Collated comments from global reviewers of CSR 49 draft (11May2005)

Reviewer	Comment	Reply
Martin Brecher	I think the csr portrays the safety profile of 300/d and 600/d Seroquel in bipolar depression too favorably. Its hard to say that Seroquel was safe and well tolerated when 26% of the 600 mg group dc for ae. I think the trial revealed issues with sedation/somnolence, eps and insulin and these should be addressed directly. Given the effect size we can conclude positive risk/benefit, but the safety issues need to be highlighted and put into context. Insulin data needs to be included with apppropriate caveats about non-fasted status. I think the description of safety results should be as objective as possible, with signals appropriately highlighted.	Have added cross-references to sedation-associated discontinuations in the common AE section. Have changed emphasis in the discussion section to note that sedation, somnolence, dizziness were more often seen in depressed bipolar patients than in acute mania or schizophrenia patients. Have noted higher discontinuation in 600 mg dose & signal for EPS in 600 mg dose Glycemic control (glucose, insulin, HOMA-R, QUICKI) now undergoing statistical analysis.
Kevin McKenna	Page 31, Bullet 13 should ALS be ALT, same page bullet 17 should "with" be "within"	Both suggested changes are correct, and CSR will be changed.
Kevin McKenna	Page 50, Table 15 The high values for crits - are they reversed for male and females. They do not line up with the hgbs for males and females.	Reviewer is correct. Data have been reanalyzed after correcting hematocrit criteria.
Kevin McKenna	Page 61, Section 5.7.4.4. last paragraph. Sentence "For this trial, suicidality was defined on the basis of adverse events only." Is this still true given we're doign the Columbia University approach.	For Study 49, we will not use the Columbia method, as the report must be finished before the extended suicidality analysis can be completed. The current plan is to apply the Columbia method to the 49 data as part of the CTD analyses.
Richard T. Owen	In the Summary of safety (Section 8.1) on p.103 it is stated that increases in SAS and BARS scales were only seen in the 600mg group. This seems to be contrary to what has been presented in poster presentations of this data where the changes were either 0 or small decreases	Reviewer is correct. Overall mean change was in negative direction for all groups in both assessments. Increase in SAS and BARS for 600 mg group was expressed only in the proportion of patients showing increase from baseline. However, other data point to a signal for more EPS in 600 mg treatment group. CSR has been rewritten to reflect full description of the data.
Kevin McKenna	Page 110 My comments are related to sedation/somnolence and pertain to other sections of the CSR where these AEs are discussed. Statement is made that these events most occurred in first 8 days. When I look at Table 45 it appears to me by "eyeball math" that most occurred in first 2 days after study drug start. Day 8 was firstscheduled assessment. Also what was time course of AE. I'm assuming that Table 41 lists AEs reported at least 1X. Of the pts reporting somnolence/sedation how many reported at Day 15. My review of Table 45, none of the pats discontinuing the study listing sedation/somnolence as an AE rated it severe. If I'm correct, I would recommend adding that in the CSR as appropriate. One none of the severe discontinued (according to Table 45) and it may add an understanding that investigators have to list an AE for discontinuation thereby artifically inflating the sedation/somnolence AE reporting.	Table reported "serious" rather than "severity". Text before Table 43 discusses severity. Apparent dose-response suggests that dc for somnolence is totally an artifact. We will have to wait on 135 data to get better estimate of strength of safety signal and degree of bias introduced by reporting requirement.
Kevin McKenna	Page 130 Tables 47 and Page 148, Table 63. The statements in the CSR stating that the EPS reported AEs do not seem to be consistent with the finding of the SAS and BARS. When one compares the results of Table 47 and the "Worsened" numbers for Table 63, there does seem to be consistency. Would it be logical to interpret the numbers that an EPS Sx would only be reported as an AE if the condition worsened. The numbers seem to line up	CSR has been rewritten to reflect full description of the data

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DATE: 5-16-08
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	better. There is still the higher rates on study drug versus placebo. As with the comments on sedation/somnolence, my comments on EPS/SAS/BARS relate to other sections of the CSR where they are mentioned.	
Kevin McKenna	Page 153, Section 9.2 Are there any efficacy measures where there is a differentiation in favor of the 600 mg dose. As the CSR is written, I would state that the 600 mg dose is at risk because of a less advantangeous safety profile v. 300 mg.	Dose effects have been covered in report of results. Discussion has been revised to reflect 600 mg disadvantages.
Kim Busch	Day 1 dosing at 300mg. was this information collected in this study. (I don't believe it was but just checking)	No, Day 1 dosing was 25 mg for the active treatment groups.
Kim Busch	In light of the elderley black box (will we need to document more in the CSR)	This CSR offers no data relevant to the elderly population as the oldest patient treated was 65 yrs old.
Kim Busch	TPC mentions a claim on life functioning (not cognitive functioning).....didn't see any specific secondary endpoints addressing this	TPC 5.1 (Seroquel is superior to placebo in improving level of functioning) will address the change from baseline in the Sheehan Disability Score which was not assessed in Study 49. Those data will be available from Study 135.
Kim Busch	Can we be more specific regarding the PROs collected from the trial. QLSEQ These will be important to know especially from a DTC perspective	Question referred to Kitty Rajagopalan.
Kim Busch	Again the TPC has a claim around suicide prevention in patients with bipolar depression. Did we capture this in the secondary endpoints in trial 49.	TPC 3.1 (Seroquel is effective in reducing suicidal ideation) addresses the change from baseline in HAM-D Item 3. Those data are displayed as descriptive statistics in Section 11 (the statistical appendices) of the report. As the baseline values for all treatment groups were constrained to ≤ 2 by a specific exclusion criterion, it is not expected that the data will offer strong support for this promotional claim. However, the data are not expected to contradict it either.
Meg Melville	Add common AEs to conclusions	Done
Meg Melville	more emphasis on akathisia	Akathisia data have been described truthfully with a relatively conservative interpretations. We do not want to overplay the value of a single study in providing accurate estimates of effect. If the Study 135 data look the same, we may have to give these data more emphasis in the CTD.
Meg Melville	expand discussion	Discussion has been restricted so as to not contradict CSR for Study 135 or CTD high-level documents. We cannot predict how additional data will affect final decisions.