond to similar treatment modalities (Marx et al. 1990; Tariot et al. 1995a; Aarsland et al. 1996; American Psychiatric Association 1997).

1.3. Pharmacotherapy of Agitation

Agitation associated with neuropsychiatric illnesses ranges in degree from mild to severe and often necessitates clinical intervention. This is the case when the level of hostility, excitement, uncooperativeness or lack of impulse control is such that the potential exists for harm to self or others, or the destruction of physical property. Particularly in patients who are psychotic or manic, untreated agitation may quickly escalate to violent, assaultive behavior. Other instances when treatment is indicated occur when high levels of agitation lead to patients' noncompliance to necessary medical care or agitation is of such a magnitude that extreme personal distress is experienced. In these instances, rapid control of agitation, over minutes to hours, is often a clinical imperative to protect the patients, medical staff, and others.

Historically, a wide range of interventions have been employed to control agitation including wet sheet packs, four-point restraints, confinement, and excessive sedation with barbiturates and other agents with hypnotic properties. Modern pharmacotherapy to rapidly control agitation relies primarily on two classes of drugs, either alone or in combination: antipsychotics and benzodiazepines. Parenteral administration of these agents is favored when a very rapid onset of action is desirable and/or when patients are unable to comply with oral preparations. (Dubin 1988; Goldberg et al. 1989; Battaglia et al. 1997). One of the most widely used IM antipsychotics for the alleviation of acute agitation in the United States is haloperidol. Both haloperidol and lorazepam, a commonly prescribed benzodiazepine given intramuscularly, have been used in previous clinical studies in the treatment of agitation (Battaglia et al. 1997; Bieniek et al. 1998).

The pharmacological treatment of agitation across the three different neuropsychiatric disorders previously mentioned is very similar. Parenteral antipsychotics are routinely used for short-term management of agitation associated with schizophrenia. It has been estimated that 20% of all hospitalized patients with schizophrenia will receive such therapy (Pilowsky et al. 1992). IM benzodiazepines are also commonly used to treat acute agitation in schizophrenia. Subsequent to IM treatment, transition to oral or depot antipsychotic treatment is necessary for long-term maintenance.

In bipolar mania, lithium, depakote, and other mood stabilizers have long been established as effective antimanic agents (Bunney 1987). Despite the efficacy of mood stabilizers, the pharmacologic management of acute mania often requires the use of adjunctive antipsychotics for (1) control of the psychotic symptoms and agitation that often accompany bipolar disorder, and (2) allowing sufficient time for mood stabilizers to take their effect. IM benzodiazepines and antipsychotics have been found useful for the control of agitation in association with mania (Dubin 1988).

In dementia, benzodiazepines and antipsychotic medications are commonly prescribed. Even though there are no IM antipsychotic medications specifically approved for the treatment of agitation in dementia, IM antipsychotics are used in this population (Schneider et al. 1990; Sunderland and Silver 1988; Tariot et al. 1995b).

Despite the commonality in pharmacological management of agitation across these three diseases, it is clear that the use of IM antipsychotics is directed not at the treatment of the core symptoms of the different diseases (psychosis, mood swings, and cognitive deficits), but is aimed at the control of agitation. IM antipsychotics are usually used for only the first several hours to quell acute agitation, in contrast to the treatment of the psychotic symptoms of schizophrenia, for example, which requires weeks to months of oral administration before remission. Thus, despite the inherent differences in the long-term approaches to the treatment of the primary disease state, the acute management of agitation is similar no matter which disease underlies the agitation.

1.4. Limitations of Current Treatment

Currently available IM medications are limited primarily by their safety concerns. IM benzodiazepines may cause respiratory depression and excessive sedation. They may also induce paradoxical behavioral disinhibition that will lead to a worsening of the patient's condition (Stimmel 1996). Currently available IM antipsychotics have a number of limitations, the most serious of which are (1) acute dystonia, (2) akathisia, (3) ECG abnormalities, (4) excessive sedation, and (5) neuroleptic malignant syndrome.

1. Acute dystonia consists of sustained contraction of the muscles of the head, neck, or upper limbs. It is painful, distressing, and frightening. It occurs in up to 25% of patients receiving typical antipsychotics, often after a single administration of the drug and always within a few days of commencing treatment, and is more common in younger male patients (Addonizio and Alexopoulos 1988). Patients who experience acute dystonia are understandably reluctant to continue maintenance therapy with the causative drug. Acute dystonia is significantly less common in patients receiving oral atypical antipsychotics such as olanzapine (Tollefson et al. 1997) or quetiapine (Peuskens and Link 1997).
2. Akathisia is a problematic and uncomfortable side effect of antipsychotics that involves persistent motor restlessness and muscle tightness. It may be misdiagnosed as a psychotic decompensation (Janicak et al. 1997) and often contributes to patients' reluctance to take antipsychotics. Severe manifestations of akathisia can lead to homicide or suicide (Drake and Ehrlich 1985; Van Putten and Marder 1987).
3. Many antipsychotics cause ECG abnormalities, particularly prolongation of the QTc interval (e.g., thioridazine) (British National Formulary 1999). Sudden unexpected death has been associated with some antipsychotics (Lader 1999; Hatta et al. 1998; Jitsufuchi et al. 1995). Because of the rapid and high peak drug concentrations (i.e., C_{max}) associated with IM antipsychotics, abnormalities in QTc may be even a greater concern than with oral preparations.
4. Sedation has frequently been reported during treatment with antipsychotics as well as benzodiazepines, and indeed a degree of sedation is desirable in the context of treating agitation. Excessively sedated patients, however, are at increased risk of respiratory complications (Heard et al. 1999; Hatta et al. 1998). These risks are so prevalent that many psychiatrists and hospitals adopt the policy of assigning a specific nurse to continuously observe a patient who have received parenteral antipsychotics and/or benzodiazepines (Walker 1997).
5. Neuroleptic malignant syndrome (NMS) is a potentially lethal side effect of antipsychotics. Its clinical presentation includes rigidity, fever, a fluctuating level of consciousness, autonomic instability, and elevated muscle enzymes. It appears some of the atypical antipsychotics are less likely to cause NMS compared with traditional neuroleptics, presumably because of lower dopamine D_2 antagonistic effects.

ECG abnormalities and excessive sedation with respiratory depression are adverse events that put the patient at risk acutely. Acute dystonia is manageable short term but often leads to a history of non-compliance with treatment due to the patient associating these drugs with acute discomfort. Clearly, there is an unmet medical need for an effective treatment for agitation that does not compromise short-term safety or long-term compliance.

1.5. Potential Advantages of Newer Atypical IM Antipsychotics

The newer oral atypical antipsychotics have significantly fewer side effects such as extrapyramidal symptoms (Remington and Kapur 2000). Acute dystonia is significantly less common in patients receiving oral atypical antipsychotics such as olanzapine (Tollefson et al. 1997), clozapine (Remington and Kapur 2000), and quetiapine (Peuskens and Link 1997). However, parenteral formulations of such drugs are not currently approved in the United States.

A key impetus for developing an IM formulation of olanzapine was its potential to offer an effective and reliable treatment for the rapid control of agitation while maximizing patient safety and tolerability. The clinical studies were designed to determine if IM olanzapine would provide the following features across different disease states:

- low incidence of extrapyramidal side effects such as acute dystonia and akathisia
- safe cardiac profile including low incidence of ECG abnormalities
- calming without excessive sedation
- rapid onset of action
- effective response to first dose, decreasing the number and frequency of subsequent injections

An IM antipsychotic with the above features would satisfy a clear and unmet need in the safe and rapid control of agitation.

2. Background

Prior to initiating a clinical development program to support the registration of IM olanzapine, Lilly met with representatives of the Food and Drug Administration (FDA) as well as a number of external academic experts to discuss and gain input on this clinical program. This section (1) summarizes the discussions with key consultants held during the design and conduct of the IM olanzapine clinical development program, (2) outlines the key regulatory considerations underlying the decision to pursue an indication for the control of agitation across different patient populations, and (3) provides a tabular summary of the clinical studies included in the new drug application (NDA) to support the approval of IM olanzapine for the treatment of agitation.

2.1. Discussions with the FDA

Lilly's initial meeting with the FDA to discuss the design of an appropriate registration plan for IM olanzapine was held on May 14, 1998. The FDA indicated that based on the anticipated use of atypical IM antipsychotics in the control of agitation across multiple medical diagnoses and patient populations, conducting registration studies only in patients with schizophrenia was not appropriate. Instead, the FDA stated that the registration of IM antipsychotics should be supported with clinical studies in agitated patients with schizophrenia as well as other disease states to support broader labeling for controlling agitation across patient populations. The FDA pointed out that analogous approaches have been used to support the registration of treatments for pain across multiple patient populations (i.e., the regulatory pain model). The FDA further stated that the studies could be of short-term duration reflecting the actual clinical use of IM atypical antipsychotics, and also suggested that the inclusion of more than one active comparator treatment (e.g., IM haloperidol, IM lorazepam) in the studies would provide useful clinical information.

Based on this direction from the FDA, Lilly, in consultation with a number of academic experts, designed the clinical program described in this briefing document. The clinical program consisted of four pivotal efficacy and safety studies evaluating IM olanzapine in the control of agitation across three distinct patient populations (i.e., two studies in agitated patients with schizophrenia, one study in agitated patients with bipolar mania, and one study in agitated patients with dementia). Each of the studies included a placebo-control group and an active comparator treatment group: IM haloperidol in the studies in agitated patients with schizophrenia, and IM lorazepam in the studies in agitated patients with bipolar mania and dementia.

Prior to initiating this clinical program, Lilly discussed the proposed plan with the FDA during a November 12, 1998 teleconference. During that teleconference, Lilly sought the FDA's agreement on the acceptability of the proposed clinical plan for a new agitation indication. Key design aspects of the plan discussed during the teleconference included: (1) the number and type of patient populations selected for the four clinical efficacy and

safety studies in three agitated patient populations, (2) the anticipated patient safety exposures to IM olanzapine (i.e., approximately 650 agitated patients and 70 volunteers), and (3) the proposed efficacy measures. The FDA stated agreement that the three patient populations selected (i.e., schizophrenia, bipolar mania, and dementia) provided a broad enough sample and that the anticipated patient safety exposures were adequate, noting the extensive patient exposures to oral olanzapine. Regarding the proposed efficacy measures of agitation, the FDA acknowledged they had no previous experience in this area, but noted that it would be necessary to select one primary measure for the studies. The FDA concluded the teleconference with the recommendation to provide a written summary of the proposed clinical plan for formal feedback, which Lilly responded to with the submission of a written plan on January 15, 1999.

As the IM olanzapine clinical program neared completion and in preparation for the June 2000 submission of the IM olanzapine NDA, a pre-NDA meeting between representatives of Lilly and the FDA was held on January 6, 2000. The FDA agreed during the pre-NDA meeting that the IM olanzapine clinical program conducted by Lilly was consistent with their previous recommendations and that an NDA for an agitation indication based on these four pivotal studies in three agitated patient populations would be fileable. The FDA did note that an agitation claim raised new questions regarding appropriate labeling. Based on this, the FDA stated their intention to convene a Psychopharmacological Drugs Advisory Committee (PDAC) meeting during the NDA review period to gain input from external consultants in the field regarding the new agitation indication.

2.2. Regulatory Considerations for an Agitation Indication

Since the clinical approach taken to support an agitation indication for IM olanzapine is analogous to previously conducted clinical programs supporting the approval of acute pain medications for use across different patient populations, it is relevant to consider the key features of the established regulatory approach for pain (i.e., regulatory pain model).

The two basic approaches commonly recognized by the FDA for pursuing new indications for drugs are outlined in the FDA's position paper for the recent March 9, 2000 PDAC meeting. One approach is to demonstrate the effectiveness and safety of the investigational drug for the treatment of a specific disease or syndrome (e.g., schizophrenia, bipolar mania, dementia). The second approach is to demonstrate the effectiveness and safety of the investigational drug for the treatment of signs or symptoms not specific to a distinct disease or syndrome (e.g., pain, fever, and agitation). In fact, a number of treatments for acute pain have been approved by the FDA based on this second approach and an FDA guidance document (Guideline for the Clinical Evaluation of Analgesic Drugs) outlining the recommended clinical approach to pursue a new indication for the treatment of acute pain across different patient populations has been issued.

The regulatory pain model outlined in the guidance document states that to support a new indication for the treatment of acute pain across patient populations, substantial evidence of efficacy needs to be established in several different pain models (e.g., postoperative pain, cancer pain, headache pain, postpartum pain). The guidance document also makes recommendations on appropriate labeling for pain medications to ensure that prescribers are provided with relevant information regarding the clinical program supporting the broad pain indication across patient populations. The recommended indication states, “For the management of pain (see Clinical Pharmacology).” The Clinical Pharmacology section of labeling then includes brief descriptions of the clinical studies supporting the drug’s approval.

These key features of the regulatory pain model have been applied to the IM olanzapine registration program. The four pivotal clinical efficacy and safety studies were conducted in the three distinct neuropsychiatric patient populations (schizophrenia, bipolar mania, and dementia) where IM antipsychotic treatment is commonly used to control agitation. Further, consistent with the labeling recommendations of the guidance document, the proposed label indication is:

ZYPREXA IntraMuscular [IM olanzapine] is indicated for the rapid control of agitation. The efficacy of ZYPREXA IntraMuscular for the control of agitation was established in 4 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia, Bipolar I Disorder (manic or mixed episodes), or dementia (*see* CLINICAL PHARMACOLOGY).

2.3. Summary of IM Olanzapine Clinical Development Program

Tables 1 and 2 summarize the studies conducted to support the registration of IM olanzapine for the control of agitation.

Table 1. Clinical Pharmacology Studies

Protocol #/ # of Sites/ Location	Study Design	# of Subjects Age Criteria	Patient Population	Study Drug / Dosage / Regimen /
F1D-EW-LOAC 1 Center Dundee, UK	Single- blind, crossover	N=31 M=31 18 to 65 yrs	Healthy male subjects	olanzapine IM up to 4 mg single dose; placebo IM; olanzapine 5 mg oral
F1D-EW-LOAW 1 Center Leicester, UK	Open-label, randomized crossover	N=24 M=24 18 to 65 yrs	Healthy male subjects	olanzapine 10 mg IM given as two 5 mg injections 4 hours apart; olanzapine 10 mg oral
F1D-LC-LOAV 1 Center, Indianapolis, IN USA	Open-label, crossover	N=15 M=4 F=11 21 to 40 yrs	Healthy males or females	olanzapine 2.5 mg IM; olanzapine 5 mg IM & lorazepam 2 mg IM given as single doses or in combination
F1D-BD-HGIO 1 Center, Paris, France	Open-label, crossover	N=18 M=18 18 to 45 yrs	Healthy male subjects	olanzapine 5 mg oral; olanzapine 5 mg IM dissolved in saline; olanzapine 5 mg IM dissolved in water each given as a single dose
F1D-MC-HGJA 2 Centers United States	Open-label	N=43 M=39 F=4 18 to 65 yrs	Non-agitated patients with schizophrenia	olanzapine 30 mg IM given as three 10 mg injections at least 4 hours apart

Table 2. Clinical Studies in Agitated Patients

Protocol #/ # of Sites/ Location	Study Design	# of Patients Age Criteria	Patient Population	Duration of IM Period	Study Drug / Dosage / Regimen /
F1D-MC-HGHV 14 Sites Multinational	Double- blind parallel	N=270 M=155 F=115 ≥18 yrs	Schizophrenia ^a	24 hours (primary endpoint at 2 hours)	olanzapine 2.5, 5, 7.5, & 10 mg IM; haloperidol 7.5 mg IM; placebo IM
F1D-MC-HGHB 51 Sites Multinational	Double- blind, parallel	N=311 M=204 F=107 ≥18 yrs	Schizophrenia ^a	24 hours (primary endpoint at 2 hours)	olanzapine 10 mg IM; haloperidol 7.5 mg IM; placebo IM
F1D-MC-HGHW 30 Sites Multinational	Double- blind, parallel	N=201 M=107 F=94 ≥18 yrs	Bipolar I disorder	24 hours (primary endpoint at 2 hours)	olanzapine 10 mg IM; lorazepam 2.0 mg IM; placebo IM
F1D-MC-HGHX 38 Sites Multinational	Double- blind, parallel	N=272 M=106 F=166 ≥55 yrs ^b	Dementia ^c	24 hours (primary endpoint at 2 hours)	olanzapine 2.5 & 5 mg IM; lorazepam 1.0 mg IM; placebo IM
F1D-EW-LOAR 1 Center Krugersdorp, South Africa	Open- label	N=26 M=26 18 to 65 yrs	Acute non- organic psychosis	3 days	olanzapine 2.5 to 10 mg IM
F1D-EW-LOAT 2 Centers George, South Africa	Open- label	N=92 M=63 F=29 ≥18 yr	Acute non- organic psychosis	3 days	olanzapine 2.5, 5, 7.5, 10, or 12.5 mg IM

^a Diagnosis of schizophreniform or schizoaffective disorder was also acceptable.

^b One patient, Patient 015-1510, was 54 years of age at time of randomization.

^c Patients in study HGHX were eligible for participation if they met criteria for Alzheimer's dementia, vascular or mixed dementia according to the DSM-IV or National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

3. Pharmacokinetic Overview

IM olanzapine is a sterile lyophilized parenteral product, which must be reconstituted prior to use. Based on the extensive clinical experience with oral olanzapine, a very important part of the biopharmaceutics characterization includes a comparison of the pharmacokinetics of olanzapine when administered orally versus intramuscularly. The results of carefully planned clinical pharmacology studies identified pharmacokinetic similarities and differences that arose because of the route of administration.

Fundamental pharmacokinetic characteristics of olanzapine such as half-life, plasma clearance, and the volume of distribution are not significantly affected by the route of administration (Table 3). The most obvious pharmacokinetic differences principally involve the rate of absorption after administration. The rate of absorption is much more rapid after the administration of an IM dose. The faster rate of absorption produces a higher maximum plasma concentration of olanzapine that occurs more quickly after IM injection compared with oral administration (Figure 1).

Table 3. Mean and Standard Deviation of Pharmacokinetic Parameters Comparing the Fundamental Pharmacokinetic Characteristics for Intramuscularly and Orally Administered Olanzapine

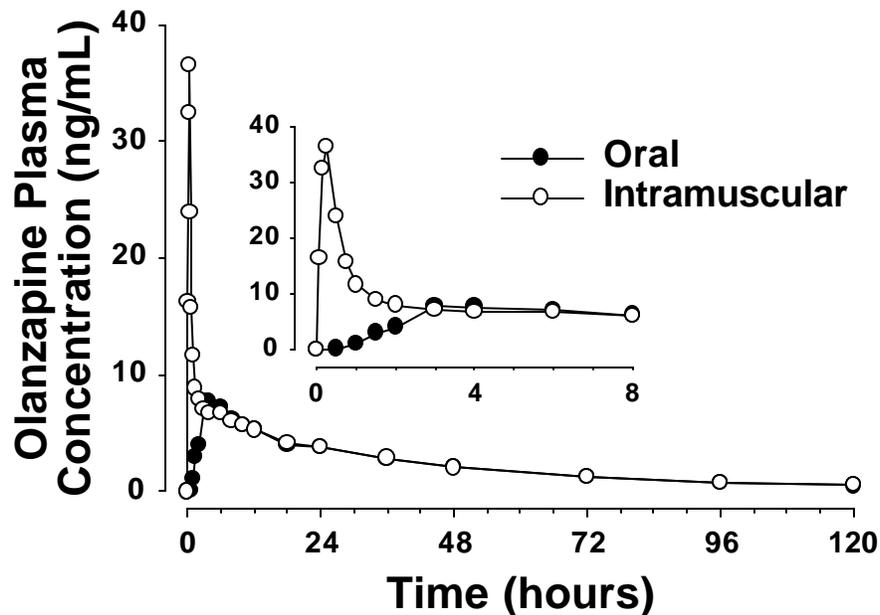
Parameter	2 mg IM	4 mg IM	5 mg Oral	10 mg Oral
	n=22 ^a	n=15 ^b	n=9	n=6
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ng/mL)	6.93 ± 2.92	20.2 ± 9.51	4.54 ± 1.43	13.6 ± 3.92
T_{max} (hr)	0.35 ± 0.16	0.27 ± 0.12	6.1 ± 2.7	2.92 ± 1.36
t_{1/2} (hr)	37.6 ± 17.3	33.7 ± 11.5	38.5 ± 9.49	29.8 ± 7.16
CL_p/F (L/kg/hr)	0.364 ± 0.137	0.361 ± 0.161	0.427 ± 0.143	0.412 ± 0.164
Vd_{ss}/F (L/kg)	15.8 ± 4.14	14.1 ± 3.67	22.1 ± 7.25	15.6 ± 3.97
MRT (hr)	49.6 ± 23.4	43.5 ± 16.4	53.9 ± 13.1	40.8 ± 10.5

Abbreviations: C_{max}=maximum plasma concentration, T_{max}=observed sampling time of C_{max}, t_{1/2}=apparent terminal elimination half-life, CL_p/F=plasma clearance/bioavailability, Vd_{ss}/F=volume of distribution at steady state/bioavailability, MRT=mean residence time.

^a For mean t_{1/2}, CL_p/F, Vd_{ss}/F, and MRT parameters, n=19.

^b For mean t_{1/2}, CL_p/F, Vd_{ss}/F, and MRT parameters, n=12.

Reference: Study FID-EW-LOAC

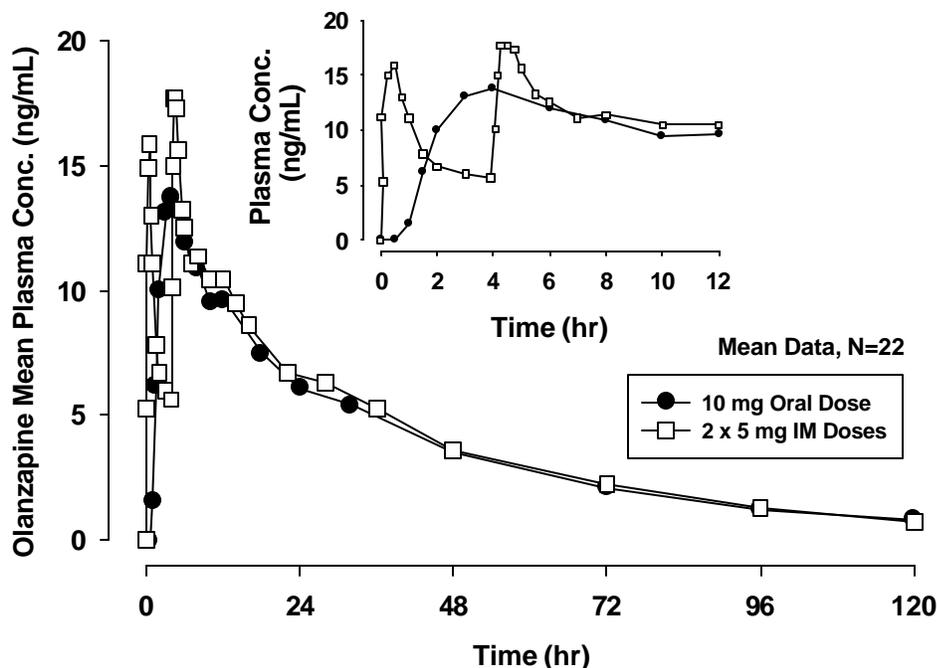


Reference: Study FID-MS-HGIO

Figure 1. Plasma concentration profiles following a 5-mg IM or 5-mg oral dose of olanzapine.

It is important to fully appreciate that the higher olanzapine concentrations following IM administration are transient and that substantial concentration differences are only apparent for 1 to 3 hours after IM injection (Figure 1).

The area under the curve (AUC) achieved after an IM dose is similar to that of an oral administration of the same dose. Further, two IM administrations of a given dose within 4 hours achieve nearly the same exposure profile as the cumulative IM dose administered as a single oral dose (Table 4). This is illustrated in Figure 2, which shows the profile of two 5-mg IM doses given 4 hours apart versus a 10-mg oral dose of olanzapine.



Reference: Study F1D-EW-LOAW

Figure 2. Mean olanzapine plasma concentrations following administration of one 10-mg dose orally or two 5-mg doses given intramuscularly 4 hours apart.

Table 4. Mean and Range of Olanzapine Pharmacokinetic Variables for Subjects Who Received a Single Dose of Olanzapine as 10 mg Orally Versus 10 mg Intramuscularly, Administered as Two 5-mg Doses 4 hours Apart

Pharmacokinetic Variable N=22 male subjects ^a	(units)	Orally-Administered Olanzapine 10 mg		Intramuscularly-Administered Olanzapine 2x5mg 4 hrs Apart	
		Mean	(range)	Mean	(range)
C_{max}	(ng/mL)	15.1	(6.6 to 22.4)	23.7	(13.1 to 43.2)
AUC_{0-t}	(ng×hr/mL)	462	(265 to 725)	487	(334 to 706)
$AUC_{0-\infty}$	(ng×hr/mL)	499	(287 to 838)	522	(353 to 792)
CL_p	(L/hr)	22.1	(11.9 to 34.8)	20.2	(12.6 to 28.3)
$t_{1/2}$	(hr)	31.0	(20.0 to 44.2)	30.4	(20.4 to 39.1)
Vd_{β}	(L/kg)	12.2	(7.4 to 23.5)	11.1	(7.3 to 16.3)

Abbreviations: C_{max} =maximum plasma concentration, AUC_{0-t} =area under the curve from time 0 to time of last concentration above BQL, BQL=below quantitation limit of assay, $AUC_{0-\infty}$, CL_p =plasma clearance, $t_{1/2}$ =apparent terminal elimination half-life, Vd_{β} =apparent volume of distribution.

^a Of 24 subjects enrolled, 22 completed the study.

Reference: Study F1D-EW-LOAW

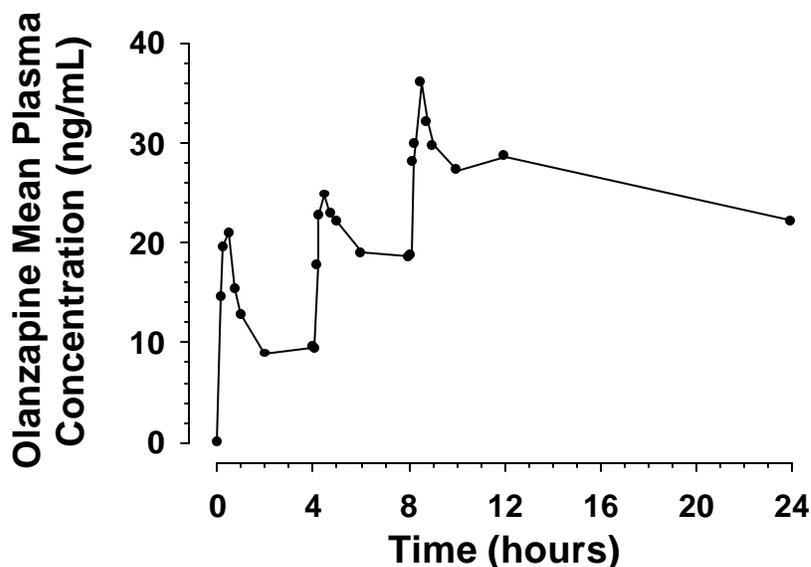
The maximum doses of IM olanzapine recommended in the proposed labeling are (1) single injections of 10 mg and (2) up to three 10 mg injections within 24 hours. To support the proposed labeling recommendations, data from a clinical study (N=43 non-agitated patients with schizophrenia) were collected to evaluate the safety (N=43) and pharmacokinetic characteristics (N=24) of up to three consecutive 10 mg injections given approximately 4-hours apart. This regimen was safe and well tolerated, and the pharmacokinetic characteristics (Table 5) were similar to those after a single dose. Consistent and predictable from the half-life of olanzapine, the C_{max} and AUC increased slightly for each consecutive dose (Figure 3). The average C_{max} for Dose 1 was 27.1 ng/mL, for Dose 2 was 29.5 ng/mL, and for Dose 3 was 41.5 ng/mL. Correspondingly, the average AUC for Dose 1 was 45.2 ng×hr/mL, for Dose 2 was 79.5 ng×hr/mL, and for Dose 3 was 115 ng×hr/mL. Nonetheless, all measured concentrations of olanzapine were less than 100 ng/mL (overall highest C_{max} was 93.5 ng/mL). Thus, measured olanzapine plasma concentrations following up to three 10 mg IM injections were all within the range of observed steady-state olanzapine plasma concentrations that have been maintained for periods of acute and chronic treatment by administration of recommended daily oral doses of olanzapine (i.e., 5 to 20 mg/day).

Table 5. Pharmacokinetic Parameter Values for IM Olanzapine after Two or Three 10 mg Injections

	$t_{1/2}$ (hr)	Cl_p/F (L/hr)	V_{1z}/F (L/kg)
Mean	29.5	22.9	11.2
SD	5.81	7.25	2.76
Minimum	20.1	10.6	7.83
Maximum	42.9	34.7	16.9
CV%	19.7	31.6	24.6
N^a	24	24	24

Abbreviations: SD=standard deviation, CV%=coefficient of variation ([standard deviation/mean] x 100), N=number of subjects.

^a 20 patients received three injections, and four patients received two injections of IM olanzapine.



