BIPOLAR AFFECTIVE DISORDER: LITHIUM/ANTI-CONVULSANT EVALUATION (BALANCE) - AN INTERNATIONAL, RANDOMISED, OPEN-LABEL TRIAL OF COMBINATION THERAPY IN RELAPSE PREVENTION IN BIPOLAR DISORDER, TYPE 1

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ABSTRACT

Background

Lithium carbonate and valproate semisodium (divalproex) are both recommended as monotherapy for prevention of relapse in bipolar disorder, but are not individually fully effective in many patients. If combination therapy with both agents is superior to monotherapy, many relapses and consequent disability could be avoided.

Methods

330 patients with bipolar disorder, type 1 from 41 sites in UK, France, USA and Italy were randomly allocated to open-label lithium carbonate (plasma level 0.4 – 1.0 mmol/l, n=110) monotherapy or valproate semisodium (750 to1250mg, n=110) monotherapy or both agents in combination (n=110), after an active run-in of 4-8 weeks on the combination. Participants were followed for up to 24 months. The primary outcome was the initiation of new treatment for an emergent mood episode which was compared between groups by Cox regression. BALANCE was registered with International Standard Randomised Controlled Trial Number Register, number ISRCTN55261332

Findings

59 people in the combination therapy group, 65 people in the lithium group and 76 people in the valproate semisodium group experienced a primary outcome event during follow-up. The hazard ratio (HR) for the primary outcome was 0.59 (95% confidence interval 0.42 to 0.83, p=0.002) for combination therapy compared to valproate semisodium, 0.82 (95% confidence interval 0.58 to 1.17, p=0.27) for combination therapy compared to lithium and 0.71 for lithium compared with valproate semisodium (95% CI 0.51 to 1.00, p=0.05),

Interpretation

For people with bipolar disorder, type 1 for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate semisodium, and lithium monotherapy are more likely to prevent relapse than valproate semisodium monotherapy. This relative benefit appears to be irrespective of baseline severity of illness and maintained for up to two years. BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy.

INTRODUCTION

Bipolar disorder is a disabling mental illness characterized by episodes of both elevated or irritable mood and depression[1]. Although acute episodes may be succeeded by a period of remission, most patients have a recurrent or chronic illness making bipolar disorder one of the most important causes of disability at ages 15-44 years[2]. Lithium carbonate was the standard maintenance treatment for more than four decades and reduces the risk of relapse and suicide: but it is not helpful for all patients [3-8]. It has a narrow therapeutic index and can cause adverse effects that some patients cannot tolerate at all, or may lead to suboptimal adherence. The limitations of lithium therapy led to the search for alternative therapies for the long-term treatment of bipolar disorder. Anticonvulsants and second generation antipsychotic drugs have increasingly been proposed as alternatives although their relative safety and efficacy long-term compared to lithium remains uncertain [4,8].

Notwithstanding this lack of good comparative evidence, there have been major shifts in prescribing away from lithium, particularly in North America [9-12]. One commonly used agent is sodium valproate which is an effective antimanic agent and probably effective in relapse prevention[13,14]. In the USA, the prescription of lithium in out-patients nearly halved between 1992-1996 and 1996-1999 while the rate of prescribing of valproate almost tripled[12].

Many patients do not respond to monotherapy and combinations of drugs are often recommended despite little evidence[4,5,16]. Lithium plus valproate is often recommended following failure of first line monotherapy[3-5,]. Should this combination have additive pharmacological effects and prove superior to monotherapy, it could be an appropriate first-line therapy[17,18]. We report BALANCE, a randomised clinical trial designed to determine if lithium plus valproate semisodium is superior to monotherapy with either drug alone in the prevention of relapse in bipolar disorder, type 1.

