BMS/Otsuka Response to Clarification Questions

General request

1. **Priority request:** Please supply the trial protocol for NCT00110461.

The protocol, extracted from the clinical study report (CSR), has been provided along with this response.

2. **Priority request:** Please supply the draft CHMP assessment report.

The final CHMP assessment has recently been published online (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000471/WC500138620.pdf) and has been provided along with this response.

3. **Priority request:** Please supply electronic versions of all the mixed treatment comparisons undertaken.

All inputs into the mixed treatment comparison have been provided in a WinBUGS file along with this response.

Literature searching

4. **Priority question:** Please clarify why adult data was not deemed as relevant to this review of aripiprazole. Could inferences from such data be made for older children?

Expert opinion is that children and adolescents have different symptoms to adults and are treated more intensively (see Appendix 14 in original submission). Compared to adult-onset bipolar disorder, children and adolescents often experience more severe manifestations, which may lead to worse outcomes in the long term.[1] Children and adolescents appear to undergo more rapid changes in disease states, and are more prone to some adverse events such as weight gain.[2-5] Moreover, the indication in children is restricted to the treatment of acute episodes, rather than long term maintenance as for adults.

Therefore it would not be appropriate to generalise adult clinical data to children and adolescents given the particular clinical characteristics of bipolar disorder in younger individuals, and the mismatch in treatment duration.

5. **Priority question:** Searches were conducted up to January 19th 2012 (pages 267 and 280 of the submission). The ERG's enquires indicate that for the period from 2012 to current there are 307 unique records for the clinical effectiveness search; 705 unique records for the cost effectiveness search; and 216 unique records in clinicaltrials.gov register. Please update the searches and associated results to include data published before January 2013 and confirm that no further studies have been missed.

A literature review was conducted on 4th February 2013 to update the systematic review carried out previously to include any new information published from January 2012 to present on the treatment of children with bipolar disorder with aripiprazole,

risperidone, quetiapine or olanzapine. This was a non-systematic review due to time constraints.

Monthly aripiprazole publication alerts, provided by BMS, were searched for the terms child, adolescent and bipolar, in turn.

PubMed was searched for aripiprazole RCTs in children with bipolar disorder, from 2012 to present, using the terms “aripiprazole, children/pediatric/adolescent, bipolar” where children, pediatric and adolescent were replaced in turn. Only articles published since 2012 were included. The same searches were also carried out for RCTs of competitors by replacing aripiprazole with risperidone, quetiapine or olanzapine. Google Scholar was searched using the same terms as above but no additional studies were identified.

Clinicaltrials.gov was searched for studies first received or last updated from 1st January 2012 to present using the terms aripiprazole/ risperidone/ quetiapine/ olanzapine, in turn, and bipolar.

PubMed was searched for any non-RCTs for aripiprazole, risperidone, quetiapine and olanzapine in children with bipolar. The search for aripiprazole studies was conducted by searching for “aripiprazole bipolar children” with no date filter. The search for risperidone, quetiapine and olanzapine non-RCTs in children with bipolar was performed by searching for “risperidone/quetiapine/olanzapine children/adolescent bipolar” with no date filter. Search results were filtered by articles that were clinical trials.

Articles that have been identified that fulfil the original inclusion criteria of the systematic review (patients aged <18 with manic or mixed episodes of bipolar I disorder) have been tabulated in Appendix 1. None of the identified articles report results that would affect the MTC or cost-effectiveness results. Findling 2011[6] and Biederman 200[77] were identified as open-label non-RCTs of aripiprazole in the treatment of any type of bipolar disorder.

6. **Priority question:** Searches for adverse events were limited to RCT evidence. Whilst one MeSH term-"Epidemiologic study characteristics/" was used within the RCT filter in the identification of studies search strategies to capture non-RCTs - this term used alone is inadequate. The subject heading is not recognised in a number of databases searched. The ERG’s own search strategies (see appendix to this clarification letter) for adverse events have found a further 400 records for non-RCTs records in Medline and Embase (direct and comparators). Please provide the reasons for not carrying out separate adverse events searches and confirm that no non-RCT evidence has been missed.

Please see the response to question 5 for details on the non-systematic literature review undertaken.

7. **Priority question:** Please provide any relevant study data (regarding YMRS response or adverse events) for the following trials. If any of the trials were identified and subsequently excluded from the searches in the submission please state the explicit reasons for exclusion:

- NCT00194012 -"Study of Aripiprazole (Abilify) Versus Placebo in Children (5-17) With Subsyndromal Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/record/NCT00194012
- NCT00102518- "Aripiprazole Open-Label, Safety and Tolerability Study (APEX 241)" http://www.clinicaltrials.gov/ct2/show/NCT00102518
- NCT00181779- "Aripiprazole for the Treatment of Mania in Children and Adolescents With Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/NCT00181779
- NCT00221416- "An Open-Label Trial of Aripiprazole in Children and Adolescents With Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/NCT00221416

NCT00194012

This trial investigated aripiprazole in patients with subsyndromal bipolar disorder, who are patients who do not meet the full criteria for bipolar disorder. Therefore it was previously excluded.

No data are available from this study.

NCT00102518

This is the extension trial to the pivotal RCT in children and adolescents with bipolar disorder (NCT00110461) and also of the pivotal RCT in children and adolescents with schizophrenia (NCT00102063). It was originally excluded as data are only presented for the bipolar and schizophrenia patients combined. These data are presented below.

Table 1: YMRS Response from NCT00102518

	NCT00102063 and NCT00110461 Subjects
Number of Participants Analyzed [units: participants] (All subjects had either completed or had withdrawn from the double-blind extension phase of studies NCT00102063 and NCT00110461)	82
Change in Young Mania Rating Scale (Y-MRS) Total Score [units: points] Mean ± Standard Deviation	-7.74 ± 11.73

Safety
Adverse event data were collected as spontaneous reports at all scheduled visit. Serious AEs were monitored until the subject's health returned to baseline status or other parameters returned to normal or were otherwise explained.

Table 2: Serious Adverse Events from NCT00102518

	NCT00102063 and NCT00110461 Subjects
Total, serious adverse events	
# participants affected / at risk	20/325 (6.15%)
Infections and infestations	
Bronchitis acute [*1]	
# participants affected / at risk	1/325 (0.31%)
Hepatitis A [*1]	
# participants affected / at risk	1/325 (0.31%)
Injury, poisoning and procedural complications	
Electrocution [*1]	
# participants affected / at risk	1/325 (0.31%)
Intentional overdose [*1]	
# participants affected / at risk	1/325 (0.31%)
Psychiatric disorders	
Acute psychosis [*1]	
# participants affected / at risk	1/325 (0.31%)
Aggression [*1]	
# participants affected / at risk	3/325 (0.92%)
Bipolar disorder [*1]	
# participants affected / at risk	3/325 (0.92%)
Depression [*1]	
# participants affected / at risk	1/325 (0.31%)
Hallucination, auditory [*1]	
# participants affected / at risk	1/325 (0.31%)
Homicidal ideation [*1]	
# participants affected / at risk	1/325 (0.31%)
Impulsive behavior [*1]	
# participants affected / at risk	1/325 (0.31%)
Intentional self injury [*1]	
# participants affected / at risk	1/325 (0.31%)
Psychotic disorder [*1]	

# participants affected / at risk	2/325 (0.62%)
Schizophrenia * 1	
# participants affected / at risk	4/325 (1.23%)
Suicidal ideation * 1	
# participants affected / at risk	1/325 (0.31%)

* Events were collected by non-systematic assessment

1 Term from vocabulary, MedDRA 9.1

Table 3: Other Adverse Events occurring in ≥5% patients

	NCT00102063 and NCT00110461 Subjects
Total, other (not including serious) adverse events	
# participants affected / at risk	230/325
Gastrointestinal disorders	
Nausea * 1	
# participants affected / at risk	25/325 (7.69%)
Vomiting * 1	
# participants affected / at risk	18/325 (5.54%)
Infections and infestations	
Nasopharyngitis * 1	
# participants affected / at risk	18/325 (5.54%)
Investigations	
Weight increased * 1	
# participants affected / at risk	25/325 (7.69%)
Metabolism and nutrition disorders	
Increased appetite * 1	
# participants affected / at risk	15/325 (4.62%)
Nervous system disorders	
Akathisia * 1	
# participants affected / at risk	27/325 (8.31%)
Extrapyramidal disorder * 1	
# participants affected / at risk	48/325 (14.77%)
Headache * 1	
# participants affected / at risk	31/325 (9.54%)

Somnolence * 1	
# participants affected / at risk	42/325 (12.92%)
Tremor * 1	
# participants affected / at risk	19/325 (5.85%)
Psychiatric disorders	
Insomnia * 1	
# participants affected / at risk	26/325 (8.00%)

* Events were collected by non-systematic assessment

1 Term from vocabulary, MedDRA 9.1

NCT00181779

This non-RCT (Biederman 2007[7]) was identified by the systematic review, but was excluded as it included patients with bipolar II disorder and bipolar disorder not otherwise specified, as well as patients with bipolar I disorder.

It was an 8-week, open-label, prospective study of aripiprazole monotherapy in outpatients aged 6-17 years of age with a diagnosis of bipolar disorder. The aim was to assess the efficacy and tolerability of aripiprazole in this patient population. Adverse events were assessed through spontaneous self-reports, vital signs weight monitoring, and laboratory analysis.[7]

The study only enrolled 19 patients, of which 15 (79%) completed the study. Aripiprazole treatment was associated with clinically and statistically significant improvement in mean Young Mania Rating Scale scores (p<.0001).[7] Other scales are presented in Table 4.

Metabolic outcomes and adverse effects are presented in Table 5 and Figure 3. There were no statistically significant changes in weight, metabolic, or cardiovascular parameters from baseline to endpoint (Table 2). The most commonly reported adverse events were sedation (57%), gastrointestinal complaints (42%), cold symptoms (32%), and headache (32%). The high rate of sedation in this sample did not account for the improvement in symptoms of mania: at study endpoint, the mean change YMRS score was not statistically different (p=0.7) in those who had experienced sedation (–17.5 ± 8.1) than in those who had not been sedated (–18.9 ± 5.3). Two cases of extrapyramidal symptoms caused the patients to discontinue medication and withdraw from the study.[7]

Table 4: Rating scale scores and baseline and week 8 from NCT00181779

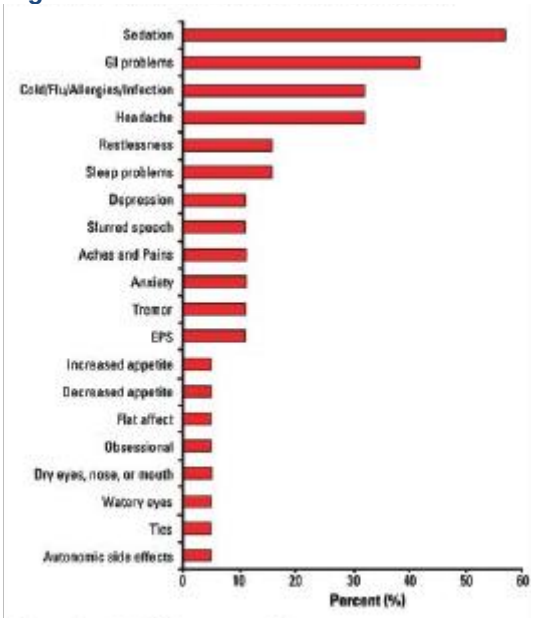
Score	Baseline, mean (SD)	Endpoint at week 8, mean (SD)	P value
YMRS	27.3 (4.8)	9.2 (6.3)	<0.001
BPRS	38.9 (7.6)	28.8 (9.9)	=0.0003
Resistance (mania symptoms)	12.9 (3.1)	7.7 (2.9)	<0.001
Positive symptoms	7.4 (2.3)	5.8 (1.2)	=0.01
Negative symptoms	5.5 (3.3)	5.1 (3.6)	=0.7
Psychological discomfort	111.9 (4.1)	9.0 (4.4)	=0.02

(anxiety/depression)			
CDRS	38.6 (11.2)	32.6 (17.4)	=0.1

Table 5: Metabolic outcomes from NCT00181779

Score	Baseline, mean (SD)	Endpoint at week 8, mean (SD)	P value
Cholesterol (mg/dL)	116.7 (57.0)	149.8 (27.2)	=0.1
High density lipoprotein (mg/dL)	49.3 (17.2)	50.1 (14.9)	=0.9
Low density lipoprotein (mg/dL)	98.2 (67.6)	79.6 (24.8)	=0.5
Triglycerides (mg/dL)	127.0 (67.1)	100.7 (48.5)	=0.4
Glucose (mg/dL)	92.3 (15.1)	89.3 (12.0)	=0.6
Prolactin (mg/dL)	19.4 (21.9)	3.2 (4.7)	=0.1
Weight (kg)	41.1 (19.3)	42.0 (19.9)	=0.2

Figure 1: adverse events from NCT00181779



GI=gastrointestinal; EPS=extrapyramidal symptoms.