Reference: Study F1D-MC-HGJA

Figure 3. Mean olanzapine plasma concentrations for 20 patients who received three injections of 10 mg IM olanzapine during a 24-hour period.

Importantly, a similar metabolite profile for olanzapine was observed following oral and IM olanzapine administration. The profile was qualitatively identical and quantitatively very similar after either IM or oral administration. No new metabolites were identified after IM administration.

The key pharmacokinetic characteristics of intramuscularly-administered olanzapine, which have been compared with oral administration, can be summarized as follows:

- Fundamental pharmacokinetic characteristics such as half-life, plasma clearance, and volume of distribution are similar when olanzapine is administered either orally or by IM injection. Nevertheless, the plasma concentration-time profiles differ after oral or IM injection due to a faster rate of absorption after IM administration.
- Data from a clinical pharmacology study indicate that IM administration of 5 mg olanzapine produces a C_{max} that is, on average, about 5-fold higher than the C_{max} produced when the same dose is administered orally. In addition, the C_{max} occurs earlier after IM injection compared with oral dosing.
- The AUC achieved after an IM dose is similar to that of an oral administration of the same dose.
- As with oral use, C_{max} and the area under the curve after IM administration are directly proportional to the dose administered.

- Plasma concentrations of olanzapine following the maximum cumulative recommended dose of three 10 mg injections given within a 24 hour period were consistent and predictable from the half-life of olanzapine, and were within the range of olanzapine concentrations achieved at steady state for recommended doses of orally-administered olanzapine.
- The metabolic profiles following IM and oral use are quantitatively similar and qualitatively identical.

4. Clinical Methodology and Rationale

There is no regulatory precedent for the development of an IM atypical antipsychotic for the control of agitation across different patient populations. Accordingly, the design of the IM olanzapine clinical development plan necessitated careful consideration of the key design features. Further, it was necessary to ensure that the clinical study designs: (1) facilitated the collection of appropriate safety and efficacy data to support registration, and (2) were representative of actual clinical use. This section summarizes the key considerations and rationale underlying the following key design aspects of the four IM olanzapine pivotal clinical studies:

- efficacy measures for assessing agitation
- patient populations
- study duration
- active comparators

4.1. Efficacy Measures for Assessing Agitation

During the planning of the clinical development for IM olanzapine, Lilly conducted an extensive literature review and identified 50 clinical studies of agitation to select a scale for the assessment of agitation (Appendix 1). Lilly also consulted extensively with academic and clinical expert psychiatrists from Europe, South Africa, Australia, the United States, and Canada. It became apparent from the review of the literature as well as the consultations with consultants that there is no single scale recognized by the field as the “gold standard” scale for the assessment of agitation. However, several suitable scales that had been used in previous clinical studies of agitation were identified. Based on the absence of a single "gold standard" scale and the similarities among the scales used in previous studies of agitation, Lilly chose the approach of defining a battery of scales for measuring agitation in the four IM olanzapine pivotal efficacy and safety studies. The inclusion of a battery of scales in each of the four pivotal studies offered the advantage of providing a broader and more robust measure of agitation compared with relying solely on a single scale. As discussed below, the battery of scales used in the pivotal IM olanzapine studies included the PANSS Excited Component, the Corrigan Agitated Behavior Scale, and the Cohen-Mansfield Agitation Inventory. An additional scale developed by Eli Lilly and Company, the Agitation-Calmness Evaluation Scale (ACES), was also included to evaluate whether or not a reduction in agitation is associated with excessive sedation.

4.1.1. PANSS Excited Component

The PANSS Excited Component was selected as the primary efficacy measure for each of the four pivotal studies and includes the items:

- poor impulse control
- tension
- hostility
- uncooperativeness
- excitement

It was derived by factor analysis from the PANSS by the scale originators (Kay et al. 1987). These five items represent the core psychiatric symptoms prevalent in other scales designed to assess agitation (Appendix 1).

The numeric values of the PANSS Excited Component are based on the 1 to 7 scoring system of severity:

- 1 = absent
- 2 = minimal
- 3 = mild
- 4 = moderate
- 5 = moderate severe
- 6 = severe
- 7 = extreme

The total score for the five items of the PANSS Excited Component could range from 5 through 35.

The PANSS Excited Component was chosen as the primary efficacy measure for the four IM olanzapine pivotal clinical studies because:

- The PANSS Excited Component was derived by factor analysis from the PANSS, a widely used and validated measure with broad recognition, and can be generalized across different patient populations.
- In an extensive review of the literature, core phenomenological features of agitation were identified and these were reflected in the items of the PANSS Excited Component (Appendix 1).
- Data from agitated and non-agitated patients with schizophrenia who had participated in a registration trial of oral olanzapine (HG AJ, n=1996) provided confirmatory validation of the PANSS Excited Component. It met all of the criteria established *a priori* in the validation plan for internal consistency, validity (construct and discriminant), responsiveness and reliability.

- It is rated by clinician observation as opposed to requiring the patient's verbal response, which contributes to its utility in a clinical trial in agitated patients. This observation rating allows data to be collected from all patients, even if patients are uncooperative.
- Ratings can be completed rapidly which allows it to be administered frequently. This was important in order to assess the onset of action of IM olanzapine.

4.1.2. Agitation-Calmness Evaluation Scale

The ACES was used as an additional efficacy measure in all four pivotal studies. The scale was designed to differentiate between the agitated, calm, and sleep states by utilizing a specially developed 9-point scale:

- 1 = Marked Agitation
- 2 = Moderate Agitation
- 3 = Mild Agitation
- 4 = Normal
- 5 = Mild Calmness
- 6 = Moderate Calmness
- 7 = Marked Calmness
- 8 = Deep Sleep
- 9 = Unarousable

Scores could range from a single score of 1 to 9.

4.1.3. Corrigan Agitated Behavior Scale

The Corrigan Agitated Behavior Scale is a validated instrument (Corrigan 1987) and has been used previously to assess agitation in patients with mania, psychoactive substance abuse, psychosis (not otherwise specified), schizophrenia and schizophreniform disorder (Battaglia 1997). For the IM olanzapine clinical studies, the Corrigan Agitated Behavior Scale was included as an additional efficacy measure in the two studies in agitated patients with schizophrenia, and in the one study in agitated patients with mania. It is a 14-item scale that required ratings of the degree to which specific behaviors were observed:

- 1 = absent
- 2 = present to a slight degree
- 3 = present to a moderate degree

4 = present to an extreme degree

Scores could range from 14 to 56.

4.1.4. Cohen-Mansfield Agitation Inventory

The Cohen-Mansfield Agitation Inventory is a validated instrument designed to assess manifestations of agitated behaviors in the elderly (Cohen-Mansfield 1989; Finkel 1992). It is widely used in dementia patient populations, as both a research and a clinical assessment tool (Cohen-Mansfield 1992). The Cohen-Mansfield Agitation Inventory is a questionnaire consisting of 30 agitated behaviors, with scoring based on the frequency of those behaviors occurring over periods of time ranging from an hour to a week. For use in the agitation in dementia study, the Cohen-Mansfield Agitation Inventory was adapted based on expert advice for use in shortened, more frequent observation periods. This adaptation required each behavior to be assessed as either present or absent (score of either 0 or 1), rather than assessed at a frequency score ranging from 1 to 7. With this modified scoring, total scores of the adapted Cohen-Mansfield Agitation Inventory could range from 0 to 30.

4.1.5. Efficacy Measures- Training and Reliability

All investigators underwent training on the PANSS Excited Component, ACES, Corrigan Agitated Behavior Scale, and Cohen-Mansfield Agitation Inventory. The training included videotapes that provided a series of simulated patient scenarios/interactions for the investigators to observe and rate, followed by a review and discussion of the results. Investigators were tested and had to score within a pre-defined range or be re-trained to be certified to participate as raters in the pivotal studies.

4.2. Patient Populations

The criteria used to select the disease states for study were:

- agitation commonly occurs in the disease state and poses a need for intervention
- agitation is frequently treated with IM medication during the course of the disease

Three patient populations were chosen for study based on these criteria: schizophrenia, bipolar mania, and dementia. These conditions represent the three most common neuropsychiatric conditions where IM antipsychotic medications are used. Further, they included both psychotic and nonpsychotic patients, patients with varying degrees of agitation from moderate to severe, a wide range of ages from young adult to elderly patients, and underlying disease states with different pathophysiologies (i.e., neurodegenerative and non-neurodegenerative). Although each of these three patient populations present with agitation, with a common symptom presentation and similar

treatment approaches short-term, the diseases are clearly different in their long-term course and treatment.

4.3. Study Duration

Study duration in each of the four pivotal studies for the injectable treatment period was 24 hours as IM olanzapine is intended for short-term use. When continuation of antipsychotic treatment is clinically indicated, IM medications are typically discontinued and replaced by oral antipsychotic therapy as soon as practicable. Therefore, one of the studies in agitated patients with schizophrenia included a 4-day oral transition period following the 24-hour injectable period of the study.

4.4. Active Comparators

Each of the four pivotal studies was placebo-controlled.

The two pivotal studies in agitated patients with schizophrenia also included an IM haloperidol active comparator, which is the most frequently used IM antipsychotic for the treatment of acute agitation.

The two pivotal studies in agitated patients with bipolar mania and dementia included an IM lorazepam active comparator because IM benzodiazepines are also frequently used in controlling agitated patients and are used as an alternative to IM antipsychotics.

4.4.1. Active Comparator Dose Selection

In choosing the doses of IM haloperidol and IM lorazepam and their frequency of administration in the pivotal clinical studies, it was critical neither to provide an efficacy advantage to IM olanzapine by choosing too low a dose of an active comparator nor to provide a safety advantage by choosing too high a dose.

The dose of 7.5 mg of IM haloperidol was chosen based on the literature (Reschke 1974; Anderson 1976; Neborsky 1981; Levy 1996) and clinical experience indicating that both 5 mg and 10 mg doses are commonly used to treat acute agitation and thus 7.5 mg represents a compromise between these doses. In addition, a dose-response analysis suggests that escalating doses up to 7.5 mg result in incremental enhancement of efficacy but doses that exceed 7.5 mg to 10 mg do not appreciably increase immediate efficacy for most patients but only cause additional side effects (Baldessarini 1998).

The doses of IM lorazepam were chosen based on the literature (Saltzman 1991; Battaglia 1997; Foster 1997; Bieniek 1998) and consultation with experts.

5. Study Designs

The study designs for the four IM olanzapine pivotal efficacy and safety studies in agitated patients with schizophrenia, bipolar mania, and dementia are summarized in the sections below (Figures 4 to 7).

5.1. Agitation in Schizophrenia – Dose Ranging

The dose ranging study in agitated patients with schizophrenia was a multi-center, double-blind, active comparator (IM haloperidol) and placebo controlled study in 270 patients randomized to injections of 2.5, 5, 7.5 or 10 mg IM olanzapine, 7.5 mg IM haloperidol, or IM placebo in a 1:1:1:1:1 ratio. Each patient received 1 to 3 injections over 24 hours, to a maximum cumulative dose of 30 mg for IM olanzapine, or 22.5 mg for IM haloperidol.

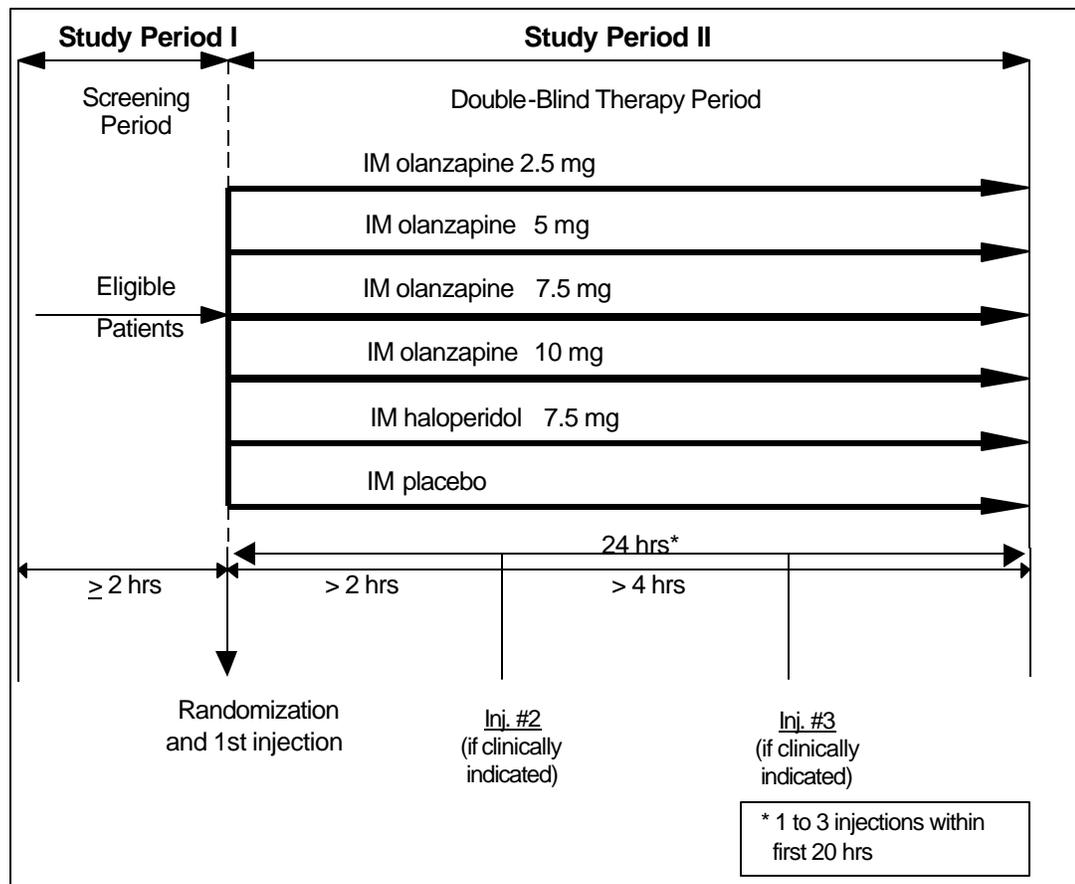


Figure 4. Agitation in Schizophrenia—Dose Ranging Study Design

5.2. Agitation in Schizophrenia – Fixed-Dose, Transition to Oral

The fixed-dose study in agitated patients with schizophrenia was a multi-center, double-blind, active comparator (IM haloperidol) and placebo controlled study in 311 patients randomized to injections of 10 mg IM olanzapine, 7.5 mg IM haloperidol or IM placebo, in a 2:2:1 ratio. Each patient received 1 to 3 injections over 24 hours, to a maximum cumulative dose of 30 mg for IM olanzapine, or 22.5 mg for IM haloperidol. Patients then entered a 4-day oral treatment period where patients initially assigned to IM olanzapine or IM placebo received oral olanzapine (5 to 20 mg per day) and patients initially assigned to IM haloperidol received oral haloperidol.

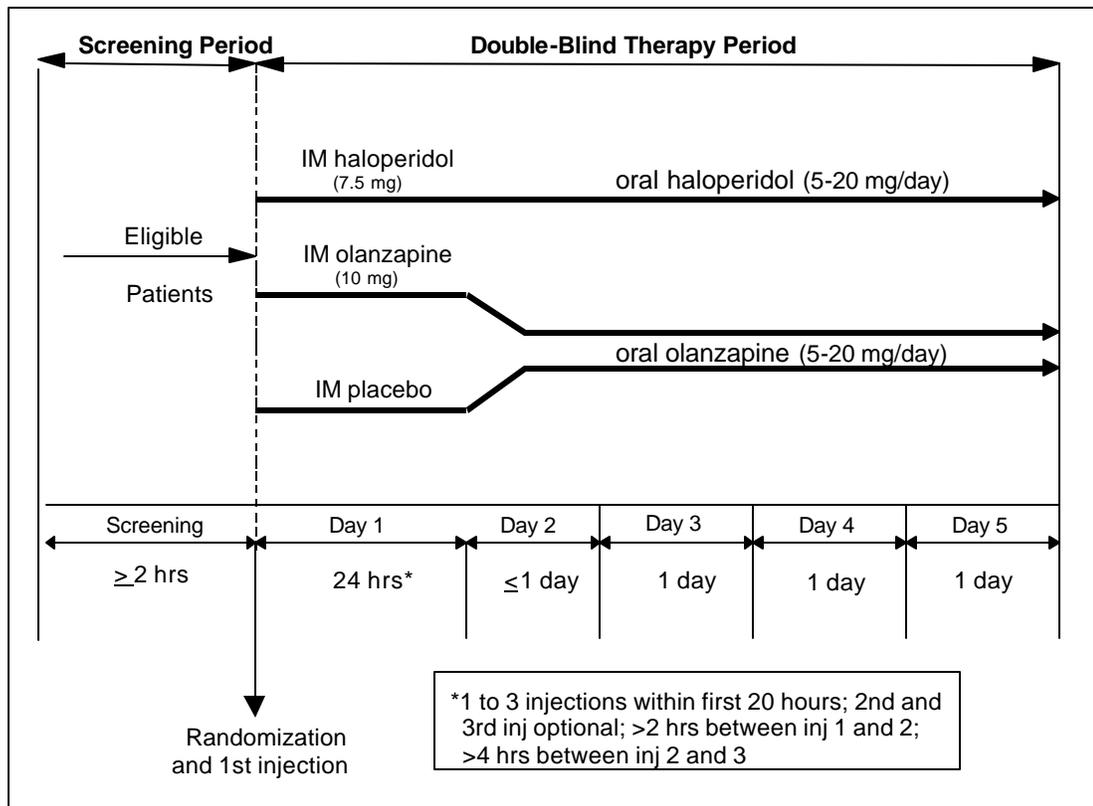


Figure 5. Agitation in Schizophrenia Study Design

5.3. Agitation in Bipolar Mania

The study in agitated patients with bipolar mania was a multi-center, double-blind, active comparator (IM lorazepam) and placebo controlled study in 201 patients. Patients were randomized to 1 to 3 injections over 24 hours of IM olanzapine (10 mg, 10 mg, and 5 mg), IM lorazepam (2 mg, 2 mg, and 1 mg), or IM placebo (third injection, if administered, was IM olanzapine 10 mg) in a 2:1:1 ratio. The maximum possible cumulative dose was 25 mg for IM olanzapine, or 5 mg for IM lorazepam.

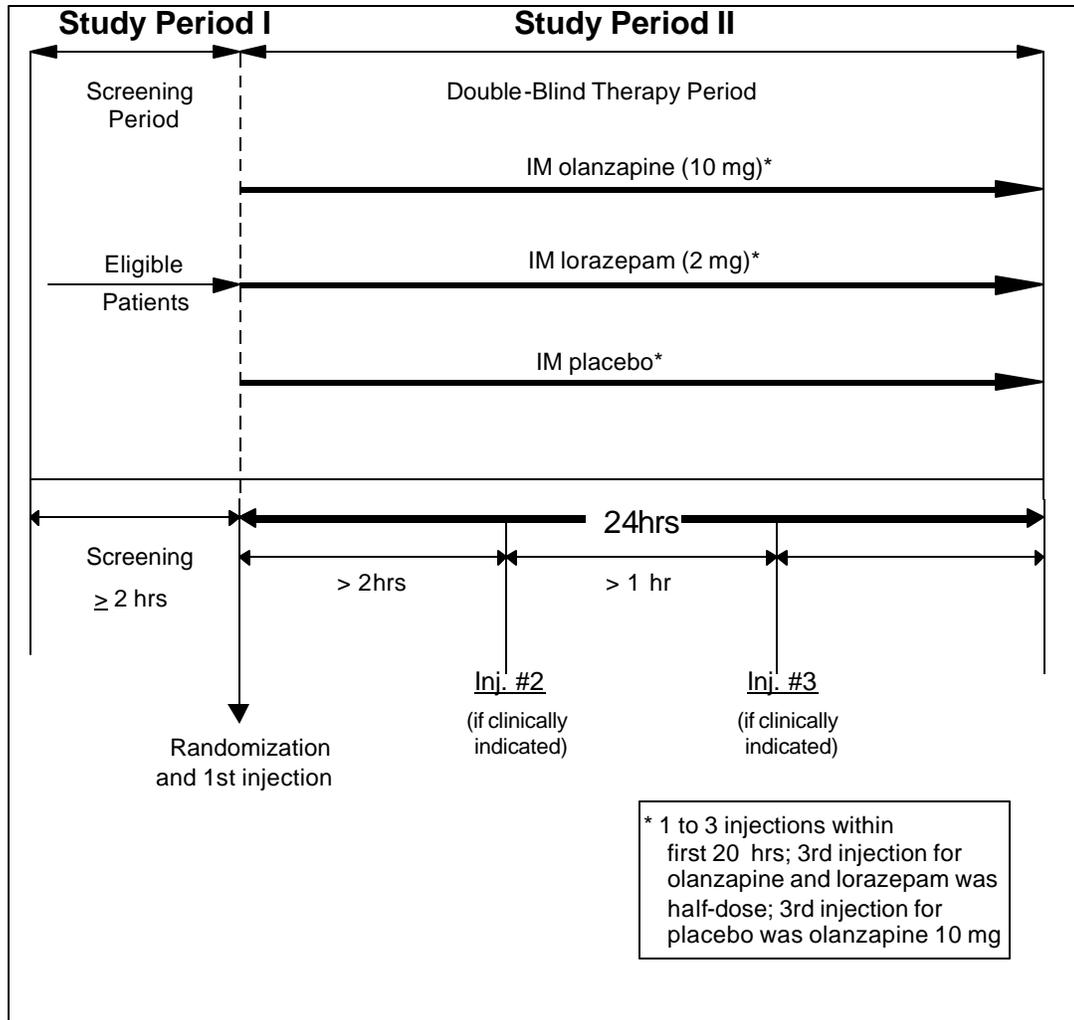


Figure 6. Agitation in Bipolar Mania Study Design

5.4. Agitation in Dementia

The study in agitated patients with dementia was a multi-center, double-blind, active comparator (IM lorazepam) and placebo controlled study in 272 patients. Patients were randomized to 1 to 3 injections over 24 hours of IM olanzapine 5 mg (5, 5, and 2.5 mg), IM olanzapine 2.5 mg (2.5, 2.5, and 1.25 mg), IM lorazepam 1 mg (1, 1, or 0.5 mg) or IM placebo (if administered, third injection was 5 mg IM olanzapine), in a 1:1:1:1 ratio. The maximum possible cumulative dose was 12.5 mg for IM olanzapine or 2.5 mg for IM lorazepam.

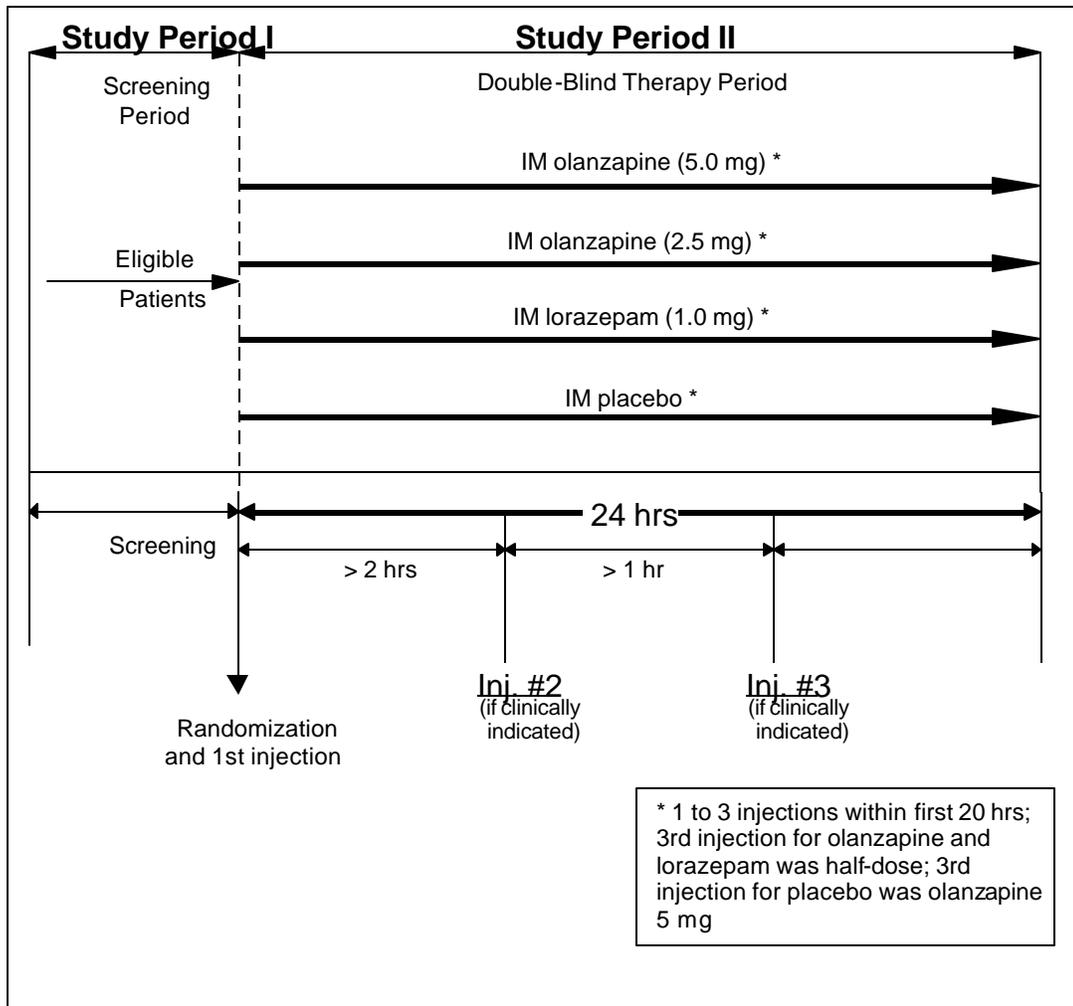


Figure 7. Agitation in Patients with Dementia Study Design

6. Patient Characteristics

This section summarizes the key entry criteria and the patient characteristics at baseline for the four IM olanzapine pivotal studies.

6.1. Agitation Criteria

All patients entered into the four pivotal studies were required to meet the following agitation criteria:

- A minimum total score of ≥ 14 on the five items comprising the PANSS Excited Component (poor impulse control, tension, hostility, uncooperativeness, and excitement) and at least one individual item score ≥ 4 using the 1 to 7 scoring system
- and
- Judged to be clinically agitated and to be appropriate candidates for IM treatment by the investigator

6.2. Diagnostic Criteria

In the two pivotal studies for agitated patients with schizophrenia, patients must have met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. In the pivotal study for agitated patients with bipolar mania, patients must have met DSM-IV criteria (confirmed through structured clinical interview [SCID]) for bipolar I disorder and currently displaying an acute manic or mixed episode. In the pivotal study for agitated patients with dementia, patients must have met DSM-IV or National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's dementia, vascular dementia, or mixed dementia. Patients were excluded if they had any other diagnosis of a serious neurological condition other than Alzheimer's disease or vascular dementia (including Parkinson's disease, Lewy body disease, seizure disorder, intracranial space-occupying lesion, hydrocephalus, or history of significant head trauma) that could contribute to psychosis or dementia.

6.3. General Entry Criteria

All patients must have been inpatients at study entry. Key exclusion criteria included:

- The agitation was considered caused by substance abuse.
- Treatment with benzodiazepines within 4 hours prior to the first IM study drug administration.
- Treatment with an oral or short-acting IM antipsychotic within 2 hours (schizophrenia studies) or 4 hours (bipolar and dementia studies) prior to study drug administration.

- Treatment with an injectable depot neuroleptic or injectable zuclopenthixol acetate within one injection interval prior to study drug administration.
- Treatment with psychostimulants or reserpine within 1 week prior to study drug administration.
- Laboratory or ECG abnormalities considered clinically significant by the investigator or qualified designee that would have clinical implications for the patient's participation in this study.
- Serious, unstable illnesses including current jaundice, hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease such that death is anticipated within 1 year or intensive care unit hospitalization for the disease is anticipated within 6 months.

6.4. Baseline Characteristics

6.4.1. Demographics

Table 6 shows the demographics for each of the four pivotal studies in agitated patients.

Table 6. Agitated Patient Study Demographics with Mean Baseline and Upper Limit PANSS Excited Component Scores

Demographic ^a	Schizophrenia-Dosing Study (N=270)	Schizophrenia Study (N=311)	Bipolar Mania Study (N=201)	Dementia Study (N=272)
<u>Age:</u>				
Mean	36	38	39	77
Minimum	18	18	18	54
Maximum	73	72	79	97
<u>Sex: n (%)</u>				
Males	155 (57.4)	204 (65.6)	107 (53.2)	106 (39.0)
Females	115 (42.6)	107 (34.4)	94 (46.8)	166 (61.0)
<u>Origin: n (%)</u>				
Caucasian	178 (65.9)	226 (72.7)	146 (72.6)	251 (92.3)
African Descent	65 (24.1)	59 (19.0)	32 (15.9)	16 (5.9)
Hispanic	0	17 (5.5)	12 (6.0)	4 (1.5)
Asian	4 (1.5)	3 (1.0)	8 (4.0)	0
Other	23 (8.5)	6 (1.9)	3 (1.5)	1 (0.4)
<u>PANSS Excited Component</u>				
Mean Baseline	19.01	18.28	17.75	19.75
Upper Limit	32.00	29.00	30.00	34.00

a There were no statistical differences between treatment groups in baseline measures for the four pivotal studies.

