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ARTICLE

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Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone *vs*. haloperidol

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Abstract

To compare the remission rate and its time-course over 196 wk of double-blind treatment with an atypical antipsychotic, ziprasidone (80–160 mg/d given b.i.d., or 80–120 mg/d given q.d.), or a conventional antipsychotic, haloperidol (5–20 mg/d). Outcome assessments included attainment of remission (Andreasen criteria) by longitudinal analysis. Positive and Negative Syndrome Scale (PANSS) scores, Global Assessment of Functioning Scale (GAF) scores, and quality-of-life (QLS) were also assessed in the initial 40-wk study phase ($n=599$) and the 3-yr extension study ($n=186$). Discontinuation rates in the initial 40-wk core and follow-up extension studies were comparable between groups: 64% and 65% for the 80–160 mg/d ziprasidone group, 65% and 58% for the 80–120 mg/d ziprasidone group, and 60% and 66% for the 5–20 mg/d haloperidol group, respectively. Mean change scores from baseline to LOCF endpoint (week 40 or early termination) for PANSS negative and GAF (primary efficacy variables) were not statistically significantly different between ziprasidone and haloperidol. During the 3-yr extension study, ziprasidone-treated subjects (80–160 mg/d) were more likely to achieve remission (51%) than haloperidol-treated (40%) subjects ($p=0.04$), while there was a favourable trend associated with 80–120 mg/d ziprasidone (48%). Compared to the haloperidol group, subjects assigned to the 80–160 mg/d ziprasidone group showed a gradual and persistent improvement in remission ($p=0.006$) and quality-of-life ($p=0.004$) in the longitudinal analyses. Significant differences in the trajectory of PANSS total and GAF scores favouring the 80–160 mg/d ziprasidone group were also observed. In this long-term, double-blind study, ziprasidone treatment was more likely to result in remission than haloperidol treatment, and was associated with greater improvement in quality-of-life.

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Introduction

Schizophrenia is the third most common cause of disability worldwide for individuals aged between 15 and 45 yr (Brundtland, 2001). There is considerable debate about the degree to which persistent symptoms can be successfully treated during maintenance phase treatment, as well as potential differences between available antipsychotic agents in facilitating better outcomes. The available data are almost entirely based on longitudinal observational studies. In a 23-yr follow-up of 208 psychotic patients, about 20% were judged to be fully recovered (Bleuler & Ganzoni, 1978). Applying modern DSM-IV diagnostic criteria to the original sample, a 12–15% recovery rate was observed by Modestin *et al*. (2003). In the Iowa 500 study, 685 persons with schizophrenia were followed for an average of 35 yr. Of these subjects 20–35% had a good outcome in marital, residential, occupational, and/or psychiatric status (Tsuang *et al*. 1979). The Bonn

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Hospital Study followed 502 schizophrenia patients for an average of 22.4 yr. Twenty-two percent are described as having complete remission of symptoms, with 56% having 'socially recovered' (Huber *et al*. 1975). The Vermont Longitudinal Research Project (Harding *et al*. 1987) followed 118 persons for 32 yr and retrospectively rediagnosed them using DSM-III criteria. At follow-up and following an innovative rehabilitation programme, 43% displayed no psychiatric symptoms. In contrast, the Cologne Long-Term Study (Marneros *et al*. 1989) followed 97 patients with schizophrenia and showed that only 10% had full remission. The only studies to consider the diagnosis of schizoaffective disorder as a possible diagnostic confound were the Cologne study (Marneros *et al*. 1989) and that of Modestin *et al*. (2003). In both studies, schizoaffective patients had much better outcomes and much higher rates of remission (50% in the Cologne sample). It is possible that the inclusion of schizoaffective subjects in the other studies may partly account for the higher rates of remission observed.

The possibility that treatment with second generation antipsychotics may enhance remission is an important consideration when making long-term cost-benefit treatment evaluations. However, most antipsychotic comparative data are derived from reatively short study periods, which may limit the potential to adequately differentiate between conventional and atypical treatment outcomes. Few long-term, double-blind studies have evaluated longitudinal outcomes (Herz *et al*. 1991; Marder *et al*. 2003), including the time-course of symptom remission in schizophrenia (Kane *et al*. 2007). Andreasen & colleagues (2005) operationalized the concept of remission as requiring a score of $\leqslant 3$ (mild or less) for at least 6 months in eight specified Positive and Negative Syndrome Scale (PANSS) items: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). Utilizing these published criteria for remission in schizophrenia, we conducted a *post-hoc* analysis of subjects who had completed a double-blind, 40-wk initial treatment period and were subsequently enrolled in a 3-yr (156-wk), double-blind extension study comparing ziprasidone and haloperidol.

Schizophrenia is a highly complex disorder characterized by a diversity of symptoms that have been grouped as positive (e.g. hallucinations and paranoia), negative (e.g. social withdrawal and ahedonia), as well as many other symptoms that interfere social and occupational functioning. As with all available antipsychotic agents, ziprasidone targets neurotransmission at dopamine D_2 receptors in the mesolimbic pathway; dopamine dysfunction is hypothesized to be the key neurochemical disturbance associated with schizophrenia. Like many other atypical antipsychotic agents, ziprasidone is a serotonin-2A (5-HT_{2A})/dopamine D_2 antagonist; however, its *in-vitro* 5-HT_{2A}/D_2 receptor affinity ratio is higher than that of the other first-line atypical antipsychotic agents (namely, risperidone, olanzapine, quetiapine, and aripiprazole). Ziprasidone also exhibits potent interaction with 5-HT_{2C}, 5-HT_{1D}, and 5-HT_{1A} receptors in human brain tissue, characteristics that may predict negative symptom relief, enhanced modulation of mood, cognitive improvement, and reduced motor symptoms. Ziprasidone also has moderate affinity for serotonin and norepinephrine reuptake sites, consistent with predictions of antidepressant/anxiolytic activity. On the other hand, ziprasidone's low affinity for histamine H_1 and muscarinic M_1 receptors suggest few cognitive side-effects, sedation, and weight gain. Its low affinity for α_1-adrenoceptors suggest little orthostatic hypotension (Stahl & Shayegan, 2003). In clinical studies ziprasidone is characterized by a neutral effect on weight, favourable effects on serum lipids, and no untoward effects on glucose metabolism (Lieberman *et al*. 2005; Parsons *et al*. 2009; Simpson *et al*. 2004, 2005). Efficacy and tolerability data from short-term (Addington *et al*. 2004; Daniel *et al*. 1999; Keck *et al*. 1998; Simpson *et al*. 2004) and long-term (Arato *et al*. 2002; Hirsch *et al*. 2002; Simpson *et al*. 2005) trials to date indicate that ziprasidone's clinical activity is consistent with its receptor profile. In contrast haloperidol targets neurotransmission at dopamine D_2 receptors but has relatively weak effects at serotonin receptors 5-HT_{2A}, 5-HT_{1A} and 5-HT_{2C}, as well as at histamine H_1 and muscarinic M_1 in human brain tissue.

Method

Subjects

The study included two treatment periods: (i) a 40-wk, randomized, double-blind core phase, with subjects having a chronic or subchronic schizophrenia or schizoaffective disorder (DSM-III-R) diagnosis, no hospitalization for psychosis for at least 12 wk prior to screening, PANSS negative score >10, PANSS hostility and uncooperativeness item scores <4 (moderate), Clinical Global Impression – Improvement (CGI-I) score <6 (much worse) at baseline (compared to screening), and Global Assessment of Functioning Scale

(GAF) score >30; and (ii) a 3-yr, double-blind, extension phase including subjects who had completed the initial 40-wk trial with a GAF score >30. The study was conducted from July 1994 to September 2000 in 40 centres in the USA and Canada. Institutional review board approval was obtained at each site, and all participants provided written informed consent.