NCT00221416

This non-RCT was not previously identified.

It was a 6-week, open-label, prospective study that aimed to assess the safety and efficacy of aripiprazole monotherapy in children and adolescents aged 7 to 18 years old, diagnosed with bipolar I disorder, manic or mixed episode.[8]

The study was extremely small, as it enrolled only 16 patients, of which 13 (81.25%) completed the study. Treatment with aripiprazole was associated with significant improvement in the mean YMRS score at week 42 (mean = 6.47+/-7.8) compared to baseline (mean = 29.67+/-5.02). Significant improvement in CGI-S scores (mean

change of 2.46+/-1.06) and final mean CGI-I scores (1.47+/- 0.9; 95%CI 0.96-1.97) were also found.[8]
Aripiprazole was well tolerated, with no extrapyramidal adverse events. There was a mean weight gain of 0.99+1.4 kg (p=0.16). The most common adverse events were appetite changes, nausea/vomiting and sleep problems.[8]

8. Please clarify whether the references of the full economic evaluations were checked for appropriate utility / cost data.

The adult cost-effectiveness references have been checked for relevant utility and cost data; no data more relevant that the current inputs into the de novo model were identified. The information found has been outlined below.

The utility/cost information provided by the evaluations identified from the previous NICE systematic review is as follows:

- Keck 1996:[9] Reported resource use and costs for a US adult population with bipolar disorder. More applicable data for children/adolescents in the UK was sourced and therefore non-UK data was disregarded.
- Revicki 2005:[10] Provided quality of life (not utilities) and cost data for US adults with bipolar disorder, which were not considered relevant to adolescents in the UK.
- Bridle 2004:[11]
  - Reported hospital length of stay from US adult patients used by the Keck evaluation. More applicable data from the UK was sourced and therefore non-UK data was disregarded.
  - Reported the overall costs of outpatient stay used in Zajecka 2000 in US dollars for valproate (US$554) and olanzapine (US$1109).
  - Reported resource use and costs from the Eli Lilly economic model for UK adults with bipolar disorder. Resource use in adults was assumed not to be applicable to adolescents, based on expert opinion. The resource use did not differentiate between atypical antipsychotics.
  - Reported overall costs from the Sanofi-Synthelabo model, but not unit costs or resource use.

The utility/cost information provided by the economic evaluations identified in our systematic review:

- Calvert 2006[12]: provided some resource use and unit cost data for adults with bipolar disorder in the US. This was not considered relevant to adolescents in the UK. The study reported the following utilities derived from SF-36 from the lamotrigine pivotal trial: 0.8 euthymic, 0.7 manic. These were not sufficiently detailed for input into our *de novo* model.

- Despiegel 2011[13], Faluta 2011[14], Ramirez de Arellano 2010a[15] (abstracts only), Muzina 2006[16] (commentary only): provided no utility or cost data

- Klok 2007[17]: Provided unit costs in Euros from 2003. More applicable data from the UK was sourced and therefore non-UK data was disregarded.

- McKendrick 2007[18]: Provided UK unit costs (from 2003) and resource use for the prevention of acute episodes in adults. Adult resource use was assumed not to be applicable for children/adolescents. Better quality, more recent cost data were available and therefore this was not used.

- Ramirez de Arellano 2010b[19] (abstract only): Provided cost per day for hospitalisation (347.90 Euros) and length of hospitalisation associated with BD (18.1 days) from a Spanish adult study. More applicable data from the UK was sourced and therefore non-UK data was disregarded.

- Schumock 2007[20]: Provided cost and resource data from the US. More applicable data from the UK was sourced and therefore non-UK data was disregarded.

- Soares-Weiser 2007[21]: Reported costs of mental health professional time. These were assumed to have been updated in the more recent version of the Unit Costs of Health and Social Care.[22]

- Woodward 2010[23]: Provided cost and resource data from the US. More applicable data from the UK was sourced and therefore non-UK data was disregarded.

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify the purpose and conduct of the 28 day screening period prior to randomisation referred to on page 51 of the submission.

The screening period was 7-28 days, which was a wash-out period for prior mood-stabilising medication, psychotropics or antidepressants. Any mood-stabilising medication, psychotropic or antidepressant had to be discontinued for at least five half-lives prior to administration of study drug. Fluoxetine in particular had to be discontinued for 28 days prior to randomisation into the study, making the screening period a maximum of 28 days.

Patients in NCT00110461

A2. Please clarify the following:
- How many patients were inpatients throughout the screening period, at baseline and throughout the study?
- If patients were not inpatients at baseline, how day 1 of the acute phase (page 52 of the submission) was observed.

Unfortunately, the proportions of patients who were inpatients during the screening phase and at baseline are not reported in the clinical study report (CSR).

The tables below present the number of hospitalisations that were observed during the acute phase and during the entire study period.

Table 6: Number of hospitalisations in the acute phase

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		

Table 7: Number of hospitalisations in the entire study period (30 weeks)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		

Patients enrolled in the study were either outpatients or inpatients. Therefore, if they were not inpatients, then they were observed at week 1 and subsequent weeks during an outpatient visit.

A3. Please clarify how many patients at baseline were in a manic state and how many patients were in a mixed state.

Data collection relating to this clinical characteristic was not required by the study protocol and was assessed post-hoc. Accordingly, there is a high proportion of missing data. As could be expected in such a population,[24] a substantial proportion of patients were experiencing a mixed episode.

Table 8: Manic and mixed state status at baseline in study NCT00110461[25]

Baseline characteristic	**Placebo** (n=99)	**Aripiprazole 10 mg** (n =98)	**Aripiprazole 30 mg** (n = 99)	**Total** (n=296)
Current episode at baseline, n (%)				
Mixed	43 (43.4%)	43 (43.9%)	39 (39.4%)	125 (42.2%)
Manic	38 (38.4%)	41 (41.8%)	40 (40.4%)	119 (40.2%)
Unknown	18 (18.2%)	14 (14.3%)	20 (20.2%)	52 (17.6%)

A4. Please clarify what percentage of patients were rapid cyclers, that is patients who experience four or more episodes a year.

Data collection relating to this clinical characteristic was not required by the study protocol and was assessed post-hoc. Accordingly, there is a relatively high proportion of missing data.

Table 9: Rapid cyclers in study NCT00110461[25]

Baseline characteristic	Placebo (n=99)	Aripiprazole 10 mg (n =98)	Aripiprazole 30 mg (n = 99)	Total (n=296)
Rapid cycling*, n (%)				
Yes	15 (15.2%)	17 (17.4%)	13 (13.1%)	45 (15.2%)
No	51 (51.5%)	49 (50.0%)	46 (46.5%)	146 (49.3%)
Unknown	33 (33.5%)	32 (32.7%)	40 (40.4%)	105 (35.5%)

* Rapid cycling defined by DSM-IV criteria as patients who experience four or more manic, hypomanic or mixed episodes during the previous year

A5. **Priority question**: Please clarify if patients in the trial received psychotherapy and if so, please provide the numbers involved in each of the trial arms.

The protocol did not preclude use of non-pharmacological therapy. However, this was not explicitly recorded.

Outcomes in NCT00110461

A6. **Priority question**: On page 271 of the submission it is stated that medication adherence and well-being were measured but not reported.

- Please describe and provide the data for adherence.
- Please describe and provide the data for well-being.

[redacted]

A7. Please clarify why relapse/recurrence of manic episode was not measured in this trial as stated on page 80 of the submission.

Measurement of relapse/recurrence was not the aim of the trial. The trial was not designed to assess relapse/recurrence after discontinuation of treatment. A different design would be necessary to measure relapse/recurrence after stopping treatment, whereby all patients receive drug initially, reach a period of sustained remission, and then are randomly taken off drug and allocated to blinded placebo.

A8. Please clarify whether recurrence of depression was measured and not reported, or if it was not measured in the trial.

Measurement of relapse/recurrence was not the aim of the trial. The effect of treatment on depressive symptoms was measured throughout the trial, though.

These results were not reported in the original submission in order to focus the original submission on the effects of aripiprazole on manic symptoms, which is the indication under review. The 4-week data on depressive symptoms has been published (Findling 2009[25]), and both the 4-week and 30-week results are presented below. As can be seen from the data, no negative effect on depression with aripiprazole treatment was seen, and at week 30 the 30 mg aripiprazole dose actually had a significant positive effect on change in depression symptoms compared to placebo as measured by the CGI-BP severity scale.

Severity of depression was monitored throughout the trial via the following secondary endpoints:

- CGI-BP Severity Score for Depression
- Children's Depression Rating Scale-Revised (CDRS-R) Score
- GBI Total Score in Parent/Guardian Version for Depression
- GBI Total Score in Subject Version for Depression

Week 4:

Table 10: Depression outcomes at week 4[25] (efficacy sample, LOCF dataset)[a,b]

	Placebo (n=99)	Aripiprazole 10 mg (n =98)		Aripiprazole 30 mg (n = 99)	
	Value	Value	P value vs. placebo	Value	P value vs. placebo
CGI-BP severity score depression					
Baseline	2.8 (n=94)	2.9 (n=96)		2.9 (n=99)	
LS mean change at week 4	-0.6 (n=92)	-0.9 (n=96)		-0.9 (n=99)	
Treatment difference at week 4 (95% CI)		-0.25 (-0.54 to 0.04)	0.0878	-0.26 (-0.55 to 0.03)	0.0752
CDRS-R score					
Baseline	33.8 (n=86)	35.2 (n=91)		34.1 (n=94)	
LS mean change at week 4	-4.9 (n=85)	-7.2 (n=91)		-6.1 (n=64)	
Treatment difference at week 4 (95% CI)		-2.28 (-4.81 to 0.25)	0.0767	-1.19 (-3.69 to 1.32)	0.3515
GBI total scores - parent/guardian (depression)					
Baseline	13.4 (n=93)	13.4 (n=95)		12.4 (n=96)	
LS mean change at week 4	-3.8 (n=91)	-5.9 (n=95)		-4.1 (n=96)	
Treatment difference at week 4 (95% CI)		-2.13 (-4.20 to -0.07)	0.0430	-0.31 (-2.37 to 1.76)	0.7696
GBI total scores - patient (depression)					
Baseline	10.5 (n=93)	12.1 (n=96)		11.3 (n=96)	
LS mean change at week 4	-3.4 (n=91)	-3.4 (n=96)		-3.3 (n=96)	
Treatment difference at week 4 (95% CI)		0.07 (-1.73 to 1.86)	0.9418	0.19 (-1.61 to 1.98)	0.8377

[a]Variation in n numbers reflects rating scales not completed for all subjects
[b]A negative change signifies improvement on all scales reported here
CI, confidence interval; LOCF, last observation carried forward; LS least squares

Week 30:

Table 11: Depression outcomes at week 30[26] (efficacy sample, LOCF dataset)[a,b]

	Placebo (n=99)	Aripiprazole 10 mg (n =98)		Aripiprazole 30 mg (n = 99)	
	Value	Value	P value vs. placebo	Value	P value vs. placebo
CGI-BP severity score depression					
LS mean change at week 30[26]	-0.5	-0.7	NS	-0.9	<0.05
Treatment difference at week 30 (95% CI)[27]				[redacted]	[redacted]
CDRS-R score					
LS mean change at week 30[27]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GBI total scores - parent/guardian (depression)					
LS mean change at week 30[26]	-2.8	-5.0	<0.05	-4.1	NS
GBI total scores - patient (depression)					
LS mean change at week 30[26]	-3.2	-4.0	NS	-4.4	NS

[a]Variation in n numbers reflects rating scales not completed for all subjects
[b]A negative change signifies improvement on all scales reported here
CI, confidence interval; LOCF, last observation carried forward; LS least squares; NR, not reported; NS, not significant

Statistical analysis of NCT00110461

A9. **Priority question:** In table B8, page 70 of the submission, it is stated that an intention-to-treat analysis was not done for this trial.