Few patients discontinued during the four pivotal studies, with the overall completion rates of the 24-hour IM treatment period ranging from 90.4% to 99.3%.

6.4.2. Level of Agitation

The patients enrolled in the studies were representative of moderately to severely agitated patients (Figures 8 to 11). Baseline scores covered the full spectrum of agitation with scores not clustered around the minimum required score of 14. Baseline PANSS Excited scores reached as high as 34 with 54% (n=1054) of patients across the four studies having at least one item score of 5 (moderately severe) on the PANSS Excited Component items.

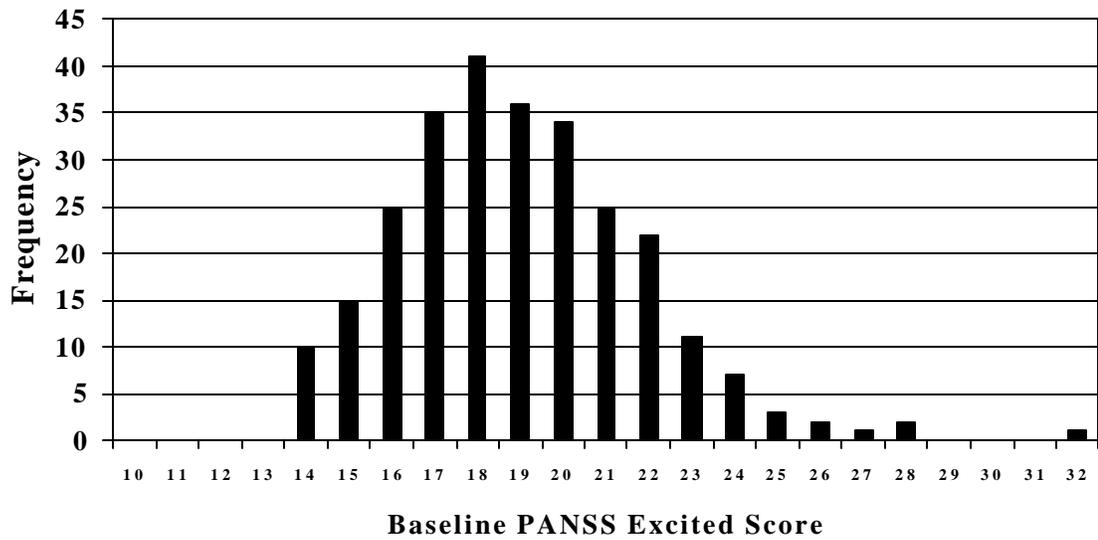


Figure 8. Frequency Distribution of Baseline PANSS Excited Component Agitation in Schizophrenia—Dose Ranging Study

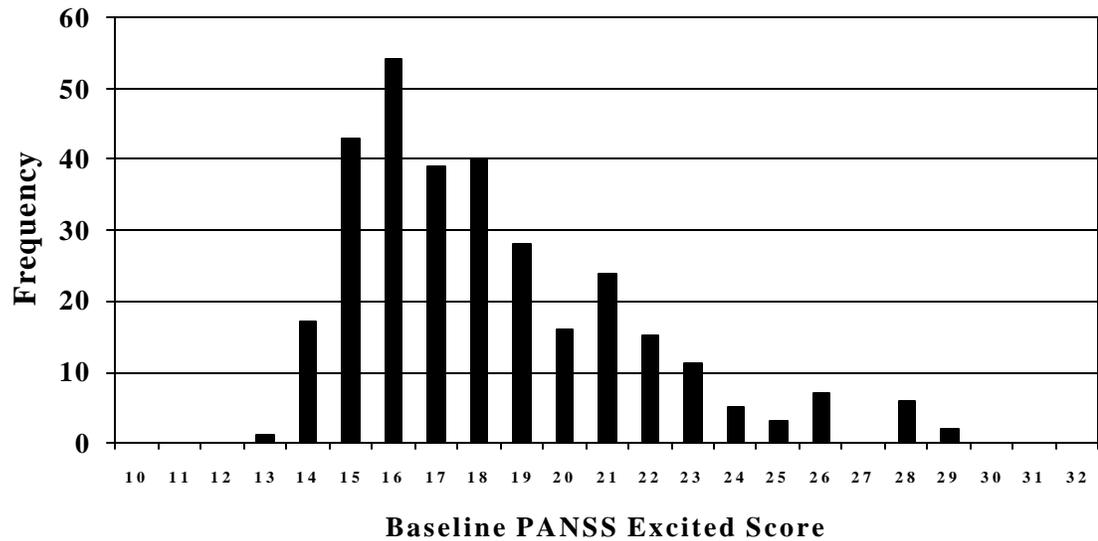


Figure 9. Frequency Distribution of Baseline PANSS Excited Component Agitation in Schizophrenia Study

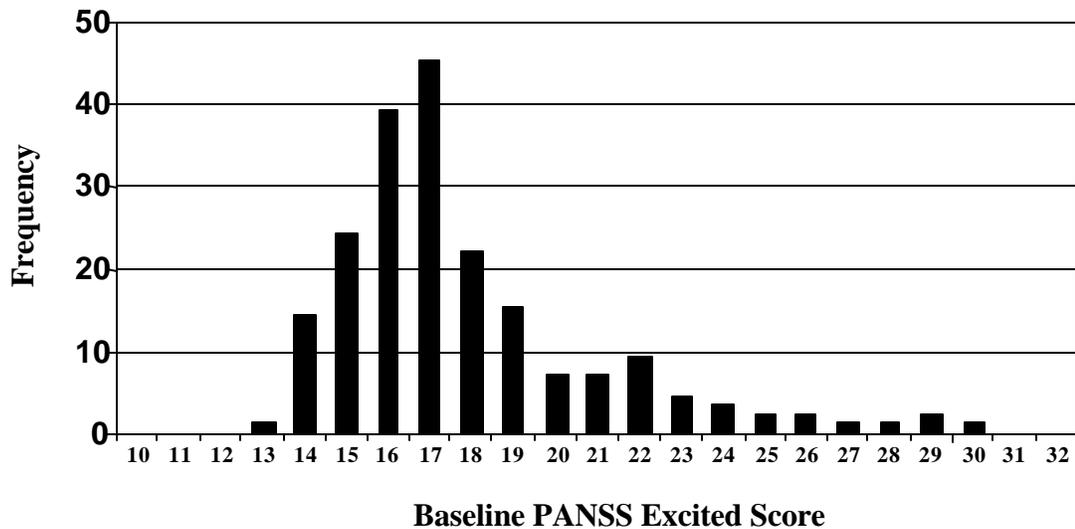


Figure 10. Frequency Distribution of Baseline PANSS Excited Component Agitation in Bipolar Mania Study

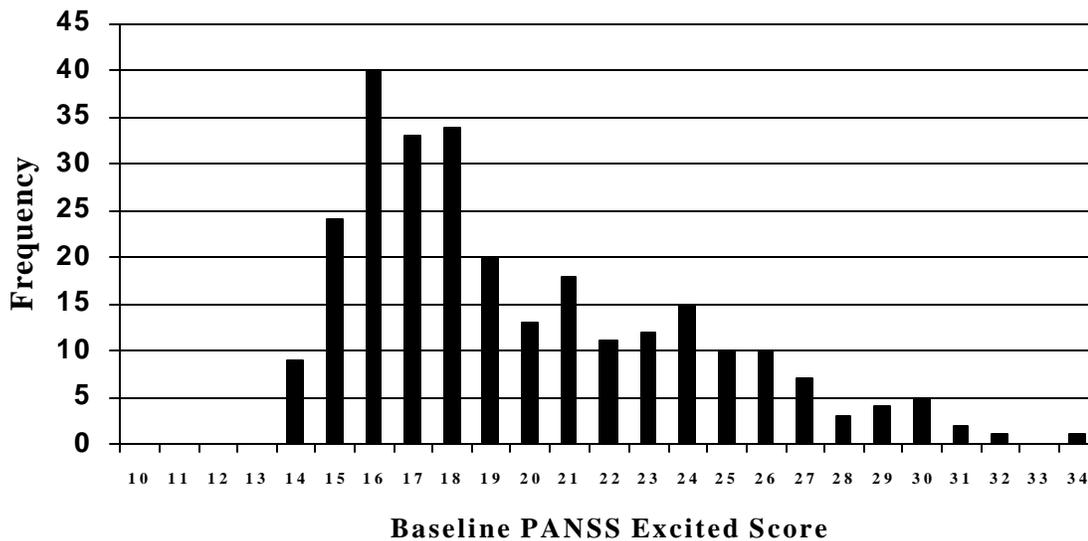


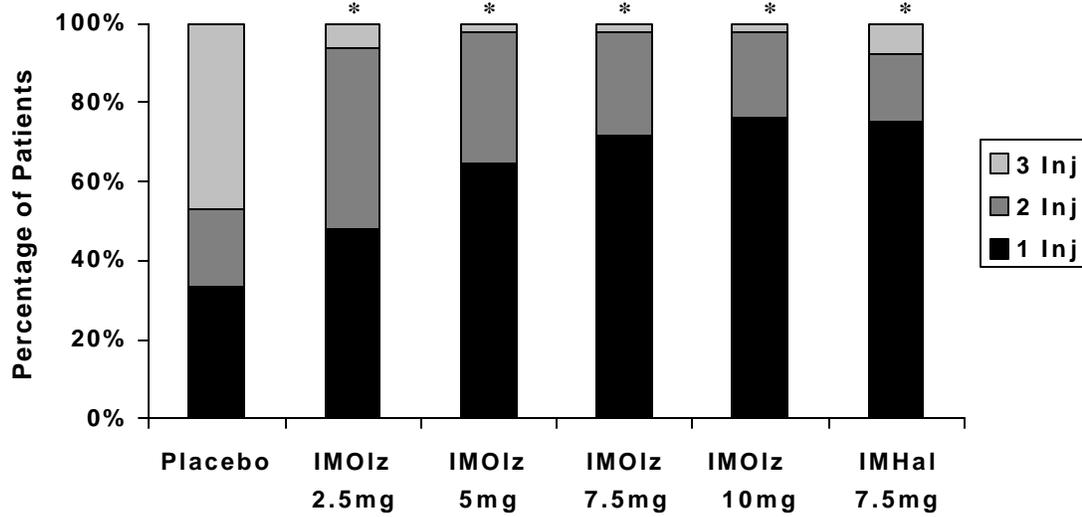
Figure 11. Frequency Distribution of Baseline PANSS Excited Component Agitation in Dementia Study

6.5. Injection Frequency

In each of the four pivotal studies the maximum number of injections was three. Consistent with clinical practice, the decision whether to administer a second or third IM injection of study drug was based on the investigator’s judgment. In the agitation in

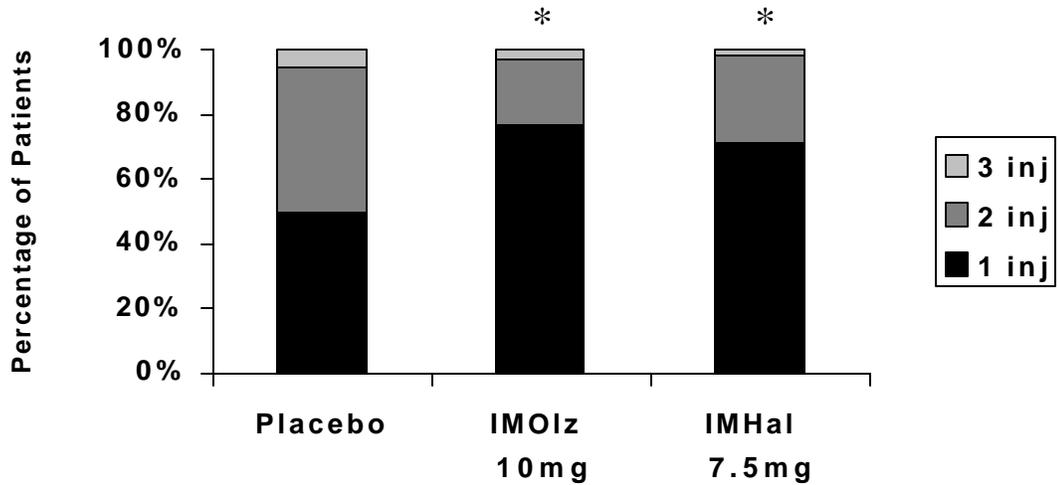
bipolar mania and dementia studies, the placebo group received IM olanzapine as the third injection.

The majority of IM olanzapine-treated agitated patients received either one or two injections in all four pivotal studies. A summary of injection frequency for the pivotal studies is shown in Figures 12 to 15.



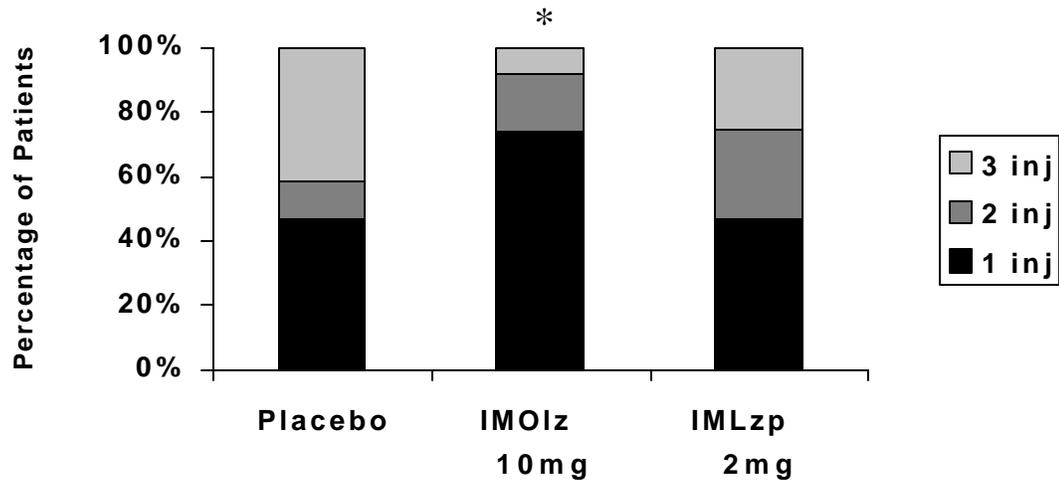
* p<0.05 vs placebo

Figure 12. Number of IM injections During 24 hours Agitation in Schizophrenia Dose-Ranging Study



* p<0.05 vs placebo

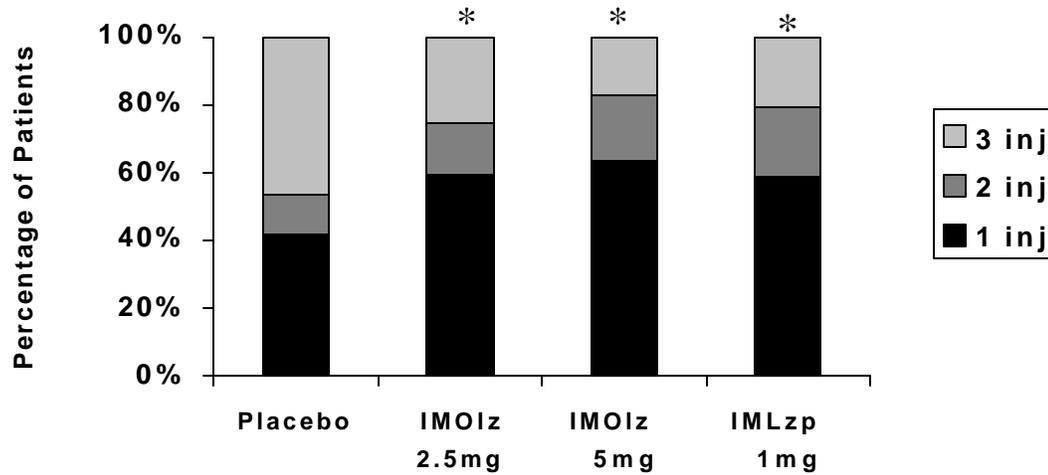
Figure 13. Number of IM injections During 24 hours Agitation in Schizophrenia Study



* p<0.05 vs placebo

The third injection for patients receiving IM olanzapine was IM olanzapine 5 mg and for patients receiving IM lorazepam was IM lorazepam 1 mg. The third injection for patients receiving IM placebo was IM olanzapine 10 mg.

Figure 14. Number of IM injections During 24 hours Agitation in Bipolar Mania Study



* $p < 0.05$ vs placebo

The third injection for patients receiving IM olanzapine 5 mg was IM olanzapine 2.5 mg and for patients receiving IM olanzapine 2.5 mg was IM olanzapine 1.25 mg. The third injection for patients receiving IM lorazepam was IM lorazepam 0.5 mg. The third injection for patients receiving IM placebo was IM olanzapine 5 mg.

Figure 15. Number of IM injections During 24 hours Agitation in Dementia Study

7. Efficacy Results

7.1. Core Efficacy Measures

The results of all four pivotal studies support the efficacy of IM olanzapine in controlling agitation across different patient populations. In all four pivotal studies, the primary efficacy measure of the mean change from baseline to endpoint in the PANSS Excited Component at 2 hours following the first IM injection showed that IM olanzapine was superior to placebo. This finding occurred for all IM olanzapine dose arms (2.5, 5, 7.5, and 10 mg). The additional efficacy measures of agitation yielded similar results. In each of the pivotal studies (agitation in schizophrenia dose ranging, agitation in schizophrenia and agitation in bipolar mania) where the Corrigan Agitated Behavior Scale and the ACES were used, the mean change from baseline to endpoint at 2 hours following the first IM injection for both scales showed that IM olanzapine was superior to placebo. In the agitation in dementia study where the ACES and Cohen-Mansfield Agitation Inventory were used, both scales again showed that IM olanzapine was superior to placebo within at least one of the IM olanzapine dose arms studied.

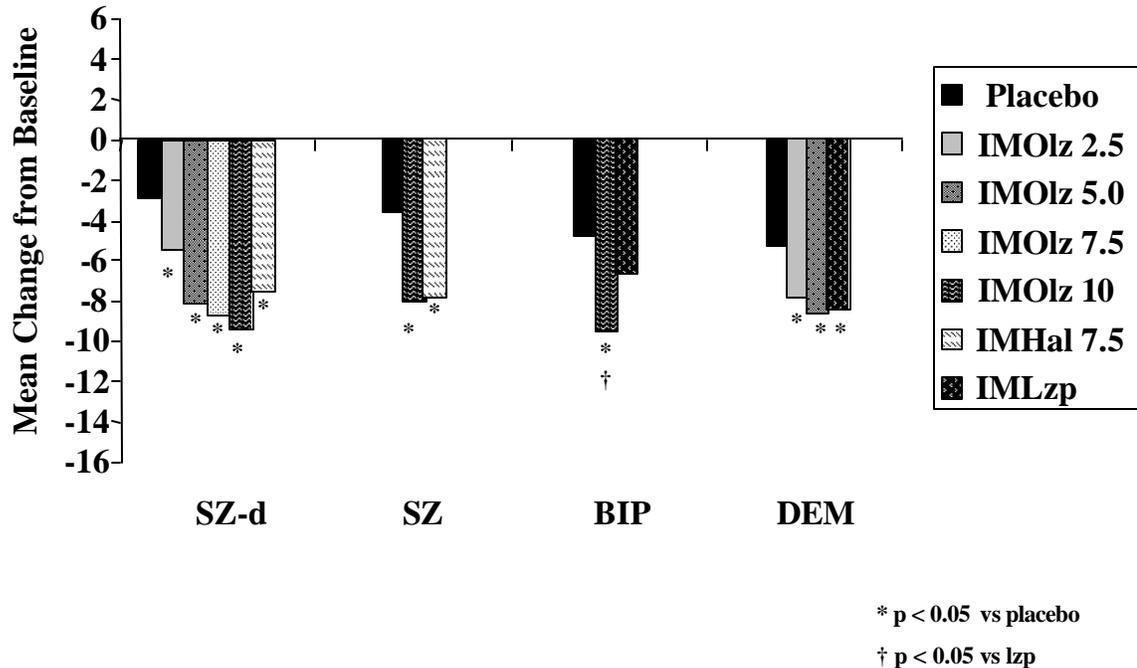
In addition to the primary efficacy data collected at 2 hours following the first IM injection, additional efficacy data were collected at the 24-hour endpoint. These additional results are confounded by a number of factors including 1) the varying number of IM injections given to patients across the treatment groups; 2) the variable time of the optional second and third injections; and 3) the use of benzodiazepine rescue medication in the studies in schizophrenia (note: benzodiazepine rescue medication was not permitted in any of the four pivotal studies prior to the 2-hour time point. In the two studies in agitated patients with schizophrenia, benzodiazepine rescue medication was permitted beginning one hour following the second injection). These confounding factors, however, are representative of standard clinical care for the treatment of agitation. In all four studies, all IM olanzapine dose arms showed superior control of agitation compared with placebo at 24 hours on the PANSS Excited Component.

Efficacy results for the four pivotal studies at the 2-hour time point are summarized in this section for the scales used to assess agitation: PANSS Excited Component, Corrigan Agitated Behavior Scale, ACES, and Cohen-Mansfield Agitation Inventory. The summaries below identify only statistically significant results. In the fixed dose agitation in schizophrenia study, a test of non-inferiority for the PANSS Excited Component was performed. The lower limit of non-inferiority was defined *a priori* as 40% of the observed mean change from baseline to 2 hours after the first injection of IM haloperidol. A lower bound of the one-sided 97.5% confidence interval ≤ 0 but > -3 , the lower limit, indicated no difference between IM olanzapine and IM haloperidol and thus non-inferiority was concluded. In the dose-ranging agitation in schizophrenia study, IM olanzapine doses higher than 2.5 mg were not significantly different from IM haloperidol on the PANSS Excited Component at 2 hours. In the agitation in dementia study, IM

olanzapine doses of 2.5 and 5 mg were not significantly different from IM lorazepam for any agitation measure at 2 hours.

7.1.1. PANSS Excited Component

Figure 16 shows the 2-hour change from baseline to endpoint last observation carried forward (LOCF) in the PANSS Excited Component for the four pivotal studies.



Abbreviations: SZ-d=Agitation in Schizophrenia—Dose Ranging Study, SZ=Agitation in Schizophrenia Study, BIP=Agitation in Bipolar Mania Study, DEM=Agitation in Dementia Study.

**Figure 16. PANSS Excited Component
Mean Change from Baseline to 2 Hours (LOCF)
Following the First IM Injection**

7.1.1.1. Agitation in Schizophrenia—Dose Ranging Study

All the IM olanzapine treatment groups (2.5, 5, 7.5 and 10 mg) demonstrated a significantly greater mean improvement compared with IM placebo ($p=0.010$ for IM olanzapine 2.5 mg, $p<0.001$ for IM olanzapine 5, 7.5, and 10 mg). IM haloperidol was also superior to IM placebo ($p<0.001$).

Using step-down linear contrasts, the minimum effective IM olanzapine dose, as determined by the PANSS Excited Component during the 2 hours following the first IM injection period, was shown statistically to be 2.5 mg. A significant monotonic dose

response relationship was shown to exist across the IM olanzapine dose range (2.5 to 10 mg) used in this study ($p < 0.001$).

Individual treatment group comparisons also revealed significant differences between the IM olanzapine 2.5 mg treatment group and each of the other active treatment groups ($p < 0.05$). Thus, while the IM olanzapine 2.5 mg dose resulted in a significantly greater mean improvement compared with IM placebo, all higher doses of IM olanzapine and also IM haloperidol were superior in last observation carried forward analyses.

7.1.1.2. Agitation in Schizophrenia Study

The IM olanzapine treatment group showed a significantly greater mean improvement in the PANSS Excited Component compared with IM placebo ($p < 0.001$). The IM haloperidol treatment group also showed a significantly greater mean improvement in the PANSS Excited Component compared with IM placebo ($p < 0.001$).

7.1.1.3. Agitation in Bipolar Mania Study

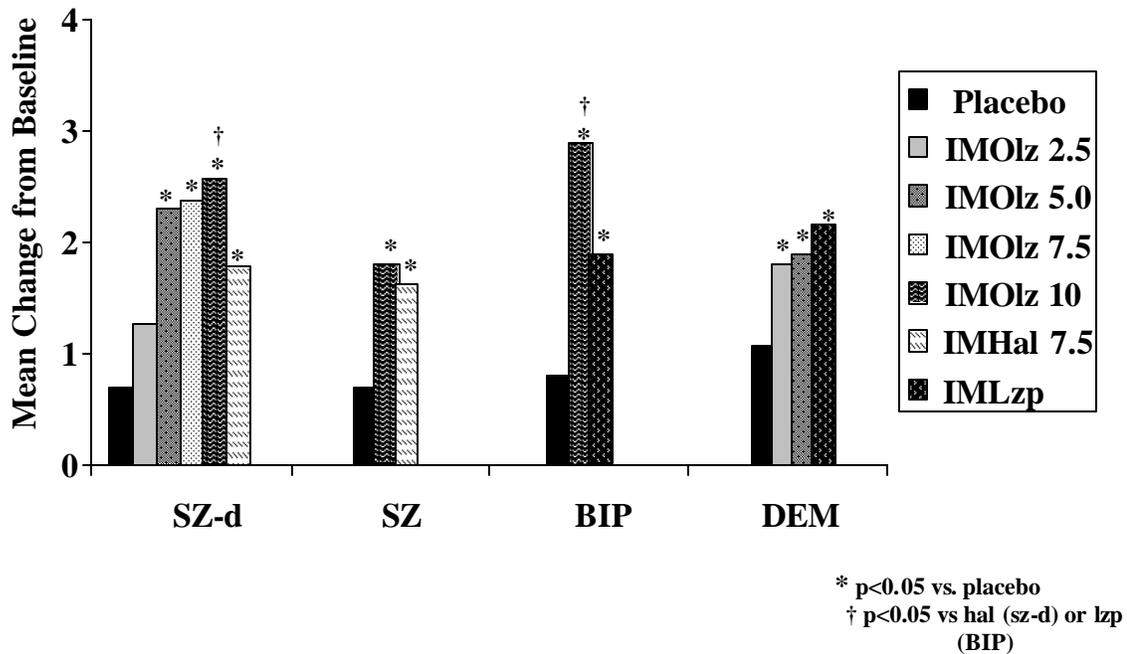
The IM olanzapine treatment group showed a significantly greater mean improvement in the PANSS Excited Component compared with the IM placebo and the IM lorazepam treatment groups ($p < 0.001$ and $p = 0.001$, respectively).

7.1.1.4. Agitation in Dementia Study

Both the IM olanzapine treatment groups (2.5 and 5 mg) demonstrated a significantly greater mean improvement in the PANSS Excited Component compared with IM placebo ($p = 0.004$ for IM olanzapine 5 mg versus IM placebo and $p = 0.024$ for IM olanzapine 2.5 mg versus IM placebo). The IM lorazepam treatment group also showed greater mean improvement in the PANSS Excited Component compared with IM placebo ($p = 0.004$).

7.1.2. Agitation-Calmness Evaluation Scale

Figure 17 shows the 2-hour change from baseline to endpoint (LOCF) in the ACES for the four pivotal studies.



Abbreviations: SZ-d=Agitation in Schizophrenia—Dose Ranging Study, SZ=Agitation in Schizophrenia Study, BIP=Agitation in Bipolar Mania Study, DEM=Agitation in Dementia Study.

**Figure 17. Agitation-Calmness Evaluation Scale
Mean Change from Baseline to 2 Hours (LOCF)
Following the First IM Injection**

7.1.2.1. Agitation in Schizophrenia-Dose Ranging Study

IM olanzapine doses of 5, 7.5 and 10 mg, but not 2.5 mg, showed a significantly greater mean improvement compared with IM placebo ($p=0.064$ for IM olanzapine 2.5 mg, $p<0.001$ for IM olanzapine 5, 7.5, and 10 mg). The difference between the IM haloperidol treatment group and IM placebo was also significant ($p=0.001$). The IM olanzapine 10 mg treatment group had a significantly greater mean improvement than the IM haloperidol treatment group ($p=0.025$). IM olanzapine doses of 5, 7.5, and 10 mg all showed a significantly greater mean improvement compared with IM olanzapine 2.5 mg ($p=0.001$ for IM olanzapine 5 mg, $p<0.001$ for IM olanzapine 7.5, and 10 mg).

7.1.2.2. Agitation in Schizophrenia Study

Both the IM olanzapine and IM haloperidol treatment groups showed a significantly greater mean improvement compared with IM placebo (both $p<0.001$).