Subjects were required to discontinue any antipsychotic medications within the 4 wk immediately preceding the baseline visit, any antidepressant within 3 wk of screening or any fluoxetine, specifically, within 5 wk of screening. Lithium or other mood stabilizers were required to be discontinued within 2 wk of screening. Concomitant medications for stable medical conditions (e.g. replacement hormones excluding insulin, anti-hypertensives, diuretics, and oral hypoglycaemics) were permitted.

Treatment

Randomization was performed according to a computer-generated schedule, with a permuted-block design in a 3:3:2 ratio, to two flexible ziprasidone dosing regimens (80–160 mg/d, ZSTD; or 80–120 mg/d, ZLOW), or haloperidol (5–20 mg/d). A limited dose of lorazepam (no more than 7 mg/wk) or episodic chloral hydrate (500–1000 mg) for treatment of insomnia or anxiety/agitation was allowed to be continued into the double-blind drug treatment phase at the investigator's discretion. At baseline, doses of any extrapyramidal medications were gradually decreased to achieve full discontinuation by week 3. If subjects experienced movement disorders at any time during the study, appropriate medications could be continued or reinstated as necessary.

Efficacy and safety assessments

The primary efficacy measures for the 40-wk, randomized, double-blind core phase were PANSS negative subscale score (Kay *et al*. 1987) and GAF (Hall, 1995). Movement Disorder Burden Score (MDBS) was included as a primary outcome variable (Addington *et al*. 2004).

The efficacy assessments in the 3-yr extension study were based on PANSS, Quality-of-Life scale (QLS; Heinrichs *et al*. 1984), and GAF. Remission as defined by Andreasen *et al*. (2005) was the key derived endpoint in this *post-hoc* analysis. The remission criteria require attaining a score ⩽3 (mild or less) for at least 6 months in eight specified PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6).

PANSS and QLS scores were evaluated at baseline (initiation of study drug), weeks 6, 16, 28, 40 (start of the double-blind, extension study phase), 68, 92, 124, 148, 172, and 196. The remission rate calculated at each visit was based on maintenance of ratings over two consecutive scheduled visits (24- to 28-wk period), of mild or less on all eight specified PANSS items. The remission rate at week 40 (start of the 3-yr extension study) was calculated based on maintenance of mild or less PANSS ratings from weeks 16–40.

Safety and tolerability assessments included the Simpson–Angus Rating Scale (SAS; Simpson & Angus, 1970), Barnes Akathisia Rating Scale (BAS; Barnes, 1989), Abnormal Involuntary Movement Scale (AIMS, 1988), treatment-emergent adverse events, vital signs, electrocardiograms, and laboratory tests.

Statistical analysis

The statistical analysis plan (SAP) including the analysis dataset, endpoints, and statistical methods were agreed upon prior to conducting the *post-hoc* analyses presented in this paper. Deviations from and additions to the SAP are noted below.

Initial 40-wk core study

The initial randomized, double-blind, 40-wk core study ($n=599$) was designed to detect a difference of 3 points (S.D. = 8 points) in PANSS negative score between treatment groups, with 88% power adjusted for a 40% drop-out rate. For this initial 40-wk core study ($n=599$), the protocol specified last observation carried forward (LOCF)-ANCOVA model was applied to estimate treatment effects (80–160 mg/d ziprasidone *vs*. haloperidol; and 80–120 mg/d ziprasidone *vs*. haloperidol) on the primary efficacy measures (PANSS negative and GAF scores) at week 40, adjusted for baseline score and centre effects. Missing data were imputed by an individual's last observed measurement, using the LOCF method as specified in the protocol.

3-yr double-blind extension study phase

For the 3-yr double-blind extension study ($n=186$), the primary analysis sample was based on all eligible subjects who met the *a priori* protocol-specified inclusion and exclusion criteria, including the completion of the initial 40 wk of study treatment. Subjects were enrolled from 40 centres (>20 centres had <4 patients per centre) in the USA and Canada. The focus of analyses was to compare the development of

remission, its relationship to the QLS score, and their time-courses over long-term, double-blind treatment with ziprasidone (80–160 mg/d, or 80–120 mg/d) or haloperidol (5–20 mg/d). The definition of remission (severity and 6-month components) was based on Andreasen *et al*. (2005).

To assess potential drop-out bias and how the treatment groups differed in their response profiles and drop-out patterns, we applied the pattern-mixture approach to analyse baseline characteristics and post-baseline responses (raw means), stratified by completers and subgroups corresponding to different drop-out times, i.e. weeks 16, 28, and 40 for the core study, and weeks 68, 92, 124, 148, 172, and 196 for the extension study. Two key statistical approaches were used: Generalized Estimating Equations (GEE; Diggle *et al*. 2001) to estimate the change in proportion of subjects who attained remission (log odds) by treatment group, and likelihood-based mixed-effects model for repeated-measures method (MMRM; Fitzmaurice *et al*. 2004) to estimate the change in continuous variable such as PANSS total, GAF and QLS. The logistic regression method, which included terms for treatment, treatment exposure duration, and baseline characteristics (symptom severity and QLS), was applied to estimate the proportion of subjects attaining remission during the 3-yr extension study. In the longitudinal analysis, the time-course for remission *vs*. no remission (dichotomized remission variable) was analysed using GEE (Diggle *et al*. 2001). The GEE model took into account the positive correlations among repeated measurements within a subject. In the secondary analyses, time-courses for PANSS total, GAF and QLS scores (continuous endpoints) were analysed using MMRM. The fixed-effects model included terms for visit, treatment × visit, treatment, and baseline characteristics (symptom severity status, and QLS total scores). The focus of inference was on differences in slope between the treatment groups in the extension phase for weeks 40–196. Random variability due to centres and subjects (nested within centre) was accounted for in the covariance model for random effects (Fitzmaurice *et al*. 2004; Willett *et al*. 1998). To best fit the data to the linear function in the slope analysis and to avoid convergent problems, a first-order autoregressive covariance AR(1) structure was used to adjust for correlations among repeated measures within subjects. The goodness of fit was checked using an unstructured covariance model in by-visit MMRM analyses. Mediator analysis (Kraemer *et al*. 2002) was applied to evaluate if treatment effect on achieving remission also mediated improvement in QLS total score.

The robustness of these results was checked in sensitivity analyses by using both the conventional LOCF method, and the conditional model approach developed by Wu *et al*. (2001) to adjust for informative drop-out measures in longitudinal analyses. Specifically, the latter approach involved including drop-out time and other drop-out summary measures as covariates in a linear mixed-effects model. Our models included drop-out time and baseline scores, to take into account the probability that drop-out at each visit may depend on the individual's slope of response (Wu *et al*. 2001) and underlying initial baseline value (Rosenheck *et al*. 2006). Qualitatively, similar results obtained from both mixed-effects (MMRM) and GEE models, with and without adjustment for informed drop-out measures, strengthen the conclusions drawn from the analyses.

The protocol-specified LOCF analyses of efficacy measures (PANSS negative and GAF scores) were also conducted, comparing change scores between treatment groups adjusted for initial baseline values (week 0). We present the mean change scores using an ANCOVA model and rate of change (per week) using a linear mixed-effects model. The purpose of analysing rate of change (per week) is to account for marked variations in treatment duration due to drop-outs in the 3-yr extension study.