- Please explain why an intention-to-treat analysis was not undertaken.
- If the evidence is available, please conduct an intention-to-treat analysis.

Subjects were analysed as per randomised group, regardless of protocol violation. The efficacy ITT population was defined as all randomised subjects evaluated as per randomised group regardless of protocol violation. For the endpoints measured as "change from baseline" (including the primary endpoint) a modified ITT analysis was necessarily performed where patients must have recorded at least one post-baseline score to be included in the dataset.

Therefore an ITT analysis of the whole randomised population in the strict sense was not applicable and was not performed.

Results from NCT00110461

A10. **Priority question:** Please clarify why the number of patients in the placebo group at week 30 in Table B95 (page 321 of the submission) is higher than the number of patients at week 4 in table B9 (page75 of the submission).

Ninety-nine patients were randomised to placebo. For the rating scales, the variation in the n numbers reflects the fact that rating scales were not always completed for all subjects at all visits.[25] For change from baseline analysis by visit, only subjects who had both baseline and post-baseline values were included in the LOCF datasets. A greater number of subjects would be expected to be included in the LOCF analysis at week 30 than at weeks 1-4 for placebo, since there was no value to impute in LOCF until a post-baseline visit was recorded.

A11. Please confirm why the observed case analysis was not available as stated on page 74 of the submission, but appeared to be available for quality of life (page 82) and also for Tables B13, B14 and B15 on pages 83-84.

The statement on page 74 is incorrect; the observed case is available and has been presented as described in the question above.

Mixed treatment comparison

A12. **Priority question**: Page 110 states that "data are available in very few studies for this analysis, and each study compares a different pair of treatments. There is therefore not enough evidence to support the estimation of a random-effects model." Please conduct a random effects model assuming a homogeneous between-study variance model, which should be subject to sensitivity analyses. Suggested priors for the between study standard deviation are U(0, 0.6), U(0, 1) and U(0, 2). Please conduct this for both the base-case model and the sensitivity analyses which include the Pavaluri and Geller trials.

Unfortunately, there is not enough evidence to support a random effects model, and therefore conducting such analysis using different priors would not provide any further useful information. The uncertainty intervals around the estimates in all cases would be very large, as the model would not have sufficient information to estimate the variability around each treatment effect.

Due to these reasons, this further analysis was not conducted.

A13. Please clarify why the mixed treatment comparison was not undertaken for 13-17 year olds. Does 'point 4 on page 146 refers to the treatments other than aripiprazole as the efficacy for aripiprazole is in Table B13 (page 83).

As stated in the original submission, the age subgroup of 13-17 year olds was not used in the MTC due to the non-availability of YMRS response data for this subgroup. YMRS response was defined as the proportion of patients who had a reduction from baseline in YMRS score of 50% of more. This analysis was not run for the age subgroups.

The only YMRS data available for this subgroup was presented in the CHMP opinion report, which included only the mean changes from baseline at week 4 and week 12.

This is the data in Table B13 on page 83 and is not a suitable outcome for use in the MTC. A separate analysis on the patient-level data would need to be run to determine the proportion of patients who had a ≥50% change from baseline, and this analysis has not been run for the age subgroups.

Point 4 on page 146 therefore does refer to aripiprazole. It is also true for risperidone and quetiapine that YMRS response data is not available for the 13-17 year old subgroup of the pivotal trials, which would be needed for a mixed treatment comparison for the 13-17 year old population.

A14. **Priority question:** Please clarify the following:

- How the results based on 50,000 iterations of the WinBUGS model (page 110 of the submission) relate to the sample of 1,000 values used within the PSA.
- Why it was deemed necessary to generate 50,000 samples.

A sample of 1000 iterations was drawn at random from the 50,000 iterations of the WinBUGS model for entry into the model as PSA seeds. This was deemed sufficient to capture the variation in the results.

It was not necessary to generate 50,000 samples to obtain satisfactory posterior estimates from the model. However, the more samples are run, the more accurate the posterior estimates will be. In this analysis where data are only reported in a limited number of studies, 50,000 was deemed to be an appropriate number of samples to ensure the best estimation possible would be derived from the available data.

A15. Please clarify how convergence of the MCMC chains was assessed and confirm that the chains had converged within the burn-in phase.

The history trace plots of the parameters of interest were examined at the end of the burn-in period. These plots display the evolution of the variables against iteration number and are a good tool to assess whether the simulation has converged. In each analysis, the plots showed all the characteristics of a random series ("hairy caterpillars" plots): no trend over iteration number, values well dispersed in space and not staying in one place. They also showed that the 3 chains, initiated with different starting points, had converged towards the same values.

A16. Please clarify what goodness-of-fit tests were performed to assess the adequacy of the model to the data.

The smoothed Kernel density plots of the posterior distributions were drawn. The posterior density functions of each parameter of interest appeared to be globally unimodal and symmetric, confirming that convergence towards a sensible posterior distribution had been achieved.

The magnitude of the MC error (Monte Carlo standard error of the mean) for each parameter was also checked. A general rule commonly used is that the size of the MC error should be less than 5% of the standard deviation of the posterior distribution. This criterion was easily attained here as the MC errors were always inferior to 1%.

The history plots were also checked over the sample used to derive the results, as previously described in question A15.

A17. The summary data are expressed as relative risks, however the WinBugs model is constructed using odds ratios. Please clarify how the transformation from odds ratios to relative risks was performed.

The data inputted into the Winbugs model are the number of patients experiencing the outcome in each treatment arm, out of the total number of patients in each arm, for all studies. These are modelled in a standard manner for dichotomous data, by assuming that these data were generated from a Binomial distribution.

$n_{ik} \sim Bin(p_{ik}, N_{ik})$
Where:

- i represents the study and k the treatment arm
- n_{ik} the number of events observed in arm k of study i
- N_{ik} the total number of patients in arm k of study i
- p_{ik} the probability of an event in arm k of study i

Since the parameters of interest p_{ik} are probabilities and therefore can only take values between 0 and 1, a transformation is used to map these probabilities into a continuous measure between plus and minus infinity. For a Binomial likelihood the most commonly used link function is the logit one. In the Winbugs model, the probabilities of experiencing the event in each study and each treatment arm are therefore modelled on the logit scale as:

$logit(p_{ib(i)}) = \lambda_i$
$logit(p_{it(i)}) = \lambda_i + \theta_{i,b(i),t(i)}$
Where:

- b(i) represents the baseline treatment in study i
- t(i) the comparator in study i
- λ_i the baseline effect (log-odds) of the control treatment in study i
- $\theta_{i,b(i),t(i)}$ the log odds-ratio of t(i) relative to b(i) in study i.

In summary, although a logit transformation is used for modelling purposes, the primary parameters of interest are the probabilities of experiencing an event with each treatment. These are estimated within the model, and then combined to produce relative risks by dividing the probability of having the event with each treatment by the probability of having one with placebo.

A18. Please clarify the inclusion of the paediatric schizophrenia trial used alongside Study 149 referred to in Table B25 (page 108 of the submission)

- Did this provide any further data that could be pooled if deemed appropriate?
- Were similar studies sought for each intervention / comparator?

Study 149 included a bipolar disorder stream and a schizophrenia stream. For most outcomes extracted, the Study 149 report described the results separately for the bipolar and schizophrenia patients. However, for prolactin increase the only results presented were for the bipolar and schizophrenia patients combined. In the absence of any other data for this outcome for quetiapine in paediatric bipolar disorder, it was decided to use the combined bipolar and schizophrenia data.

This was also the case for somnolence, but there was an error in Table B25 in the submission as this was not marked.

Similar studies were not sought for the other interventions, as there was sufficient evidence in a pure bipolar population. The AstraZeneca report does provide many safety outcomes for the bipolar study 149 and the schizophrenia study 112 combined, but it would not be appropriate to use this data for outcomes where pure bipolar data is available as it would not be comparable to the competitor data.

A19. Please clarify how the placebo rates in the MTC were populated to obtain the results in Table B30 (page 114 of the submission).

The placebo rates are derived from the data within the MTC model, by taking the average of the placebo effect in each study.

The relevant lines of codes are shown below (N1 represents the number of data points for placebo):

```
for (i in 1:N.d) {lambda1[i] <- lambda[s[i]] * equals(t[i],1) }
ref <- sum(lambda1[])/N1

for (k in 1:N.t) { logit(T[k])<- ref +mu[k] }
```

In this model, the lambda parameters are trial-specific baselines, representing the log-odds of the outcome in the reference treatment. Here the reference treatment is placebo, coded as treatment 1.

A20. Pooling of all doses of interventions may not be appropriate given the potential different side effect profile and acquisition cost of each intervention. Please undertake an MTC assuming that different doses represent different treatment possibilities.

Unfortunately in the time permitted to respond to this letter it was not possible to programme a mixed treatment comparison to run these additional analyses.

This analysis was not performed in the original submission because it is believed that patients on average would tend to receive a dose somewhere between the investigated doses, in order to balance the risk-benefit profiles of the therapies according to each individual situation.

A21. Please provide, as far as possible, adverse event information corresponding to Tables B36 to B39 (pages 123-128 of the submission), for each of the studies used in the mixed treatment comparison.

Table 12: Common adverse events from Haas 2009[28] (risperidone)

		Daily dose risperidone	
	Placebo (n=58)	0.5-2.5 mg (n=50)	3-6 mg (n=61)
Common AEs, n (%)			
Total with AEs	44 (76)	45 (90)	58 (95)
Most common AEs			
Somnolence	11 (19)	21 (42)	34 (56)

Headache	19 (33)	20 (40)	23 (38)
Fatigue	2 (3)	9 (18)	18 (30)
Abdominal pain	3 (5)	9 (18)	9 (15)
Dizziness	3 (5)	8 (16)	8 (13)
Rhinitis	6 (10)	7 (14)	8 (13)
Nausea	4 (7)	8 (16)	8 (13)
Vomiting	4 (7)	6 (12)	6 (10)
Dyspepsia	2 (3)	8 (16)	3 (5)
Agitation	6 (10)	2 (4)	7 (11)
Pharyngitis	3 (5)	5 (10)	2 (3)
Serious AEs, n (%)			
Total with serious AEs	3 (5)	3 (6)	5 (8)
Psychosis manic-depressive	2 (3)	1 (2)	4 (7)
Suicide attempt	1 (2)	2 (4)	2 (3)
Manic reaction	1 (2)	0	0
Allergic reaction	0	0	1 (2)
Asthma	0	1 (2)	0
Bronchospasm	0	1 (2)	0

Numbers of common AEs and serious AEs may exceed the total number because rates are based on the number of subjects experiencing at least 1 AE, not the number of events.