7.1.2.3. Agitation in Bipolar Mania Study

Both the IM olanzapine and IM lorazepam treatment groups showed a significantly greater mean improvement compared with IM placebo ($p\leq 0.001$ and $p=0.002$, respectively). Comparisons between the IM olanzapine and IM lorazepam treatment

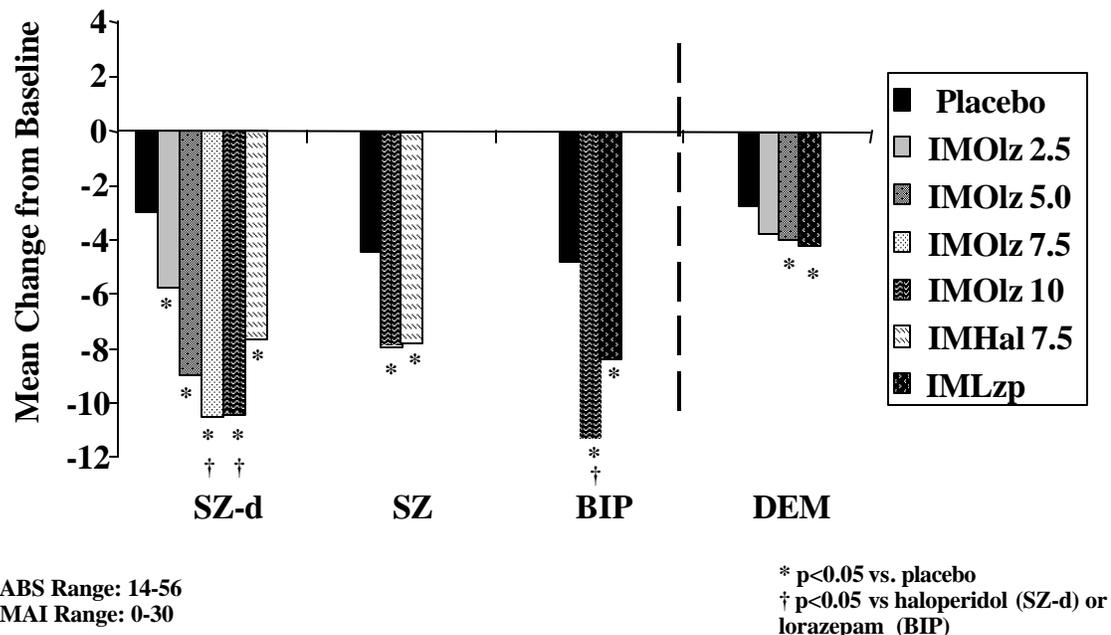
groups showed a significantly greater improvement in the IM olanzapine treatment group (p=0.001).

7.1.2.4. Agitation in Dementia Study

Both the IM olanzapine treatment groups (2.5 mg and 5 mg) and the IM lorazepam treatment group showed a significantly greater mean improvement compared with IM placebo (p=0.013, p=0.006, and p<0.001, respectively).

7.1.3. Corrigan Agitated Behavior Scale / Cohen-Mansfield Agitation Inventory

Figure 18 shows the 2-hour change from baseline to endpoint (LOCF) in the Corrigan Agitated Behavior Scale for the pivotal studies in agitated patients with schizophrenia or bipolar mania, and the Cohen-Mansfield Agitation Inventory for the pivotal study in agitated patients with dementia.



Abbreviations: SZ-d=Agitation in Schizophrenia—Dose Ranging Study, SZ=Agitation in Schizophrenia Study, BIP=Agitation in Bipolar Mania Study, DEM=Agitation in Dementia Study, CABS=Corrigan Agitation Behavior Scale, CMAI=Cohen-Mansfield Agitation Inventory.

**Figure 18. Corrigan Agitation Behavior Scale
Cohen-Mansfield Agitation Inventory
Mean Change from Baseline to 2 Hours (LOCF)
Following the First IM Injection**

7.1.3.1. Agitation in Schizophrenia-Dose Ranging Study

Each of the IM olanzapine treatment groups (2.5, 5, 7.5 and 10 mg) showed a significantly greater mean improvement on the Corrigan Agitated Behavior Scale when

compared with IM placebo ($p=0.012$ for IM olanzapine 2.5 mg, $p<0.001$ for IM olanzapine 5, 7.5, and 10 mg). The difference between the IM haloperidol 7.5 mg treatment group and IM placebo was also significant ($p<0.001$). The IM olanzapine 7.5 and 10 mg treatment groups each demonstrated a significantly greater mean improvement compared with IM haloperidol ($p=0.016$ and $p=0.023$, respectively). IM olanzapine doses of 5, 7.5 and 10 mg all showed a significantly greater mean improvement compared with IM olanzapine 2.5 mg ($p=0.005$ for IM olanzapine 5 mg, $p<0.001$ for IM olanzapine 7.5 and 10 mg).

7.1.3.2. Agitation in Schizophrenia Study

Both the IM olanzapine and IM haloperidol treatment groups showed a significantly greater mean improvement on the Corrigan Agitated Behavior Scale compared with IM placebo ($p<0.001$ and $p<0.001$, respectively).

7.1.3.3. Agitation in Bipolar Mania Study

Both the IM olanzapine and IM lorazepam treatment groups showed a significantly greater mean improvement on the Corrigan Agitated Behavior Scale compared with IM placebo ($p<0.001$ and $p=0.003$, respectively). Comparisons between the IM olanzapine and IM lorazepam treatment groups showed significantly greater improvement in the IM olanzapine treatment group ($p=0.006$).

7.1.3.4. Agitation in Dementia Study

Both the IM olanzapine 5 mg and IM lorazepam treatment groups showed a significantly greater mean improvement compared with IM placebo ($p=0.047$ and $p=0.020$, respectively).

7.2. Onset of Action

The onset of action of IM olanzapine and the active comparators was investigated across all four pivotal studies at various time points ranging from 15 minutes to 2 hours following the first IM injection. For each time point, only those patients who had both a baseline score and a post baseline score at the time point in question were included in that particular time point analysis. However, very little data were missing at any time point across studies. In each study, IM olanzapine was superior on the PANSS Excited Component at the earliest time point measured compared with IM placebo within at least one of the IM dose arms studied. In the two schizophrenia studies and in the mania study, IM olanzapine was also superior at the earliest time point measured compared with IM haloperidol and IM lorazepam within at least one of the IM olanzapine dose arms studied. Also, all doses of IM olanzapine in all studies (with the exception of IM olanzapine 2.5 mg in the agitation in schizophrenia dose ranging study and the agitation in dementia study) were superior to IM placebo at all time points measured. These data support the rapid onset of IM olanzapine in the control of agitation across patient populations.

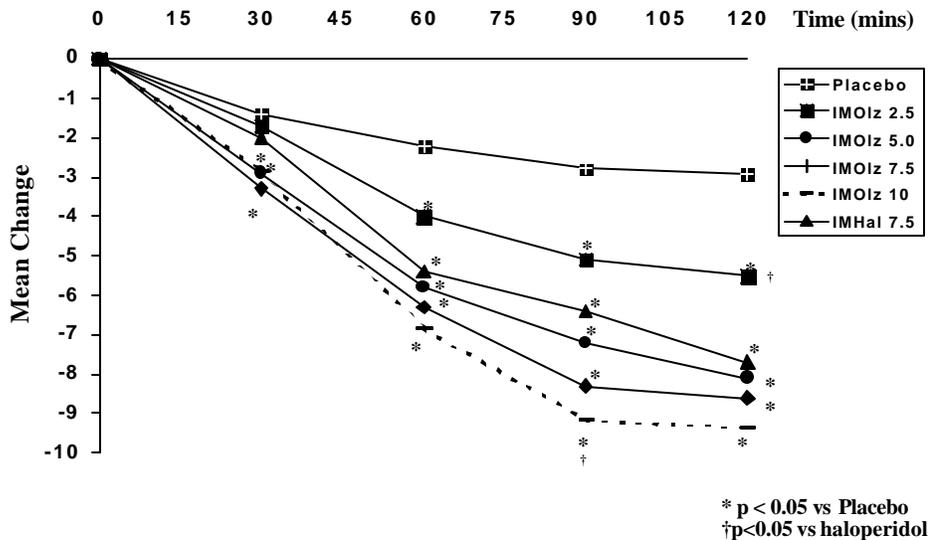
The time point-wise analyses for the primary efficacy measure (PANSS Excited Component) are summarized in the following sections for each of the four pivotal studies.

7.2.1. Agitation in Schizophrenia-Dose Ranging Study

Figure 19 shows the change from baseline to observed score (OC) for time points within the 2 hours following the first IM injection period in the PANSS Excited Component for the agitation in schizophrenia dose ranging study.

There was a significant overall treatment effect at each time point (30, 60, 90, and 120 minutes following the first IM injection). Comparisons among the treatment groups revealed a significant difference at all time points between IM placebo and the IM olanzapine 5, 7.5 and 10 mg treatment groups for the PANSS Excited Component. For IM olanzapine 2.5 mg and IM haloperidol, the significant difference compared with IM placebo was not observed until 60 minutes but was maintained until 120 minutes following the first injection.

The IM olanzapine 5, 7.5, and 10 mg treatment groups showed statistically greater mean improvement than the IM olanzapine 2.5 mg treatment group at 60 minutes which was maintained until 120 minutes ($p < 0.05$). The IM haloperidol treatment group also showed statistically greater mean improvement than IM olanzapine 2.5 mg but this difference did not differ statistically until 120 minutes ($p < 0.036$).



**Figure 19. PANSS Excited Component
Time point-wise Change from Baseline (OC)
Agitation in Schizophrenia—Dose Ranging Study**

7.2.2. Agitation in Schizophrenia Study

Figure 20 shows the change from baseline to observed score for time points within the 2 hours following the first IM injection period in the PANSS Excited Component for the agitation in schizophrenia study.

The IM olanzapine treatment group consistently showed greater mean improvement at each time point (15, 30, 45, 60, 90, and 120 minutes following the first IM injection) compared with IM placebo. The IM haloperidol 7.5 mg treatment group did not differ significantly from IM placebo until the 30-minute time point on the PANSS Excited Component, and this difference was maintained until the 120-minute time point.

The IM olanzapine treatment group showed greater mean improvement at the early time points compared with the IM haloperidol treatment group and a significant difference at 15, 30, and 45 minutes ($p < 0.001$, $p < 0.001$, $p = 0.016$, respectively) on the PANSS Excited Component.

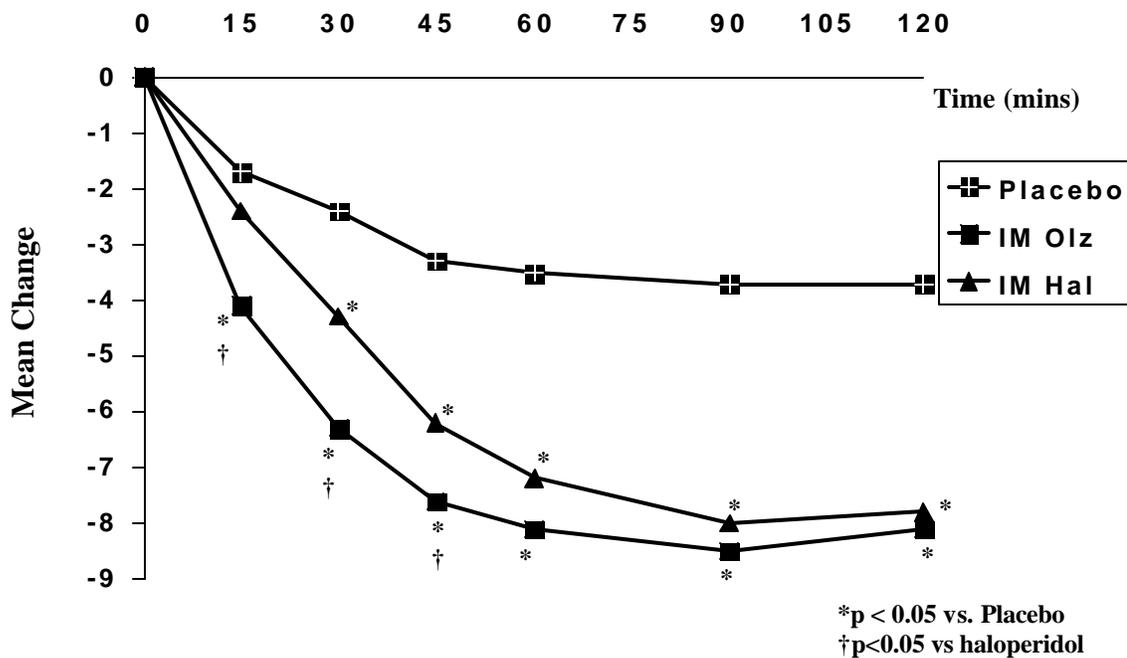
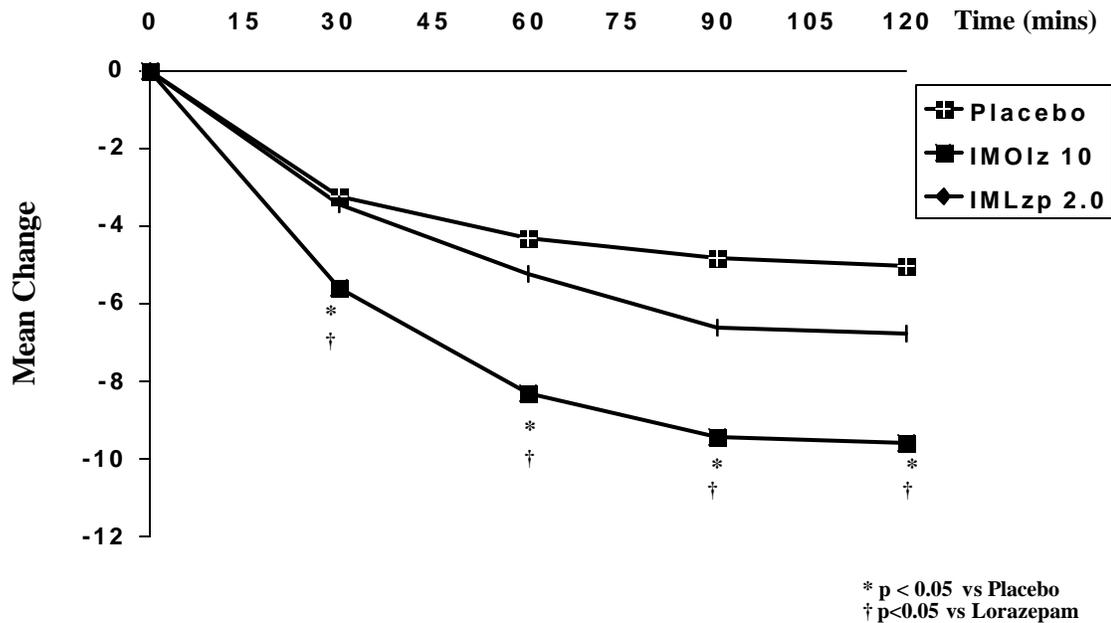


Figure 20. PANSS Excited Component
Time point-wise Change from Baseline (OC)
Agitation in Schizophrenia Study

7.2.3. Agitation in Bipolar Mania Study

Figure 21 shows the change from baseline to observed score for time points within the 2 hours following the first IM injection period in the PANSS Excited Component for the agitation in bipolar mania study.

The IM olanzapine treatment group consistently showed significantly greater mean improvement at each time point (30, 60, 90, and 120 minutes following the first IM injection) on the PANSS Excited Component compared with both the IM lorazepam treatment group and IM placebo ($p \leq 0.005$ and $p \leq 0.003$, respectively).



**Figure 21. PANSS Excited Component
Time point-wise Change from Baseline (OC)
Agitation in Bipolar Mania Study**

7.2.4. Agitation in Dementia Study

Figure 22 shows the change from baseline to observed score for time points within the 2 hours following the first IM injection period in the PANSS Excited Component for the agitation in dementia study.

The IM olanzapine 5 mg treatment group showed significantly greater mean improvement at each time point (30, 60, 90, and 120 minutes following the first IM injection) on the PANSS Excited Component compared with IM placebo ($p < 0.05$). In contrast, the IM lorazepam treatment group did not differ statistically from IM placebo until the 60-minute time point, but this difference was maintained until 120 minutes ($p \leq 0.012$). For IM olanzapine 2.5 mg, the difference versus IM placebo was only significant at 120 minutes ($p = 0.024$).

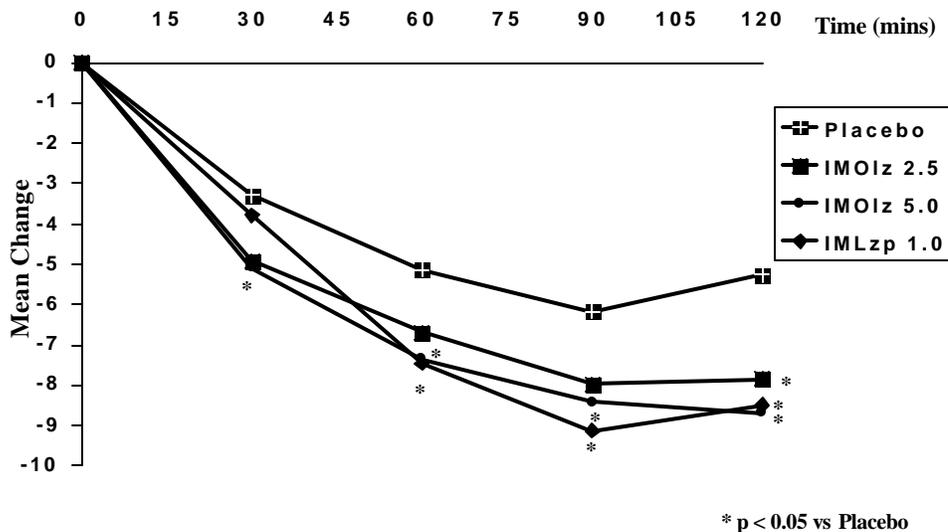


Figure 22. PANSS Excited Component
Time point-wise Change from Baseline (OC)
Agitation in Dementia Study

7.3. PANSS Excited Component—Assessment of Individual Items

The efficacy of IM olanzapine in treating each of the various aspects of agitation was evaluated using a by-item analysis of the PANSS Excited Component for each of the four pivotal studies.

The overall p-values for the PANSS Excited Component and each of the five items comprising it (poor impulse control, tension, hostility, uncooperativeness, and excitement) were significant in all studies with the exception of two items in the agitation in dementia study (poor impulse control, $p=0.058$ and excitement, $p=0.06$) (Tables 7 to 10). When examining the pairwise comparisons between the treatment groups, IM olanzapine consistently demonstrated statistical superiority compared with IM placebo across studies on the majority of PANSS Excited Component items.

These data show that each item in the PANSS Excited Component contributes to the overall significant p-value and further supports the efficacy of IM olanzapine in treating the various aspects of agitation. In the two pivotal studies in agitated patients with schizophrenia where IM haloperidol was included as an active comparator, it was also superior to IM placebo on all five items. In contrast, IM lorazepam did not generalize across the two patient populations in which it was studied (bipolar mania and dementia) in its efficacy for the five items of the PANSS Excited Component. IM lorazepam showed significant superiority to IM placebo on all five items in the agitation in dementia study but only showed significant superiority on excitement in the agitation in bipolar mania study.

**Table 7. PANSS Excited Component By-Item Analysis
Agitation in Schizophrenia—Dose Ranging Study**

PANSS Excited Item	Treatment	N	Baseline Mean ± SD	Endpoint Mean ± SD	Change Mean ± SD	p for Comparison of Change Scores Between Groups		
						Overall p-Value ^a	Pairwise p-Values	
PANSS Excited Component Total	IMOlz2.5	48	13.35 ± 2.38	7.75 ± 4.50	-5.50 ± 4.61	<0.001	0.010	Olz2.5 vs. Pla
	IMOlz5	45	14.71 ± 3.40	6.62 ± 5.96	-8.09 ± 5.30		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	13.85 ± 2.58	5.20 ± 4.95	-8.65 ± 4.98		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	14.30 ± 2.62	4.96 ± 5.00	-9.35 ± 4.88		<0.001	Olz10 vs. Pla
	IMHal7.5	40	14.28 ± 3.13	6.75 ± 5.39	-7.53 ± 5.93		<0.001	Hal vs. Pla
	IMPla	45	13.78 ± 2.83	10.87 ± 5.00	-2.91 ± 4.69			
Poor Impulse Control	IMOlz2.5	48	2.54 ± 0.71	1.54 ± 1.11	-1.00 ± 1.03	<0.001	0.130	Olz2.5 vs. Pla
	IMOlz5	45	3.22 ± 0.88	1.51 ± 1.32	-1.71 ± 1.31		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	2.87 ± 0.69	1.13 ± 1.09	-1.74 ± 1.18		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	2.93 ± 0.88	1.00 ± 1.15	-1.93 ± 1.14		<0.001	Olz10 vs. Pla
	IMHal7.5	40	2.93 ± 0.86	1.50 ± 1.20	-1.42 ± 1.36		0.001	Hal vs. Pla
	IMPla	45	2.84 ± 0.98	2.20 ± 1.18	-0.64 ± 1.13			
Tension	IMOlz2.5	48	2.98 ± 0.79	1.81 ± 1.00	-1.17 ± 1.06	<0.001	0.049	Olz2.5 vs. Pla
	IMOlz5	45	3.18 ± 0.86	1.44 ± 1.31	-1.73 ± 1.19		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	3.04 ± 0.70	1.17 ± 1.12	-1.87 ± 1.22		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	2.96 ± 0.73	1.04 ± 1.11	-1.91 ± 1.13		<0.001	Olz10 vs. Pla
	IMHal7.5	40	3.10 ± 0.74	1.50 ± 1.24	-1.60 ± 1.30		<0.001	Hal vs. Pla
	IMPla	45	3.11 ± 0.80	2.42 ± 1.12	-0.69 ± 1.10			

**Table 7. (Concluded) PANSS Excited Component By-Item Analysis
Agitation in Schizophrenia—Dose Ranging Study**

PANSS Excited Item	Treatment	N	Mean ± SD	Mean ± SD	Mean ± SD	p for Comparison of Change Scores Between Groups		
						Overall p-Value ^a	Pairwise p-Values	
Hostility	IMOlz2.5	48	2.35 ± 0.81	1.44 ± 0.94	-0.92 ± 1.05	<0.001	0.040	Olz2.5 vs. Pla
	IMOlz5	45	2.58 ± 1.01	1.22 ± 1.28	-1.36 ± 1.19		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	2.52 ± 0.89	1.07 ± 1.02	-1.46 ± 1.17		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	2.72 ± 1.00	1.07 ± 1.12	-1.65 ± 1.37		<0.001	Olz10 vs. Pla
	IMHal7.5	40	2.58 ± 1.11	1.25 ± 1.10	-1.33 ± 1.44		<0.001	Hal vs. Pla
	IMPla	45	2.49 ± 0.97	2.07 ± 1.16	-0.42 ± 1.18			
Uncooperativeness	IMOlz2.5	48	2.52 ± 0.97	1.40 ± 1.09	-1.13 ± 1.12	<0.001	0.010	Olz2.5 vs. Pla
	IMOlz5	45	2.56 ± 1.06	1.09 ± 1.33	-1.47 ± 1.09		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	2.43 ± 1.11	1.04 ± 1.21	-1.39 ± 1.14		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	2.59 ± 0.93	1.00 ± 1.26	-1.59 ± 1.17		<0.001	Olz10 vs. Pla
	IMHal7.5	40	2.43 ± 0.96	1.10 ± 1.06	-1.33 ± 1.29		0.001	Hal vs. Pla
	IMPla	45	2.51 ± 0.97	1.98 ± 1.22	-0.53 ± 1.06			
Excitement	IMOlz2.5	48	2.85 ± 0.77	1.56 ± 1.25	-1.29 ± 1.22	<0.001	0.005	Olz2.5 vs. Pla
	IMOlz5	45	3.18 ± 0.94	1.36 ± 1.38	-1.82 ± 1.25		<0.001	Olz5 vs. Pla
	IMOlz7.5	46	2.98 ± 0.83	0.78 ± 1.01	-2.20 ± 1.17		<0.001	Olz7.5 vs. Pla
	IMOlz10	46	3.11 ± 0.85	0.85 ± 1.13	-2.26 ± 1.10		<0.001	Olz10 vs. Pla
	IMHal7.5	40	3.25 ± 0.84	1.40 ± 1.39	-1.85 ± 1.44		<0.001	Hal vs. Pla
	IMPla	45	2.82 ± 0.72	2.20 ± 1.18	-0.62 ± 1.01			

**Table 8. PANSS Excited Component By-Item Analysis
Agitation in Schizophrenia Study**

PANSS Excited Item	Treatment	N	Baseline Mean ± SD	Endpoint Mean ± SD	Change Mean ± SD	p for Comparison of Change Scores Between Groups			
						Overall p-Value ^a	Pairwise p-Values		
PANSS Excited Component Total	IMOlz10	131	13.35 ± 3.36	5.34 ± 5.96	-8.01 ± 6.10	<0.001	<0.001	Olz vs. Pla	
	IMHal7.5	126	13.17 ± 3.15	5.34 ± 4.40	-7.83 ± 4.95			0.868	Olz vs. Hal
	IMPla	54	13.37 ± 3.48	9.63 ± 5.41	-3.74 ± 5.22			<0.001	Hal vs. Pla
Poor Impulse Control	IMOlz10	131	2.63 ± 0.98	1.05 ± 1.24	-1.59 ± 1.23	<0.001	<0.001	Olz vs. Pla	
	IMHal7.5	126	2.57 ± 0.99	1.05 ± 1.03	-1.52 ± 1.22			0.761	Olz vs. Hal
	IMPla	54	2.54 ± 0.97	1.89 ± 1.16	-0.65 ± 1.23			<0.001	Hal vs. Pla
Tension	IMOlz10	131	3.28 ± 0.93	1.42 ± 1.43	-1.86 ± 1.50	<0.001	<0.001	Olz vs. Pla	
	IMHal7.5	126	3.36 ± 0.91	1.53 ± 1.26	-1.83 ± 1.26			0.910	Olz vs. Hal
	IMPla	54	3.39 ± 0.88	2.52 ± 1.28	-0.87 ± 1.10			<0.001	Hal vs. Pla
Hostility	IMOlz10	131	2.10 ± 1.11	0.78 ± 1.20	-1.32 ± 1.42	0.002	0.002	Olz vs. Pla	
	IMHal7.5	126	2.13 ± 1.15	0.78 ± 0.98	-1.35 ± 1.29			0.849	Olz vs. Hal
	IMPla	54	2.13 ± 1.18	1.48 ± 1.28	-0.65 ± 1.23			0.001	Hal vs. Pla
Uncooperativeness	IMOlz10	131	2.28 ± 1.15	0.85 ± 1.33	-1.43 ± 1.57	0.005	0.002	Olz vs. Pla	
	IMHal7.5	126	2.13 ± 1.13	0.78 ± 0.95	-1.35 ± 1.20			0.698	Olz vs. Hal
	IMPla	54	2.22 ± 1.16	1.52 ± 1.44	-0.70 ± 1.33			0.005	Hal vs. Pla
Excitement	IMOlz10	131	3.05 ± 1.02	1.24 ± 1.47	-1.81 ± 1.37	<0.001	<0.001	Olz vs. Pla	
	IMHal7.5	126	2.98 ± 0.95	1.21 ± 1.12	-1.78 ± 1.29			0.944	Olz vs. Hal
	IMPla	54	3.09 ± 1.09	2.22 ± 1.41	-0.87 ± 1.17			<0.001	Hal vs. Pla

**Table 9. PANSS Excited Component By-Item Analysis
Agitation in Bipolar Mania Study**

PANSS Excited Item	Treatment	N	Baseline Mean ± SD	Endpoint Mean ± SD	Change Mean ± SD	p for Comparison of Change Scores Between Groups		
						Overall p-Value ^a	Pairwise p-Values	
PANSS Excited Component Total	IMOlz10	98	12.96 ± 3.18	3.36 ± 4.53	-9.60 ± 4.74	<0.001	<0.001	Olz vs. Pla
	IMLzp2	51	12.39 ± 2.97	5.65 ± 4.94	-6.75 ± 5.20		0.001	Olz vs. Lzp
	IMPla	50	12.72 ± 3.10	7.88 ± 5.29	-4.84 ± 4.66		0.053	Lzp vs. Pla
Poor Impulse Control	IMOlz10	98	2.79 ± 1.04	.076 ± 1.08	-2.03 ± 1.29	<0.001	<0.001	Olz vs. Pla
	IMLzp2	51	2.41 ± 1.04	1.12 ± 1.23	-1.29 ± 1.17		0.001	Olz vs. Lzp
	IMPla	50	2.62 ± 0.90	1.74 ± 1.16	-0.88 ± 1.26		0.104	Lzp vs. Pla
Tension	IMOlz10	98	3.15 ± 0.90	0.81 ± 1.09	-2.35 ± 1.31	<0.001	<0.001	Olz vs. Pla
	IMLzp2	51	3.27 ± 0.87	1.55 ± 1.38	-1.73 ± 1.40		0.007	Olz vs. Lzp
	IMPla	50	3.06 ± 0.93	1.74 ± 1.24	-1.32 ± 1.43		0.150	Lzp vs. Pla
Hostility	IMOlz10	98	2.29 ± 1.10	0.55 ± 1.00	-1.73 ± 1.26	<0.001	<0.001	Olz vs. Pla
	IMLzp2	51	2.10 ± 1.33	0.80 ± 1.13	-1.29 ± 1.32		0.035	Olz vs. Lzp
	IMPla	50	2.16 ± 1.15	1.32 ± 1.38	-0.84 ± 1.15		0.076	Lzp vs. Pla
Uncooperativeness	IMOlz10	98	1.63 ± 1.06	0.45 ± 0.77	-1.18 ± 1.08	0.008	0.007	Olz vs. Pla
	IMLzp2	51	1.43 ± 1.04	0.71 ± 1.17	-0.73 ± 1.27		0.017	Olz vs. Lzp
	IMPla	50	1.70 ± 1.09	1.04 ± 1.19	-0.66 ± 0.94		0.763	Lzp vs. Pla
Excitement	IMOlz10	98	3.10 ± 0.96	0.80 ± 1.17	-2.31 ± 1.33	<0.001	<0.001	Olz vs. Pla
	IMLzp2	51	3.18 ± 0.97	1.47 ± 1.39	-1.71 ± 1.49		0.011	Olz vs. Lzp
	IMPla	50	3.18 ± 0.96	2.04 ± 1.35	-1.14 ± 1.23		0.036	Lzp vs. Pla

