

| Table DS1 Summary table of trials included in individual patient data meta-analysis | | | | | |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 |
| Protocol numbers | GW602/SCAB2001 | GW603/SCAA2010 | SCA40910 | SCA10022 | SCA30924 |
| Participants | Bipolar disorder, type I | Bipolar disorder, type I or II | Bipolar disorder, type I | Bipolar disorder, type II | Bipolar disorder, type I |
| Inclusion criteria | HRSD (17 item) \geq 18 MDE duration 2 weeks to 12 months \geq 2 mood episodes in previous 10 years (at least one manic/mixed) | HRSD (17 item) \geq 18 MDE duration 2 weeks to 12 months If bipolar disorder I \geq 2 mood episodes in previous 10 years (at least one manic/mixed) If bipolar disorder II at least one de- pressive and two hypomanic episodes in previous 10 years | HRSD (17 item) \geq 18 MDE duration 2 weeks to 12 months \geq 2 mood episodes in previous 5 years (at least one manic/mixed) | HRSD (17 item) \geq 18 MDE duration \geq 8 weeks \geq 2 mood episodes in previous 10 years (at least one manic/mixed) \geq 3 on either HRSD Item 1 or 7 at screen and baseline | HRSD (17 item) \geq 18 MDE duration \geq 8 weeks History of full or partial hospitalisation for a mood episode |
| Exclusion criteria | Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive-compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy New course of psychotherapy Any psychoactive drug within 5 half-lives Investigational drug within 30 days | Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive-compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy Any psychoactive drug within 5 half- lives Investigational drug within 30 days | Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive-compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy Any psychoactive drug within 5 half- lives Investigational drug within 30 days \geq 10 on Mania Rating Scale < 16 MADRS | Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive-compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy Any psychoactive drug within 5 half- lives Investigational drug within 30 days > \pm 20% change on HRSD from screening to randomisation \geq 10 on Mania Rating Scale ¹ | Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive-compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy Any psychoactive drug within 5 half- lives Investigational drug within 30 days > \pm 20% change on HRSD from screening to randomisation \geq 10 on Mania Rating Scale ² |
| Treatments and daily dose | Lamotrigine 50 mg or 200 mg (only 200 mg arm included in current analysis) Placebo | Lamotrigine 100–400 mg Placebo | Lamotrigine 200 mg Placebo | Lamotrigine 200 mg Placebo | Lamotrigine 200 mg Placebo |
| Titration schedule for lamotrigine, daily dose | For 200-mg group: Weeks 1 & 2: 25 mg Week 3: 50 mg Week 4: 100 mg Weeks 5–7: 200 mg | Weeks 1 & 2: 25 mg Weeks 3 & 4: 50 mg Week 5: 100 mg Week 6: flexible (100–200 mg) Week 7: flexible (100–300 mg) Weeks 8–10: flexible (100–400 mg) | Weeks 1 & 2: 25 mg Weeks 3 & 4: 50 mg Week 5: 100 mg Weeks 6–8: 200 mg | Weeks 1 & 2: 25 mg Weeks 3 & 4: 50 mg Week 5: 100 mg Weeks 6–8: 200 mg | Weeks 1 & 2: 25 mg Weeks 3 & 4: 50 mg Week 5: 100 mg Weeks 6–8: 200 mg |
| Number randomised and included | 129 total: Lamotrigine 200 mg ($n=63$) Placebo ($n=66$) | 206 total: Lamotrigine 100–400 mg ($n=103$; bipolar disorder I=61; bipolar disorder II=41) Placebo ($n=103$; bipolar disorder I=61; bipolar disorder II=41) | 257 total: Lamotrigine 200 mg ($n=133$) Placebo ($n=124$) | 221 total: Lamotrigine 200 mg ($n=111$) Placebo ($n=109$, no post- randomisation primary outcome in 1 participant) | 259 total: Lamotrigine 200 mg ($n=131$) Placebo ($n=128$) |

(Continued)

Table DS1 (continued)

| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| Study completion rate | Lamotrigine: 71% Placebo: 71% | Lamotrigine: 66% Placebo: 67% | Lamotrigine: 61% Placebo: 73% | Lamotrigine: 73% Placebo: 67% | Lamotrigine: 60% Placebo: 57% |
| Duration of double-blind treatment | 7 weeks | 10 weeks | 8 weeks | 8 weeks | 8 weeks |
| Primary outcome | 17-item HRSD | 17-item HRSD | MADRS | MADRS | MADRS |
| Secondary outcomes | HRSD item 1, 31-item HRSD, MADRS, CGI-S, ² CGI-I ² | HRSD item 1, 31-item HRSD, MADRS, CGI-S, CGI-I | HRSD item 1, 17-item HRSD, 31-item HRSD, CGI-S, CGI-I | HRSD item 1, 17-item HRSD, 31-item HRSD, CGI-S, CGI-I | HRSD item 1, 17-item HRSD, 31-item HRSD, CGI-S, CGI-I |
| CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; TFT, thyroid function test. | | | | | |

References

- 1 Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978; **35**: 837–44.
- 2 Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised DHEW Pub. (ADM). National Institute for Mental Health, 1976.

Appendix DS1: Search strategy used to identify articles

Search history (January 2005 to November 2006)

1. exp bipolar disorder/
 2. ((bipolar OR bi?polar OR bi polar) adj5 (disorder\$ OR depress\$)).tw.
 3. (mania\$ OR manic\$ OR hypomania\$).tw.
 4. (((cyclothymi\$ OR rapid OR ultradian) adj5 cycl\$) OR RCBD).tw.
 5. OR/1-4
 6. (lamotrigin\$ OR lamictal OR lamictin OR labileno).mp.
 7. (Bw 430 C OR Bw 430c OR Bw 430c78 OR Bw430c OR Bw430c78).tw.
 8. 84057-84-1.rn.
 9. OR/6-8
 10. exp clinical trials/ OR exp clinical trial/ OR exp controlled clinical trials/
 11. exp crossover procedure/ OR exp cross over studies/ OR exp cross-over design/
 12. exp double blind procedure/ OR exp double blind method/ OR exp double blind studies/
 - OR exp single blind procedure/ OR exp single blind method/ OR exp single blind studies/
 13. exp random allocation/ OR exp randomization/ OR exp random assignment/ OR exp random sample/ OR exp random sampling/
 14. exp randomized controlled trials/ OR exp randomized controlled trial/
 15. (clinical adj2 trial\$).tw.
 16. (crossover OR cross over).tw.
 17. (((single\$ OR doubl\$ OR trebl\$ OR tripl\$) adj5 (blind\$ OR mask\$ OR dummy)) OR (singleblind\$ OR doubleblind\$ OR trebleblind\$)).tw.
 18. (placebo\$ OR random\$).mp.
 19. (clinical trial\$ OR random\$).pt. OR (random\$ OR clinical control trial).sd.
 20. animals/ NOT (animals/ AND human\$.mp.)
 21. animal\$/ NOT (animal\$/ AND human\$)
 22. (animal NOT (animal AND human)).po.
 23. (OR/10-19) NOT (OR/20-22)
 24. AND /5,9,23
 25. limit 24 to yr="2005–2007"
 26. remove duplicates from 25
- Total number of hits: 202