Table 13: Common adverse events from Pavuluri 2010[29] (risperidone)

Variable	Frequency (%)	
	Risperidone (n=32)	Divalproex Sodium (n=33)
Increased appetite	8 (25.0)	10 (31.3)
Irritable/agitated	0 (0.0)	7 (21.9)*
Stomach discomfort	6 (18.8)	5 (15.6)
Sleepiness	5 (15.6)	4 (12.5)
Fatigue/tiredness	5 (15.6)	4 (12.5)
Insomnia	0 (0.0)	4 (12.5)
Weight gain	3 (9.4)	4 (12.5)

*$p < 0.05$ for comparison of divalproex vs. risperidone

Table 14: Common adverse events from Geller 2012[30] (risperidone)

Adverse effect	Subjects, No. (%)								
	Treated with risperidone and completed ≥1 wk (n=89)			Treated with lithium and completed ≥1 wk (n=84)			Treated with divalproex sodium and completed ≥1 wk (n=97)		
	Baseline	Weeks 1-8	P value	Baseline	Weeks 1-8	P value	Baseline	Weeks 1-8	P value
Abdominal pain	0 (0.0)	0 (0.0)		5 (6.0)	34 (40.5)	<.001	11 (11.3)	26 (26.8)	0.005
Weight loss	1 (1.1)	9 (10.1)	.011	4 (4.8)	23 (27.4)	<.001	4 (4.1)	29 (29.9)	<0.001
Weight gain	11 (12.4)	85 (95.5)	<.001	7 (8.3)	58 (69.0)	<.001	7 (7.2)	71 (73.2)	<0.001
Appetite decrease	0 (0.0)	0 (0.0)		12 (14.3)	24 (28.6)	.011	10 (10.3)	21 (21.6)	0.016
Appetite increase	23 (25.8)	68 (76.4)	<.001	0 (0.0)	0 (0.0)		28 (28.9)	69 (71.1)	<0.001
Diarrhoea	0 (0.0)	0 (0.0)		1 (1.2)	9 (10.7)	.011	2 (2.1)	17 (17.5)	<0.001
Constipation	2 (2.2)	7 (7.9)	.06	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Nausea	0 (0.0)	15 (16.9)		0 (0.0)	30 (35.7)		1 (1.0)	23 (23.7)	<0.001
Vomiting	0 (0.0)	7 (7.9)		0 (0.0)	18 (21.4)		0 (0.0)	11 (11.3)	
Headache	10 (11.2)	28 (31.5)	<.001	8 (9.5)	29 (34.5)	<.001	0 (0.0)	0 (0.0)	
Difficulty arousing in AM							28 (28.9)	62 (63.9)	<0.001
Difficulty falling asleep	71 (79.8)	33 (37.1)	<.001	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Drowsiness	16 (18.0)	45 (50.6)	<.001	10 (11.9)	22 (26.2)	.019	11 (11.3)	34 (35.1)	<0.001
Sweating	1 (1.1)	6 (6.7)	.03	1 (1.2)	7 (8.3)	.03	0 (0.0)	0 (0.0)	
Tremor	0 (0.0)	0 (0.0)		0 (0.0)	7 (8.3)		0 (0.0)	0 (0.0)	
Lethargy	0 (0.0)	0 (0.0)		12 (14.3)	25 (29.8)	.012	0 (0.0)	0 (0.0)	
Dry mouth	1 (1.1)	9 (10.1)	.011	1 (1.2)	18 (21.4)	<.001	0 (0.0)	0 (0.0)	

Adverse effect	Subjects, No. (%)								
	Treated with risperidone and completed ≥1 wk (n=89)			Treated with lithium and completed ≥1 wk (n=84)			Treated with divalproex sodium and completed ≥1 wk (n=97)		
	Baseline	Weeks 1-8	P value	Baseline	Weeks 1-8	P value	Baseline	Weeks 1-8	P value
Nasal congestion	5 (5.6)	20 (22.5)	<.001	3 (3.6)	20 (23.8)	<.001	7 (7.2)	28 (28.9)	<0.001
Frequent urination	2 (2.2)	6 (6.7)	.16	2 (2.4)	24 (28.6)	<.001	4 (4.1)	14 (14.4)	0.012
Enuresis	0 (0.0)	0 (0.0)		6 (7.1)	18 (21.4)	.001	10 (10.3)	20 (20.6)	0.008
Itching	3 (3.4)	6 (6.7)	.26	0 (0.0)	0 (0.0)		5 (5.2)	16 (16.5)	0.008
Rash	3 (3.4)	6 (6.7)	.32	2 (2.4)	5 (6.0)	.26	3 (3.1)	13 (13.4)	0.004
Muscular cramps	0 (0.0)	0 (0.0)		1 (1.2)	5 (6.0)	.05	0 (0.0)	0 (0.0)	
Excessive thirst	3 (3.4)	22 (24.7)	<.001	3 (3.6)	37 (44.0)	<.001	4 (4.1)	19 (19.6)	0.002
Fever	0 (0.0)	9 (10.1)		2 (2.4	5 (6.0)	.18	1 (1.0)	9 (9.3)	0.011
Modified AIMS score									
≥1	0 (0.0)	0 (0.0)		3 (3.6)	5 (6.0)	.41	0 (0.0)	0 (0.0)	
≥2	3 (3.4)	8 (9.0)	.06				0 (0.0)	0 (0.0)	
≥3	2 (2.2)	6 (6.7)	.05				0 (0.0)	0 (0.0)	

Table 15: Common adverse events from Tohen 2007[3] (olanzapine)

Event type	Treatment		
	Olanzapine	Placebo	P value
Serious Adverse Events (n)	4	0	
Exacerbation of bipolar disorder	3	0	
Decreased neutrophil and white blood cell count	1	0	
Deaths (n)	0	0	
Baseline-to-endpoint changes: Vital signs and weight			
Supine systolic blood pressure	3.61	-2.28	0.001
Supine pulse	9.51	-0.67	<0.001
Standing pulse	8.9	-1.35	<0.001
Weight increase (kg)	3.66	0.30	<0.001
BMI increase	1.18	0.02	<0.001
Treatment-emergent weight gain ≥7% of baseline (%)	41.9	1.9	<0.001
Baseline-to-endpoint changes: Prolactin and other laboratory values			
Prolactin levels: females (ng/ml)	15.38	2.67	<0.001
Prolactin levels: males (ng/ml)	11.50	0.66	<0.001
Treatment-emergent abnormally high prolactin levels: females (%)	25.7	0	<0.001
Treatment-emergent abnormally high prolactin levels: males (%)	62.5	5	<0.001
Mean increase in aspartate transaminase (U/Liter)	7.41	-1.62	<0.002
Mean increase in alanine transaminase (U/Liter)	19.53	-1.28	0.003
Treatment-emergent abnormally high aspartate transaminase levels (%)	22.4	2.0	<0.001
Treatment-emergent abnormally high alanine transaminase levels (%)	33.7	2.1	<0.001
Mean increase in uric acid (mol/liter)	21.04	0.60	0.026
Baseline-to-endpoint changes: ECG			
Mean increase in heart rate (bpm)	9.8	-3.61	<0.001
Mean change in Fridericia-adjusted QTc interval (msec)	2.28	1.62	<0.808
Baseline-to-endpoint changes: Extrapyramidal symptoms			
AIMS	-0.10	0.00	0.289
Simpson-Angus Scale	0.02	-0.02	0.769
Barnes Scale	-0.04	0.06	0.264
Suicidality			
Report of treatment-emergent suicidal Ideation (n)	1	0	
Report of suicide attempt (n)	0	0	
Report of self-injurious behaviour (n)	0	0	

Table 16: Common adverse events from Study 149 (quetiapine)

	Quetiapine (N=193)	Placebo (N=90)
	%	%
AE potentially related to EPS	7 (3.6%)	1 (1.1%)
Akathisia n, (%)	1.0%	0%
Weight gain ≥7% of body weight (%)	12%	0%
Mean change in body weight (kg)	1.7	0.4
Clinically significant change in cholesterol ≥240 mg/dL (%)	10	3

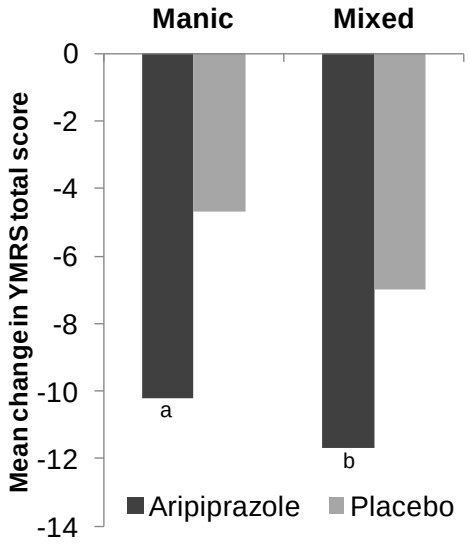
Clinically significant change in triglycerides ≥200 mg/dL (%)	22	13
Mean change in fasting glucose level (mg/dL)	3.62	-1.17

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Please clarify, with evidence, whether the ICER reported in the submission for the population experiencing manic episodes is assumed to be applicable to a population experiencing mixed episodes.

Evidence from the literature in adults with bipolar disorder has indicated that there is no difference in the YMRS responses associated with aripiprazole for patients with manic and those with mixed episodes (Figure 2).[31, 32] Therefore response data from a population with manic episodes should be applicable to a population with mixed episodes. There is no evidence that this assumption does not hold in children.

Figure 2: YMRS mean change from baseline at 3 weeks - Subgroup analysis for manic versus mixed adult bipolar I disorder patients pooled from 2 randomised, 3-week, double-blind, placebo-controlled trials[31]



[a] p<0.001; [b] p<0.01

The economic model submitted in the original submission uses clinical data for all comparators from populations that contain both manic and mixed patients. The relative proportions from each pivotal trial are presented below in Table 17 to Table 19. Therefore the ICER produced can be assumed to be applicable for both manic and mixed episodes.

Table 17: Patients with manic or mixed episodes from Haas 2009

	Placebo (N=54)	Risperidone 0.5-2.5 mg (N=50)	Risperidone 3-6 mg (N=61)	Total (N=169)
Diagnosis by DSM-IV criteria, n (%)				
Manic episode	19 (33%)	20 (40%)	21 (34%)	60 (36%)
Mixed episode	39 (67%)	30 (60%)	40 (66%)	109 (64%)

Table 18: Patients with manic or mixed episodes from Tohen 2007

	Placebo (N=54)	Olanzapine (N=107)
Current episode, n (%)		
Mixed	25 (46.3%)	61 (58.9%)
Rapid cycling	5 (10.4%)	25 (26.0%)
Psychotic features	7 (13.0%)	22 (20.8%)

Table 19: Patients with manic or mixed episodes from Study 149

	Placebo (N=89)	Quetiapine 400 mg (N=93)	Quetiapine 600 mg (N=95)	Total (N=277)
Diagnosis by DSM-IV criteria, n (%)				
Most recent episode manic, n (%)	68 (76.4%)	73 (78.5%)	72 (75.8%)	213 (76.9%)
Most recent episode manic, severe without psychotic features	14 (15.7%)	14 (15.1%)	14 (15.7%)	42 (15.2%)
Most recent episode manic, severe with psychotic features	7 (7.9%)	5 (5.4%)	5 (5.3%)	17 (6.1%)
Most recent episode mixed	0	0	1 (1.1%)	1 (0.4%)
Most recent episode mixed, severe without psychotic features	0	0	2 (2.1%)	2 (0.7%)
Most recent episode mixed, severe with psychotic features	0	1 (1.1%)	1 (1.1%)	2 (0.7%)

B2. **Priority Question:** Please clarify whether the model structure was intended to replicate the licensed duration (of 12 weeks for aripiprazole) or if it was intended to replicate real life prescribing (the ERG have been advised by its clinical experts that antipsychotics are typically used for more than 12 weeks). Within the model it is currently possible for patients to receive treatment for more than 12 weeks.

The model was developed so that this parameter was flexible, to allow the model to be adapted by different users in different settings.

There is also a lack of comparative data beyond 3 weeks, as the double blind placebo controlled phases of the pivotal RCTs that provide response rates for the MTC are only 3-4 weeks. Beyond this point, the efficacy of all comparators has to be assumed to be the same.

Therefore extending the treatment duration beyond 12 weeks is uninformative in terms of comparison between antipsychotics. Thus, although the model is flexible to incorporate longer treatment durations, it is not actually recommended that it be used for this purpose.

B3. **Priority Question:** Please comment on why depression was not included in the model, as the occurrence of depression is likely to vary with health state, and hence with treatment strategy.

Unfortunately, there was a lack of data to support the relative frequencies of depression between the different states in children. As the purpose of the model was to assess acute mania, this was not deemed to be an issue.

B4. Please clarify why only 4 adverse events were discussed in the model.

Diabetes and prolactin increase were identified as clinically significant adverse events, but were not included in the economic model. The reasons for this are outlined in section 6.4.12 of the original submission and are due to lack of data. The exclusion of these events from the model is likely to disadvantage aripiprazole compared to its comparators, evidenced by:

- The network meta-analysis demonstrated that aripiprazole-treated patients had a lower risk of clinically significant prolactin increases than the other three atypical antipsychotics (Section 5.7.6 of original submission).
- Data from adult populations has suggested that aripiprazole may have lower incidence of newly diagnosed diabetes cases than risperidone, olanzapine or quetiapine.[33]

The adverse events that were included in the model (weight gain, somnolence and EPS) were chosen based on a number of reasons:

1. From reports in the literature and based on NICE clinical guidelines, they were deemed to be the most clinically significant events.[3-5, 34, 35]
2. Previous models of the use of atypical antipsychotics in bipolar disorder have not included other adverse events.[17, 18, 21] The model produced to inform NICE clinical guideline 38 (Bridle 2004) did not include adverse events at all.[11]
3. There is a lack of data on utility decrements associated with other adverse events.
    a) Briggs 2008: reported utilities only for weight gain, diabetes, hyperprolactinemia and EPS.[36] There was a lack of data on diabetes for this to be included in the model, and there were no cases of diabetes in the aripiprazole trials.
    b) Boyle 2010: only reports utilities for weight gain.[37]
    c) Heeg 2008: reported utilities for weight gain, tardive dyskinesia, EPS, sedation and diabetes.[38] Tardive dyskinesia was included in the definition of EPS in the pivotal aripiprazole trial.