**Table 10. PANSS Excited Component By-Item Analysis
Agitation in Dementia Study**

PANSS Excited Item	Treatment	N	Baseline Mean ± SD	Endpoint Mean ± SD	Change Mean ± SD	p for Comparison of Change Scores Between Groups		
						Overall p-Value ^a	Pairwise p-Values	
PANSS Excited Component Total	IMOlz2.5	71	14.58 ± 4.11	6.72 ± 6.20	-7.86 ± 6.05	0.01	0.024	Olz2.5 vs. Pla
	IMOlz5	66	14.86 ± 3.88	6.20 ± 6.96	-8.67 ± 6.97			
	IMLzp1.0	68	14.22 ± 4.39	5.74 ± 6.56	-8.49 ± 6.55			
	IMPla	67	15.36 ± 4.71	10.09 ± 6.98	-5.27 ± 6.87			
Poor Impulse Control	IMOlz2.5	71	2.89 ± 0.98	1.49 ± 1.34	-1.39 ± 1.39	0.058	0.186	Olz2.5 vs. Pla
	IMOlz5	66	2.98 ± 0.94	1.27 ± 1.44	-1.71 ± 1.62			
	IMLzp1.0	68	2.93 ± 1.03	1.31 ± 1.56	-1.62 ± 1.45			
	IMPla	67	3.22 ± 1.22	2.16 ± 1.43	-1.06 ± 1.48			
Tension	IMOlz2.5	71	3.35 ± 1.10	1.49 ± 1.45	-1.86 ± 1.44	0.037	0.012	Olz2.5 vs. Pla
	IMOlz5	66	3.30 ± 0.94	1.48 ± 1.67	-1.82 ± 1.60			
	IMLzp1.0	68	3.16 ± 1.10	1.40 ± 1.49	-1.76 ± 1.56			
	IMPla	67	3.45 ± 1.16	2.28 ± 1.56	-1.16 ± 1.69			
Hostility	IMOlz2.5	71	2.35 ± 1.30	1.15 ± 1.36	-1.20 ± 1.49	0.016	0.172	Olz2.5 vs. Pla
	IMOlz5	66	2.73 ± 1.23	1.08 ± 1.47	-1.65 ± 1.50			
	IMLzp1.0	68	2.41 ± 1.49	0.91 ± 1.48	-1.50 ± 1.70			
	IMPla	67	2.54 ± 1.46	1.73 ± 1.58	-0.81 ± 1.84			

**Table 10. (Concluded) PANSS Excited Component By-Item Analysis
Agitation in Dementia Study**

PANSS Excited Item	Treatment	N	Mean ± SD	Mean ± SD	Mean ± SD	p for Comparison of Change Scores Between Groups		
						Overall p-Value ^a	Pairwise p-Values	
Uncooperativeness	IMOlz2.5	71	2.90 ± 1.33	1.23 ± 1.47	-1.68 ± 1.50	0.004	0.005	Olz2.5 vs. Pla
	IMOlz5	66	2.97 ± 1.28	1.15 ± 1.50	-1.82 ± 1.55		0.001	Olz5 vs. Pla
	IMLzp1.0	68	2.59 ± 1.34	0.99 ± 1.26	-1.60 ± 1.44		0.008	Lzp vs. Pla
	IMPla	67	2.87 ± 1.50	1.91 ± 1.66	-0.96 ± 1.50			
Excitement	IMOlz2.5	71	3.08 ± 1.05	1.35 ± 1.43	-1.73 ± 1.38	0.06	0.102	Olz2.5 vs. Pla
	IMOlz5	66	2.88 ± 0.92	1.21 ± 1.58	-1.67 ± 1.62		0.172	Olz5 vs. Pla
	IMLzp1.0	68	3.13 ± 1.09	1.13 ± 1.44	-2.00 ± 1.62		0.007	Lzp vs. Pla
	IMPla	67	3.28 ± 1.00	2.00 ± 1.42	-1.28 ± 1.65			

7.4. Overall Efficacy Conclusions

Four double-blind, placebo and active comparator controlled studies were conducted in agitated patients from three distinct patient populations to support the efficacy of IM olanzapine in the rapid control of agitation across different patient populations. Two of these studies were conducted with the intent of demonstrating the efficacy of IM olanzapine in agitated patients with schizophrenia and related psychoses (schizoaffective disorder and schizophreniform disorder). One study was similarly conducted in agitated patients with bipolar I disorder (manic or mixed episode). A final study was conducted in agitated patients with Alzheimer's dementia, vascular dementia, or mixed dementia.

The efficacy data support the efficacy of IM olanzapine for the rapid control of agitation across different patient populations. In all four pivotal studies, the primary analysis showed that IM olanzapine was superior to placebo. This finding occurred for all IM olanzapine dose arms (2.5, 5, 7.5 and 10 mg). The additional efficacy measures of agitation yielded similar results. Further, the onset of action of all treatment arms was investigated across all studies at various time points ranging from 15 minutes to 2 hours following first IM injection. In each study, IM olanzapine was superior at the earliest time point measured compared with IM placebo within at least one of the IM olanzapine dose arms studied. In the two schizophrenia studies and in the bipolar mania study, IM olanzapine was also superior at the earliest time point measured compared with IM haloperidol and IM lorazepam within at least one of the IM olanzapine dose arms studied. A by-item analysis of the PANSS Excited Component showed that IM olanzapine consistently demonstrated superiority compared with IM placebo across each of the four pivotal studies on the majority of the PANSS Excited Component items. These results demonstrate that IM olanzapine is effective in rapidly controlling agitation across different disease states.

8. Safety Results

Safety data are presented in this section for several controlled databases that provide the opportunity for direct comparison of IM olanzapine with IM placebo and current standard therapies.

Safety data for the patients enrolled in the pivotal studies in agitated patients with schizophrenia or bipolar mania are presented for:

- **Placebo-Controlled Database:** Pooled IM olanzapine and pooled IM placebo safety data from the two pivotal studies conducted in agitated patients with schizophrenia and the one study in agitated patients with bipolar mania are referred to as the placebo-controlled database. This database included 415 IM olanzapine-treated patients and 150 IM placebo-treated patients.
- **Haloperidol-Controlled Database:** Pooled IM olanzapine and pooled IM haloperidol safety data from the two pivotal studies in agitated patients with schizophrenia where IM haloperidol was included as an active comparator are referred to as the haloperidol-controlled database. This database included 316 IM olanzapine-treated patients and 166 IM haloperidol-treated patients.
- **Lorazepam-Controlled Database:** IM olanzapine and IM lorazepam safety data from the pivotal study in agitated patients with bipolar mania where IM lorazepam was included as an active comparator are referred to as the lorazepam-controlled database. This database included 99 IM olanzapine-treated patients and 51 IM lorazepam-treated patients.

Safety data for the geriatric patients enrolled in the pivotal study in agitated patients with dementia are presented for:

- **Geriatric Placebo-Controlled Database:** IM olanzapine and IM placebo safety data from the pivotal study in agitated patients with dementia are referred to as the geriatric placebo-controlled database. This database included 137 IM olanzapine-treated patients and 67 IM placebo-treated patients.
- **Geriatric Lorazepam-Controlled Database:** IM olanzapine and IM lorazepam safety data from the pivotal study in agitated patients with dementia are referred to as the geriatric lorazepam-controlled database. This database included 137 IM olanzapine-treated patients and 68 IM lorazepam-treated patients.

The databases for the geriatric patients with dementia have not been pooled with the other databases based on the differences in patient age and co-morbid disease characteristics between the geriatric patients and the patients enrolled in the other pivotal studies. The geriatric patients, as a group, were very old. Among the 272 patients enrolled in the

pivotal study in agitated patients with dementia, the mean age was 77 and 45.2% were age 80 or older and 8.8% were age 90 or older. These patients suffered from neurodegenerative brain disease and significant medical co-morbidity consistent with the problems encountered in typical clinical settings. In this population 41.2% had hypertension, 32.0% had some degree of coronary artery disease, including histories of myocardial infarctions, 12.9% had congestive heart failure, and 12.9% had cerebrovascular and/or peripheral vascular disease. There were 13.2% with chronic respiratory disease, 11.4% with diabetes, and 13.6% with hypothyroidism. Right bundle branch block was identified in 22 patients at baseline and 10 patients had left bundle branch block at baseline. There were 6 patients with pacemakers. To treat these co-morbid illnesses, the patients were taking significant concomitant medications.

In addition to the controlled safety databases described above, data are also presented from pooled safety data from all six IM olanzapine clinical studies conducted in agitated patients (i.e., the four pivotal studies and two open-label studies), referred to as the overall integrated database.

- **Overall Integrated Database:** This uncontrolled database included a total of 722 IM olanzapine-treated patients. Included among the 722 IM olanzapine-treated patients were 52 patients from the placebo-controlled studies, who after receiving two placebo injections required a third injection, which was IM olanzapine. Only safety data for time points after the third injection are included for the 52 patients who crossed over from IM placebo to IM olanzapine.

In the four pivotal clinical studies, patients were randomly assigned to a treatment group and received one to three injections of study drug. The decision of whether to administer the optional second or third injection of study drug was made by the investigator based on clinical judgment. The second/third injections were to be administered within 20 hours of the first injection and the summary assessments were made at approximately 24 hours. Thus, the safety data presented in this section for the 24-hour period following the first IM injection includes patients who have received up to three injections.

8.1. Safety Methodology

Safety data (treatment-emergent adverse events, clinical laboratory tests, vital signs, ECGs, and extrapyramidal symptoms) were monitored throughout each of the studies comprising the patient safety database. Adverse events were elicited by open-ended, non-directed questioning of the patient; clinical observation; and source document review. Adverse events were recorded as Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) classification terms.

When a patient discontinued the study, the investigator chose the reason for discontinuation. If the reason for discontinuation was an adverse event, the investigator identified the specific event.

For all studies the following vital signs were collected: supine and standing blood pressure and supine and standing heart rate pre-dose and at subsequent time points for all studies. This summary presents supine blood pressure and heart rate data and, to represent orthostatic challenge, orthostatic systolic blood pressure change, and standing pulse rates are presented. Orthostatic systolic blood pressure change is supine systolic blood pressure minus standing systolic blood pressure. Thus, a positive value represents a drop in standing systolic blood pressure compared with supine systolic blood pressure (i.e., lower blood pressure standing compared with supine). This value will be referred to as the “orthostatic drop.”

ECGs were performed at baseline, 2 hours following the first IM injection and 24 hours following the first IM injection for all studies. The QTc data and JTc data (terminal point of QRS complex to terminal point of T wave, corrected for heart rate) for agitated patients with dementia presented in this summary are for the Bazett correction. QTc (and JTc in the geriatric study where it was calculated) was calculated using Friderica’s correction and a data derived regression correction factor, in addition to Bazett’s correction for each of the individual studies. The analyses using Friderica’s and regression corrections are considered post hoc. Since Bazett’s correction was *a priori* considered primary and analyses using the other correction factors did not alter the overall interpretation of the results comparing IM olanzapine to IM placebo and active comparators, results using Bazett’s correction are presented here.

The ECG data were analyzed by mean change and categorical analyses. In the categorical analyses, the incidence of QTc post baseline prolongations was analyzed using alternative criteria. Based on Moss (1993), QTc intervals at or above the 97.5th percentile (≥ 430 for males and ≥ 450 for females) for healthy adults and above the 99th percentile (≥ 450 for males and ≥ 470 for females) for healthy adults were considered prolonged. Additionally, QTc intervals ≥ 500 msec were considered prolonged. The 500 msec criterion was derived from a population that would be predictive of clinical risk of torsades de pointes in younger, non-agitated, non-neurologically diseased subjects (Morganroth 1993). Only patients who had a QTc baseline interval below the predefined criterion were included in each of the categorical analyses.

The advanced age and co-morbid conditions for the geriatric patients included in the pivotal study in agitated patients with dementia raised concerns that assessment and measurement of ECG tracings for these patients would be more difficult compared with other studies. Further, in addition to the standard analyses of the QTc interval, the JTc interval was analyzed in order to evaluate a representation of ventricular repolarization time without that representation also including ventricular depolarization time, as is the case with QTc interval. Therefore, computation of the JTc interval allowed for analysis of any differential treatment influence on ventricular repolarization without the potential confound of pre-existing differences or changes in ventricular depolarization.

The potential association of IM olanzapine with excessive sedation was assessed using the ACES and by conventional adverse events collection (as described above).

Extrapyramidal symptoms were assessed by conventional adverse event collection (as described above). In addition, the specific extrapyramidal symptoms of parkinsonism and akathisia were evaluated with operationalized rating scales, the Simpson-Angus (all four pivotal studies) and Barnes Akathisia (pivotal studies in agitated patients with schizophrenia and bipolar mania) scales.

8.2. Deaths, Discontinuations Due to Adverse Events, and Serious Adverse Events

No deaths occurred among IM olanzapine-treated agitated patients during or within 5 days of discontinuation or ending participation in any of the studies.

Only 5 out of 722 agitated patients who received IM olanzapine discontinued due to an adverse event. These discontinuations included two (Patient 1-anxiety, Patient 2-maculopapular rash) in agitated patients randomized to olanzapine and three (Patient 3-agitation, Patient 4-hostility, Patient 5-tachycardia) in placebo crossover patients, where the agitated patients received two injections of placebo before receiving olanzapine.

Serious adverse events were identified according to standard FDA-defined criteria (i.e., death, initial or prolonged inpatient hospitalization, life-threatening, severe or permanent disability, cancer, congenital anomaly, or judged significant for other reason). Three IM olanzapine-treated patients experienced four serious adverse events during study participation: (1) one patient with anxiety (which also resulted in discontinuation of this patient from the study, and is included among the five patients enumerated above), (2) one patient with tachycardia (not the one leading to discontinuation described above), and (3) one patient with abnormal ECG and anemia. The case reported by the investigator as "abnormal ECG" was a case where the ECG findings at 24 hours following the IM olanzapine injection were normal sinus rhythm, rightward axis, low voltage QRS, poor R-wave progression consistent with faulty lead placement or chronic obstructive pulmonary disease, and non-specific ST and T wave abnormalities. However, these findings were also present on the screening ECG and according to the interpreting cardiologist there were no significant changes from screening to the end of study ECG. Regarding the reported "anemia," the baseline hematology results for this patient, collected 1 hour prior to study drug administration, showed a pre-existing condition of anemia with a hemoglobin of 7.45 mmol/L-Fe, a hematocrit of 33%, and a red blood cell count of 3.6 TI/L. At endpoint, 24 hours following the injection, the patient had a hemoglobin of 6.45 mmol/L-Fe, a hematocrit of 27%, and a red blood cell count of 3 TI/L and a serious adverse event was reported. Based on the pre-existing condition of anemia, any clinically relevant changes occurring during study participation were likely due to a progression of a pre-existing pattern. Although the change in hematocrit might appear clinically relevant, the changes in hemoglobin and red blood cell count suggest that the changes were likely within physiological or laboratory variability.

8.3. Treatment-Emergent Adverse Events

This section presents comparisons of treatment-emergent adverse events among the treatment groups for each of the five controlled databases described above. In the comparisons between IM olanzapine and IM placebo, treatment-emergent adverse events reported by at least 1% of IM olanzapine-treated patients (provided the event was reported for at least two patients) with an incidence greater than placebo are presented. In the comparisons between IM olanzapine and IM active comparator treatment, treatment-emergent adverse events reported by at least 1% of IM olanzapine- or IM active comparator-treated patients (provided the event was reported for at least two olanzapine- or active comparator-treated patients) and not equal in incidence between the treatment groups are presented.

In the IM olanzapine pivotal studies, no treatment-emergent adverse events occurred at a significantly greater incidence in the IM olanzapine treatment groups compared with IM placebo or the active comparator treatments (IM haloperidol or IM lorazepam). In contrast, in the two pivotal studies in agitated patients with schizophrenia where IM haloperidol was included as an active comparator, extrapyramidal syndrome (COSTART term capturing parkinsonism), amblyopia, dyspepsia, and dystonia were reported at a significantly greater incidence in IM haloperidol-treated patients compared with IM olanzapine-treated patients. In the pivotal study in agitated patients with bipolar mania where IM lorazepam was included as an active comparator, nausea and vomiting were reported at a significantly greater incidence in IM lorazepam-treated patients compared with IM olanzapine-treated patients.

8.3.1. Placebo-Controlled Database

Treatment-emergent adverse events reported by at least 1% of IM olanzapine-treated patients and with an incidence greater than IM placebo in the placebo-controlled pivotal studies in agitated patients with schizophrenia or bipolar mania are shown in Table 11. No treatment-emergent adverse events occurred at a statistically greater incidence in the IM olanzapine treatment groups compared with IM placebo.

**Table 11. Treatment-Emergent Adverse Events
Placebo Controlled Database**

Body System/Adverse Event	Percentage of Patients Reporting Event ^a		p-value
	IM Olanzapine (N=415)	IM Placebo (N=150)	
Body as a Whole			
Asthenia	2%	1%	0.688
Cardiovascular System			
Hypotension	2%	0%	0.121
Postural hypotension	1%	0%	0.332
Nervous System			
Dizziness	4%	2%	0.307
Somnolence	6%	3%	0.381
Tremor	1%	0%	0.332

^a Events reported by at least 1% of patients treated with IM olanzapine, except the following events which had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia, nervousness.

8.3.2. Haloperidol-Controlled Database

Treatment-emergent adverse events reported by at least 1% of IM olanzapine- or IM haloperidol-treated patients and not equal in incidence between groups in the two pivotal studies in agitated patients with schizophrenia where IM haloperidol was included as an active comparator are shown in Table 12. Extrapyramidal syndrome (COSTART term capturing parkinsonism), amblyopia, dyspepsia, and dystonia were reported at a significantly greater incidence in IM haloperidol-treated patients compared with IM olanzapine-treated patients. In contrast, no treatment-emergent adverse events were reported significantly more frequently in IM olanzapine-treated patients compared with IM haloperidol-treated patients. Hypotension was reported as an adverse event for 3% of IM olanzapine-treated patients and 0% of IM haloperidol-treated patients (p=0.055).

Table 12. Treatment-Emergent Adverse Events in Haloperidol-Controlled Database

Body System/Adverse Event	Percentage of Patients Reporting Event ^a		p-value
	IM Olanzapine (N=316)	IM Haloperidol (N=166)	
Cardiovascular			
Hypotension	3%	0%	0.055
Postural hypotension	1%	0%	0.304
Digestive			
Constipation	0%	1%	0.118
Dyspepsia	0%	2%	0.040
Nervous system			
Agitation	3%	6%	0.240
Akathisia	1%	4%	0.070
Anxiety	2%	4%	0.355
Dizziness	3%	2%	0.755
Dystonia	0%	7%	<0.001
Extrapyramidal syndrome ^b	0%	5%	0.001
Hypertonia	0%	2%	0.120
Insomnia	2%	4%	0.355
Somnolence	3%	6%	0.152
Tremor	1%	2%	0.419
Special Senses			
Amblyopia	0%	2%	0.040

^a Events reported for at least 1% of patients treated with IM olanzapine or IM haloperidol, except the following events which had an equal incidence in both the treatment groups: asthenia, headache, dry mouth, nervousness.

^b Extrapyramidal syndrome is the COSTART term capturing parkinsonism.

8.3.3. Lorazepam-Controlled Database

Treatment-emergent adverse events reported by at least 1% of IM olanzapine- or IM lorazepam-treated patients (provided the event was reported for at least two olanzapine- or lorazepam-treated patients) and not equal in incidence between groups in the pivotal study in agitated patients with bipolar mania where IM lorazepam was included as an active comparator are shown in Table 13. The incidences of nausea and vomiting were reported at a significantly greater incidence in IM lorazepam-treated patients compared with IM olanzapine-treated patients. In contrast, no treatment-emergent adverse events were reported significantly more frequently in IM olanzapine-treated patients compared with IM lorazepam-treated patients.

Table 13. Treatment-Emergent Adverse Events in Lorazepam-Controlled Database

Body System/Adverse Event	Percentage of Patients Reporting Event ^a		p-value
	IM Olanzapine (N=99)	IM Lorazepam (N=51)	
Body as a whole			
Asthenia	3%	4%	1.000
Back pain	0%	4%	0.114
Headache	3%	10%	0.122
Injection site pain	0%	4%	0.114
Cardiovascular			
Hypertension	2%	0%	0.548
Hypotension	1%	4%	0.267
Digestive			
Dry mouth	3%	2%	1.000
Nausea	1%	8%	0.046
Vomiting	0%	6%	0.038
Musculoskeletal			
Twitching	2%	0%	0.548
Nervous			
Abnormal gait	2%	0%	0.548
Dizziness	9%	14%	0.411
Hallucinations	2%	0%	0.548
Insomnia	2%	4%	0.605
Nervousness	3%	4%	1.000
Somnolence	13%	10%	0.609
Tremor	2%	0%	0.548
Respiratory			
Pharyngitis	2%	0%	0.548

^a There were no events reported with an incidence $\geq 1\%$ and equal in both the treatment groups

8.3.4. Geriatric Placebo-Controlled Database

Treatment-emergent adverse events reported by at least 1% of IM olanzapine-treated patients (provided the event was reported for at least two patients) and with an incidence greater than IM placebo in the placebo-controlled pivotal study in agitated patients with dementia are shown in Table 14. No treatment-emergent adverse events occurred at a statistically significantly greater incidence in the IM olanzapine treatment group compared with IM placebo.

Table 14. Treatment-Emergent Adverse Events in Geriatric Placebo-Controlled Database

Body System/Adverse Event	Percentage of Patients Reporting Event ^a		p-value
	IM Olanzapine (N=137)	IM Placebo (N=67)	
Body as a Whole			
Accidental injury	2%	0%	0.552
Headache	3%	0%	0.305
Cardiovascular System			
Electrocardiogram abnormal ^b	2%	0%	0.552
Tachycardia	1%	0%	1.000
Vasodilatation	1%	0%	1.000
Digestive System			
Vomiting	1%	0%	1.000
Nervous System			
Dizziness	2%	0%	0.552
Hallucinations	1%	0%	1.000
Somnolence	4%	3%	1.000
Tremor	1%	0%	1.000

^a Events reported for at least 1% of patients treated with olanzapine, except the following event which had an incidence equal to placebo: hypertension.

^b Actual terms reported: 1) abnormal ECG with QRS axis shifted left; 2) nonspecific T-wave abnormality; 3) ST-T elevation.

8.3.5. Geriatric Lorazepam-Controlled Database

Treatment-emergent adverse events reported by at least 1% of IM olanzapine- or IM lorazepam-treated patients (provided the event was reported for at least two olanzapine- or lorazepam-treated patients) and not equal in incidence between groups in the pivotal study in agitated patients with dementia where IM lorazepam was included as an active comparator are shown in Table 15. There were no statistically significant differences in the incidence of treatment-emergent adverse events between IM olanzapine- and IM lorazepam-treated patients.

**Table 15. Treatment-Emergent Adverse Events
Geriatric Lorazepam-Controlled Database**

Body System/Adverse Event	Percentage of Patients Reporting Event ^a		p-value
	IM Olanzapine (N=137)	IM Lorazepam (N=68)	
Body as a whole			
Accidental injury	2%	4%	0.401
Headache	3%	1%	1.000
Cardiovascular			
Electrocardiogram Abnormal ^b	2%	0%	0.552
Hypertension	1%	3%	0.601
Vasodilatation	1%	0%	1.000
Nervous System			
Dizziness	2%	3%	1.000
Hallucinations	1%	0%	1.000
Somnolence	4%	10%	0.109
Tremor	1%	0%	1.000

^a Events reported for at least 1% of patients treated with olanzapine, except the following events which had an incidence equal to lorazepam: tachycardia, vomiting.

^b Actual terms reported: 1) abnormal ECG with QRS axis shifted left; 2) nonspecific T-wave abnormality; 3) ST-T elevation.

8.4. Adverse Events Related to Injection Site Reaction

In order to assess the incidence of injection site reactions, adverse event terms were reviewed to identify all terms related to injection site reactions. In the four pivotal studies, there were reports of injection site pain such as burning sensation and stinging at the injection site in 3 of 604 IM olanzapine patients, 2 of 119 IM lorazepam patients, 0 of 166 IM haloperidol patients, and 0 of 217 IM placebo patients. In all cases, the injection site pain was self-limited.

Thus, IM olanzapine was not associated with adverse injection site reactions other than infrequent and relatively mild discomfort, and the data do not suggest an association between olanzapine and local irritant or allergic reactions.

8.5. Laboratory Analytes

There were no clinically significant findings in the analysis of laboratory analytes. Clinically insignificant but statistically significant increases in mean cell hemoglobin and sodium were noted in geriatric patients with dementia following IM olanzapine treatment.

8.6. Vital Signs

This section presents the basic analyses of vital signs for the placebo-controlled database, haloperidol-controlled database and geriatric placebo-controlled database. Additional analyses further evaluating the vital sign data are also presented. The lorazepam-

controlled and the geriatric lorazepam-controlled databases are not presented because haloperidol is believed to be the more standard treatment and the analyses with only placebo- and haloperidol-controlled groups are quite extensive. The data suggest that IM olanzapine is not associated with clinically relevant effects on vital signs except for mild and transient trends for decrements in blood pressure and heart rate. Direct comparison of IM olanzapine to IM haloperidol indicates clinically similar hemodynamic safety profiles.

8.6.1. Basic Analyses

Two types of analyses of vital signs were performed: change from baseline to the last value available up to the 2 and 24 hour endpoints following the first IM injection for each vital sign, and categorical analyses of changes to a value outside of the reference range at anytime during the 24 hour IM treatment period (including the first 2 hours) and specifically at the 24 hour endpoint for each vital sign.

The reference ranges for each vital sign are shown in Table 16. In each categorical analysis of changes to a value above or below the reference range, only patients who had values above the lower limit at baseline (for analyses of changes to values below the limit) or below the upper limit at baseline (for analyses of changes to values above the upper limit) were included in that particular analysis. Therefore, the denominators for these categorical analyses for a given treatment group can be smaller than the total number of patients in that treatment group. Some patients were abnormal at baseline and therefore not included in an analysis of change to abnormal.

Table 16. Vital Signs Reference Ranges

Parameter	Lower Limits	Upper Limits
Supine systolic blood pressure (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic blood pressure (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15
Orthostatic hypotension (mm Hg)	--	≥30 mm Hg decrease in systolic BP (supine to standing)
Standing pulse (bpm)	<50 and decrease ≥15	>120 and increase ≥15

8.6.1.1. Placebo-Controlled Database

In the mean change analysis at 2 hours, the IM olanzapine group experienced several significant decreases compared with IM placebo: supine systolic blood pressure ($p<0.001$), supine diastolic blood pressure ($p=0.039$), and supine pulse ($p=0.002$) (Figures 23 to 25). The mean change analysis at 24 hours revealed no significant differences (Figures 23 to 25). In the analysis of changes to a value outside the reference range at any time during the 24 hour period, decreases in supine diastolic blood pressure ($p=0.003$) occurred significantly more frequently in IM olanzapine-treated patients than

in IM placebo-treated patients (Figure 26). In the analysis of changes to a value outside the reference range at the endpoint of the 24-hour period, there were no statistically significant differences between IM olanzapine and IM placebo (Figure 27).