Results

Randomized, double-blind, 40-wk core study

In the initial 40-wk study phase, 599 subjects were randomly assigned in a 3:3:2 ratio to two ziprasidone dosing regimens (80–160 mg/d, $n=227$; or 80–120 mg/d, $n=221$), or haloperidol (5–20 mg/d, $n=151$). Demographics and diagnosis (>85% schizophrenia *vs*. schizoaffective) were comparable between the treatment groups at initial baseline (Table 1). Mean modal daily doses at week 40 were 111.7 mg/d in the 80–160 mg/d ziprasidone group, 95.9 mg/d in the 80–120 mg/d ziprasidone group and 11.6 mg/d in the haloperidol group (5–20 mg/d). Discontinuation rates were similar across the treatment groups: 65% (80–160 mg/d ziprasidone), 64% (80–120 mg/d ziprasidone), and 60% (haloperidol), respectively) (see Fig. 1).

The full analysis set included 536 subjects who had at least one post-baseline efficacy assessment. There were no statistically significant differences in pairwise comparisons between treatment groups in the primary efficacy measures of PANSS negative (all $p>0.51$) and GAF scores (all $p>0.31$) using the LOCF-ANCOVA method (Table 2). A statistically significant difference (in favour of ziprasidone) was seen between both of

Table 1. Demographics and baseline characteristics for core and extension studies

	Ziprasidone (80–160 mg)		Ziprasidone (80–120 mg)		Haloperidol (5–20 mg)	
	Core ($n=227$)	Extension ($n=72$)	Core ($n=221$)	Extension ($n=67$)	Core ($n=151$)	Extension ($n=47$)
Age (yr) Mean (range)	39.9 (17–78)	40.2 (19–78)	39.3 (18–76)	41.1 (20–76)	40.0 (18–82)	40.7 (18–82)
Race						
White	165 (73%)	54 (75%)	146 (66%)	47 (70%)	110 (73%)	33 (70%)
Black	39 (17%)	10 (14%)	48 (22%)	13 (19%)	30 (20%)	10 (21%)
Asian	4 (2%)	2 (3%)	1 (0.4%)	1 (2%)	1 (0.7%)	1 (2%)
Other	19 (8%)	6 (8%)	26 (12%)	6 (9%)	10 (6.6%)	3 (6%)
Primary diagnosis						
Schizophrenia disorders	198 (87%)	61 (85%)	194 (88%)	59 (88%)	130 (86%)	45 (96%)
Schizoaffective disorders	29 (13%)	11 (15%)	27 (12%)	8 (12%)	21 (14%)	2 (4%)
Age at onset of first hospitalization Mean (S.D.)	23.3 (7.8)		23 (7.0)		24.2 (9.0)	
Years since onset of first psychiatric illness Mean (S.D.)	16.4 (11)		16.1 (10.4)		15.7 (10.6)	
Number of previous psychiatric hospitalizations (S.D.)	5.4 (6.0)		5.3 (5.5)		5.0 (5.0)	
Baseline PANSS total score (S.D.)	73.7 (18.3)	71.6 (18.5)	72.5 (17.7)	71.3 (15.5)	72.6 (18.1)	70.0 (18.3)
Baseline PANSS negative subscale (S.D.)	21.4 (6.3)	20.9 (6.3)	21.1 (6.2)	22.1 (5.7)	20.8 (6.4)	20.8 (6.3)
Baseline GAF (S.D.)	49.5 (11.0)	49.9 (11.7)	49.2 (11.6)	49.5 (11.8)	49.1 (11.0)	48.9 (12.3)
Baseline QLS (S.D.)	54.9 (20.1)	57.1 (19.1)	57.5 (21.9)	53.6 (21.8)	57.8 (21.6)	61.4 (19.8)*

PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning Scale; QLS, Quality-of-Life Scale.
* $p=0.04$ for comparing baseline QLS score for 80–160 mg/d ziprasidone *vs*. haloperidol.

the ziprasidone groups and the haloperidol group for the MDBS ($p<0.002$) (Table 2).

Double-blind 3-yr extension study

Of the 220 subjects who completed the 40-wk core study, 186 (84.5%) consented to participate in the extension study. These 186 patients were considered evaluable for the remission *post-hoc* analysis. Mean modal doses for weeks 40–196 were 113 mg/d for the 80–160 mg/d ziprasidone group ($n=72$), 97 mg/d for the 80–120 mg/d ziprasidone group ($n=67$), and 13 mg/d for the haloperidol group ($n=47$).

Discontinuation rates in the extension study (weeks 40–196) were comparable between groups: 47/72 (65%) for the 80–160 mg/d ziprasidone group (median study treatment duration 128 wk), 39/67 (58%) for the 80–120 mg/d ziprasidone group (112 wk) and 31/47 (66%) for the haloperidol group (128 wk) (see Fig. 1). Table 1 shows the demographics and diagnosis (>85% schizophrenia *vs*. schizoaffective) across the treatment groups at initial baseline and at week 40 (end of core phase). Despite the progressive selectivity of subjects remaining in the trial, mean baseline PANSS and GAF scores were comparable and balanced between the 80–160 mg/d ziprasidone group and the haloperidol group across all visits from day 0 (core baseline) to week 40 (Table 1). Similar baseline PANSS scores were observed for completers (196 wk): 70 for the 80–160 mg/d ziprasidone group, 73 for the 80–120 mg/d ziprasidone group, and 69 for the haloperidol group.

LOCF analysis of protocol-specified efficacy measures

The protocol-specified LOCF analyses showed greater improvement with the 80–160 mg/d ziprasidone

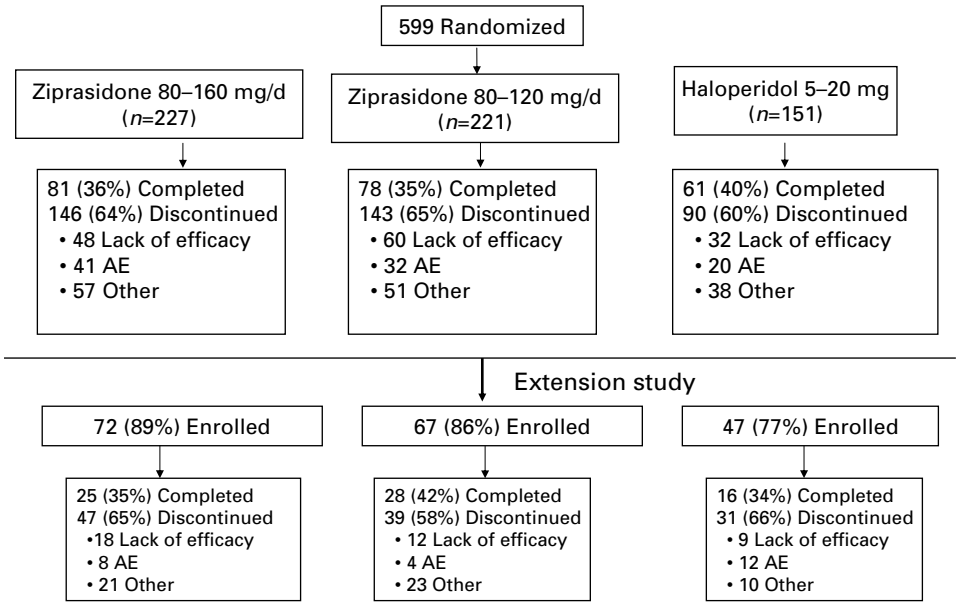


Fig. 1. Flow chart of study.

group compared to the haloperidol group in mean change (per week) in the primary efficacy measure – PANSS negative ($p<0.05$, $t=-1.98$, d.f.$=182$). Analyses of GAF scores showed trends favouring ziprasidone (80–120 mg/d) but the treatment difference was not significant ($p=0.09$, $t=1.72$, d.f.$=182$) (Table 2). No statistically significant differences in these efficacy measures were observed for ziprasidone (80–120 mg/d) *vs*. haloperidol (Table 2).