Model parameters

B5. On page 145 it is stated that the starting age of 15 years is not based on the trial data. Please provide sensitivity analyses using 13 and 17 years and the mean age from the trial.

The mean age from NCT00110461 was 13.4 years. Decimal ages cannot be entered into the model. Therefore the sensitivity analysis below, using a starting age of 13 years, reflects the mean age of the trial population.

Table 20: Aged 13 years, 5 year time horizon

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£98,793	£97,742	£97,975	£98,537	-£1,050	-£818	-£256
QALYs	4.05384	4.06605	4.06493	4.06426	0.01221	0.01109	0.0104
ICER					Dominant	Dominant	Dominant

Table 21: Aged 17 years, 1 year time horizon

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£49,090	£48,388	£48,636	£49,027	-£702	-£454	-£63
QALYs	0.86316	0.86713	0.86594	0.86569	0.00397	0.00278	0.0025
ICER					Dominant	Dominant	Dominant

B6. Please clarify whether mean or median values were used to calculate the proportion of responders at weeks 1 and 2. Table B54 (pages 168-172 of the submission) indicates the former, Section 6.6.3 (page 214) the latter.

The probabilities of response results produced by the network meta-analysis are medians. Therefore Table B54 is incorrect. The proportion of week 3 responders who responded by week 2, and the proportion of week 2 responders who responded by week 1, are ratios of medians.

B7. Where values from the mixed treatment comparison are reported in Table B54, please clarify if the point estimates relate to means or medians.

The probabilities of response results produced by the network meta-analysis are medians.

B8. Please clarify whether the non-proprietary costs for quetiapine were used or the costs for branded Seroquel in Table 57 (page 177 of the submission).

The non-proprietary costs for quetiapine were used in the cost-effectiveness and budget impact analyses; these are stated in Table B67 of the original submission and the results reflect this non-proprietary cost.

Please disregard any mention of branded Seroquel in the original submission. The non-proprietary costs only became available late in the development of the submission and the mention of branded Seroquel in Table B57 was not updated to reflect the change.

B9. Please clarify how the standard errors for the first five rows of Table B62 (page 192 of the submission) have been derived.

Table 22 presents the explanation for the calculations of the standard errors (SEs) of the utilities.

Table 22: Explanation of the standard error calculations for the utilities

Health state	Mean utility for health state	SE	Explanation
Acute mania	0.69	0.0408	SE=0.0408 was based on the interquartile range reported in Hayhurst 2006 (0.69 to 0.80) using the formula (UQR-LQR)/(2*1.349); however, it was not used in the PSA. Values for uAcuteMania in the PSA were derived by multiplying the sampled value of uResponderObservation by the ratio of mean uAcuteMania to uResponderObserved utilities (0.69/0.85=0.8117). The resulting standard error of the 1000 values derived this way in the PSA is 0.0848 producing an interquartile range of 0.577 to 0.806. This method was used to ensure that all sampled values made logical sense; that is the utility of acute mania was always lower than responder observation and euthymic health states.
Responder observation	0.85	0.1075	SE=0.1075 is based on the interquartile range reported in Hayhurst 2006 (0.71 to 1.0)
Euthymic treated	0.85	0.1075	SE and sampled values for euthymic treated state are equal to those for responder observation
Euthymic not treated	0.85	0.1075	SE and sampled values for euthymic untreated state are equal to those for responder observation
Therapy resistance	0.72	0.1223 (reported as 0.0842 in original submission, which was an error)	SE=0.0842 as presented in the original submission is an error. Correct SE based on the interquartile range reported in Hayhurst 2006 (0.67 to 1) is 0.1223; however, it was not used in the PSA. Values for uTherapyResistance in the PSA were derived by multiplying the sample value of uResponderObservation by the ratio of mean uTherapyResistance to uResponderObservation utilities (0.72/0.85=0.847). The resulting standard error of the 1000 values derived this way in the PSA is 0.0885 producing an interquartile range of 0.602 to 0.841. This method was used to ensure that all sampled values made logical sense; that is the utility of therapy restance was always lower than responder observation and euthymic health states.

B10. Please clarify how the 'age of population' and 'proportion male in population' values for the Hospitalisation state in Table B62 (page 192 of the submission) have been derived.

The source of information for the utility decrement for hospitalisation (from Mental Health Research Review 2000[39]) stated that all patients were male. However, this source did not give the mean age of the population. Therefore, the mean age for this population was assumed to be equivalent to that of Hayhurst et al. (2006), the reference used to derive the majority of utilities.

This assumption has been tested in the sensitivity analysis below, by varying the assumed age from 30 years to 50 years. It can be seen that the results hardly change, indicating that this assumption does not influence the final conclusions.

Table 23: Base case

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£75,066	£74,133	£74,379	£74,888	-£932	-£686	-£178
QALYs	2.51637	2.52466	2.52348	2.52297	0.00830	0.00712	0.0066
ICER					Dominant	Dominant	Dominant

Table 24: Assumed population from Mental Health Research Review had mean age of 30 years

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£75,066	£74,133	£74,379	£74,888	-£932	-£686	-£178
QALYs	2.51696	2.52525	2.52407	2.52356	0.00829	0.00711	0.0066
ICER					Dominant	Dominant	Dominant

Table 25: Assumed population from Mental Health Research Review had mean age of 50 years

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£75,066	£74,133	£74,379	£74,888	-£932	-£686	-£178
QALYs	2.51579	2.52409	2.52291	2.52238	0.00830	0.00712	0.0066
ICER					Dominant	Dominant	Dominant

Results from the model

B11. Please report results with a half cycle correction.

Half cycle correction can be turned on under the 'Index' tab of the model. The results using half cycle correction are only minimally different from the base case:

Table 26: Cost-effectiveness results using half cycle correction

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£72,840	£71,908	£72,105	£72,662	-£932	-£735	-£178
QALYs	2.50269	2.51097	2.50996	2.50927	0.00828	0.00727	0.0066
ICER					Dominant	Dominant	Dominant

Figure 3: Scatter plot of strategy 2 (aripiprazole second line) vs Strategy 1 (usual care)

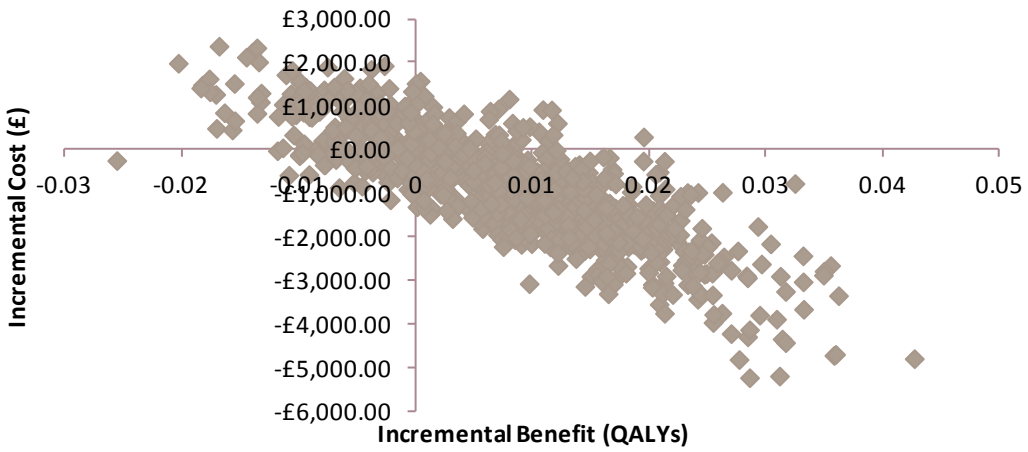


Figure 4: Scatter plot of strategy 3 (aripiprazole first line) vs Strategy 1 (usual care)

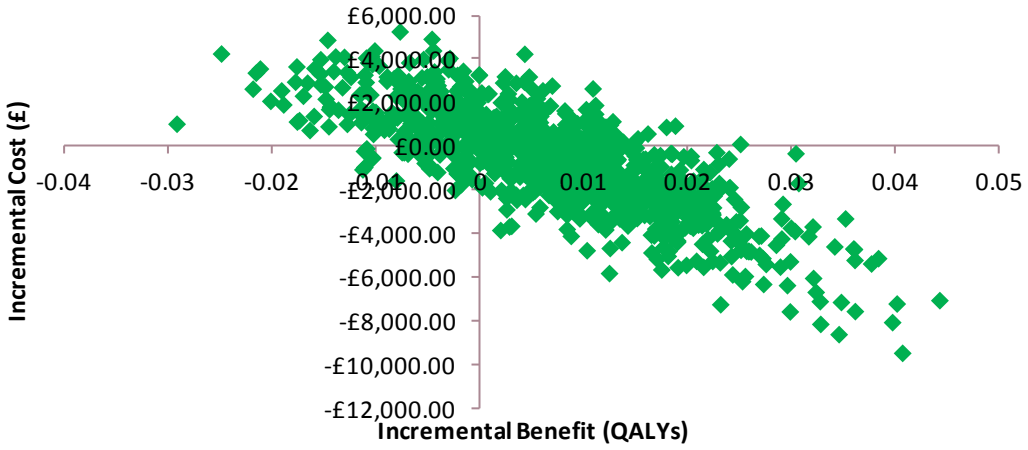
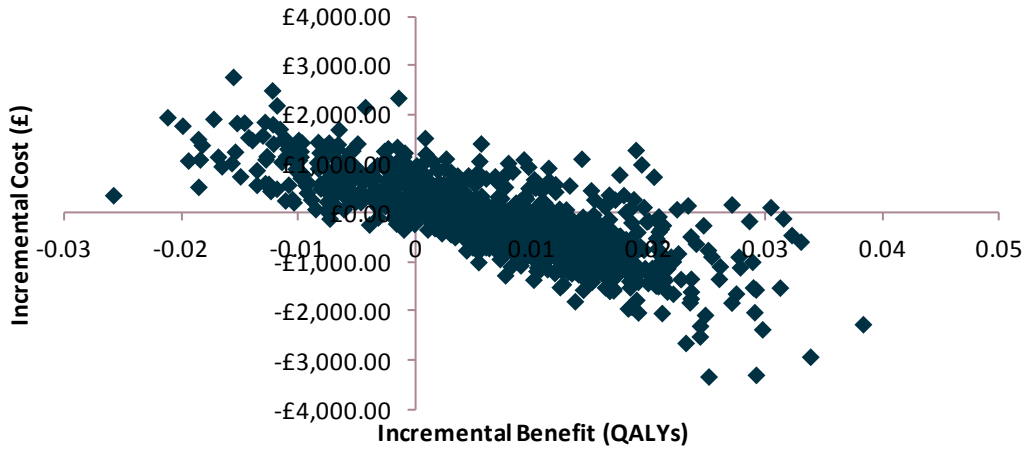


Figure 5: Scatter plot of strategy 4 (aripiprazole third line) vs Strategy 1 (usual care)



B12. **Priority question**: Please provide cost-effectiveness results using results from a Bayesian random effects model rather than a fixed effect model (see question A12). Please do this for both the base-case random effects results and the sensitivity analyses results which include the Pavaluri and Geller trials.

Referring to question A12 above, there is not enough evidence to support a random effects model and therefore this analysis was not performed.

B13. Regarding section 6.6.3 (page 214 of the submission), please comment, supported by appropriate evidence, on whether including uncertainty in both resource use for maintenance states and unit costs would significantly alter the results.

For hospitalised states, the only resource use including in the costing is days in hospital. As patients have to be hospitalised for the whole time during these states, it would not make sense to vary the number of days hospitalised from 7. Therefore only resource use in the outpatient states has been investigated in sensitivity analysis, and the results are presented below in Table 27. All cases for each aripiprazole-containing strategy remain dominant over usual care.