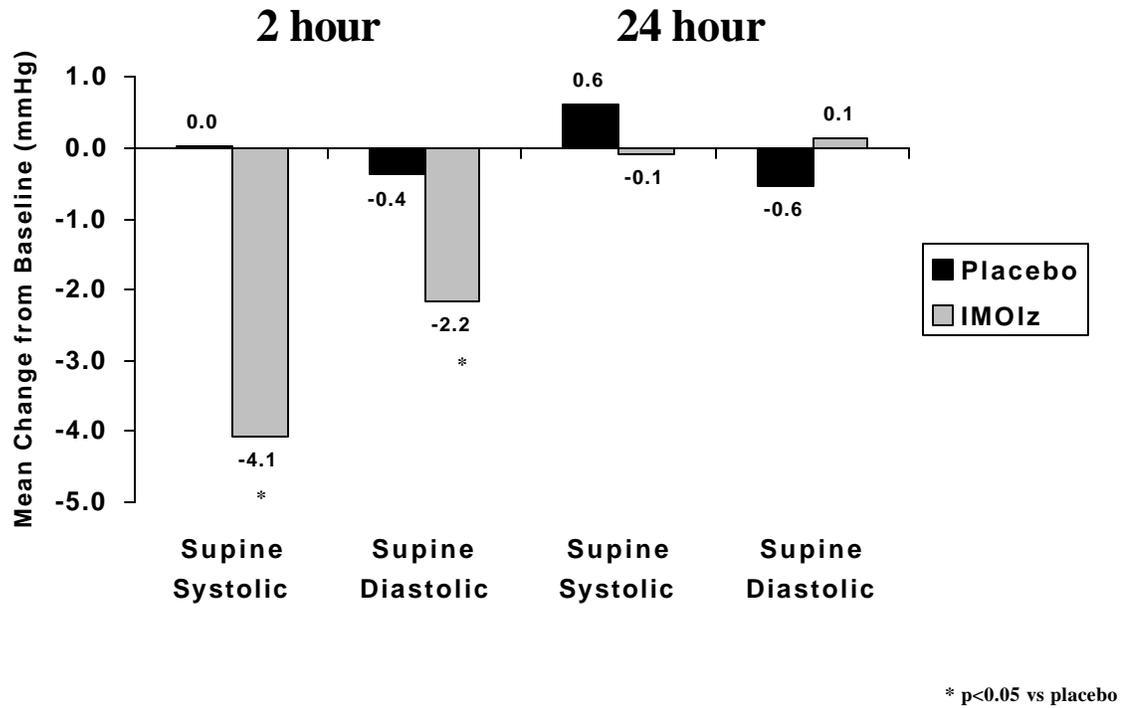
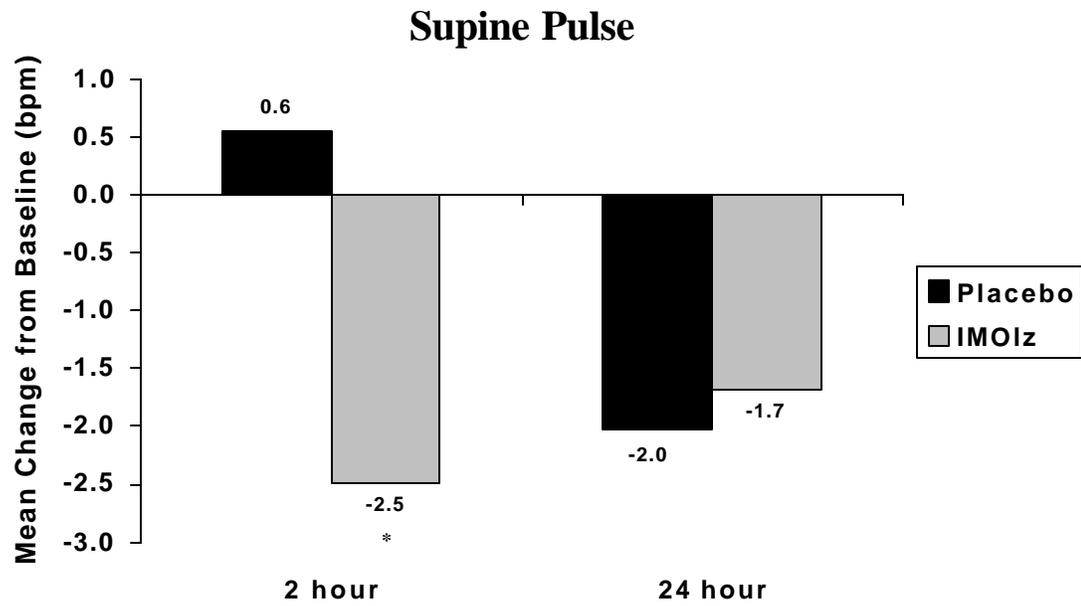
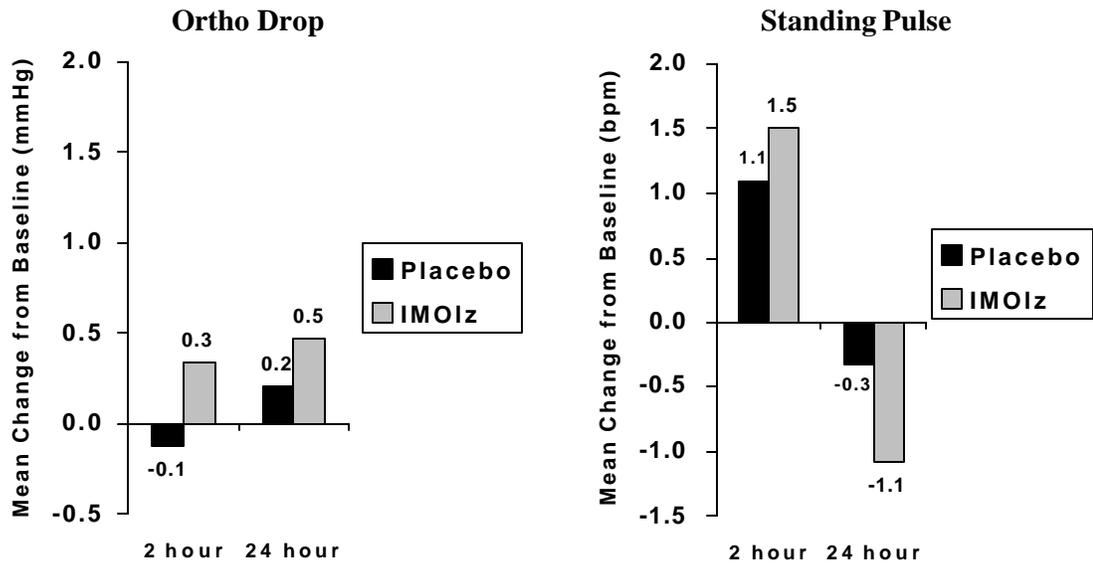


Figure 23. Supine Systolic and Supine Diastolic Blood Pressure Mean Change at 2 and 24 Hours Placebo-Controlled Database



* p<0.05 vs placebo

Figure 24. **Supine Pulse**
Mean Change at 2 and 24 Hours
Placebo-Controlled Database



N.S.D. difference between Olz and Pla on any measure

**Figure 25. Orthostatic Drop and Standing Pulse
Mean Change at 2 and 24 hours
Placebo-Controlled Database**

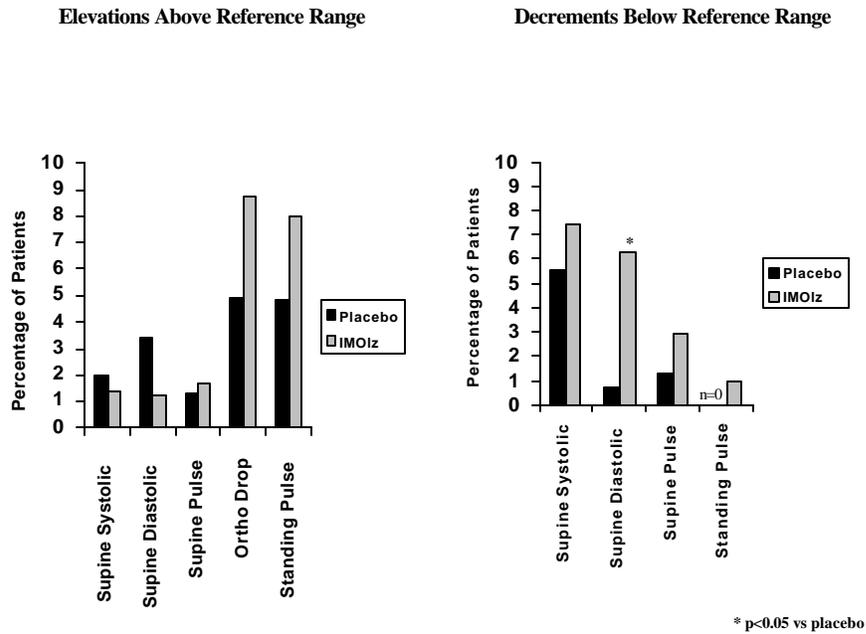


Figure 26. Change to Value Outside of Reference Range at Any Time During the 24 Hours Placebo-Controlled Database

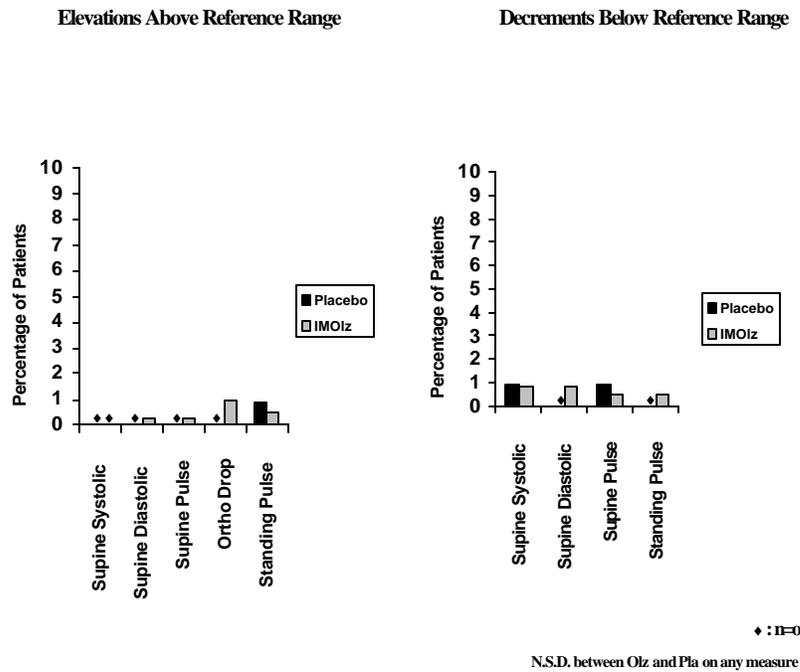
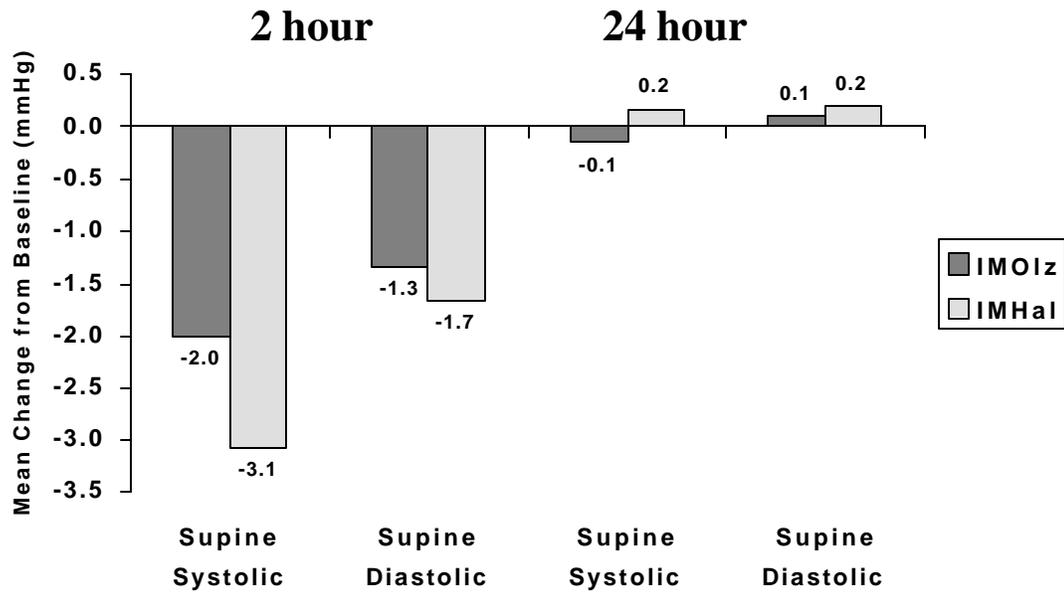


Figure 27. Change to Value Outside of Reference Range at Endpoint of the 24-Hour Period Placebo-Controlled Database

These data, taken together, suggest a small and not clinically significant decrement in blood pressure and heart rate for IM olanzapine compared with IM placebo. Whereas the continuous analysis of mean change at 2 hours indicated a statistically significant decrease in supine pulse for IM olanzapine compared with IM placebo, this statistically significant difference was not reflected in the categorical analyses or in the mean change analysis at 24 hours. In fact, a decrease in supine diastolic blood pressure for IM olanzapine compared with IM placebo was the only vital sign where a significant difference was observed in both continuous and categorical analyses (at any time, not at 24 hours). Further, no significant differences were observed in either continuous or categorical analyses for orthostatic systolic blood pressure drop or standing pulse. Thus, the small decrement in blood pressure in IM olanzapine-treated patients compared with IM placebo-treated patients was observed more under resting conditions than upon orthostatic challenge.

8.6.1.2. Haloperidol-Controlled Database

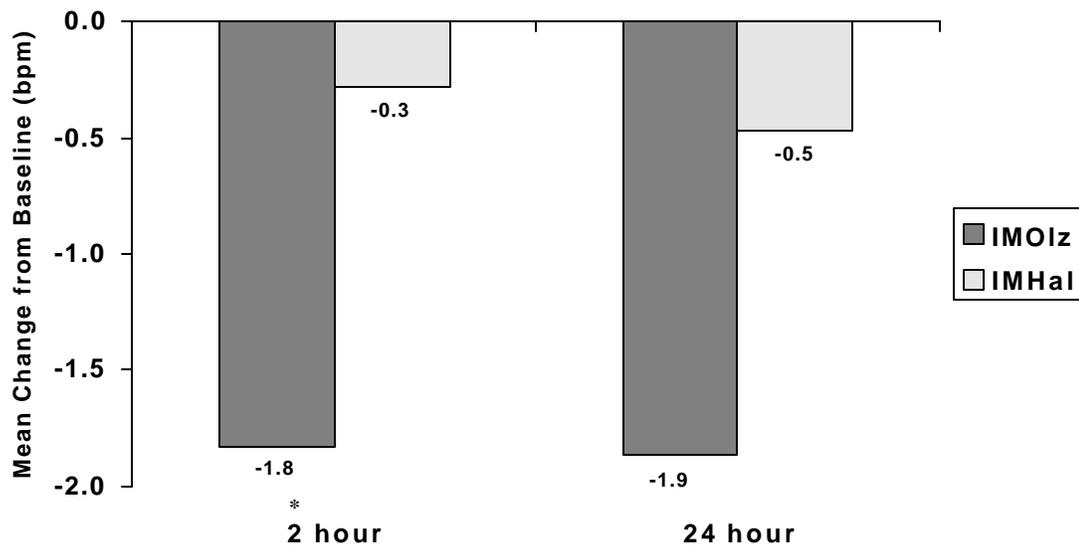
In the mean change analyses at 2 and 24 hours, the IM olanzapine treatment group experienced a significant decrease in supine pulse ($p=0.011$) at 2 hours, and an increase in orthostatic drop in systolic blood pressure ($p=0.035$) at 24 hours compared with the IM haloperidol treatment group (Figures 28 to 30). In the analysis of changes to a value outside the reference range at anytime during the 24 hour IM treatment period or at endpoint of the 24 hour IM treatment period, no significant differences were revealed between IM olanzapine and IM haloperidol (Figures 31 and 32).



N.S.D. between Olz and Hal on any measure

Figure 28. Supine Systolic and Supine Diastolic Blood Pressure Mean Change at 2 and 24 hours Haloperidol-Controlled Database

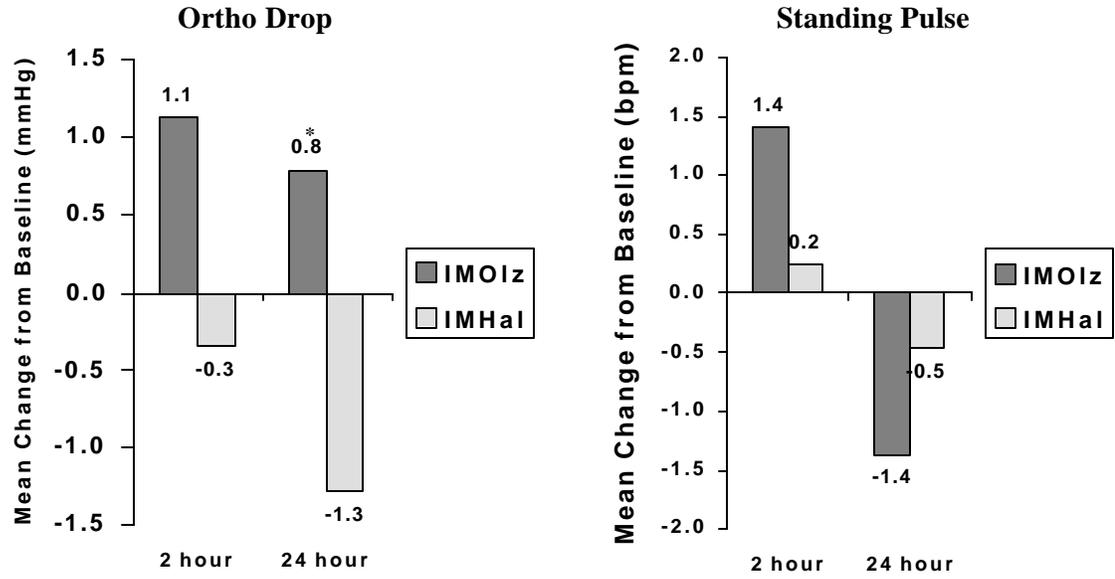
Supine Pulse



* p<0.05 Olz vs Hal

Figure 29.

Supine Pulse
Mean Change at 2 and 24 Hours
Haloperidol-Controlled Database



* p<0.05 Olz vs Hal

Figure 30. Orthostatic Drop and Standing Pulse Mean Change at 2 and 24 Hours Haloperidol-Controlled Database

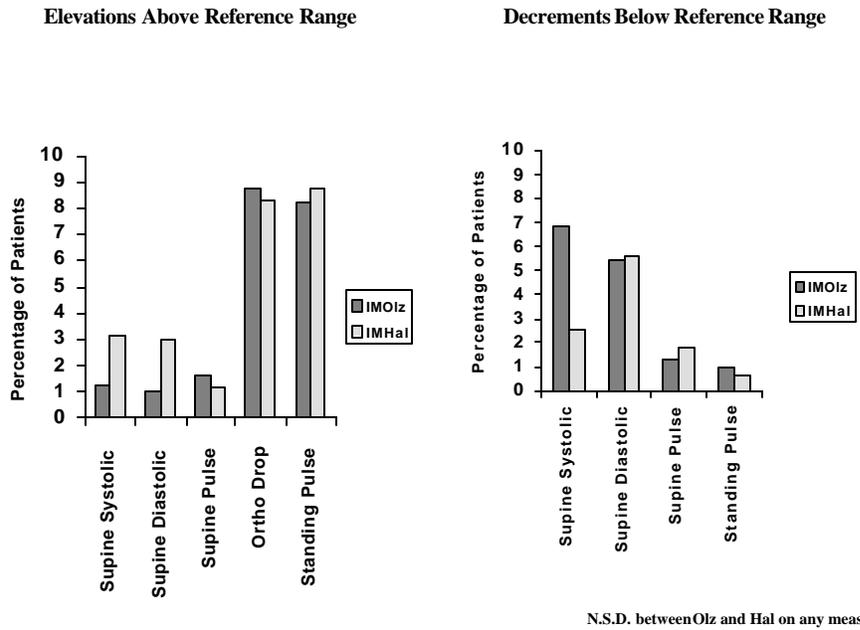


Figure 31. Change to Value Outside of Reference Range at Any Time During the 24 Hours Haloperidol-Controlled Database

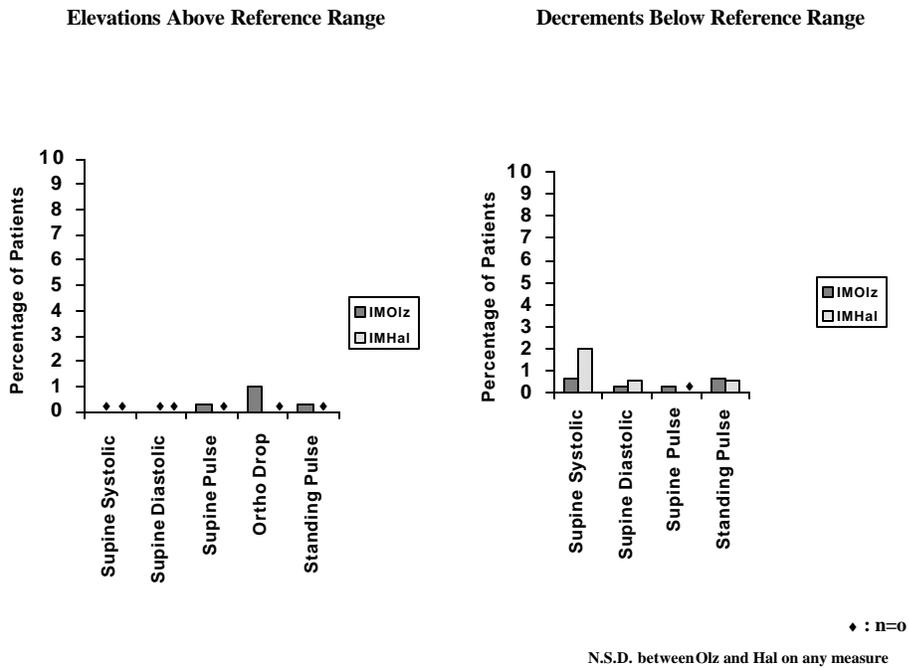
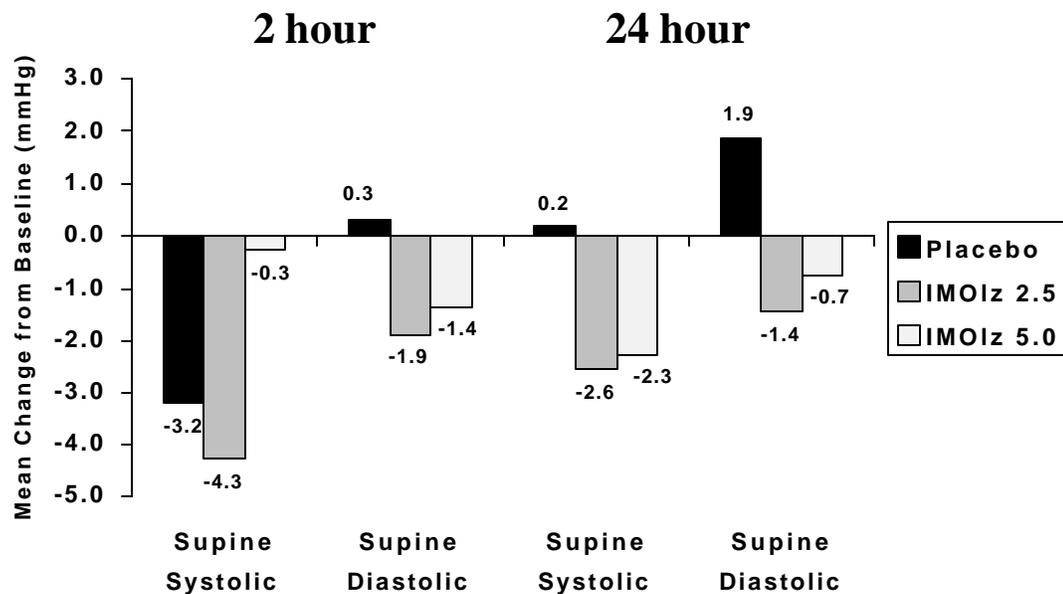


Figure 32. Change to Value Outside of Reference Range at Endpoint of the 24-Hour Period Haloperidol-Controlled Database

While these data suggest a slight increase in the orthostatic drop in blood pressure for IM olanzapine compared with IM haloperidol, the resulting difference does not appear to be clinically significant. The mean change analysis at 24 hours indicated a statistically significant difference in orthostatic systolic blood pressure drop. However, this difference was not reflected in either the mean change analysis at 2 hours or in the categorical analyses. Further, the statistical difference in the mean change analysis at 24 hours appears to result, to a large extent, from a paradoxical decrease in orthostatic systolic blood pressure drop for IM haloperidol.

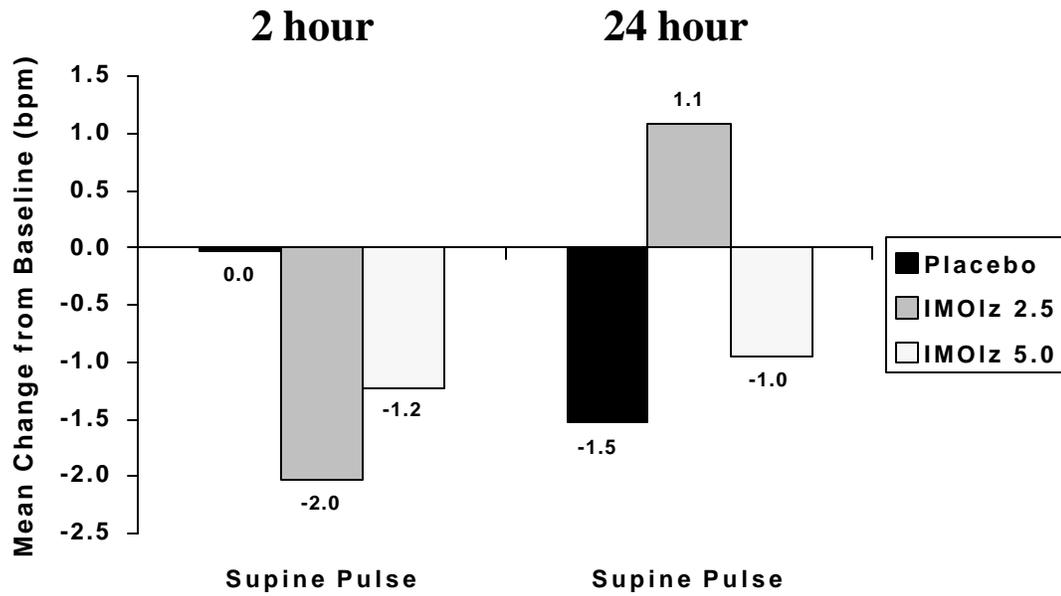
8.6.1.3. Geriatric Placebo-Controlled Database

No significant differences were found between IM olanzapine and IM placebo for vital sign changes in either the mean change analyses at 2 hour or 24 hour endpoints (Figures 33 to 35) or the analyses of changes to a value outside the reference range at any time (Figure 36) or at endpoint (Figure 37) of the 24 hour IM treatment period. IM olanzapine had no clinically relevant effects on blood pressure or heart rate in these elderly, medically compromised patients.