Analysis of remission rates

In this *post-hoc* analysis, the 80–160 mg/d ziprasidone group was significantly more likely to achieve remission than the haloperidol group (at least one remission episode) during the 3-yr extension study (51% and 40%, respectively; $t=2.02$, d.f.$=166$, $p=0.04$, logistic regression) (Fig. 2), as well as in the final 6 months of extension treatment [80–160 mg/d (43%) *vs*. haloperidol (26%); $t=2.68$, d.f.$=166$, $p=0.007$, logistic regression]. Trends favouring the 80–120 mg/d ziprasidone group were not statistically significant compared to the haloperidol group (48% during the study or 34% in the final 6 months; both $t>1.75$, d.f.$=166$, $p>0.08$).

In the longitudinal analyses using available data at all visits, we found a differential time profile (slope) for the remission rate favouring the ziprasidone (80–160 mg/d) *vs*. the haloperidol group during the extension study phase (80–160 mg/d ziprasidone *vs*. haloperidol: z$=2.75$, $p=0.006$; 80–120 mg/d ziprasidone *vs*. haloperidol: z$=1.68$, $p=0.092$) (Table 3). Main treatment effects terms for remission rate at week 40 were not statistically significant (all $p>0.11$). The 80–160 mg/d ziprasidone group showed significantly greater likelihood of attaining remission than haloperidol at weeks 124 (z$=2.33$, $p=0.02$, GEE model), 148 (z$=2.60$, $p=0.01$), and 196 (z$=2.42$, $p=0.01$) (see Fig. 3). No statistically significant differences were found for the lower ziprasidone dose group *vs*. haloperidol at these visits.

Supportive analyses

Longitudinal analysis of QLS score

Ziprasidone-treated subjects were also associated with gradual and persistently improved QLS, in contrast to haloperidol during the extension phase (80–160 mg/d ziprasidone *vs*. haloperidol, $t=2.86$, $p=0.004$; 80–120 mg/d ziprasidone *vs*. haloperidol, $t=1.79$, $p=0.07$) (Fig. 3, Table 4). The overall improvement in quality-of-life favouring ziprasidone was partially mediated through remission achieved over long-term treatment ($p<0.001$).

Longitudinal analyses of PANSS and GAF scores

To check the consistency of remission analysis results with those of PANSS or GAF scores, we performed a linear mixed-effects model analysis. Raw and least-squares estimates of mean PANSS total score (with loess-smoothed curve) for the three treatment groups are presented in Fig. 4. The 80–160 mg/d ziprasidone group showed a significantly greater rate of

Table 2. Primary efficacy variables for LOCF endpoint: 40-wk core phase followed by 3-yr extension phase (all subjects)

	Ziprasidone (80–160 mg) Mean change (S.D.)	Ziprasidone (80–120 mg) Mean change (S.D.)	Haloperidol Mean change (S.D.)	Ziprasidone (80–160 mg) *vs.* Haloperidol			Ziprasidone (80–120 mg) *vs.* Haloperidol		
				Least squares Mean (95% CI)	*p* value	*t*	Least squares Mean (95% CI)	*p* value	*t*
40-wk core phase (LOCF-ANCOVA)									
PANSS negative change score	−2.05 (6.12)	−1.65 (5.63)	−1.31 (5.59)	−0.38 (−1.5 to 0.7)	0.51	−0.66	−0.22 (−1.3 to 0.9)	0.71	−0.38
GAF change score	1.59 (13.01)	0.60 (13.37)	1.74 (12.41)	−0.25 (−2.8 to 2.3)	0.85	−0.19	−1.32 (−3.9 to 1.2)	0.31	−1.0
MDBS	0.23 (0.58)	0.31 (0.63)	0.49 (0.68)	−0.26 (−0.4 to −0.1)	<0.001		−0.21 (−0.3 to −0.1)	0.002	
3-yr extension phase (LOCF analyses of change score per week)[a]									
PANSS negative Change score	−4.86 (7.64)	−2.87 (6.48)	−3.17 (6.15)	−0.014 (−0.03 to −0.002)	<0.05	−1.98	0.003 (−0.012 to 0.017)	0.71	0.38
GAF Change score	6.78 (16.34)	4.55 (12.62)	4.87 (16.93)	0.026 (−0.004 to 0.056)	0.09	1.72	0.007 (−0.023 to 0.038)	0.63	0.48

PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning Scale; MDBS, Movement Disorder Burden Score.
This mixed-effects model produces the conventional LOCF-ANCOVA estimate of treatment effects adjusted for baseline score when LOCF_visit_time (continuous variable) is replaced by baseline *vs.* post-baseline visit (dichotomized visit variable = 0 for baseline and 1 for post-baseline LOCF endpoint) (Liang & Zeger, 2000).
[a] PANSS negative or GAF (change score per week) = LOCF_visit_time (continuous) + (CENTER and SUBJECT nested within CENTRE are random effects).

Fig. 2. Remission rate during double-blind 3-year extension study. * $p = 0.04$ [80–160 mg/d ziprasidone (Zip) *vs.* haloperidol] for attainment of remission any time during the double-blind 3-yr extension study.

improvement in PANSS total compared to haloperidol in the slope analysis, which adjusted for individual variations in treatment durations (range >40 to 196 wk) and used available data at all visits in a linear mixed-effects model (Fig. 4). In the by-visit analysis, subjects treated with ziprasidone (80–160 mg/d) demonstrated significantly greater improvement than haloperidol-treated subjects in PANSS total score at weeks 124, 148, and 172 (numeric difference only at the week 196 visit). Similar results were observed in GAF score, showing a significantly greater rate of improvement in the ziprasidone (80–160 mg/d) group when compared to haloperidol (Table 4). These longitudinal results took into account the duration of treatment (attrition) for each subject using slope analyses, unlike standard LOCF analysis which ignores treatment duration differences.

Sensitivity analyses

Drop-out pattern analysis

To assess the impact of potential drop-out bias, we adopted a pattern-mixture analysis approach to compare mean response profiles stratified for the completers and subgroups corresponding to the different drop-out time (drop-out cohorts) (Fig. 5). In the 40-wk core study phase, the ziprasidone group (80–160 mg/d) showed comparable or less severe PANSS score (*vs.* haloperidol) in all subgroups corresponding to drop-out time at weeks 16, 28, and 40. However, for drop-outs which occurred at the first scheduled visit (week 6 drop-out cohort; Fig. 5*a*), worsening mean PANSS score was observed in the ziprasidone groups [representing 31% of the intention-to-treat

Table 3. Longitudinal analysis (GEE) of remission rates

Parameter[a]	Estimate	S.E.	Robust *z*	*p* value
Intercept	−2.29	0.4504	−5.09	<0.0001
Visit time[b]	−0.005	0.0031	−1.79	0.0733
Visit time × treatment (slope difference for 80–160 mg ziprasidone *vs*. haloperidol)	0.011	0.0039	2.75	0.0060
Visit time × treatment (slope difference for 80–120 mg ziprasidone *vs*. haloperidol)	0.007	0.0041	1.68	0.0925
Baseline QLS total	0.027	0.0075	3.65	0.0003
Baseline remit status (0/1)	1.408	0.3665	3.84	0.0001

GEE, Generalized Estimating Equations; QLS, Quality-of-Life Scale.
AR(1) structure was used to adjust for within-subject correlations among repeated measures within subjects.
Unstructured covariance model was used in by-visit analysis (treating visit as a categorical variable) which showed 80–160 mg ziprasidone *vs*. haloperidol was significant at weeks 124, 148, and 196 (see Fig. 3*a*). No statistically significant differences were found for the lower ziprasidone dose group *vs*. haloperidol at these visits.
[a] Non-significant treatment effect terms (for initial week 40 period) were dropped from the model: ziprasidone *vs*. haloperidol ($p > 0.25$).
[b] Centre visit time (week) = 40, 68, 92, 124, 148, 172, and 196 (minus 40).

