## Introduction

Good Morning. My name is Stephen Cheng and I am with the Health Outcomes Research Division of Eli Lilly and Company.

- Thank you for the opportunity to comment on Zyprexa today. Since the atypical antipsychotic class was last reviewed by the Idaho P&T Committee, there have been 2 new meta-analytical studies comparing antipsychotics in the treatment of persons with schizophrenia.
- These meta-analyses were conducted by a team of experts who systematically synthesized data from a total of 227 studies including about 35,000 patients. The researchers also conducted sensitivity analyses to examine potential bias, including industry sponsorship bias. Both of these meta-analytical studies provide valuable comparative information that also helps to highlight the benefits and risks of Zyprexa when compared to first-generation antipsychotics and other second-generation antipsychotics.
- Since the 2 new meta-analyses included 9 second-generation antipsychotics and 3 of them— Solian, Nipolept, and Serdolect—are not available in the US, I will focus on findings applicable to the antipsychotics available in the US.

## Leucht et al, 2009<sup>1</sup>

- The first meta-analytical study was funded by the National Institute of Mental Health.<sup>1</sup> It compared first- and second-generation antipsychotics in the treatment of schizophrenia and included 150 double-blind, randomized studies with about 21,000 participants. This study evaluated the efficacy and safety of 9 second-generation antipsychotics compared to first-generation antipsychotics, primarily Haldol, and it focused on overall efficacy as the primary outcome measure.
- This meta-analysis found that only 4 of the 9 second-generation antipsychotics were more efficacious than first-generation antipsychotics, with small to medium effect sizes. These 4 second-generation antipsychotics include Clozaril, Zyprexa, and Risperdal. The other 5— which included Seroquel, Abilify, and Geodon—were only as efficacious as first-generation antipsychotics. Importantly, this study measured potential industry sponsorship bias, and found that when industry-sponsored studies were excluded, Risperdal was no longer significantly more efficacious than first-generation antipsychotics; but the results for Zyprexa and Seroquel were unchanged.
- On secondary outcome measures, Clozaril, Zyprexa, and Risperdal were better than firstgeneration antipsychotics on positive and negative symptoms. Seroquel was also found to be less efficacious than first-generation antipsychotics on positive symptoms. NS022609KM
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- On depressive symptoms, Clozaril, Zyprexa, Abilify, and Seroquel were significantly better than first-generation drugs, whereas Risperdal was not.
- On relapse prevention, Zyprexa and Risperdal were better than first-generation antipsychotics, and on quality of life, all second-generation antipsychotics—except Clozaril did not significantly differ from first-generation antipsychotics.
- When compared on extrapyramidal symptoms, patients treated with Zyprexa and all other second-generation antipsychotics drugs experienced fewer extrapyramidal symptoms than patients treated with Haldol, even when Haldol was used in lower doses. With the exception of Clozaril, Zyprexa, and Risperdal, second-generation drugs have not been shown to be better than low-potency first-generation antipsychotic drugs with respect to EPS.
- Patients treated with Clozaril and Zyprexa experienced significantly fewer EPS than did firstgeneration antipsychotic drugs despite prophylactic antiparkinsonian medication, but the effect size was relatively small.
- There was no significant difference in the incidence of sedation between patients treated with Zyprexa and first-generation antipsychotics; whereas a greater percentage of patients treated with Clozaril and Seroquel experienced sedation compared to patients treated with firstgeneration antipsychotics. Patients treated with Abilify experienced less sedation than patients treated with first-generation antipsychotics. Compared with patients treated with lowpotency first-generation antipsychotic drugs, only patients treated with Clozaril experienced significantly more sedation.
- Concerning weight gain, most second-generation antipsychotics (except Abilify and Geodon) were associated with more weight gain than high potency, but not more than low potency, first-generation antipsychotics. Patients treated with Clozaril and Zyprexa experienced the greatest weight gain.

# Leucht et al, 2008<sup>2</sup>

- Since indirect comparisons of first- and second-generation antipsychotics are limited in their ability to support any differences in efficacy between second-generation antipsychotics, the authors performed a second meta-analysis,<sup>2</sup> comparing the 9 second-generation antipsychotics head-to-head.
- This meta-analysis used data from 78 blinded studies with about 13,000 patients and was sponsored by several sources, including the NIMH. The study found that on overall efficacy the primary outcome measure—Zyprexa proved superior to Abilify, Seroquel, Risperdal, and

NS022609KM Quality Reviewed (Haya Ascher-Svanum, Stacey Bledsoe) 2/6/09 Approved by GHO Neuroscience Platform Manager (Pete Watson) 2/10/09 Approved by Legal (Andrew Kantra, Colin Ewing) 2/25/09 Geodon, but was not significantly different from Clozaril. The authors note that most of the differences between drugs were due to positive symptoms rather than negative symptoms. The effect sizes range between 1.9 (between Zyprexa and Risperdal) and 8.3 (between Zyprexa versus Geodon) PANSS points. These effect sizes are small to medium differences. The clinical relevance of the difference between Zyprexa and Risperdal based on a large sample size is especially doubtful.

- Zyprexa also proved superior to Seroquel, Risperdal, and Geodon on dropout rates due to lack of medication efficacy, a finding consistent with the CATIE Phase 1 results.<sup>3</sup>
- Importantly, results of the second meta-analysis were also robust with regard to the lack of industry sponsorship bias.
- In first-episode and treatment-resistant population, five first-episode studies showed no difference between second-generation antipsychotics. Most studies of treatment-resistant patients involved Clozaril, which was not more efficacious than Zyprexa.
- Safety assessments were not included in this clinical trial meta-analysis.

## Conclusions

- In conclusion, the first meta-analyses showed the superior efficacy of Zyprexa compared to first-generation antipsychotics, while highlighting Zyprexa's safety and tolerability profile, including its higher rate of weight gain, fewer EPS, and non-significant sedation (when compared with first-generation antipsychotics). The second meta-analysis showed Zyprexa to have superior efficacy compared to Risperdal, Seroquel, Abilify, and Geodon.
- Although these studies were sponsored by the NIMH, conducted by credible experts, and used multiple sensitivity analyses to assess robustness of the findings, these meta-analyses can only be as good as the underlying studies. It is important to note that in both studies, the effect sizes for the differences between the antipsychotics were of small to medium size and the clinical implications of these differences need further study.
- Because the second-generation antipsychotics differ in many properties, including efficacy, adverse events, cost and pharmacology, neither these drugs nor the first-generation antipsychotics form a homogeneous class.
- Addressing these findings, the authors concluded that "Schizophrenia afflicts patients for life and even a small benefit may be important... There are substantial differences between individual patients in how they respond to these drugs. The balancing of efficacy and side effects must be tailored to the individual patient, the setting, and the health system."<sup>2</sup>

#### References

- 1. Leucht et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; 373:31-41.
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