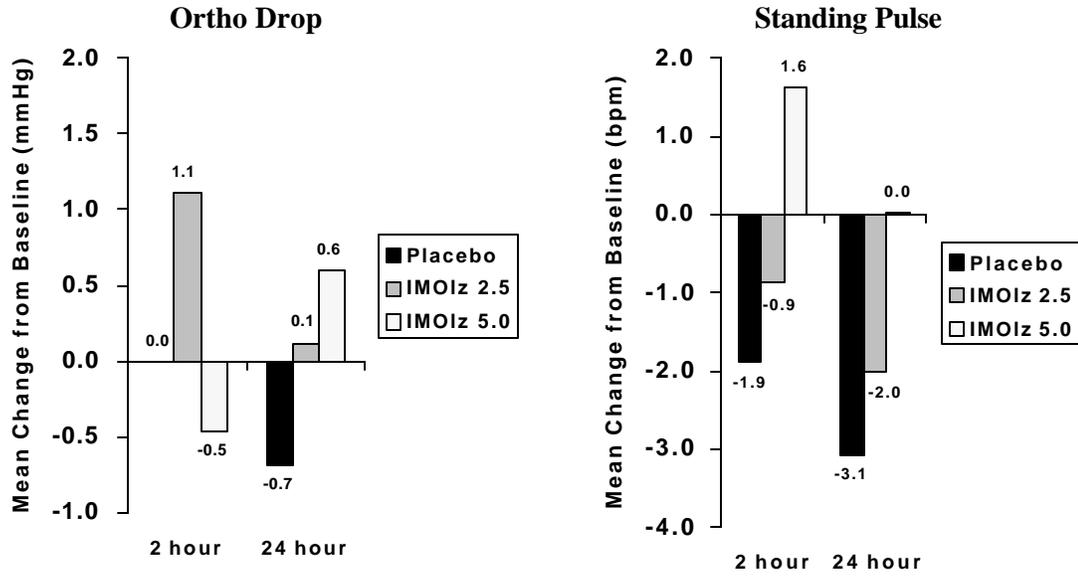
N.S.D. between Olz and Pla on any measure

Figure 33. Supine Systolic and Supine Diastolic Blood Pressure Mean Change at 2 and 24 Hours Geriatric Placebo-Controlled Database



N.S.D. between Olz and Pla on any measure

**Figure 34. Supine Pulse
Mean Change at 2 and 24 Hours
Geriatric Placebo-Controlled Database**



N.S.D. between Olz and Pla on any measure

Figure 35. Orthostatic Drop and Standing Pulse Mean Change at 2 and 24 Hours Geriatric Placebo-Controlled Database

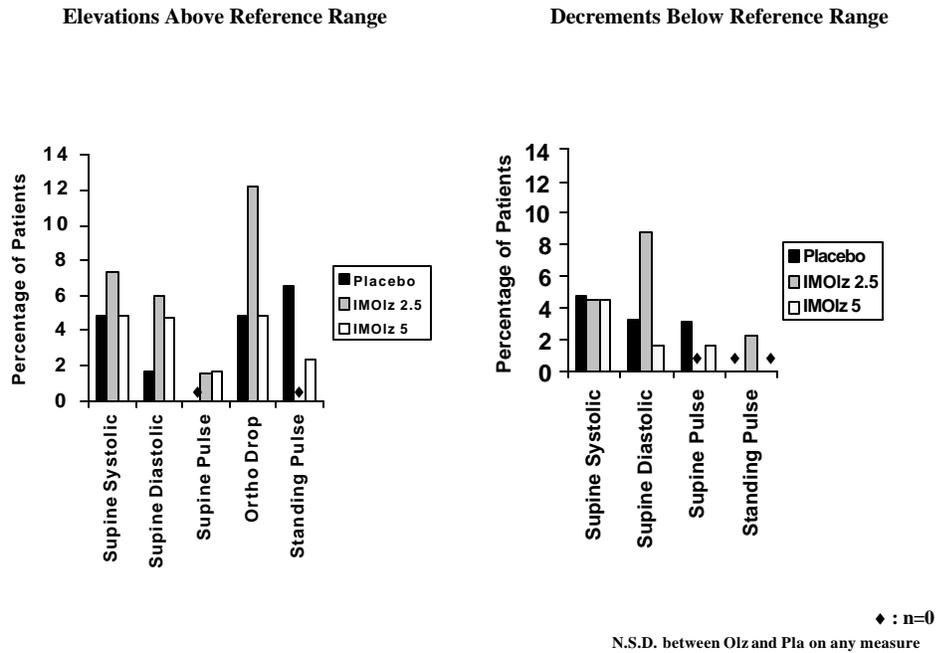


Figure 36. Change to Value Outside of Reference Range at Any Time During the 24 Hours Geriatric Placebo-Controlled Database

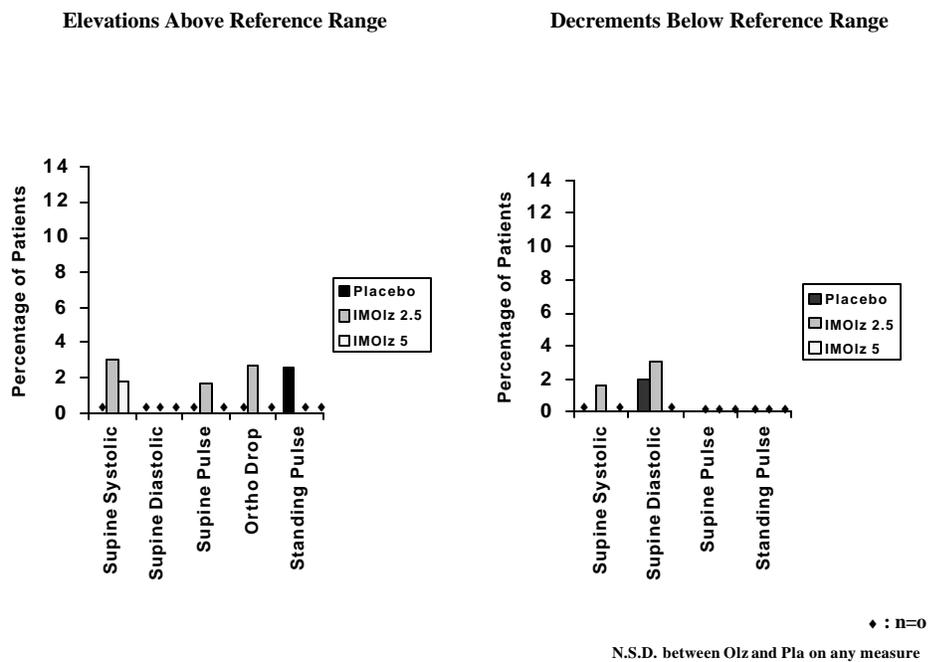


Figure 37. Change to Value Outside of Reference Range at Endpoint of the 24 Hour Period Geriatric Placebo-Controlled Database

8.6.2. Specific Considerations Regarding Decrements in Blood Pressure and Heart Rate

IM olanzapine, in comparison to IM placebo, was not associated with any effects on vital signs except for small and infrequent decrements in blood pressure and heart rate that did not appear to be clinically relevant. When compared with IM haloperidol, these differences (i.e., the differences seen for IM olanzapine versus placebo) were essentially lost.

To further investigate decrements in blood pressure and heart rate reported during treatment with IM olanzapine, a review of all IM olanzapine studies was undertaken to identify and review any cases where potentially clinically significant decreases in heart rate and blood pressure were observed together following IM olanzapine treatment (see Appendix 2, Table 33, for criteria used to identify potentially clinically significant changes) in patients treated with IM olanzapine. Infrequent occurrences of such cases were identified. Of the 765 patients treated with IM olanzapine to date (i.e., comprised of 722 agitated patients in the overall integrated database plus 43 non-agitated schizophrenia patients from a clinical pharmacology study), only 5 cases were identified where decrements in blood pressure and heart rate were observed together. Further, a direct comparison of IM olanzapine to IM haloperidol from the pool of 316 olanzapine-treated and 166 haloperidol-treated patients in the haloperidol-controlled database identified one case (one of the five total cases noted above) with IM olanzapine where decrements of heart rate and blood pressure were observed together compared with no cases with IM haloperidol. The 95% confidence interval about this difference in incidence is -0.003 to 0.010 .

Clinical evaluation of these individual cases indicated that they were consistent with the physiologic mechanism of neurally mediated reflex bradycardia/syncope (NMRB). NMRB is a relatively common form of vasovagal decrement in heart rate, reported to account for about 40% or more of cases of syncope (Linzer et al. 1997). In NMRB/syncope an abnormal reflex response to a decrement in blood pressure leads to sinus bradycardia and / or sinus pauses usually accompanied by peripheral vasodilatation. This may lead to dizziness or syncope. The autonomic reflex mechanism is responsible for slowing of the heart rate and no intrinsic cardiac arrhythmias are present. NMRB/syncope is both a common and relatively benign cause of postural dizziness and syncope in otherwise healthy individuals. Factors leading to a degree of venous pooling or drop in blood pressure (e.g., orthostatic challenge) are necessary to initiate the NMRB cascade of events of venous pooling/drop in blood pressure \rightarrow increased cardiac contractility \rightarrow bradycardia and decreased vascular tone. NMRB in patients treated with olanzapine may result from a combination of its α_1 -adrenergic receptor antagonism resulting in decreased peripheral vascular resistance and the sedation that frequently results in those who receive the medication assuming a supine posture for extended periods, facilitating venous pooling.

Decrements in resting blood pressure and increases in the drop in systolic blood pressure (i.e., orthostatic hypotension) and NMRB/syncope are clearly distinct physiologic phenomena. The decrements in resting blood pressure and the orthostatic hypotension are likely direct pharmacologic effects of IM olanzapine with its α_1 -receptor antagonism. Based on categorical definitions for objective vital signs these phenomena will occur in the range between 5% and 10% of the adult clinical population treated with IM olanzapine.

NMRB/syncope, in contrast, is not a direct effect of IM olanzapine. Its clinical expression is facilitated by the decrement in blood pressure and orthostatic hypotension that occur during IM olanzapine treatment but occurs in individuals with the pre-existing abnormal reflex.

The potential clinical significance of these vital signs findings was investigated by evaluating hemodynamic or possibly hemodynamic-related effects of sufficient clinical consequence to be reported as adverse events. A direct comparison of IM olanzapine to IM haloperidol from the pool of 316 olanzapine-treated and 166 haloperidol-treated patients in the haloperidol-controlled database in hemodynamic-related adverse events revealed no deaths, serious adverse events, or discontinuations from either IM olanzapine or IM haloperidol for any hemodynamic or possibly hemodynamic related event (e.g., dizziness). The analysis of treatment-emergent adverse events revealed no cases of syncope in either treatment group, and no other appreciable differences except for resting hypotension with greater incidence among IM olanzapine-treated patients ($p=0.055$) (Table 17). Similar analyses for treatment-emergent adverse events comparing IM olanzapine to IM lorazepam in agitated patients with bipolar mania (lorazepam-controlled database) and in medically-compromised geriatric patients with dementia (geriatric lorazepam-controlled database) revealed no substantial differences among the treatment groups (Tables 18 and 19).

Table 17. Treatment-Emergent Adverse Events Related to Bradycardia or Hypotension Haloperidol-Controlled Database

Event Classification	IM Olanzapine (N=316)		IM Haloperidol (N=166)		p-value
	n	%	n	%	
Dizziness	8	2.5%	3	1.8%	0.755
Postural Hypotension	4	1.3%	0	0%	0.304
Syncope	0	0%	0	0%	--
Hypotension	8	2.5%	0	0%	0.055
Bradycardia ^a	1	0.3%	0	0%	1.000

^a Includes the COSTART terms "sinus bradycardia" and "bradycardia."

Table 18. Treatment-Emergent Adverse Events Related to Bradycardia or Hypotension Lorazepam-Controlled Database

Event Classification	IM Olanzapine (N=99)		IM Lorazepam (N=51)		p-value
	n	%	n	%	
Dizziness	9	9.1%	7	13.7%	0.411
Postural Hypotension	1	1.0%	1	2.0%	1.000
Syncope	1	1.0%	0	0%	1.000
Hypotension	1	1.0%	2	3.9%	0.267
Bradycardia ^a	1	1.0%	0	0%	1.000

^a Includes the COSTART terms "sinus bradycardia" and "bradycardia."

Table 19. Treatment-Emergent Adverse Events Related to Bradycardia or Hypotension Geriatric Lorazepam-Controlled Database

Event Classification	IM Olz 2.5 mg (N=71)		IM Olz 5 mg (N=66)		IM Lzp (N=68)		p-value	
	n	%	n	%	n	%	Olz 2.5 vs Lzp	Olz 5 vs Lzp
Dizziness	2	2.8%	1	1.5%	2	2.9%	1.00	1.00
Postural Hypotension	0	0%	0	0%	0	0%	--	--
Syncope	0	0%	0	0%	0	0%	--	--
Hypotension	0	0%	1	1.5%	1	1.5%	0.489	1.00
Bradycardia ^a	0	0%	1	1.5%	0	0%	--	--

^a Includes the COSTART terms “sinus bradycardia” and “bradycardia.”

8.6.3. Vital Signs Conclusions

Direct comparison of IM olanzapine to IM haloperidol indicated clinically similar hemodynamic safety profiles with a slightly greater incidence of hypotension as an adverse event (IM olanzapine 2.5%, IM haloperidol 0%; $p=0.055$). This difference in blood pressure was not as great when categorical decreases in resting blood pressure were assessed by objective criteria (incidence of decrements in supine systolic blood pressure at any time: IM olanzapine 6.8%, IM haloperidol 2.5%, $p=0.053$; incidence of decrements in supine diastolic blood pressure at any time: IM olanzapine 5.4%, IM haloperidol 5.6%, $p=1.000$).

In summary, IM olanzapine appears to have the capacity to facilitate a slight decrement in resting blood pressure and to slightly increase the decrement in systolic blood pressure observed on orthostatic challenge. The changes observed upon orthostatic challenge were even smaller than those observed at rest. Infrequently, decrements in blood pressure can occur together with decrements in heart rate. Some degree of decrement in resting blood pressure differentiated IM olanzapine from IM haloperidol in clinical use in these studies but did not result in any significant differences in relevant clinical adverse events (dizziness, syncope) or in discontinuation or serious events in clinical studies. Similarly, comparison of IM olanzapine to IM lorazepam revealed no substantial differences in clinical adverse events (dizziness, syncope).

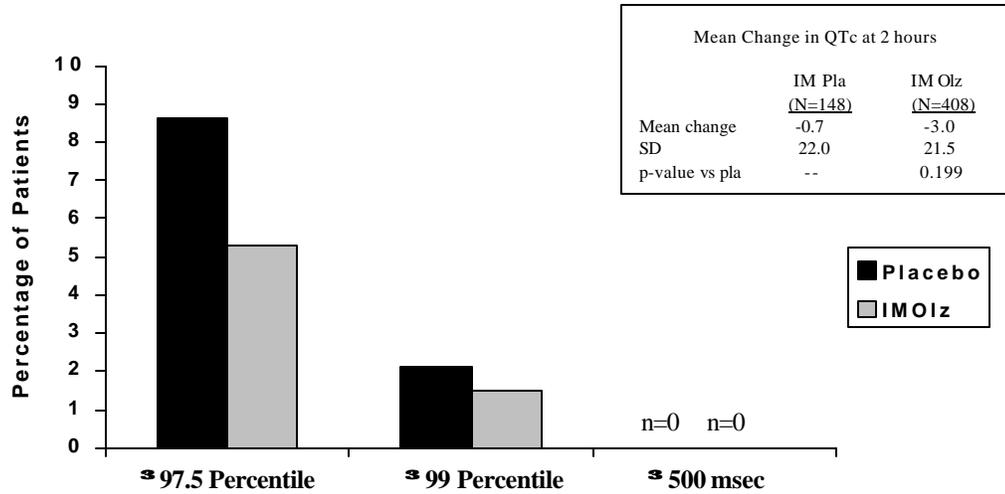
It should be noted that agitated patients generally have elevated heart rates and blood pressures (Harvey 1996). Some of the observed decrements may result from the calming therapeutic effects of IM olanzapine.

8.7. Electrocardiograms

The analyses of ECG data included continuous analyses of change from baseline to endpoint at 2 hours and 24 hours following the first IM injection, and categorical analyses of ECG changes from normal at baseline to abnormal at 2 hours and 24 hours following the IM injection. This section summarizes the results of these analyses of ECG intervals and heart rate for the placebo-controlled database, haloperidol-controlled database, and geriatric placebo-controlled database. The lorazepam-controlled and the geriatric lorazepam-controlled databases are not presented because haloperidol is believed to be the more standard treatment (sometimes in combination with lorazepam) and the analyses with just placebo- and haloperidol-controlled groups are quite extensive. Historically, some antipsychotics have been associated with the capacity to delay ventricular repolarization. Based on this, this section presents the IM olanzapine QTc data in greater detail for each of the three databases. All of the results from the IM olanzapine clinical studies indicate that IM olanzapine had no clinically relevant effect on any ECG interval, including QTc, or heart rate.

8.7.1. Placebo-Controlled Database

The mean change and categorical analyses of ECGs revealed no statistically significant differences accounted for by an increase in ECG intervals (PR, QRS, QR, and QTc) for IM olanzapine compared with IM placebo. The only statistically significant difference in either the continuous or categorical QTc analyses was an increased incidence of **IM placebo-treated patients** exhibiting prolonged QTc intervals (Moss [1993] 97.5 percentile: ≥ 430 msec males, ≥ 450 msec females) compared with IM olanzapine-treated patients in the categorical analysis at 24 hours (Figures 38 and 39). Tables 34 and 35 in Appendix 3, provide the data for mean change in QTc interval from baseline to 2 hours and to 24 hours.

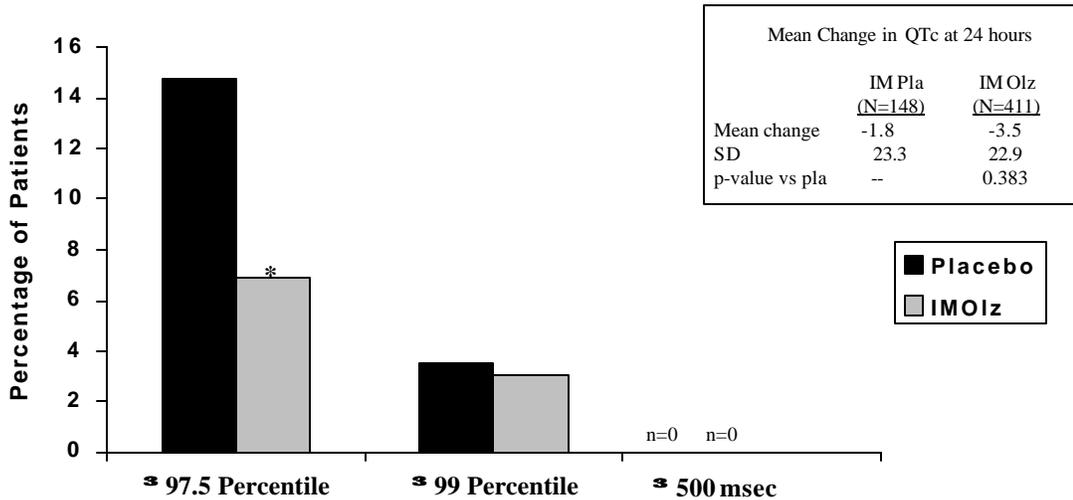


Moss (1993) \geq 97.5 Percentile: \geq 430 msec male
 \geq 450 msec female

Moss (1993) \geq 99 Percentile: \geq 450 msec male
 \geq 470 msec female

N.S.D. on any measure vs placebo

Figure 38. QTc Interval: Normal to Prolonged at 2 hrs and Mean Change Placebo-Controlled Database



Moss (1993) \geq 97.5 Percentile: \geq 430 msec male
 \geq 450 msec female

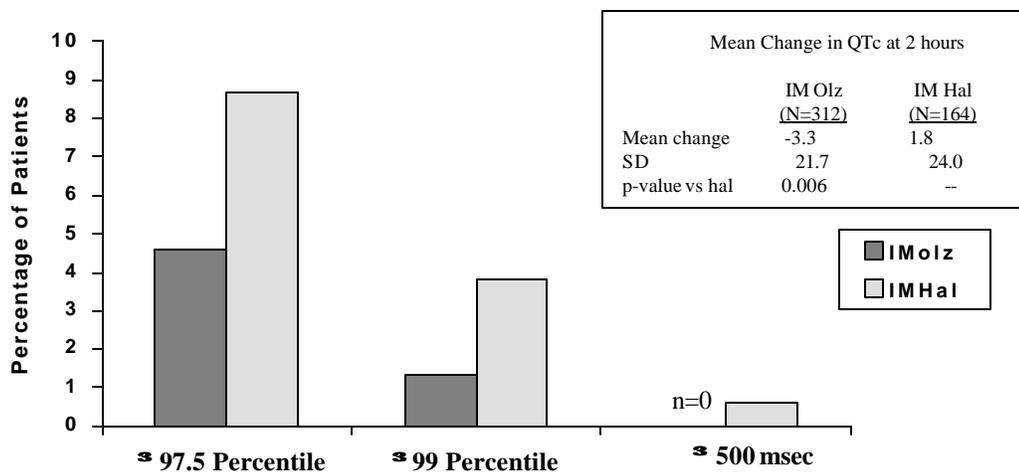
Moss (1993) \geq 99 Percentile: \geq 450 msec male
 \geq 470 msec female

* p<0.05 vs placebo

Figure 39. QTc Interval – Normal to Prolonged at 24 hrs and Mean Change Placebo-Controlled Database

8.7.2. Haloperidol-Controlled Database

Analysis of the pooled data from the 2 studies in agitated patients with schizophrenia where IM haloperidol was included as the active comparator revealed no statistically significant differences accounted for by an increase in ECG intervals (PR, QRS, QR, and QTc) for IM olanzapine compared with IM haloperidol. The mean change and categorical analyses of QTc intervals for IM olanzapine compared with IM haloperidol are shown in Figures 40 and 41. The only statistically significant difference in any of the QTc analyses was a mean decrease in QTc interval in the IM olanzapine group versus a mean increase in the IM haloperidol group at the 2-hour time point that was statistically significant at 2 hours (IM olanzapine: -3.3 msec, IM haloperidol: $+1.8$ msec; $p=0.006$). Tables 36 and 37 in Appendix 3 provide the data for mean change in QTc interval from baseline to 2 hours and to 24 hours.

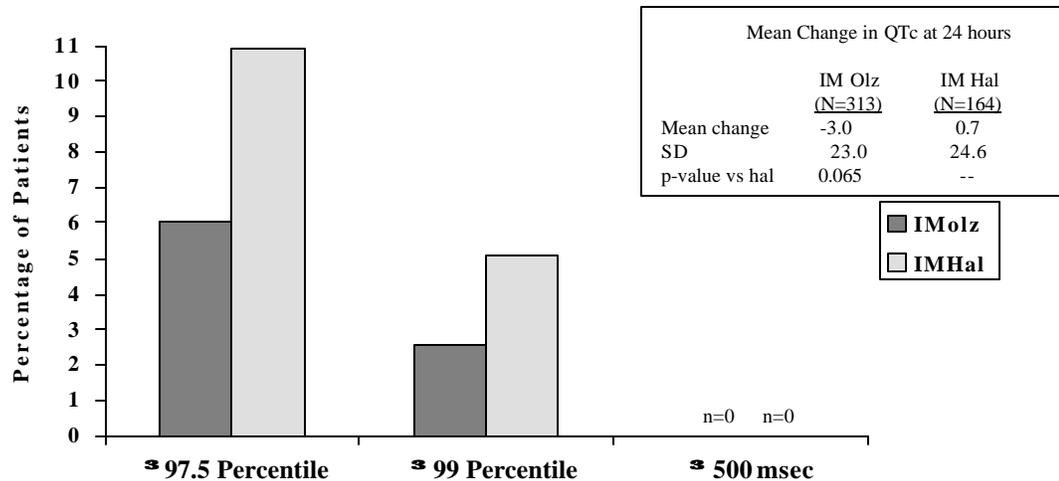


Moss (1993) ≥ 97.5 Percentile: ≥ 430 msec male
 ≥ 450 msec female

Moss (1993) ≥ 99 Percentile: ≥ 450 msec male
 ≥ 470 msec female

N.S.D. on any measure vs haloperidol

Figure 40. QTc Interval: Normal to Prolonged at 2 hrs and Mean Change Haloperidol-Controlled Database



Moss (1993) ≥97.5 Percentile: ≥ 430 msec male
≥ 450 msec female

Moss (1993) ≥99 Percentile: ≥ 450 msec male
≥ 470 msec female

N.S.D. between on any measure vs. haloperidol

Figure 41. QTc Interval: Normal to Prolonged at 24 hrs and Mean Change Haloperidol-Controlled Database

8.7.3. Geriatric Placebo-Controlled Database

In the pivotal study conducted in agitated patients with dementia, the ECG analyses revealed baseline differences among the treatment groups (Table 20). The mean baseline QTc interval in the IM olanzapine 5 mg treatment group was statistically significant lower than the mean in the other three treatment groups. There was also an extreme variance in the QTc values at baseline as reflected in Figures 42 and 43.

Table 20. QTc Interval Mean Baseline QTc Values Agitation in Dementia Study

Treatment Group	Baseline QTc (msec)		p-value versus IM Olanzapine 5 mg
	N	Mean ± SD	
IM Olanzapine 2.5 mg	69	430.3 ± 29.2	0.036
IM Olanzapine 5 mg	61	419.0 ± 26.3	--
IM Lorazepam	64	432.1 ± 37.8	0.021
IM Placebo	62	432.6 ± 31.8	0.019

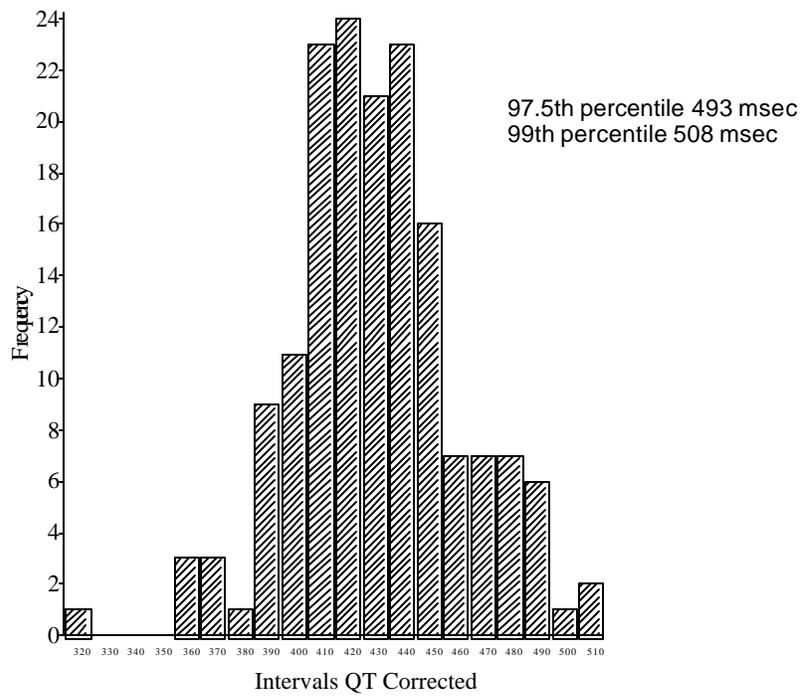


Figure 42. The Frequency Distribution of Baseline QTc Intervals for Females Agitation in Dementia Study

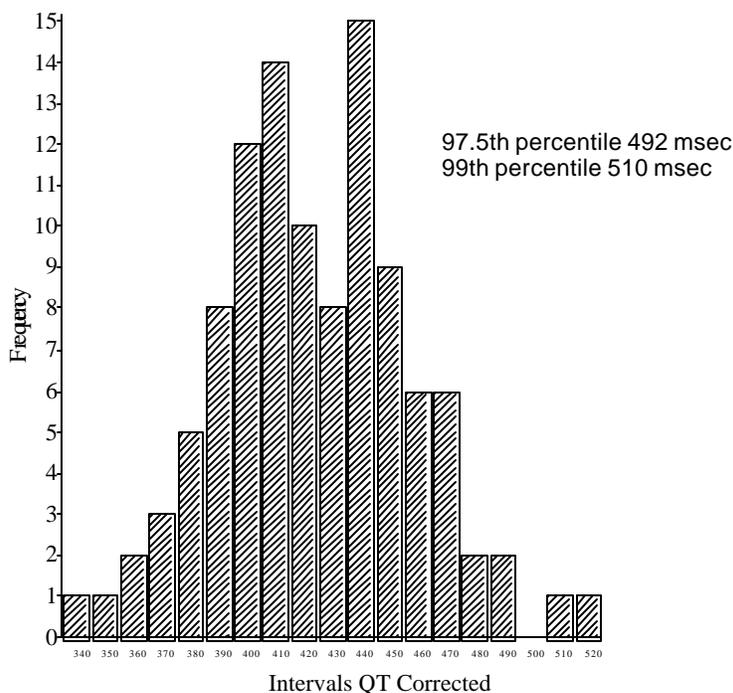
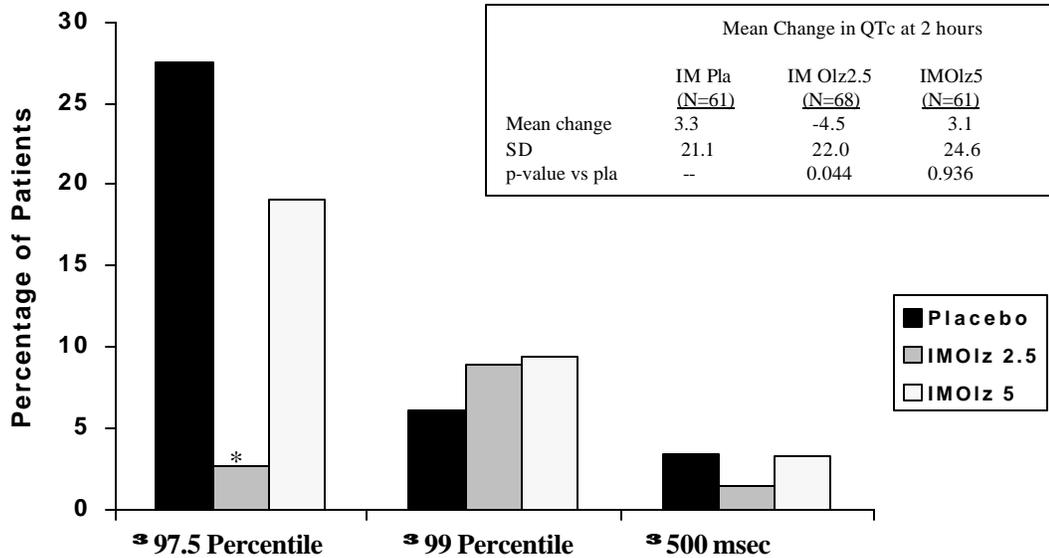


Figure 43. The Frequency Distribution of Baseline QTc Intervals for Males Agitation in Dementia Study

These findings at baseline led to a review by external cardiology consultants with special expertise in cardiac repolarization and geriatric cardiology. The recommendation was that all the ECG tracings from this study should be independently re-read by two established ECG core laboratories. The blinded re-read results from the two laboratories were closely correlated (baseline correlation $r=0.79$). The data from the two independent laboratories were averaged for the analyses of the ECG data presented in this section.

The mean change and categorical analyses of these ECG data revealed no statistically significant differences accounted for by an increase in ECG intervals (QRS, QR, QTc, and JTc) for IM olanzapine compared with IM placebo. The analyses of QTc intervals for IM olanzapine compared with IM placebo are shown in Figures 44 and 45. The only statistically significant difference in the categorical analyses of QTc was an increased incidence of **IM placebo-treated patients** exhibiting prolonged QTc intervals compared with IM olanzapine 2.5 mg-treated patients in the categorical analysis at 2 and 24 hours (97.5 percentile ≥ 430 msec males, ≥ 450 msec females; Moss [1993]). The only statistically significant difference in the mean change analyses was a **mean decrease** in the IM olanzapine 2.5 mg group versus a mean increase in the IM placebo group at both 2 and 24 hours. Tables 38 and 39 in Appendix 3, provide the data for mean change in QTc interval from baseline to 2 hours and to 24 hours.