(ITT) ziprasidone subjects], while the haloperidol group showed no change from baseline (representing 29% of the ITT haloperidol subjects).

These results demonstrate the limitations of LOCF analyses of long-term data and show how the treatment groups differ in mean response over time in this study. Worsening mean PANSS scores observed in the ziprasidone week-6 drop-out cohort are assumed to remain constant following drop-out at week 6 throughout the 40 wk of the core study in the LOCF analysis. A relatively less severe PANSS total score was carried forward in the haloperidol arm which showed no change from baseline. To address this limitation, a MMRM analysis was conducted. At week 40, MMRM estimate of treatment differences were −3.26 (S.E. = 2.36) numerically favouring 80–160 mg ziprasidone (*vs*. haloperidol; $p = 0.17$, $t = 1.38$, d.f. = 403), and −1.58 (S.E. = 2.39) for 80–120 mg ziprasidone (*vs*. haloperidol; $p = 0.51$, $t = 0.66$, d.f. = 403). The difference between groups remained non-significant at all visits (weeks 6–40) in this analysis (treatment × visit: $p = 0.23$, $F = 1.32$, d.f. = 8, 403).

Similar drop-out pattern analyses were conducted for the extension phase. Figure 5*b* shows mean response profiles of ziprasidone and haloperidol groups stratified for the completers and subgroups corresponding to the different drop-out times (drop-out cohorts) at weeks 68, 92, 124, 148, 172, and 196. Subjects assigned to the ziprasidone (80–160 mg/d) group showed comparable or less severe PANSS scores (*vs*. haloperidol) in all drop-out cohorts and completers, with the exception of the week 68 drop-out cohort (prior to adjustment for observed difference in baseline score). Differential patient characteristics (baseline PANSS and QLS total scores) by treatment groups were observed at some visits (Fig. 5). These results suggest that the likelihood of drop-outs may depend on the slope of response [informed drop-outs are defined as missing not at random (MNAR), meaning that the probability that responses are missing is related to missingness or the specific values that should have been obtained] and/or baseline scores.

Informative drop-out models

To check the robustness of results, sensitivity analyses were performed using the conditional model approach to adjust for informed drop-out covariates (drop-out time × visit and baseline × visit covariates). We found a similar trend showing a differential time profile (slope) for remission rate over the 3-yr period favouring ziprasidone (*vs*. haloperidol) after adjusting

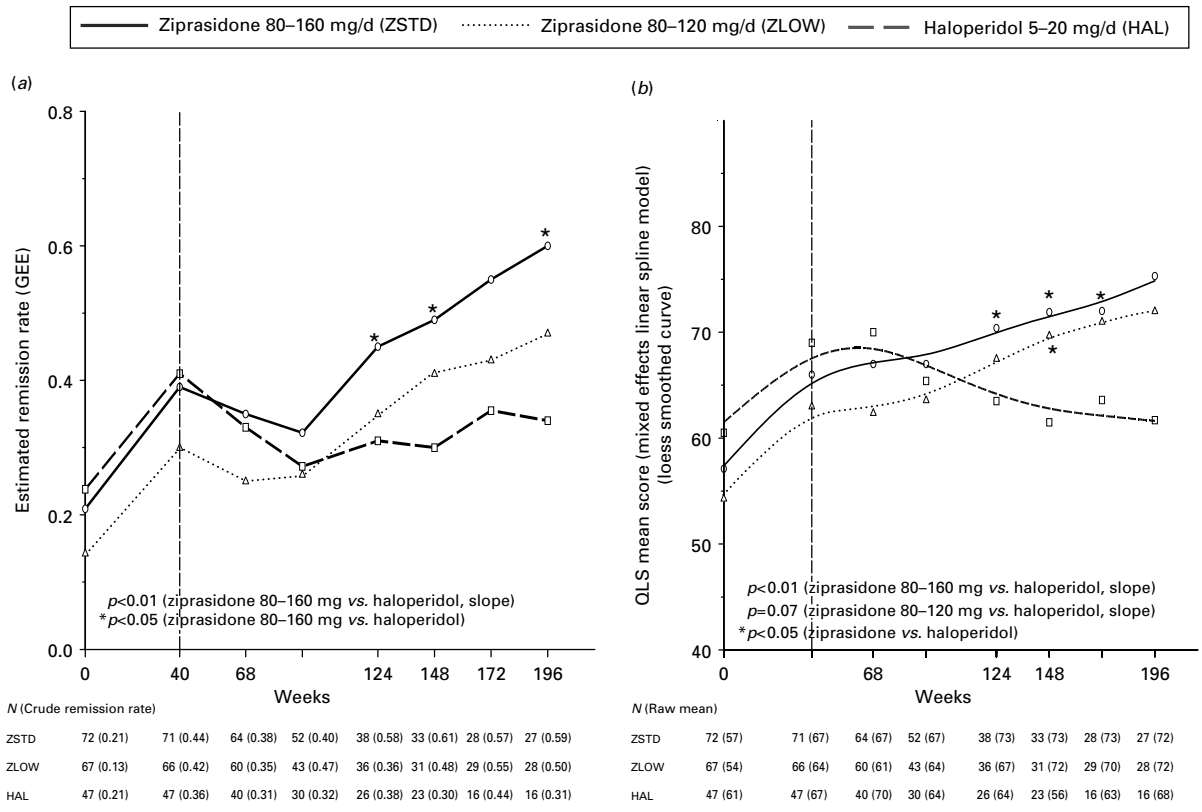


Fig. 3. Remission and quality-of-life during the double-blind 3-yr extension study. (*a*) Remission rates over time from GEE model. ZSTD *vs.* HAL ($p=0.006$, slope analysis). ZLOW *vs.* HAL ($p=0.092$, slope analysis). ZSTD *vs.* HAL in by-visit analysis: weeks 124, 148, and 196 (all $p<0.02$). No statistically significant differences were found for the ZLOW group *vs.* HAL at these visits. (*b*) Mean QLS Total over time and loess-smoothed curve from mixed-effects linear spline model. ZSTD *vs.* HAL ($p=0.004$, slope analysis). ZLOW *vs.* HAL ($p=0.07$, slope analysis). ZSTD *vs.* HAL in by-visit analysis: weeks 124, 148, 172 (all $p<0.05$). ZLOW *vs.* HAL in by-visit analysis: week 148 ($p<0.05$).

for drop-out measures (80–160 mg/d ziprasidone *vs.* haloperidol, robust $z=2.79$, $p=0.005$; 80–120 mg/d ziprasidone *vs.* haloperidol, robust $z=2.00$, $p=0.045$). Similar results were also obtained for PANSS and QLS total scores (Table 5). It is interesting to note that both the GEE and mixed-effects models yielded similar results after adjustment for drop-out measures, strengthening the conclusions drawn from the analyses.