METHODS

BALANCE was a randomised, open-label, 3-arm trial of maintenance therapy with up to 24 months of follow-up[19-21]. Patients initially entered an active run-in phase to confine randomisation to those patients who tolerated both drugs in the short-term and were likely to take the randomly allocated study treatment for 2 years[22]. The run-in was usually 4-8 weeks long but could be extended if clinically required. During the run-in patients received 4 to 8 weeks of treatment with both lithium carbonate (*Priadel,* at doses producing a serum level between 0.4 and 1.0 mmol per litre) and valproate semisodium (*Depakote,* at least 750mg per day with a target daily dose of 1250 mg or the highest dose tolerated). For participants starting one or both treatments, medicines were titrated to the target dose over 4 weeks. Participants taking higher doses of valproate semisodium at study entry could continue at the same dose during the trial. Lower doses of valproate were permitted if required for tolerability and the serum level was at least 50 microg/ml prior to randomisation. BALANCE was designed to be as simple as possible and no appointments additional to those needed for routine clinical practice were required for the trial.

Participants and eligibility

Recruitment took place at 41 sites in UK, USA, Italy and France between May 31st 2001 and February 22nd 2007. The protocol was approved by the appropriate institutional review boards/ethics committees. Men and women aged 16 and over, with a clinical diagnosis of bipolar disorder, type 1 (based on a previous episode of mania meeting DSM-IV criteria[23]) were eligible for entry into the active run-in provided that 1) informed consent was given 2) patient was not suffering from an acute episode and long-term drug therapy was considered clinically indicated to prevent relapse; 3) it was considered clinically reasonable to try combination therapy with lithium plus valproate semisodium; 4) there was no medical disorder or condition contraindicating either of the investigational drugs; 5) the patient was normally resident in one country and had a residential address.

Participants proceeded to randomisation if: 1) there was clinical uncertainty and no clear treatment preference; 2) the lithium level was between 0.4 to 1.0 mmol/litre; 3) valproate semisodium dose at least 750mg, or valproic acid serum level at least 50 microgram/millilitre; 4) the combination of lithium and valproate semisodium was tolerated at trial doses; 5) adherence during the run-in phase was judged by the investigator to be at least 70%.

Participants were randomly allocated to one of three arms: 1) combination therapy with lithium and valproate semisodium; 2) lithium monotherapy – valproate semisodium withdrawn and lithium continued at the dose established during the run-in; 3) valproate semisodium monotherapy – lithium withdrawn and valproate semisodium continued. Allocated drugs were continued at the dose established in the run-in. In the monotherapy arms the discontinued drug was withdrawn over four weeks to reduce the risk of relapse associated with abrupt discontinuation[24]. Doses of the investigational drugs could be increased if the serum level dropped below the minimum threshold (post-randomisation serum levels could be done but were optional) and decreased (within the trial ranges) if side-effects became troublesome. Participants remained on the allocated treatment for 2 years or until treatment failure. Non-investigational co-therapies could be continued during the course of the trial.

The primary outcome was time to new intervention for an emerging mood episode including drug treatment (which could be the commencement of a new drug, restarting a discontinued drug or increasing the dose of the investigational drug in response to an emergent mood episode) and/or admission to hospital). Secondary outcomes included 1) time to new intervention for an emerging depressive episode, 2) time to new intervention for an emerging manic episode, 3) global assessment of functioning scale[25], 4) episodes of deliberate self-harm, 5) quality of life using the EuroQol (EQ-5D)[26], 6) adverse events including both emergent serious adverse events and participant-reported adverse effects, 7) withdrawal from study treatment, 8) adherence to study treatment estimated by investigator[27].

Sample size and randomisation

A total of 231 participants were needed to give 90% power at 2-sided 5% significance level to detect a 40% relative reduction in the hazard from an expected value of 70%[6], assuming a 20% rate of drop-out from allocated treatment. A secondary objective was to determine if the study treatments had differential effects on preventing depressive and manic episodes. To detect a 40% reduction in hazard ratio for a depressive episode requiring new treatment with 80% power at 5% significance level required 115 per group giving a total sample size of 345.