Table 27: Deterministic sensitivity analysis on outpatient state resource use

Parameter	Change	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
ICER Strategy 2 vs Usual care				
Consultant visits, euthymic treated	+30%	-£930	0.00830	Dominant
	-30%	-£935	0.00830	Dominant
Consultant visits, euthymic not-treated	+30%	-£909	0.00830	Dominant
	-30%	-£956	0.00830	Dominant
Consultant visits, therapy resistance	+30%	-£1,001	0.00830	Dominant
	-30%	-£864	0.00830	Dominant
Psychologist visits, euthymic treated	+30%	-£932	0.00830	Dominant
	-30%	-£933	0.00830	Dominant
Psychologist visits, euthymic not-treated	=euthymic treated phase (0.5 per month)	-£893	0.00830	Dominant
Psychologist visits, therapy resistance	+30%	-£951	0.00830	Dominant
	-30%	-£914	0.00830	Dominant
ICER Strategy 3 vs Usual care				
Consultant visits, euthymic treated	+30%	-£683	0.00712	Dominant
	-30%	-£689	0.00712	Dominant
Consultant visits, euthymic not-treated	+30%	-£663	0.00712	Dominant
	-30%	-£710	0.00712	Dominant
Consultant visits, therapy resistance	+30%	-£754	0.00712	Dominant
	-30%	-£618	0.00712	Dominant
Psychologist visits, euthymic treated	+30%	-£686	0.00712	Dominant
	-30%	-£687	0.00712	Dominant
Psychologist visits, euthymic not-treated	=euthymic treated phase (0.5 per month)	-£647	0.00712	Dominant
Psychologist visits, therapy resistance	+30%	-£704	0.00712	Dominant
	-30%	-£668	0.00712	Dominant

ICER Strategy 4 vs Usual				
Consultant visits, euthymic treated	+30%	-£176	0.0066	Dominant
	-30%	-£181	0.0066	Dominant
Consultant visits, euthymic not-treated	+30%	-£157	0.0066	Dominant
	-30%	-£200	0.0066	Dominant
Consultant visits, therapy resistance	+30%	-£246	0.0066	Dominant
	-30%	-£110	0.0066	Dominant
Psychologist visits, euthymic treated	+30%	-£178	0.0066	Dominant
	-30%	-£179	0.0066	Dominant
Psychologist visits, euthymic not-treated	=euthymic treated phase (0.5 per month)	-£141	0.0066	Dominant
Psychologist visits, therapy resistance	+30%	-£196	0.0066	Dominant
	-30%	-£160	0.0066	Dominant

Regarding unit costs, the unit costs for mental health services were investigated in deterministic sensitivity analysis previously performed, as presented in the original submission (Table B70) and below in Table 27. None of the changes in unit costs changed the ICER from being dominant for any strategy and this is why they are not reported in Section 6.7.7 of the original submission.

Table 28: Deterministic sensitivity analysis performed on mental health service costs in the original submission

Mental health services costs	Base Case (£)	Scenario
Inpatient day	602.10	±30%
Haematology	3.36	±30%
Initial consultant visit: outpatient setting	419.00	±30%
Follow-up consultant visit: outpatient setting	229.00	±30%

B14. Regarding section 6.6.3 (page 214 of the submission), please comment, supported by appropriate evidence, on whether including uncertainty in the utility multiplier would significantly alter the results.

The utility multiplier is calculated by dividing the observed utility value by the estimated utility for the general population based on age and gender demographics of the population from which the utility was derived. The utility values were investigated in a scenario sensitivity analysis in the original submission and were found not to greatly influence the model results (Table B84 of original submission).

The estimated general population utilities have now been investigated through deterministic sensitivity analysis, and the results are presented below in Table 29. In this analysis, the utility values from the respective references were kept the same as the base case. The general population utility values were increased and decreased by 30%; where increasing the value raised it above 1, the value was capped at 1 as utility values cannot be greater than 1. For somnolence, there was no general population utility as the value from the reference was itself a utility multiplier. Therefore this utility multiplier was subjected to deterministic sensitivity analysis.

Strategies that included aripiprazole remained dominant over usual care in the majority of cases, apart from when the general population utility for hospitalisation was decreased by 30% and when all general population utilities were all decreased by 30%, which is an unlikely scenario.

Table 29: Deterministic sensitivity analysis on utility multiplier

Parameter	Change	Incremental costs (£) vs. Usual Care	Incremental QALYs vs. Usual Care	ICER (£) (cost per QALY) vs. Usual Care
ICER Strategy 2 vs Usual care				
General population utility – acute mania	1	-£932	0.00854	Dominant
	-30%	-£932	0.00765	Dominant
General population utility – responder observation	1	-£932	0.00787	Dominant
	-30%	-£932	0.00848	Dominant
General population utility – euthymic treated	1	-£932	0.00784	Dominant
	-30%	-£932	0.00849	Dominant
General population utility – euthymic not-treated	1	-£932	0.00477	Dominant
	-30%	-£932	0.00983	Dominant
General population utility – therapy resistance (IP & OP)	1	-£932	0.01155	Dominant
	-30%	-£932	0.00126	Dominant
General population utility – hospitalisation	1	-£932	0.00828	Dominant
	-30%	-£932	0.00836	Dominant
General population utility – EPS	1	-£932	0.00803	Dominant
	-30%	-£932	0.00883	Dominant
General population utility – weight gain	1	-£932	0.01003	Dominant
	-30%	-£932	0.00460	Dominant
Utility multiplier - somnolence	1	-£932	0.00946	Dominant
	-30%	-£932	0.00498	Dominant
General population utility – **all states**	1	-£932	0.00973	Dominant
	-30%	-£932	-0.00440	Inferior
ICER Strategy 3 vs Usual care				
General population utility – acute mania	1	-£686	0.00740	Dominant
	-30%	-£686	0.00638	Dominant
General population utility – responder observation	1	-£686	0.00677	Dominant
	-30%	-£686	0.00727	Dominant
General population utility – euthymic treated	1	-£686	0.00666	Dominant
	-30%	-£686	0.00731	Dominant
General population utility – euthymic not-	1	-£686	0.00361	Dominant
	-30%	-£686	0.00864	Dominant

treated				
General population utility – therapy resistance (IP & OP)	1	-£686	0.01037	Dominant
	-30%	-£686	0.00008	Dominant
General population utility – hospitalisation	1	-£686	0.00709	Dominant
	-30%	-£686	0.00722	Dominant
General population utility – EPS	1	-£686	0.00667	Dominant
	-30%	-£686	0.00802	Dominant
General population utility – weight gain	1	-£686	0.00887	Dominant
	-30%	-£686	0.00337	Dominant
Utility multiplier - somnolence	1	-£686	0.00909	Dominant
	-30%	-£686	0.00147	Dominant
General population utility – **all states**	+30%	-£686	0.00926	Dominant
	1	-£686	-0.00787	Inferior
ICER Strategy 4 vs Usual care				
General population utility – acute mania	+30%	-£178	0.0066	Dominant
	-30%	-£178	0.0066	Dominant
General population utility – responder observation	+30%	-£178	0.0062	Dominant
	-30%	-£178	0.0068	Dominant
General population utility – euthymic treated	+30%	-£178	0.0062	Dominant
	-30%	-£178	0.0068	Dominant
General population utility – euthymic not-treated	1	-£178	0.0034	Dominant
	-30%	-£178	0.0080	Dominant
General population utility – therapy resistance (IP & OP)	1	-£178	0.0099	Dominant
	-30%	-£178	-0.0004	Inferior
General population utility – hospitalisation	1	-£178	0.0066	Dominant
	-30%	-£178	0.0066	Dominant
General population utility – EPS	1	-£178	0.0064	Dominant
	-30%	-£178	0.0070	Dominant
General population utility – weight gain	1	-£178	0.0077	Dominant
	-30%	-£178	0.0041	Dominant
Utility multiplier - somnolence	1	-£178	0.0075	Dominant
	-30%	-£178	0.0041	Dominant
General population utility – **all states**	1	-£178	0.0075	Dominant
	-30%	-£178	-0.0036	Inferior

Additional sensitivity analyses

B15. Where additional sensitivity analyses are performed, please provide details of the input data / assumptions used, with the resulting costs, and QALYs and ICERs for each strategy.

The inputs, assumptions and results of all additional sensitivity analyses have been detailed under the relevant questions.

B16. **Priority question:** Please provide sensitivity analyses assuming that there is a reduction in efficacy as the drug moves further down the treatment line, thus for example there is X% reduction between lines 1 and 2, and between lines 2 and 3.

Multipliers have been added to the model (version 'B16 REVISED' supplied along with this response), which affect the transition probabilities at each week for all treatments (in the Trans Matrices). Cells G112 and G113 on the Input sheet can be edited to alter these multipliers.

A selection of scenarios has been tested and the results provided below. The base case results are robust to a reduction in efficacy as the drug moves further down the treatment line.

Table 30: 5% reduction in efficacy between lines 1 and 2, 10% reduction in efficacy between lines 2 and 3

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£75,473	£74,540	£74,793	£75,301	-£933	-£680	-£172
QALYs	2.51181	2.52054	2.51928	2.51833	0.00873	0.00748	0.0065
ICER					Dominant	Dominant	Dominant

Table 31: 10% reduction in efficacy between lines 1 and 2, 15% reduction in efficacy between lines 2 and 3

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£75,777	£74,881	£75,142	£75,608	-£896	-£635	-£169
QALYs	2.50872	2.51736	2.51602	2.51523	0.00864	0.00730	0.0065
ICER					Dominant	Dominant	Dominant

Table 32: 15% reduction in efficacy between lines 1 and 2, 20% reduction in efficacy between lines 2 and 3

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£76,085	£75,227	£75,498	£75,919	-£858	-£587	-£166
QALYs	2.50554	2.51405	2.51262	2.51200	0.00851	0.00709	0.0065
ICER					Dominant	Dominant	Dominant

Table 33: 50% reduction between lines 1 and 2, 75% reduction between lines 2 and 3

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£78,804	£78,147	£78,504	£78,728	-£657	-£300	-£76
QALYs	2.47300	2.48095	2.47856	2.47613	0.00795	0.00556	0.0031
ICER					Dominant	Dominant	Dominant

B17. **Priority question:** Please provide sensitivity analyses using 4 treatment lines.

This sensitivity analysis would require substantial alteration to be made to the model. We would be happy to perform this sensitivity analysis if deemed necessary; however, we cannot do so within the timeframe allowed.

B18. **Priority question:** The ERG have been advised by clinical experts that switching treatment at 3 weeks due to <50% YMRS response is unlikely to happen in clinical practice. Please provide sensitivity analysis where patients are maintained on initial treatment for a longer duration.

A tunnel state for a 4th acute week of treatment had already been built into the model and had previously been switched off. This has now been turned on in version 'B18 REVISED' (supplied along with this response), so now patients spend one week longer on a given treatment before trying another assuming that they've neither failed nor responded.

To generate the response and discontinuation transition probabilities for this 4th acute week, the ratio of responders and discontinuers at week 4 for aripiprazole was compared to that at week 3 for aripiprazole (pooled dose from the pivotal trial NCT00110461). These ratios were then applied to the other comparators, whose trials did not report 4 week results.

A risk ratio of 1.15 was derived for response and 1.50 for discontinuation for probability at week 4 compared to week 3. However, when entered into the model, the probability of events for risperidone at week 4 added to more than 1, which sometimes happens when applying risk ratios greater than 1 to already large proportions. To resolve this issue, odds ratios were calculated from the aripiprazole data instead and were applied to the risk at week 3 using the following formula: (OR/(1-BR(1-OR))*BR, where BR is the baseline risk. The odds ratios derived were 1.33 for response and 1.61 for discontinuation.

The results for this scenario analysis are presented below in Table 34. Aripiprazole strategies remain dominant compared to usual care in the case where patients are kept on treatment for 4 weeks before they change due to non-response.

Table 34: Scenario analysis involving a 4th line of acute treatment before switching treatment due to non-response

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£76,045	£74,769	£75,213	£75,732	-£1,277	-£832	-£314
QALYs	2.52942	2.53711	2.53536	2.53497	0.00769	0.00594	0.0055
ICER					Dominant	Dominant	Dominant

B19. **Priority question:** The ERG has been advised by its clinical experts that patients are likely to be maintained on antipsychotics for at least 6 -12 months. Please provide sensitivity analyses whilst treatment is maintained during euthymic state for 6 and 12 months.

Treatment duration in the euthymic treated phase can be changed in the model by altering cell B47 on the Index sheet.

When treatment is maintained in the euthymic state for 6 months (24 cycles; Table 35) or 12 months (48 cycles; Table 36), the strategies including aripiprazole remain dominant over standard care (without aripiprazole), except for 12 months treatment when aripiprazole is used first line. In this latter case the ICER is £7,568 per QALY, which can be considered cost-effective at a £20,000 per QALY willingness-to-pay threshold.