Analysis of safety variables

At the last visit, haloperidol was associated with significantly higher BAS (0.72 from baseline 0.87) compared to ziprasidone (0.40 from baseline 0.81; $p=0.02$ controlling for baseline). SAS and AIMS were generally stable for both haloperidol (2.0 from baseline 2.0 for SAS, and 2.4 from baseline 2.4 for AIMS, respectively) and ziprasidone (1.7 from baseline 2.3 for SAS, and 1.5 from baseline 1.4 for AIMS, respectively) ($p>0.27$ controlling for baseline). The proportion of subjects taking anti-muscarinics for Parkinsonism was somewhat higher for haloperidol (77%) than ziprasidone (61%). The most common (>15%) treatment-related adverse events during the 3-yr extension study were, for ziprasidone *vs.* haloperidol, respectively: akathisia (18.7%/23.4%), EPS (8.6%/17%), insomnia (18%/15%), somnolence (22%/23%), and tremor (5%/17%). Adverse events were predominantly mild-to-moderate in severity. No subjects had a QTc interval >480 ms over the 196-wk study period.

Discussion

Traditional LOCF analyses of group mean psychopathology changes do not address the proportion of subjects who improve to the point of symptom remission, a major goal in treating schizophrenia. By defining improvement in terms of an absolute threshold of symptom severity over a minimum time period, the recent consensus-based remission criteria

Table 4. Linear mixed-effects splines function models for PANSS total, QLS and GAF scores

	PANSS total[a]				QLS total[b]				GAF[c]			
Parameter	Estimate	S.E.	*t*	*p* value	Estimate	S.E.	*t*	*p* value	Estimate	S.E.	*t*	*p* value
Intercept	88.29	1.71	51.50	<0.0001	11.89	1.93	6.16	<0.0001	35.88	1.34	26.75	<0.0001
Core phase (visit)[d]	−0.31	0.030	−10.42	<0.0001	0.22	0.033	6.62	<0.0001	0.217	0.024	9.12	<0.0001
Extension phase $(\text{visit}-40)_+$[e]	0.33	0.043	7.74	<0.0001	−0.27	0.053	−5.13	<0.0001	−0.226	0.035	−6.41	<0.0001
Slope difference for 80–160 mg ziprasidone *vs*. haloperidol $(\text{visit}-40)_+ \times$ treatment	−0.06	0.027	−2.43	0.015	0.12	0.041	2.86	0.004	0.052	0.018	2.81	0.005
Slope difference for 80–120 mg ziprasidone *vs*. haloperidol $(\text{visit}-40)_+ \times$ treatment	−0.009	0.027	−0.32	0.747	0.075	0.042	1.79	0.074	0.024	0.019	1.27	0.206

PANSS, Positive and Negative Syndrome Scale; QLS, Quality-of-Life Scale; GAF, Global Assessment of Functioning Scale.

AR(1) structure was used to adjust for within-subject correlations among repeated-measures within subjects.

Random effects include intercept, slope, centre, subjects (nested in centre).

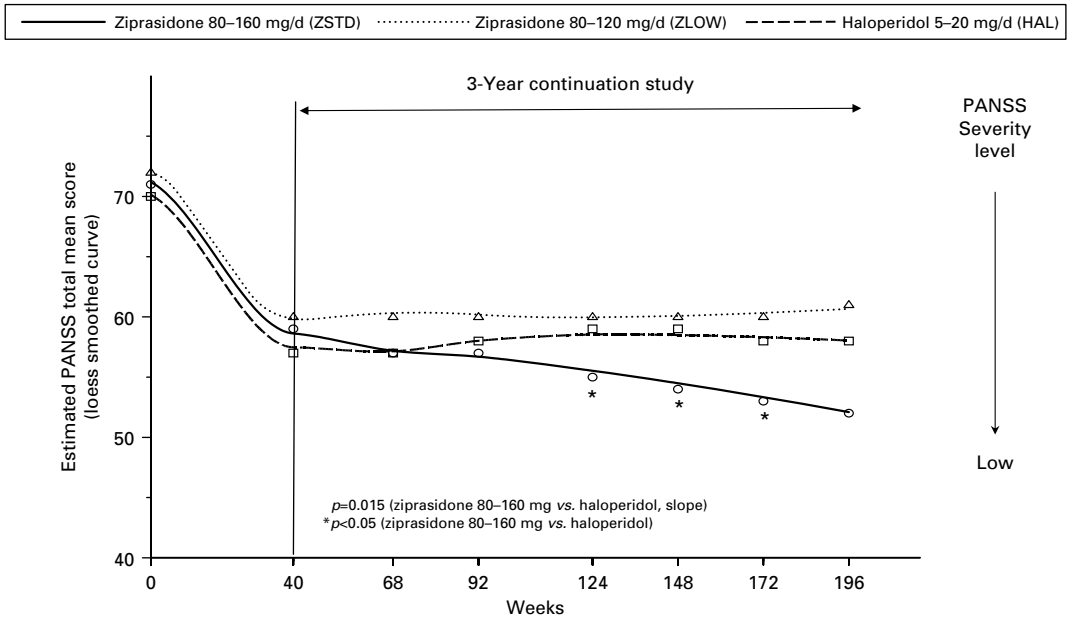
[a] Non-significant treatment effect terms were dropped from the model for PANSS: ziprasidone *vs*. haloperidol (all $p > 0.78$), treatment × visit (core phase) (all $p > 0.11$).

[b] Non-significant treatment effect terms were dropped from the model for QLS: ziprasidone *vs*. haloperidol (all $p > 0.53$), treatment × visit (core phase) (all $p > 0.26$).

[c] Non-significant treatment effect terms were dropped from the model for GAF: ziprasidone *vs*. haloperidol (all $p > 0.22$), treatment × visit (core phase) (all $p > 0.37$). Significant baseline QLS covariate was included in models for PANSS, QLS total, and GAF (all $p < 0.001$).

[d] Visit (week) = 0, 40, 68, 92, 124, 148, 172, and 196.

[e] $(\text{visit}-40)_+ = (\text{visit}-40)$ if visit > 40.



N (Raw mean)								
ZSTD	72 (72)	71 (55)	64 (58)	52 (55)	38 (49)	33 (51)	28 (49)	27 (51)
ZLOW	67 (72)	66 (59)	60 (63)	43 (60)	36 (55)	31 (54)	29 (54)	28 (54)
HAL	47 (70)	47 (58)	40 (59)	30 (60)	26 (56)	23 (60)	16 (57)	16 (56)

Fig. 4. Long-term trajectory of Positive and Negative Syndrome Scale (PANSS) total score: mixed-effects linear spline model. ZSTD *vs.* HAL ($p=0.015$, slope analysis). ZLOW *vs.* HAL ($p=0.747$, slope analysis). ZSTD *vs.* HAL in by-visit analysis: weeks 124, 148, 172 (all $p<0.05$). No statistically significant differences were found for ZLOW *vs.* HAL at these visits.

(Andreasen *et al*. 2005) have provided a useful outcome measure with greater sensitivity for detecting long-term treatment effects (De Hert *et al*. 2007; Mortimer, 2007). The clinical relevance of these remission criteria was supported by a mediator analysis which assessed the impact of attaining remission on quality-of-life and functioning. This analysis showed a significant longitudinal relationship between remission and improvement in quality-of-life over time.

Longitudinal analysis of the response to haloperidol suggests that haloperidol will reach a plateau after about 40 wk, and that patients who have not achieved remission by then are unlikely to do so over the next 3 yr. In contrast, ziprasidone was associated with a gradual and sustained improvement in remission rate and quality-of-life during the extension treatment period. The current analysis, based on an almost 4-yr follow-up of subjects receiving ziprasidone or haloperidol treatment under double-blind conditions, suggests that differential patterns of remission and quality-of-life can emerge in the course of long-term antipsychotic treatment. These results also illustrate that remission is an attainable goal in the treatment of schizophrenia and that patients can accrue benefit from sustained antipsychotic treatment. The importance of continuous treatment is further highlighted by noting that no differences in either remission, quality-of-life or other outcomes were observed within the initial 40-wk study period, a finding consistent with recent comparative studies of similar treatment duration (Jones *et al*. 2006; Lieberman *et al*. 2005).