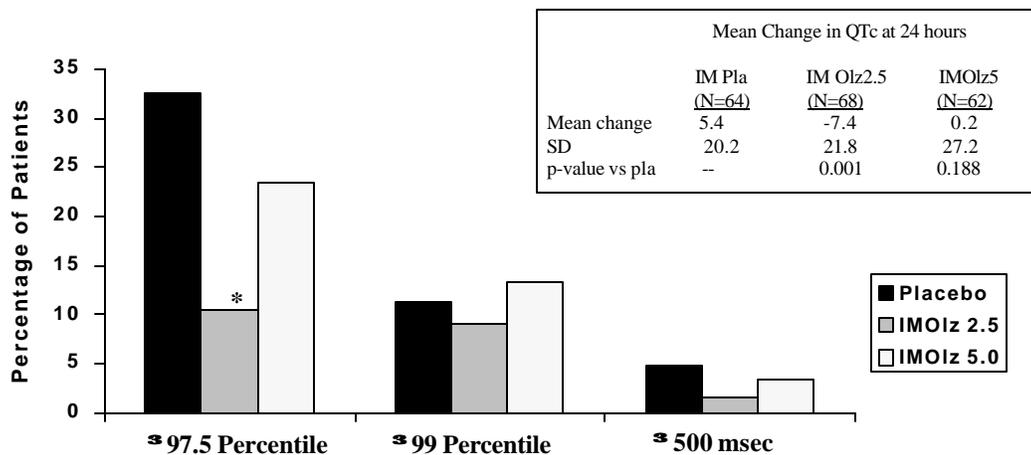


Moss (1993) ≥ 97.5 Percentile: ≥ 430 msec male
 ≥ 450 msec female

Moss (1993) ≥ 99 Percentile: ≥ msec 450 male
 ≥ msec 470 female

* p<0.05 vs placebo

**Figure 44. QTc Interval: Normal to Prolonged at 2 hrs
 Mean Change
 Geriatric Placebo-Controlled Database**



Moss (1993) ≥ 97.5 Percentile: ≥ 430 msec male
 ≥ 470 msec female

Moss (1993) ≥ 99 Percentile: ≥ 450 msec male
 ≥ 470 msec female

*p<0.05 vs. Placebo

**Figure 45. QTc Interval: Normal to Prolonged at 24 hrs
 Mean Change
 Geriatric Placebo-Controlled Database**

In addition to the analyses presented above, further analyses of QTc intervals were conducted for all four pivotal studies. These included an examination of the incidence of changes from baseline of ≥ 30 , ≥ 60 , and ≥ 75 msec. There were no statistically or clinically significant differences among the treatment groups in any of these analyses.

8.7.4. Electrocardiogram Conclusions

All of the results from the IM olanzapine clinical studies indicate that IM olanzapine had no clinically relevant effect on any ECG interval, including QTc, or heart rate. In the categorical analyses of QTc interval, the only statistically significant differences seen were an increased incidence of **IM placebo-treated patients** exhibiting prolonged QTc interval (increase above the 97.5 percentile: ≥ 430 msec males, ≥ 450 msec females; Moss [1993]) compared with IM olanzapine-treated patients in both the placebo-controlled and geriatric placebo-controlled databases. In the mean change analyses of QTc interval, the only statistically significant differences seen were a mean decrease in the IM olanzapine 2.5 mg group versus a mean increase in the IM placebo group in the geriatric placebo-controlled database and a mean decrease in the IM olanzapine group versus a mean increase in the IM haloperidol group in the haloperidol-controlled database.

8.8. Sedation

This section evaluates the potential association of IM olanzapine with excessive sedation for each of the five IM olanzapine controlled databases. Two approaches were used: evaluation of the ACES data, and conventional adverse event collection.

For the ACES evaluations, categorical analyses were conducted of the proportions of patients with scores of 8 (deep sleep) or 9 (unarousable) at any time during the 24-hour IM treatment period of the pivotal studies. For the adverse event evaluations, the COSTART adverse event terms of somnolence, CNS depression, stupor, or coma were identified as potentially related to excessive sedation by sponsor physician review of all adverse terms from the studies included in the overall patient database. The incidence of these adverse event terms was then assessed for each of the controlled databases.

The results of the ACES and adverse event evaluations for each of the five IM olanzapine controlled databases are presented below. In the IM olanzapine pivotal clinical trials, IM olanzapine was not associated with excessive or adverse sedation.

8.8.1. Agitation-Calmness Evaluation Scale

The proportions of patients in each of the five controlled databases with an ACES score of 8 or 9 at any time during the 24-hour IM period are shown in Tables 21 to 25. The only statistically significant difference in any of the five databases, was an increased incidence of IM olanzapine-treated patients versus IM placebo-treated patients having a score of 8 in the placebo-controlled database (4.3% versus 0.7%, $p=0.033$). Only one

patient (an IM-lorazepam-treated patient) had an ACES score of 9 at anytime during the 24-hour period.

**Table 21. Maximum ACES Score of 8 or 9
Placebo-Controlled Database
24-Hours Following the First IM Injection Period**

Maximum	IM Olanzapine (N=414)		IM Placebo (N=149)		p-value ^a
	n	%	n	(%)	
ACES Score of 8	18	4.3%	1	0.7%	0.033
ACES Score of 9	0	0%	0	0%	--

^a Frequencies are analyzed using a Fisher's Exact test.

**Table 22. Maximum ACES Score of 8 or 9
Haloperidol-Controlled Database
24 Hours Following the First IM Injection Period**

Maximum	IM Olanzapine (N=316)		IM Haloperidol (N=166)		p-value ^a
	n	%	n	%	
ACES Score of 8	12	3.8%	2	1.2%	0.154
ACES Score of 9	0	0%	0	0%	--

^a Frequencies are analyzed using a Fisher's Exact test.

**Table 23. Maximum ACES Score of 8 or 9
Lorazepam-Controlled Database
24 Hours Following the First IM Injection Period**

Maximum	IM Olanzapine (N=98)		IM Lorazepam (N=51)		p-value ^a
	n	%	n	(%)	
ACES Score of 8	6	6.1%	2	3.9%	0.716
ACES Score of 9	0	0%	1	2.0%	0.342

^a Frequencies are analyzed using a Fisher's Exact test.

**Table 24. Maximum ACES Score of 8 or 9
Geriatric Placebo-Controlled Database
24 Hours Following the First IM Injection Period**

Maximum	IM Olanzapine (N=137)		IM Placebo (N=67)		p-value ^a
	n	%	n	%	
ACES Score of 8	10	7.3%	3	4.5%	0.552
ACES Score of 9	0	0%	0	0%	--

^a Frequencies are analyzed using a Fisher's Exact test.

**Table 25. Maximum ACES Score of 8 or 9
Geriatric Lorazepam-Controlled Database
24 Hours Following the First IM Injection Period**

Maximum	IM Olanzapine (N=137)		IM Lorazepam (N=68)		p-value ^a
	n	%	n	%	
ACES Score of 8	10	7.3%	6	8.8%	0.784
ACES Score of 9	0	0%	0	0%	--

^a Frequencies are analyzed using a Fisher's Exact test.

8.8.2. Incidence of Sedation-Related Adverse Events

The proportions of patients in each of the five controlled databases with treatment-emergent adverse events related to sedation are shown in Tables 26 to 30. The only sedation-related adverse event identified in the five databases was somnolence. Analysis of the proportions of patients with somnolence revealed no statistically significant differences between treatment groups in any of the five IM olanzapine controlled databases. No patients had treatment-emergent CNS depression, stupor, or coma.

Table 26. Treatment-Emergent Adverse Events Related to Sedation Placebo-Controlled Database 24 Hours Following the First IM Injection Period

Event Classification	IM Olanzapine (N=415)		IM Placebo (N=150)		p-value
	n	%	n	%	
Somnolence	23	5.5%	5	3.3%	0.381

Table 27. Treatment-Emergent Adverse Events Related to Sedation Haloperidol-Controlled Database 24 Hours Following the First IM Injection Period

Event Classification	IM Olanzapine (N=316)		IM Haloperidol (N=166)		p-value
	n	%	n	%	
Somnolence	10	3.2%	10	6.0%	0.152

Table 28. Treatment-Emergent Adverse Events Related to Sedation Lorazepam-Controlled Database 24 Hours Following the First IM Injection Period

Event Classification	IM Olanzapine (N=99)		IM Haloperidol (N=51)		p-value
	n	%	n	%	
Somnolence	13	13.1%	5	9.8%	0.609

Table 29. Treatment-Emergent Adverse Events Related to Sedation Geriatric Placebo-Controlled Database 24 Hours Following the First IM Injection Period

Event Classification	IM Olanzapine (N=137)		IM Placebo (N=67)		p-value
	n	%	n	%	
Somnolence	5	3.6%	2	3.0%	1.00

Table 30. Treatment-Emergent Adverse Events Related to Sedation Geriatric Lorazepam-Controlled Database 24 Hours Following the First IM Injection Period

Event Classification	IM Olanzapine (N=137)		IM Lorazepam (N=68)		p-value
	n	%	n	%	
Somnolence	5	3.6%	7	10.3%	0.109

8.8.3. Sedation Conclusions

Based on the ACES results and the low incidence of treatment-emergent adverse events related to sedation, IM olanzapine was not associated with qualitatively excessive or adverse sedation. Although a small percentage of olanzapine-treated patients were given an ACES rating of 8, no olanzapine-treated patients were given an ACES rating of 9.

Further, no olanzapine-treated patients were considered to have experienced an adverse event labeled with the COSTART terms of stupor, coma, or CNS depression.

8.9. Extrapyramidal Symptoms

8.9.1. *Extrapyramidal Symptoms as Assessed by Treatment-Emergent Adverse Events*

Extrapyramidal symptoms were assessed by grouping treatment-emergent extrapyramidal adverse events into one of five categories: 1) dystonic events, 2) parkinsonian events, 3) akathisia events, 4) dyskinesic events, and 5) residual events, and then reported treatment-emergent events were summarized in the overall category, "any extrapyramidal event."

The number of patients who exhibited one or more extrapyramidal treatment-emergent adverse events was tabulated in the following manner:

- If a patient exhibited one or more extrapyramidal treatment-emergent events that mapped to one of the five extrapyramidal categories, the patient was counted once in that category.
- If a patient exhibited events that mapped to more than one extrapyramidal category, the patient was counted once in each applicable category.
- The total number and percentage of patients who exhibited at least one extrapyramidal treatment-emergent adverse event (regardless of category) are listed in the "Any extrapyramidal event" row. (Thus, even though a patient may have been counted in more than one extrapyramidal category, the patient was counted only once in the "Any extrapyramidal event" row.)

Treatment-emergent adverse event data from each of the two pivotal studies testing multiple doses of IM olanzapine are presented to assess the incidence of extrapyramidal symptoms by dose. The numbers and percentages of patients in the five categories, for the IM olanzapine, IM haloperidol, and IM placebo treatment groups in the pivotal dose ranging study in agitated patients with schizophrenia are shown in Table 31. There were no statistically significant differences between any of the IM olanzapine groups and the IM placebo group for any of the five categories or for the overall category of any extrapyramidal event. In contrast, the analysis revealed a significant increase in the IM haloperidol group compared with the IM placebo group in the overall category of any extrapyramidal event ($p=0.020$).

Table 31. Analysis of Extrapyramidal Treatment-Emergent Adverse Events by Category of Event Agitation in Schizophrenia - Dose Ranging Study

	IM Placebo (N=45)	IM Olanzapine 2.5 mg (N=48)		IM Olanzapine 5 mg (N=45)		IM Olanzapine 7.5 mg (N=46)		IM Olanzapine 10 mg (N=46)		IM Haloperidol 7.5 mg (N=40)	
Extrapyramidal Category	n (%)	n (%)	p-value ^a	n (%)	p-value ^a	n (%)	p-value ^a	n (%)	p-value ^a	n (%)	p-value ^a
Dystonic events ^b	0 (0%)	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--	2 (5.0%)	0.218
Parkinsonian events ^c	0 (0%)	2 (4.2%)	0.495	1 (2.2%)	1.000	0 (0%)	--	0 (0%)	--	3 (7.5%)	0.100
Akathisia events ^d	0 (0%)	1 (2.1%)	1.000	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--
Dyskinetic events ^e	0 (0%)	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--
Residual events ^f	0 (0%)	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--	0 (0%)	--
Any extrapyramidal event	0 (0%)	2 (4.2%)	0.495	1 (2.2%)	1.000	0 (0%)	--	0 (0%)	--	5 (12.5%)	0.020

a Fisher's Exact p-value versus placebo.

b Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

c Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

d Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

e Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

f Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The numbers and percentages of patients in the five categories, for the IM olanzapine and IM placebo treatment groups in the pivotal study in agitated patients with dementia are shown in Table 32. For the IM lorazepam group included in this study, no patients experienced extrapyramidal symptoms. There were no statistically significant differences between any of the IM olanzapine groups and the IM placebo group for any of the five categories or for the overall category of any extrapyramidal event.

Table 32. Analysis of Extrapyramidal Treatment-Emergent Adverse Events by Category of Event Agitation in Dementia Study

Extrapyramidal Category	IM Placebo (N=67)	IM Olanzapine 2.5 mg (N=71)		IM Olanzapine 5 mg (N=66)	
	n (%)	n (%)	p-value ^a	n (%)	p-value ^a
Dystonic events ^b	0 (0%)	0 (0%)	--	0 (0%)	--
Parkinsonian events ^c	0 (0%)	1 (1.4%)	1.000	1 (1.5%)	0.496
Akathisia events ^d	0 (0%)	0 (0%)	--	0 (0%)	--
Dyskinetic events ^e	1 (1.5%)	0 (0%)	0.486	0 (0%)	1.000
Residual events ^f	0 (0%)	0 (0%)	--	0 (0%)	--
Any extrapyramidal event	1 (1.5%)	1 (1.4%)	1.000	1 (1.5%)	1.000

^a Fisher's Exact p-value versus placebo.

^b Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

^c Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked faces, tremor.

^d Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

^e Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

^f Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

8.9.2. Extrapyramidal Symptoms as Assessed by Rating Scales

Extrapyramidal symptoms were assessed in the four IM olanzapine pivotal studies using analyses of mean change from baseline to 24 hours following the first IM injection for the Simpson-Angus Scale total score and the Barnes Akathisia Scale global score (Figures 46 to 49). The results show that there were no statistically significant differences between IM olanzapine and IM placebo in any of the four pivotal studies. In contrast, the analyses of the two pivotal studies in agitated patients with schizophrenia where IM haloperidol 7.5 mg was included as an active comparator showed a significant worsening of symptoms in the IM haloperidol treatment group versus IM placebo on one or both of the rating scales. In the agitation in schizophrenia dose-ranging study, there was a significant difference between each of the IM olanzapine treatment groups compared with IM haloperidol on both the Simpson-Angus and Barnes Akathisia Scales.

In the agitation in schizophrenia study, the treatment difference in mean change for IM olanzapine- and IM haloperidol-treated patients was statistically significant again for both scales.

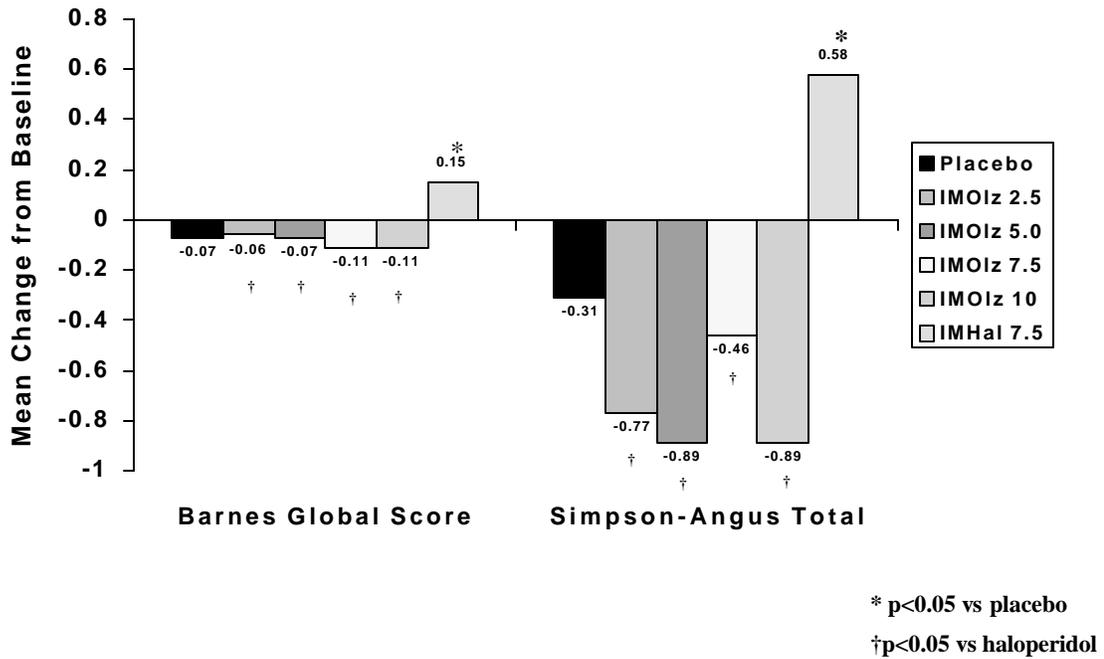


Figure 46. Analysis of Extrapyramidal Symptoms by Rating Scales Agitation in Schizophrenia Dose-Ranging Study

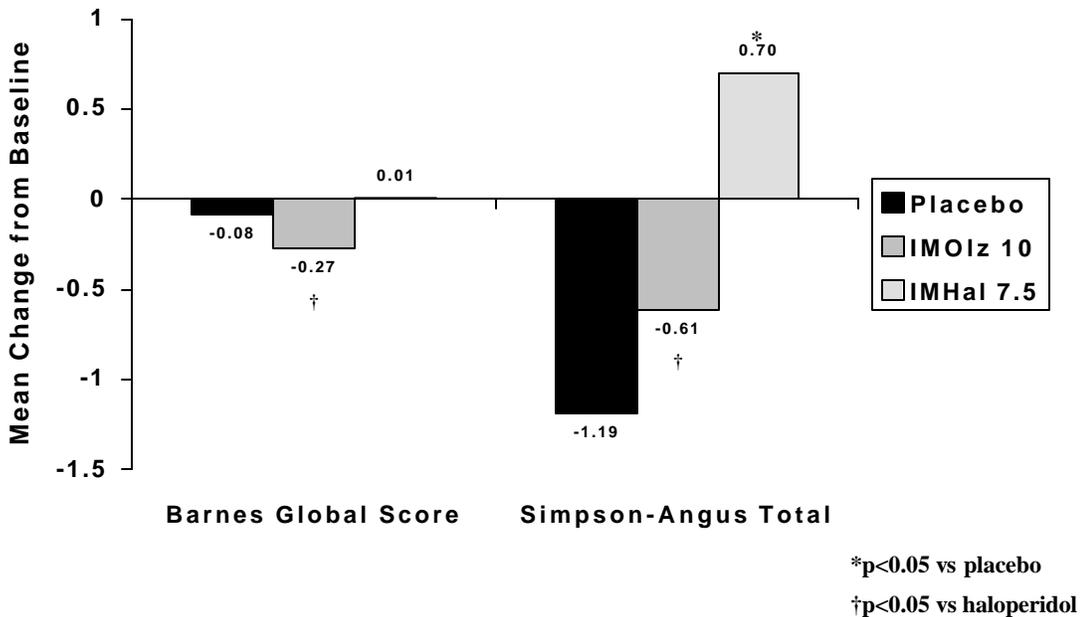
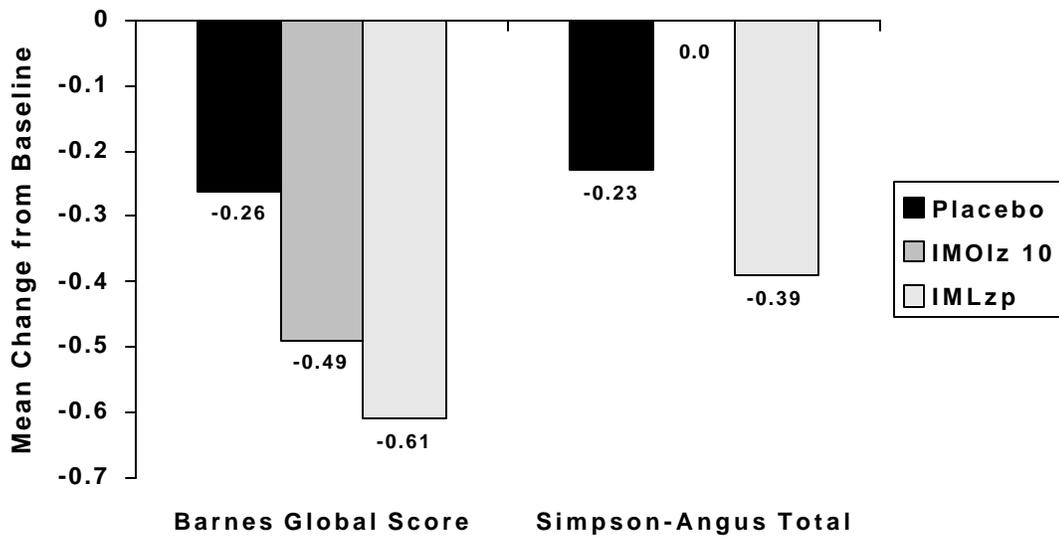
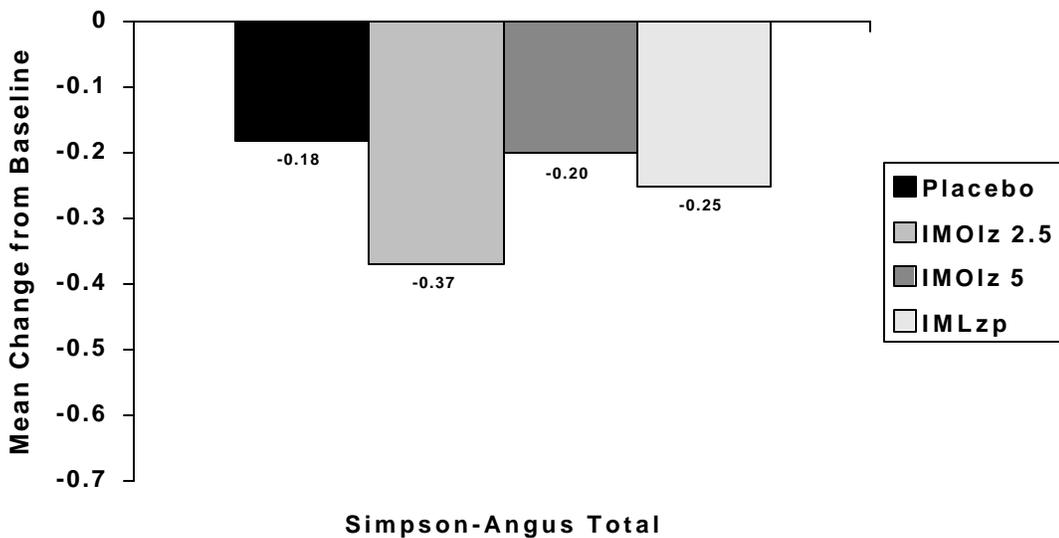


Figure 47. Analysis of Extrapyramidal Symptoms by Rating Scales Agitation in Schizophrenia Study



N.S.D. between any measures vs placebo

Figure 48. Analysis of Extrapyramidal Symptoms by Rating Scales Agitation in Bipolar Mania Study



N.S.D. between any measure vs placebo

Figure 49. Analysis of Extrapyramidal Symptoms by Rating Scales Agitation in Dementia Study

8.10. Overall Safety Conclusions

The IM olanzapine clinical trial safety data establish IM olanzapine as a safe and well tolerated therapy for the control of agitation. In the IM olanzapine clinical studies, the incidence of adverse events leading to discontinuation and serious adverse events was relatively low. Further, no treatment-emergent adverse events occurred at a statistically significantly greater incidence in IM olanzapine-treated patients compared with IM placebo-treated patients, or compared with IM haloperidol- or IM lorazepam-treated patients. The assessment of laboratory analytes and ECGs revealed no clinically significant changes associated with IM olanzapine. Notably, the analyses of ECG data in all four pivotal studies revealed no significant QTc interval prolongations associated with IM olanzapine at any dose when compared with IM placebo. The lack of the QTc abnormalities in the agitation in dementia study is particularly relevant due to the advanced age and presence of co-morbid medical conditions in this patient population. In the assessment of vital signs in these controlled clinical study databases, IM olanzapine was not associated with any effects except for mild and transient decrements in blood pressure and heart rate that were not clinically significant. IM olanzapine did not produce excessive or undesirable sedation. For extrapyramidal symptoms, IM olanzapine exhibited a favorable profile compared with IM haloperidol. In the IM olanzapine clinical studies, the incidence of extrapyramidal symptoms in IM olanzapine-treated patients was comparable to IM placebo-treated patients whereas IM haloperidol-treated patients experienced a significant higher incidence of extrapyramidal symptoms compared with IM placebo-treated patients.

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**Appendix 1.
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Appendix 2.
Criteria to Identify Potentially Clinically Significant
Changes

Table 33. Descriptive Vital Sign and ECG Data Combinations to Identify Potentially Clinically Significant Changes in Heart Rate and Blood Pressure

Combination of Potentially Clinically Significant Vital Signs	Indication
Supine Pulse Low and Standing Pulse Low	Supine and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)
Supine Pulse Low and Orthostatic Systolic Blood Pressure Drop	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and ≥ 30 mmHg decrease in systolic BP (supine to standing)
ECG Heart Rate Low and Standing Pulse Low	ECG heart rate ≤ 40 bpm and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)
ECG Heart Rate Low and Orthostatic Systolic Blood Pressure Drop	ECG heart rate ≤ 40 bpm and ≥ 30 mmHg decrease in systolic BP (supine to standing)
Supine Pulse Low and Supine Systolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
Supine Pulse Low and Supine Diastolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine diastolic blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)
ECG Heart Rate Low and Supine Systolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
ECG Heart Rate Low and Supine Diastolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)

Appendix 3.
QTc Interval—Mean Change from Baseline to Endpoint

**Table 34. QTc Interval (msec)
Mean Change from Baseline to 2 Hours
Placebo-Controlled Database**

Treatment	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Change Mean \pm SD	p-value for change vs pla
IM Olanzapine	408	410.5 \pm 27.1	407.4 \pm 26.8	-3.0 \pm 21.5	0.199
IM Placebo	148	412.8 \pm 25.6	412.1 \pm 25.4	-0.7 \pm 22.0	--

**Table 35. QTc Interval (msec)
Mean Change from Baseline to 24 Hours
Placebo-Controlled Database**

Treatment	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Change Mean \pm SD	p-value for change vs pla
IM Olanzapine	411	410.5 \pm 27.1	407.0 \pm 25.4	-3.5 \pm 22.9	0.383
IM Placebo	148	412.8 \pm 25.6	411.0 \pm 24.7	-1.8 \pm 23.3	--

**Table 36. QTc Interval (msec)
Mean Change from Baseline to 2 Hours
Haloperidol-Controlled Database**

Treatment	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Change Mean \pm SD	p-value for change vs hal
IM Olanzapine	312	407.4 \pm 26.4	404.2 \pm 27.7	-3.3 \pm 21.7	0.006
IM Haloperidol	164	408.1 \pm 28.1	410.0 \pm 28.4	1.8 \pm 24.0	--

**Table 37. QTc Interval (msec)
Mean Change from Baseline to 24 Hours
Haloperidol-Controlled Database**

Treatment	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Change Mean \pm SD	p-value for change vs hal
IM Olanzapine	313	407.4 \pm 26.4	404.4 \pm 25.5	-3.0 \pm 23.0	0.065
IM Haloperidol	164	408.1 \pm 28.1	408.9 \pm 26.5	0.7 \pm 24.6	--

**Table 38. QTc Interval (msec)
Mean Change from Baseline to 2 Hours
Geriatric Placebo-Controlled Database**

Treatment	N	Baseline	Endpoint	Change	p-value for change vs pla
		Mean \pm SD	Mean \pm SD	Mean \pm SD	
IM Olanzapine 2.5 mg	68	436.9 \pm 31.3	432.4 \pm 30.6	-4.5 \pm 22.0	0.044
IM Olanzapine 5 mg	61	430.5 \pm 28.6	433.5 \pm 32.2	3.1 \pm 24.6	0.936
IM Lorazepam	63	437.4 \pm 31.0	431.2 \pm 30.2	-6.2 \pm 20.6	0.019
IM Placebo	61	436.2 \pm 28.0	439.5 \pm 28.4	3.3 \pm 21.1	--

**Table 39. QTc Interval (msec)
Mean Change from Baseline to 24 Hours
Geriatric Placebo-Controlled Database**

Treatment	N	Baseline	Endpoint	Change	p-value for change vs pla
		Mean \pm SD	Mean \pm SD	Mean \pm SD	
IM Olanzapine 2.5 mg	68	436.9 \pm 31.3	429.5 \pm 30.2	-7.4 \pm 21.8	0.001
IM Olanzapine 5 mg	62	431.1 \pm 28.8	431.3 \pm 32.4	0.2 \pm 27.2	0.188
IM Lorazepam	65	437.4 \pm 31.2	439.7 \pm 32.7	2.3 \pm 21.3	0.426
IM Placebo	64	436.1 \pm 27.4	441.5 \pm 29.2	5.4 \pm 20.2	--