Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 – 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 – 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 – 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 – 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated Hba1C (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as…quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 – 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 – 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Sernyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 – 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 – 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members, NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fac, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools…across parameters / measures…across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; $P<0.001$). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; $P<0.001$ and 0.53; $P<0.001$, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.

Donna K Arnett

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