600 mg dose in Bipolar Depression

CFT Bipolar

June 1st 2005

Issue

- There is a risk that there will be consequences in label if the 600 mg/day dose doesn't demonstrate advantages compared to 300 mg/day. in worst case 600 mg per day will not be part of the label
  - Data from study 135 are still not available but will be critical in defining a final strategy for dose recommendation in the Bipolar Depression submission

This slide set describes different scenario and evaluate their consequences for the brand (commercially) and for other ongoing clinical programs

Background (1)

- Mania label describes a efficacy range of 400-800 mg/day with a target dose at 600 mg/day
- Bipolar depression program (studies 049, 135, 134 and 001) are conducted with fixed doses of 300 and 600 mg/day given once daily. Continuation phase in studies 135 / 001 will be analyzed by pooling data both by doses (300 and 600 mg) and across studies
- Results from study 049 (BOLDER) shows no major difference in efficacy between the two doses of quetiapine on the primary endpoint (potentially differences in completers, in MMRM analysis, in subgroups and by onset), but somewhat worse tolerability for 600 mg/day (especially higher discontinuation rate due to AE and higher increase in insulin)

Background (2)

- Bipolar maintenance program uses flexible doses of 400-800 mg day (adjunct, studies 126 and 127) and 300-800 mg/day (monotherapy, study 144), both given b.i.d.
- Clinical programs in MDD and GAD will investigate fixed doses of quetiapine SR 50, 150 and 300 mg/day (GAD and MDD)

Possible scenarios

Four scenarios were identified when comparing the dose groups (300 and 600 mg/day). The comparisons are based on results from pooled data from both studies (049 and 135)

Scenario	Outcome
A	600 mg/day offers significant advantages compared to 300 mg/day (efficacy and/or tolerability)
B	600 mg/day is similar to 300 mg/day with regard to efficacy and tolerability
C	600 mg/day has both advantages and disadvantages compared to 300 mg/day, either better efficacy and worse tolerability, or worse efficacy and better tolerability (the latter seems to be less likely)
D	600 mg/day is clearly inferior to 300 mg/day with regard to efficacy and/or tolerability

Possible scenarios

Efficacy / Tolerability	600 better than 300	600 equal to 300	600 worse than 300
600 better than 300 (not likely)	A	A	C
600 equal to 300	A	B	D
600 worse than 300	C	D	D

Scenario A

600 mg/day offers significant advantages compared to 300 mg/day (efficacy and/or tolerability)

Likelihood	• Judged to be low with the result from study 049 in mind where efficacy is similar but tolerability somewhat worse
Consequences:	• The 600 mg dose will be defended in submission • Label recommendation will range from 300 to 600 mg/day
Actions needed	• No changes compared to existing planning

Scenario B

600 mg/day is similar to 300 mg/day with regard to efficacy and tolerability

Likelihood	• Judged to be low. • Need better tolerability for 600 mg than 300 mg/day in study 135, which is not likely
Consequences:	• The 600 mg dose can probably still be defended in submission. • Label recommendation will probably range from 300 to 600 mg/day.
Actions needed	• No changes compared to existing planning • Actions are already taken in study 135 with regard to study conduct (e.g. reporting procedures for reasons for withdrawals and procedures for sampling)

Scenario C

600 mg/day has both advantages and disadvantages compared to 300 mg/day (e.g. better efficacy but worse tolerability)

Likelihood	• Judged to be high (better efficacy but worse tolerability)
Consequences:	• 600 mg dose might be defended in submission. However, success is uncertain. • Label recommendation might range from 300 to 600 mg/day or will be only 300 mg/day.
Actions needed	• We will try to defend the 600 mg/day dose in CTD by claiming a similar or positive risk/benefit ratio vs 300 mg/day. • Additional post-hoc analyses are most likely needed for submission, as well as for regulatory defense. • Contingency planning for the case where 600 mg will be dropped needs to be done in advance (i.e. before final decision by FDA) • No delay in submission is expected • Final strategy depends on the detailed results of study 135

Scenario D

600 mg/day is clearly inferior to 300 mg/day with regard to efficacy and/or tolerability

Likelihood	• Judged to be moderate (Inferior in tolerability). • This scenario might happen if the results from study 049 is confirmed in study 135 (even if the tolerability profile for 600 mg is similar to 300 mg in study 135, this is not likely to balance the findings we have already seen in study 049)
Consequences:	• It is judged that 600 mg dose cannot be defended in submission. Trying to do that could potentially lead to: - disagreement with the FDA and delay in approval - endangering the perception of Seroquel as an substance with a favorable safety profile • Therefore, it is recommended that proposed label should only contain the 300 mg/day dose
Actions needed	• See separate slide

Consequences if 600 mg/day cannot be defended for the label (1)

US bipolar depression program	• Not judged to be a showstopper for the submission. • 300 mg/day will be the only recommended dose in the proposed label. • We might be criticized by FDA of not defining a dose range, especially for not identifying minimal effective dose. Regulatory defense should be prepared. • No changes to TFLs in CTD prototype are expected. However, text and conclusions in the documents need to be changed accordingly if 600 mg/day is dropped prior to submission. • No delay in submission is expected. If 600 mg/day is included and FDA disagree, there might be a delay in approval.

Consequences if 600 mg/day cannot be defended for the label (2)

Commercial implications	• Need to build a story to manage that a higher dose is used in adjunct maintenance treatment compared to in acute monotherapy • Communication of dosing messages across indications & SR formulation becomes more complicated • Potential reduction on sales/NPV forecasts as a result of lower doses used in clinical practice to be determined

Consequences if 600 mg/day cannot be defended for the label (3)

Other ongoing clinical program	• Interpretation of results in European bipolar program will be more complicated. Do we automatically need to drop 600 mg/day in Europe as well? Can 600 mg/day data still be used for analysis of continuation phase if that dose is dropped from acute label? • Adjunct maintenance program is conducted outside the approved doses for bipolar depression. Need to argue that a range of 400-800 mg/day in the maintenance studies is probably needed for also preventing against manic events. • Judged to be no major consequences for maintenance bipolar monotherapy as dose range include the 300 mg/day dose • Judged to be no consequences for MDD and GAD programs as 600 mg/day is not included in these programs

Conclusions (1)

- Results from study 049 shows no major difference in efficacy between the two doses of quetiapine on the primary endpoint (potentially differences in completers, in MMRM analysis, in subgroups and by onset), but somewhat worse tolerability for 600 mg/day
- The final evaluation of the 300 and 600 mg/day doses requires study results from both studies. Thus, we need to wait for 135 data before final strategy can be decided upon
- The planned strategy is we will try to defend the 600 mg/day dose in the proposed label (assuming scenario C, still somewhat worse tolerability but some improved efficacy)
- Awareness that the situation might change into scenario D when results from study 135 becomes available (worse tolerability clearly confirmed but no evidence of improved efficacy for 600 mg/day)
- Need to decide at time of data interpretation meeting for study 135 if 600 mg/day should be included in proposed label

Conclusions (2)

If 600 mg/day is dropped (Scenario D or a failed scenario C) there will be consequences:

- Commercially (dose story and communication of dosing messages, and effects on sales/NPV forecasts TBD)
- On other clinical programs
  - Adjunct maintenance: need to defend that a range of 400-800 mg/day in the maintenance studies is needed for preventing manic events.
  - European bipolar depression: need to defend that 600 mg should still be part of continuation analysis