Results for the 80–160 mg/d ziprasidone group were generally better than for the 80–120 mg/d ziprasidone group. This may be partially attributable to the lower maximum allowable dose in the 80–120 mg/d group (120 *vs*. 160 mg/d for the 80–160 mg/d group, respectively), but plasma levels of ziprasidone were not available to confirm a dose–response relationship. Mauri *et al*. (2007) showed a significant linear relationship between ziprasidone plasma levels and change in PANSS negative score ($r=0.67$, $p<0.05$) in a study of 13 schizophrenia in-patients after an acute exacerbation phase. However, they did not find significant correlations between the oral ziprasidone dose and plasma concentrations, or between plasma ziprasidone levels and PANSS positive symptom changes although the small numbers may have underestimated such relationships. Movement disorder rates were higher for haloperidol, but these events were generally mild-to-moderate in nature. Despite

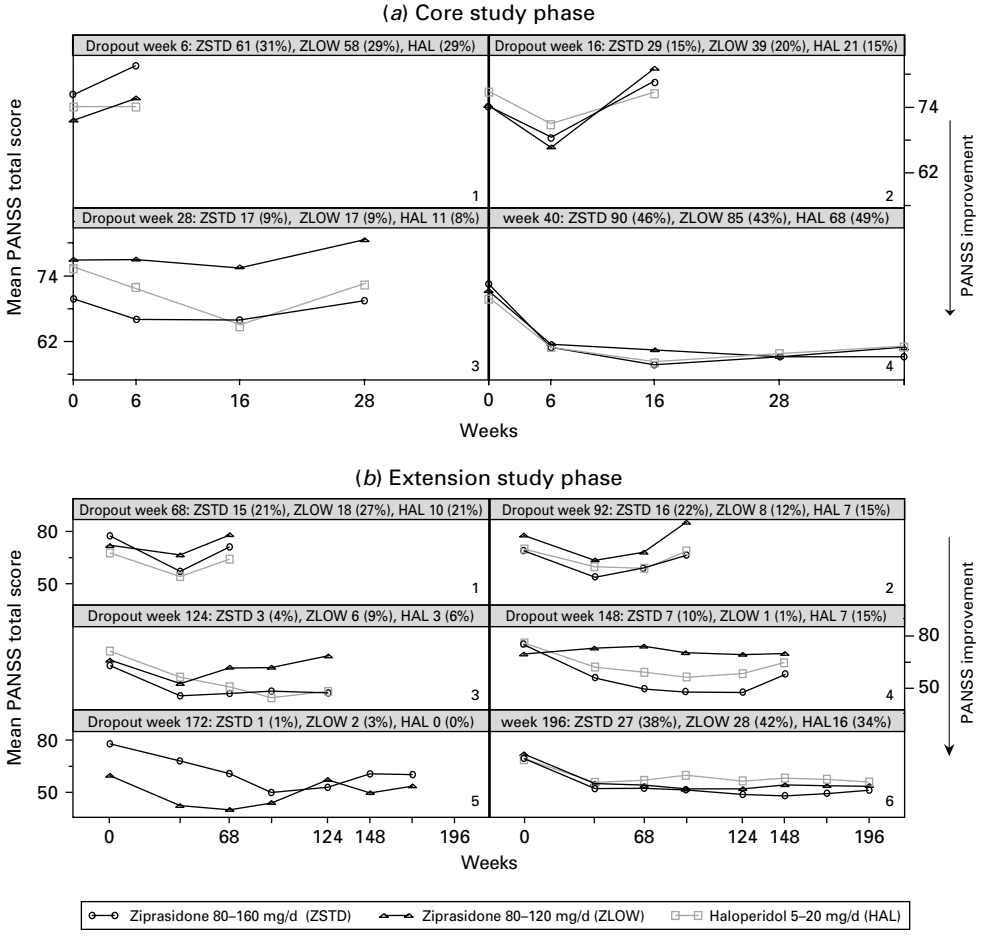


Fig. 5. Drop-out patterns for 40-wk core and 3-yr extension studies. Raw mean Positive and Negative Syndrome Scale (PANSS) total score corresponding to drop-outs at each follow-up visit during the 196-wk double-blind treatment with ziprasidone or haloperidol.

the relatively wide, flexible dose ranges permitted for each agent, mean modal doses could conceivably not be fully optimized for either agent in this study. Subjects were required to have a PANSS negative score >10 to enter the trial. In several population-based studies, as well as acute and long-term randomized clinical trials, subjects with schizophrenia displayed a similar degree of negative symptoms thus making the study population here representative of schizophrenia patients in general.

To our knowledge, to date there have not been other double-blind, comparative antipsychotic trials of this duration (almost 4 yr) published in the English-language literature; previous double-blind trials have generally ranged up to 2 yr (Herz *et al*. 1991; Marder *et al*. 2003). Therefore, the present study presented a unique opportunity to evaluate the potential for differential treatment effects between a conventional antipsychotic compound (haloperidol) and a new-generation or atypical agent (ziprasidone), focusing on the key outcomes of remission and quality-of-life and their time-courses. The major findings reported here –that clinically relevant outcome differences were detected over the course of long-term treatment – add to the debate regarding the degree to which newer agents represent a therapeutic advance (Leucht *et al*. 2007). Further investigation is warranted to detect whether the differential effects of ziprasidone *vs*. haloperidol observed in this study are in fact generalizable to other antipsychotic agents, and to explore the potential underlying pharmacological mechanisms for any differences between these and other agents.

As indicated, mean PANSS change scores from baseline to LOCF endpoint between groups were not statistically significant in the commonly used ANCOVA analysis. The expected large variations in treatment duration in this 196-wk follow-up study (range 40–196 wk) make LOCF-ANCOVA analysis

Table 5. Sensitivity analysis using conditional model approach to adjust for informative drop-out measures

Parameter estimate (robust S.E.) (p value)	Remission[a]	PANSS Total		QLS Total	
	GEE	GEE	Mixed-effects model	GEE	Mixed-effects model
Intercept	−2.15 (S.E. = 0.49) ($p < 0.001$)	33.3 (S.E. = 7.6) ($p < 0.001$)	37.5 (S.E. = 7.8) ($p < 0.001$)	32.7 (S.E. = 7.80) ($p < 0.001$)	32.2 (S.E. = 7.4) ($p < 0.001$)
Visit (week)	−0.03 (S.E. = 0.007) ($p < 0.001$)	0.46 (S.E. = 0.08) ($p < 0.001$)	0.45 (S.E. = 0.08) ($p < 0.001$)	−0.24 (S.E. = 0.09) ($p = 0.01$)	−0.22 (S.E. = 0.08) ($p = 0.01$)
Slope difference for ZSTD *vs.* HAL	0.009 (S.E. = 0.003) ($p = 0.005$)	−0.04 (S.E. = 0.016) ($p = 0.006$)	−0.03 (S.E. = 0.02) ($p = 0.04$)	0.08 (S.E. = 0.027) ($p = 0.002$)	0.08 (S.E. = 0.025) ($p = 0.002$)
Trt (ZSTD *vs.* HAL) × visit					
Slope difference for ZLOW *vs.* HAL	0.006 (S.E. = 0.003) ($p = 0.045$)	−0.007 (S.E. = 0.02) ($p = -0.46$)	0.01 (S.E. = 0.02) ($p = 0.49$)	0.058 (S.E. = 0.026) ($p = 0.01$)	0.049 (S.E. = 0.025) ($p = 0.05$)
Trt (ZLOW *vs.* HAL) × visit					
Baseline score	1.73 (S.E. = 0.53) ($p = 0.001$)	0.24 (S.E. = 0.06) ($p < 0.001$)	0.07 (S.E. = 0.07) $p = 0.33$	0.73 (S.E. = 0.06) ($p < 0.001$)	0.61 (S.E. = 0.08) ($p < 0.001$)
Drop-out time × visit interaction terms	0.0001 (S.E. = 00003) ($p < 0.001$)	All $p < 0.001$	$p = 0.001$ to 0.004	$p = 0.0005$ to 0.96	$p = 0.0002$ to 0.822
Baseline score × visit interaction terms	−0.004 (S.E. = 0.004) ($p = 0.368$)	$p = 0.48$ to 0.001	$p = 0.001$ to 0.95	$p = 0.19$ to 0.98	$p = 0.15$ to 0.81
Baseline QLS	0.03 (S.E. = 0.008) ($p < 0.001$)	−0.20 (S.E. = 0.04) ($p < 0.001$)	−0.19 (S.E. = 0.05) ($p < 0.001$)	0.73 (S.E. = 0.06) ($p < 0.001$)	0.61 (S.E. = 0.08) ($p < 0.001$)
Random effects	All sources combined	All sources combined	Centre, subject (centre), intercept, slope	All sources combined	Center, subject (centre), intercept, slope
Covariance structure	Unstructured	Unstructured	Unstructured	Unstructured	Unstructured

