EXHIBIT 9

Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
+ Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the hadoperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 – 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (± 9.6) kg at week 104, 5.7 (± 10.9) kg at week 156, and 6.7 to 7.3 (± 9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

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

Donna K. Arnett, Ph.D., M.S.P.H.