Please note that the use of aripiprazole for children aged 13-17 years with manic episodes of bipolar disorder for longer than 12 weeks is outside of its proposed marketing authorisation. It should also be noted that the lack of data on long-term treatment for comparators is disadvantageous to aripiprazole in any analysis modelling longer term treatment, as weight gain and side effects associated with prolactin increases are known to develop and would become more costly in the longer term (Figure 4 in Arango 2009[40]; Correll 2007[41]).

Table 35: Treatment for 6 months in euthymic state ('Time in euthymic treated before euthymic not treated' under the Index tab changed from 4 to 24 weeks)

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£69,505	£68,640	£69,203	£69,354	-£865	-£302	-£151
QALYs	2.51989	2.53294	2.53183	2.52925	0.01305	0.01194	0.0094
ICER					Dominant	Dominant	Dominant

Table 36: Treatment for 12 months in euthymic state ('Time in euthymic treated before euthymic not treated' under the Index tab changed from 4 to 52 weeks)

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£64,773	£63,994	£64,892	£64,657	-£780	£119	-£116
QALYs	2.52225	2.53897	2.53797	2.53348	0.01672	0.01571	0.0112
ICER					Dominant	£7,568	Dominant

B20. **Priority question:** Please provide a sensitivity analysis that combines all of the previous 4 sensitivity analyses described in B15-B19.

The tables below present the sensitivity analysis (adapting version 'B18 REVISED') where there is:

- a 4th line of acute treatment before switching treatment,
- a decrease in efficacy between 1st and 2nd line of 10%,
- a decrease in efficacy between 2nd and 3rd line of 15%,
- 6 months (Table 37) or 12 months (Table 38) treatment in the euthymic state

The strategies including aripiprazole remain dominant over standard care (without aripiprazole), except for 12 months treatment when aripiprazole is used first line. In this latter case the ICER is £14,599 per QALY, which can be considered cost-effective at a £20,000 per QALY willingness-to-pay threshold.

Table 37: 4th acute line of treatment before switch; 10% reduction in efficacy between lines 1 and 2, 15% reduction in efficacy between lines 2 and 3; treatment for 6 months in euthymic state

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£70,730	£69,576	£70,450	£70,455	-£1,153	-£280	-£275
QALYs	2.52671	2.53900	2.53739	2.53464	0.01228	0.01067	0.0079
ICER					Dominant	Dominant	Dominant

Table 38: 4th acute line of treatment before switch; 10% reduction in efficacy between lines 1 and 2, 15% reduction in efficacy between lines 2 and 3; treatment for 12 months in euthymic state

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£66,164	£65,115	£66,363	£65,932	-£1,049	£199	-£231
QALYs	2.52922	2.54430	2.54285	2.53843	0.01507	0.01362	0.0092
ICER					Dominant	£14,599	Dominant

B21. **Priority question:** Please provide sensitivity analyses where the costs of drug-related adverse events in the inpatient setting is not assumed to be incorporated into the HRG.

Cases of both EPS and somnolence were assumed to incur additional psychiatric consultant time, at £267 per patient-related hour (Unit costs of health and social care 2011[22]). It is unknown how much additional consultant time would be required per week for each type of adverse event, and therefore scenarios investigating 1 and 3 additional hours were performed.

Medications do exist for the treatment of EPS, but in children it is believed that they would have their dose reduced or their treatment discontinued rather than be prescribed benzodiazepines or beta-blockers. Therefore medication costs for EPS were not included in the model.

The cost of inpatient care in the acute and responder observation phases were adjusted for each antipsychotic based on the relative incidence of EPS and somnolence estimated from the MTC (Table B30 in original submission). No incidence was available for olanzapine for either EPS or somnolence. Therefore the conservative assumption was made that the incidence for olanzapine would be equal to the lowest incidence for the other atypical, which was risperidone for both EPS and somnolence. The costs used are elaborated on in Table 39 (1 hour additional consultant time) and Table 40 (3 hours of additional consultant time).

At 1 hour of additional consultant time per case of EPS and somnolence, aripiprazole remained dominant over usual care when used in the 2nd and 1st line (Table 41). At 3rd line, aripiprazole had an ICER compared to usual care of £4,270 per QALY, which can be considered cost-effective at a £20,000 per QALY willingness-to-pay threshold. At 3 hours of additional consultant time per case of EPS and somnolence, aripiprazole remained dominant over usual care when used in the 2nd line (Table 42).

Table 39: Costs associated with EPS and somnolence assuming 1 additional hour of consultant time per week

Treatment	Incidence EPS	Incremental cost per week due to EPS	Incidence somnolence	Incremental cost per week due to somnolence	Cost used in acute states	Cost per week used in responder observation states
ARP	0.158	£42.19	0.463	£123.62	£4,416.39 (£4,483.06 in 1st week)	£4,416.39
RIS	0.112	£29.90	0.266	£71.02	£4,316.00	£4,316.00
QTP	0.116	£30.97	0.273	£72.89	£4,346.85	£4,346.85
OLA	0.112	£29.90	0.266	£71.02	£4,324.84	£4,325.04

Table 40: Costs associated with EPS and somnolence assuming 3 additional hours of consultant time per week

Treatment	Incidence EPS	Incremental cost per week due to EPS	Incidence somnolence	Incremental cost per week due to somnolence	Cost used in acute states	Cost per week used in responder observation states
ARP	0.158	£126.56	0.463	£370.86	£4,748.00 (£4,814.67 in 1st week)	£4,748.00
RIS	0.112	£89.71	0.266	£213.07	£4,517.85	£4,517.85
QTP	0.116	£92.92	0.273	£218.67	£4,554.58	£4,554.58
OLA	0.112	£89.71	0.266	£213.07	£4,526.69	£4,526.90

Table 41: Cost-effectiveness assuming 1 additional hour of consultant time per week for EPS and somnolence

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£76,425	£75,760	£76,198	£76,453	-£665	-£227	£28
QALYs	2.51637	2.52466	2.52348	2.52297	0.00830	0.00712	0.0066
ICER					Dominant	Dominant	£4,270

Table 42: Cost-effectiveness assuming 3 additional hours of consultant time per week for EPS and somnolence

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£79,143	£79,014	£79,834	£79,584	-£129	£691	£441
QALYs	2.51637	2.52466	2.52348	2.52297	0.00830	0.00712	0.0066
ICER					Dominant	£97,147	£66,838

B22. The ERG has been advised by its clinical experts that the estimated 5% relapse rate (page 160 of the submission) is too low. Please conduct sensitivity analyses with higher relapse rate values.

Please find below the sensitivity analyses using relapse rates of 10%, 15% and 20% for treated states. Aripiprazole-containing strategies remain dominant compared to usual care in all cases.

Table 43: Relapse rate of 10% for treated states

	Usual care	**Strategy 2**	**Strategy 3**	**Strategy 4**	**Strategy 2 vs Usual care**	**Strategy 3 vs Usual care**	**Strategy 4 vs Usual**
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£84,204	£83,040	£83,250	£83,764	-£1,164	-£954	-£441
QALYs	2.49972	2.50835	2.50731	2.50678	0.00863	0.00759	0.0071
ICER					Dominant	Dominant	Dominant

Table 44: Relapse rate of 15% for treated states

	Usual care	**Strategy 2**	**Strategy 3**	**Strategy 4**	**Strategy 2 vs Usual care**	**Strategy 3 vs Usual care**	**Strategy 4 vs Usual**
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£94,567	£93,189	£93,367	£93,868	-£1,378	-£1,200	-£699
QALYs	2.48183	2.49061	2.48971	2.48918	0.00878	0.00788	0.0073
ICER					Dominant	Dominant	Dominant

Table 45: Relapse rate of 20% for treated states

	Usual care	Strategy 2	Strategy 3	Strategy 4	Strategy 2 vs Usual care	Strategy 3 vs Usual care	Strategy 4 vs Usual
First line	RIS	RIS	ARI	RIS	RIS	ARI	RIS
Second line	QTP	ARI	RIS	QTP	ARI	RIS	QTP
Third line	OLA	QTP	QTP	ARI	QTP	QTP	ARI
Costs	£106,176	£104,618	£104,766	£105,241	-£1,558	-£1,410	-£935
QALYs	2.46290	2.47165	2.47088	2.47038	0.00875	0.00798	0.0075
ICER					Dominant	Dominant	Dominant

Section C: Textual clarifications and additional points

C1. Please confirm the typing errors in Table B1 (page 47 of the submission)

- RCT NCT00110461 has 11 associated articles. This is correct
- RCT NCT00116259 has 2 associated articles. This is correct

C2. Please confirm the valproate dose in Geller 2012. On page 98 of the submission, it is stated that the dose of divalproex is 111-125 µg/mL and on page 107 the dose of valproate is 110-125 µg/mL.

The maintenance dose of valproate in Geller 2012 was 111-125 µg/mL

C3. On page 102 of the submission, it is stated that the dose of divalproex is 15mg/kg/day plus placebo and the dose of risperidone is 0.5-2.0 mg/day plus placebo. On page 107 it is stated that the dose of valproate in the Pavaluri 2010 study is 60-120 µg and the dose of risperidone is 0.5-2.5mg. Please clarify the typing error for the risperidone dose and confirm the valproate doses are equivalent.

In Pavaluri 2010, the dose of valproate was titrated *up to* 15 mg/kg/day over 3 days. The optimal dose that was aimed for was 80-120 µg/ml. In the abstract of the paper, it states that the dose for valproate was 60-120 µg/ml; it is not clear whether this was the range seen in patients or a typing error.

The dose for risperidone was 0.5-2.0 mg/day.

C4. Please clarify why valproate is included in Table B24 (page 107 of the submission) but not lithium.

Geller 2012 was the only study that included a lithium arm. Therefore, the data on lithium from this trial does not inform the mixed treatment comparison at all. Lithium was not considered a comparator in this submission.

C5. Please confirm the typing error in Table B36, on page 123 of the submission, where in the 6th column “relative risk for aripiprazole 10mg” should be 30mg instead of 10mg.

That was a typing error; this should state 30 mg.

C6. Please confirm the typing error on page 138 of the submission, where section 5.9.4 is referenced instead of section 5.10.4.

That was a typing error; this should state section 5.10.4.

C7. Please clarify that the reported utility for hospitalisation is a decrement in Table B54 (pages 168-172 of the submission).

Yes, the utility value for hospitalisation in Table B54 is a decrement.

C8. Please include the treatment costs for lithium in Table B54 (pages 168-172 of the submission).

Treatment cost of lithium per day is £0.04, as stated in Table B67.

C9. Please confirm a typing error in Table B60 (page 184 of the submission) in the first exclusion criteria 'QoL/utilities some patients < 18' which should be >18.

This is not a typing error. It is meant to say that only *some* patients in these trials were <18. This is actually equivalent to saying that some patients were >18, and therefore it does not actually matter which symbol is used.

C10. Please clarify the discrepancy between Table B8 (page 70) where it is stated that there is no evidence to suggest outcomes were measured and not reported and the table in section 9.3.1 (page 271), in which it is stated that medication adherence and well-being outcomes were measured and not reported.

Table B8 is incorrect and should state 'Yes', that there is evidence that outcomes were recorded but not reported. Table B8 was completed based on the publication and was not updated when the CSR became available.

The CSR states that "subjects were to be contacted by telephone at the end of Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29 to assess medication compliance and assure the subjects' well-being". These outcomes were not specifically reported in the CSR.