PANSS, Positive and Negative Syndrome Scale; QLS, Quality-of-Life Scale; GEE, Generalized Estimating Equations; ZSTD, Ziprasidone 80–160 mg/d; ZLOW, ziprasidone 80–120 mg/d; HAL, haloperidol 5–20 mg/d.

[a] Non-significant main treatment effects term ($p > 0.27$) were deleted from the model.

difficult to interpret, since the latter assumes data are missing completely at random, and that responses following drop-out remain the same at the last observed value after drop-out for the full study duration (Fitzmaurice *et al*. 2004). The drop-out patterns in Fig. 5 show that such assumptions are questionable and unrealistic. In fact, LOCF assumptions are generally violated in a typical clinical trial (Leon *et al*. 2006). In our study, for example, a subject who dropped out for any reason at week 68 would be assumed to have the same symptom ratings at week 196, more than 2 yr later.

Limitations of the LOCF-ANCOVA model are apparent in that only the last observation is used and treatment time is ignored in the analysis. It is interesting to note that mixed-effects models produced the conventional LOCF-ANCOVA estimates of treatment effects, when dichotomized measure of treatment duration was used (visit-time variable = 0 for baseline *vs*. 1 for LOCF post-randomization response) (Liang & Zeger, 2000). By analysing mean changes as a function of treatment time (slope), using all available visit data in a mixed-effects or GEE model, we found consistent differential effects between treatment groups in both remission rate and PANSS total score.

The strengths of this study include the double-blind design and length of treatment duration (up to 196 wk) which permitted evaluation of the time-course of remission (Andreasen *et al*. 2005). A limitation of this analysis is that the remission criteria used as the key endpoint were not specified *a priori* in the protocol (these criteria were not available at the time the study was conducted). However, the primary analysis for remission *vs*. no remission (dichotomous variable) was agreed upon before the conduct of the *post-hoc* analyses using a GEE model appropriate for

analysing mean change in remission rate over time (i.e. log odds of remission averaged over subjects in each treatment group).

Further, in long-term studies such as this, drop-outs are the rule, not the exception, which can create challenges for the analysis and interpretation of results. The chronic schizophrenia patients enrolled in the CATIE schizophrenia study (Lieberman *et al*. 2005) only remained on their randomly assigned treatment for 18 months for a mean of 120 days (early drop-out rate 74%). In the two open-label, random-assignment of first-episode patient studies, 42% and 70% of subjects, respectively, completed 1 yr of treatment with their assigned agents (McEvoy *et al*. 2007; Kahn *et al*. 2008). Fewer than 58% of these subjects were diagnosed as having schizophrenia compared to 89.7% of our subjects. Eligible subjects in this extension study were required to meet the *a priori* specified inclusion/exclusion criteria in the protocol which included the completion of the initial 40-wk study. We showed that about 37% of subjects remained on treatment for years and, when they did, accrued additional benefits including remission and an enhanced quality-of-life.

Drop-outs can introduce selection bias, resulting in misleading conclusions regarding treatment effects. To avoid conclusions based on only those completing the week-196 visit, our primary endpoint was the slope of the time-course which integrated data from all 186 subjects across visits in the extension study. We also assess the potential drop-out bias by showing the results in each drop-out cohort, derived by dividing the entire sample into subgroups corresponding to all drop-out time (drop-out pattern-mixture approach) (Fig. 5). Subjects assigned to the 80–160 mg/d ziprasidone group showed comparable or less severe PANSS scores (*vs.* haloperidol) across all subgroups stratified according to their drop-out time (weeks 92–196) (Fig. 5*b*). Consistency of result across these drop-out cohorts strengthens the conclusions of analyses. Our analyses of remission and other outcome measures also addressed the issues of drop-out bias using a conditional model approach. These results show that both GEE and mixed-effects models yield similar results across efficacy measures and sensitivity analyses (Tables 3–5). When drop-outs are not completely at random and potentially informative, it is generally challenging to identify a unique model for any repeated-measures data, where drop-out patterns and some key aspects of the model are unknown *a priori*. Sensitivity analyses based on models adjusted for a range of informative drop-out measures are useful. Regardless of the methods used in the analyses with or without adjustment for drop-out measures to account for the time-dependent drop-out process (Rosenheck *et al*. 2006; Wu *et al*. 2001), we found similar results across efficacy measures and sensitivity analyses (Tables 3–5). Given the *post-hoc* nature of analyses these findings should be confirmed in subsequent investigations.

Overall, our findings demonstrate that remission can occur with long-term antipsychotic treatment, and suggests that attainment of remission may have a positive impact on quality-of-life and ultimately, on overall patient outcomes. Specifically, extended ziprasidone treatment may increase rates of remission and improve quality-of-life more than haloperidol treatment. These findings have important implications for the use of atypical agents and our understanding of long-term outcomes in the treatment of schizophrenia.

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Statement of Interest

Steven Potkin received grant support, funding, and has been a consultant to Pfizer that has contributed to this study. He also received grant support, funding, or has been a consultant to the following companies that make medication related to schizophrenia and related disorders: Wyeth Research, Bristol–Myers Squibb, Eli Lilly and Company, Merck & Co. Inc., AstraZeneca AB, Novartis Pharmaceuticals Corporation, Elan Corporation plc, Bioline, Dainippon–Sumitomo, Fujisawa, Janssen Pharmceutica, Ono, Organon/Schering Plough, Otsuka Pharmaceuticals, Solvay Pharmaceuticals, Roche Laboratories, Vanda, Cortex, and Forest Laboratories. Peter Weiden has received grant support, funding or has been a consultant to the following companies: AstraZeneca, Bristol–Myers Squibb/Otsuka America Pharmaceutical, Ortho-McNeil Janssen, Organon, Pfizer, Shire, Vanda, and Wyeth. Dr Weiden's family member has served as a consultant for Pfizer within the last 3 years. Drs Loebel, Watsky and Warrington were full-time employees of Pfizer Inc. during development and writing of the manuscript. Cynthia Siu was a paid consultant to Pfizer in connection with the statistical analysis and development of this manuscript and has served as a consultant to Pfizer, Dainippon Sumitomo Pharma America, Memory Pharmaceutical, Wyeth, and Prescient.

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