References

1. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, Nelson E. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry 2006;45:305-313.
2. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: A review of the existing literature. Development and Psychopathology. 2006;18:1023-1035.
3. Tohen M, Kryzhanovskaya L, Carlson G, DelBello M, Wozniak J, Kowatch R, Wagner K, Findling R, Lin D, Robertson-Plouch C, Xu W, Dittmann RW, Biederman J. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. American Journal of Psychiatry. 2007;164:1547-1556.
4. Roke Y, van Harten PN, Boot AM, Buitelaar JK. Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. Journal of Child and Adolescent Psychopharmacology 2009;19:403-414.
5. Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. The Journal of clinical psychiatry 2008;69:26.
6. Findling R, McNamara N, Youngstrom E, Stansbrey R, Frazier T, Lingler J, Otto B, Demeter C, Rowles B, Calabrese J. An open-label study of aripiprazole in children with a bipolar disorder. J Child Adolesc Psychopharmacol 2011;21:345-51.
7. Biederman J, Mick E, Spencer T, Doyle R, Joshi G, Hammerness P, Kotarski M, Aleardi M, Wozniak J. An open-label trial of aripiprazole monotherapy in children and adolescents with bipolar disorder. CNS Spectr 2007;12:683-9.
8. Danielyan A, Cannon M, Kowatch A. An Open Prospective Trial of Aripiprazole in Children and Adolescents with Bipolar I Disorder. Biol Psychiatry 2010;67:233S.
9. Keck PE, Jr., Nabulsi AA, Taylor JL, Henke CJ, Chmiel JJ, Stanton SP, Bennett JA. A pharmacoeconomic model of divalproex vs. lithium in the acute and prophylactic treatment of bipolar I disorder. J Clin Psychiatry 1996;57:213-22.
10. Revicki DA, Hirschfeld RM, Ahearn EP, Weisler RH, Palmer C, Keck PE, Jr. Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical trial. J Affect Disord 2005;86:183-93.
11. Bridle C, Palmer S, Bagnall AM, Darba J, Duffy S, Sculpher M, Riemsma R. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technol Assess 2004;8:iii-iv, 1-187.
12. Calvert NW, Burch SP, Fu AZ, Reeves P, Thompson TR. The cost-effectiveness of lamotrigine in the maintenance treatment of adults with bipolar I disorder. Journal of Managed Care Pharmacy. 12 (4) (pp 322-330), 2006. Date of Publication: May 2006. 2006;12:322-330.
13. Despiegel N, Davie AM, Corson H, Beillat M, Sapin C. Cost-minimisation analysis of asenapine monotherapy versus other antipsychotics in bipolar I disorder in two nordic countries. Value in Health. Conference: ISPOR 14th

Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7) (pp A293), 2011. Date of Publication: November 2011. 2011;14:A293.

14. Faluta T, Rdzanek M, Pierzgalska K. The economic and social consequences of seroquel xr (quetiapine prolonged release tablets) reimbursement in bipolar disorder treatment for patients currently treated with seroquel (quetiapine immediate release tablets) in Poland: Analysis of the impact on the health care system. Value in Health. Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7) (pp A290), 2011. Date of Publication: November 2011. 2011.
15. Ramirez De Arellano A, Rubio-Terres C, Baca E, Riesgo Y, Luque J, Mena E. Cost analysis of adverse events associated with treatment of bipolar disorder: A comparison between aripiprazole and olanzapine in the Spanish health system. Value in Health. Conference: ISPOR 13th Annual European Congress Prague Czech Republic. Conference Start: 20101106 Conference End: 20101109. Conference Publication: (var.pagings). 13 (7) (pp A447-A448), 2010. Date of Publication: November 2010. 2010.
16. Muzina DJ. Divalproex and lithium are similarly cost effective for adults with bipolar disorder. Evidence-Based Mental Health. 9(1):15, 2006 Feb. 2006;9:15.
17. Klok RM, Al Hadithy AFY, van Schayk NPJT, Antonisse AJJ, Caro JJ, Brouwers JRBJ, Postma MJ. Pharmacoeconomics of quetiapine for the management of acute mania in bipolar I disorder. Expert Review of Pharmacoeconomics and Outcomes Research. 7 (5) (pp 459-467), 2007. Date of Publication: Oct 2007. 2007;7:459-467.
18. McKendrick J, Cerri KH, Lloyd A, D'Ausilio A, Dando S, Chinn C. Cost effectiveness of olanzapine in prevention of affective episodes in bipolar disorder in the United Kingdom. Journal of Psychopharmacology. Vol.21(6), Aug 2007, pp. 588-596. 2007;21:588-596.
19. Ramirez De Arellano A, Rubio-Terres C, Baca E, Riesgo Y, Luque J, Mena E. Economic evaluation analysis in the treatment of bipolar disorder with aripiprazole and other atypical antipsychotic drugs in Spain. Value in Health. Conference: ISPOR 13th Annual European Congress Prague Czech Republic. Conference Start: 20101106 Conference End: 20101109. Conference Publication: (var.pagings). 13 (7) (pp A452), 2010. Date of Publication: November 2010. 2010.
20. Schumock GT, Walton SM, Gupta SR, Cramer JA. Cost analysis of divalproex sodium extended-release compared to valproic acid in the treatment of bipolar disorder. Current Medical Research and Opinion. 23 (8) (pp 1997-2004), 2007. Date of Publication: Aug 2007. 2007;23:1997-2004.
21. Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, Geddes J, Gilbody S, Palmer S, Woolacott N. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health technology assessment (Winchester, England). 11 (39) (pp iii-iv, ix-206), 2007. Date of Publication: Oct 2007. 2007;11:ix-206.
22. Curtis L. Unit Costs of Health and Social Care 2011, 2011.

23. Woodward TC, Tafesse E, Quon P, A. L. Cost effectiveness of adjunctive quetiapine fumarate extended-release tablets with mood stabilizers in the maintenance treatment of bipolar I disorder. References. PharmacoEconomics. Vol.28(9), Sep 2010, pp. 751-764. 2010;28:751-764.
24. McClellan J, Kowatch R, Findling R, Work Group on Quality Issues. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Bipolar Disorder. J. Am. Acad. Child Adolesc. Psychiatry 2007;46:107-125.
25. Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, Ivanova S, Carson WH, Chang K. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: A randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 2009;70:1441-1451.
26. Findling RL, Nyilas M, Aurang C, van Beek A, Jin N, Marcus R, Iwamoto T, Carson WH, Carlson G. Long term efficacy of aripiprazole in children (ages 10-17 years) with bipolar I disorder. American College of Neuropsychopharmacology 46th Annual Meeting, 2007.
27. Otsuka Pharmaceutical Development & Commercialization Inc. Aripiprazole (Abilify, OPC-14597, BMS-337039) Clinical Study Report. Protocol No. 31-03-240. 2007.
28. Haas M, DelBello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, Quiroz J, Kusumakar V. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: A randomized, double-blind, placebo-controlled study. Bipolar Disorders. 2009;11:687-700.
29. Pavuluri MN, Henry DB, Findling RL, Parnes S, Carbray JA, Mohammed T, Janicak PG, Sweeney JA. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. Bipolar Disorders. 2010;12:593-605.
30. Geller B, Luby J, Joshi P, Dineen Wagner K, Emslie G, Walkup J, Axelson D, Bolhofner K, Robb A, Wolf D, Riddle M, Birmaher B, Nusrat N, Ryan N, Vitiello B, Tillman R, Lavori P. A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents. Arch Gen Psychiatry. 2012;69:515-528.
31. Suppes T, Eudicone J, McQuade R, Pikalov A, Carlson B. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. Journal of Affective Disorders 2008;107:145-54.
32. Jody D, McQuade R, Carson W, Iwamoto T, Abou-Gharbia N, Hardy S, Archibald D. Efficacy of aripiprazole in sub-populations of bipolar disorder. American Psychiatric Association Annual Meeting, New York 2004.
33. Chabroux S, Haffen E, Penfornis A. [Diabetes and second-generation (atypical) antipsychotics]. Ann Endocrinol (Paris) 2009;70:202-10.
34. NICE. Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. National Institute for Health and Clinical Excellence 2006;Clinical Guideline 38.
35. Pikalov A, McQuade RD, Carson WH, Nyilas M, Forbes RA, Iwamoto T, Mankoski R, Mathew SJ. Somnolence and sedation in child and adolescent patients with bipolar I disorder treated with aripiprazole in an acute study with long term follow-up. Bipolar Disorders. Conference: 8th International Conference on Bipolar Disorder. 2009;11(S1);69 2009.

36. Briggs A, Wild D, Lees M, Reaney M, Dursun S, Parry D, Mukherjee J. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. Health and Quality of Life Outcomes 2008;6:105.
37. Boyle S, Jones G, Walters S. Physical activity, quality of life, weight status and diet in adolescents. Quality Life Res 2010;19:943-954.
38. Heeg B, Buskens E, Botteman M, Caleo S, Ingham M, Damen J, de Charro F, van Hout B. The Cost-Effectiveness of Atypicals in the UK. Value in Health 2008;11:1007-1021.
39. Mangalore R. Mental Health Research review 7, May 2000: The utility approach to valuing health states in schizophrenia.
40. Arango C, Robles O, Parellada M, Fraguas D, Ruiz-Sancho A, Medina O, Zabala A, Bombin I, Moreno D. Olanzapine compared to quetiapine in adolsecents with a first psychotic episode. Eur Child Adolesc Psychiatry 2009;18:418-28.
41. Correll C. Comparison of hyperprolactinaemia in adolescents/paeds with APs over time. International Congress on Schizophrenia Research 2007.

Appendix 1: Results of the updated literature review

Table 46: RCTs of aripiprazole published since 1st January 2012

Reference (Authors and journal)	PubMed ID	Title	Notes
Findling R.L., Youngstrom E.A., Zhao J., Marcus R., Andersson C., McQuade R., Mankoski R J Affective Disord 2012;143(1-3):231-235	PMID:23044285	Respondent and item level patterns of response of aripiprazole in the acute treatment of pediatric bipolar i disorder	post-hoc analysis of NCT00110461
Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, Rowles BM, Demeter CA, Frazier TW, Calabrese JR J Clin Psychiatry. 2012 Jan;73(1):57-63. doi: 10.4088/JCP.11m07104.	PMID:22152402	Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder	Children aged 4-9 years, therefore not relevant to decision problem

Table 47: RCTs of risperidone, quetiapine and olanzapine published since 1st January 2012

Reference (Authors and journal)	PubMed ID	Title	Notes
Pavuluri MN, Passarotti AM, Fitzgerald JM, Wegbreit E, Sweeney JA J Am Acad Child Adolesc Psychiatry. 2012 Feb;51(2):157-170.e5	PMID:22265362	Risperidone and divalproex differentially engage the fronto-striato-temporal circuitry in pediatric mania: a pharmacological functional magnetic resonance imaging study	NCT00176202 six-week, double-blind, randomized trial of risperidone plus placebo versus divalproex plus placebo for patients with mania (n = 21; 13.6 ± 2.5 years of age) No outcomes of relevance for comparison to aripiprazole. Inclusion criteria of 'DSM-IV diagnosis of mixed or manic bipolar disorder'; doesn't specify bipolar I disorder
Olsen BT, Ganocy SJ, Bitter SM, Findling RL, Case M, Chang K, Tohen M, DelBello MP Compr Psychiatry. 2012 Oct;53(7):1000-5	PMID:22520085	Health-related quality of life as measured by the child health questionnaire in adolescents with bipolar disorder treated with olanzapine	Parent assessment of child's quality of life: Child Health Questionnaire-Parental Form 50 at baseline, before receiving medication, and then again at the end of participation in a 3-week double-blind placebo-controlled study of

			olanzapine No utility values reported

Table 48: non-RCTs of aripiprazole not previously identified

Reference (Authors and journal)	PubMed ID	Title	Notes
Danielyan A, Cannon M, Kowatch A. Biol Psychiatry 2010;67:233S.	Not in PubMed	An Open Prospective Trial of Aripiprazole in Children and Adolescents with Bipolar I Disorder	8-week, open-label, prospective study of aripiprazole Only 16 patients NCT00221416

Table 49: non-RCTs of risperidone, quetiapine and olanzapine not previously identified

Reference (Authors and journal)	PubMed ID	Title	Notes
Frazier JA, Biederman J, Tohen M, Feldman PD, Jacobs TG, Toma V, Rater MA, Tarazi RA, Kim GS, Garfield SB, Sohma M, Gonzalez-Heydrich J, Risser RC, Nowlin ZM J Child Adolesc Psychopharmacol. 2001 Fall;11(3):239-50	PMID:11642474	A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder	8-week, open-label, prospective study of olanzapine monotherapy. Does not explicitly state bipolar I disorder, but refers to the DSM-IV criteria for manic, mixed and hypomanic states, which are sub-categories of bipolar I disorder in the DSM-IV. N=23 patients, therefore a very small trial. Overall, olanzapine was well tolerated, and extrapyramidal symptom measures were not significantly different from baseline. Body weight increased significantly over the study (5.0 ± 2.3 kg, $p < 0.001$).

Table 50: Trials from clinicaltrials.gov, updated since 1st January 2012

Reference (Authors and journal)	Clinicaltrials.gov ID	Title	Notes
AstraZeneca	NCT00090311	Quetiapine Fumarate (SEROQUEL) Compared to Placebo in the Treatment of Children & Adolescents With Bipolar I Mania (ANCHOR 149)	No data uploaded This is Study 149, which has been included in the original submission