The computerised randomization programme included a minimisation algorithm to ensure balanced allocation of participants across the intervention groups for the following prognostic factors: (i) nature of most recent episode (mania/non-mania); (ii)

number of previous psychiatric admissions (<2 /≥ 2); (iii) previous maintenance treatment (yes/no); (iv) age (under 35 / 35 plus); (v) sex; (vi) region. Treatment allocation was via the 24 hour telephone service at the Clinical Trial Service Unit, University of Oxford. Investigators telephoned the service and logged the patient as eligible for randomisation. The investigator was then informed of the treatment allocation. Treatment was open because of the complexities of blinding lithium therapy and the concern that it would limit participation and generalizability[21]. The consequent risk of performance and ascertainment biases was managed by restricting randomisation to patients for whom there was no strong treatment preference on the part of the patient of clinician and by careful verification of outcomes. All outcome events were considered by the trial management team, blind to treatment assignment. In the case of any doubt, a description of the event was sent to an independent adjudicator.

Statistical methods

The analysis followed a detailed, pre-specified plan. The time to first event during the scheduled follow up period was compared between the three arms. The follow-up period was censored at the last available assessment in patients who were lost to follow-up without experiencing an event. The time from randomisation to event was summarised by Kaplan-Meier curves, and compared using the log rank test. Hazard ratios (HR) with 95% confidence intervals were calculated using Cox's regression to estimate the size of the treatment effect. The proportional hazards assumption was tested formally using an analysis of the Schoenfeld residuals. An analysis adjusting for the minimization factors was also conducted. As BALANCE had very specific hypotheses and only one outcome of primary importance, no formal adjustment was made for multiple significance testing. Stata (Release 10) was used for all power calculations and analyses[28].

The trial was designed, conducted, analysed and interpreted by the investigators and collaborators entirely independently of the funding sources.

Protocol changes and other modifications

The protocol (cebmh.warne.ox.ac.uk/balance/balance1/document.html) was approved for the UK by the South-West Multicentre Research Ethics Committee on 4th April 2001. In July 2003, the protocol was changed to require blood samples at randomisation only. In October 2003, an end-of-trial questionnaire was added to ask about participants experiences. In August 2005, there was a change in primary

outcome and, consequently, sample size. Initially, the primary outcome was admission to hospital and the planned sample size was 1068 participants. During the early course of the trial, time to intervention became established as the primary outcome of choice in long-term trials in bipolar disorder. Change to this clinically meaningful primary outcome led to a revision of the planned sample size from 1068 to 345 (see above). All protocol changes were approved by ethics committee, data monitoring and ethics committee and the trial steering committee. Following the implementation of the EU Directive on Clinical Trials in 2004, the initial nominal academic principal investigators were replaced with principal investigators who met European Union Directive 2001/20/EC criteria.

RESULTS

Patient enrolment

Participant characteristics at screening and randomisation were broadly similar between groups (Table 1); 459 patients entered the run-in phase (Figure 1), 330 were randomised. Of the 129 who were not randomised, 49 (11% of total screened) were unable to tolerate the combination treatment, 40 (9%) chose not to enter the trial and 40 (9%) for other reasons (figure 1). Approximately a quarter of randomised patients had not previously been prescribed maintenance treatment with mood stabilizers. On entering the run-in phase, 53% of UK patients were given a lithium titration pack and 71% a valproate semisodium titration pack, indicating that more patients were already taking lithium than valproate. About 90% of participants were estimated to have >90% adherence to medication during the run-in. The randomisation levels and drug doses were mostly within the planned ranges and were similar between groups (Table 1). The most recent mood episode was manic in 48% of the randomised participants, depressive in 37%, mixed in 11% and cycling between mania and depression in 4%. Substance abuse was considered to be clinically significant in 8% of participants. The randomised participants were followed for a total of 589.8 (combination 201.1, lithium 191.6 and valproate 197.2) person years, of which 452.6 (combination 149.0, lithium 148.5 and valproate 155.1) person years were on the allocated therapy.

Primary outcome: time to first new treatment for a mood episode

During the follow-up period the primary outcome occurred in 59/110 (54%) of participants on combination therapy, 76/110 (69%) on valproate semisodium and 65/110 (59%) on lithium carbonate (Table 2 and Figure 2). The hazard of the primary outcome in participants allocated to combination therapy was statistically significantly lower than in those allocated to valproate semisodium monotherapy (HR 0.59, 95% CI 0.42 to 0.83, p=0.002) but not significantly lower than in those allocated to lithium monotherapy (HR 0.82 (95% CI 0.58 to 1.17, p=0.27). The hazard of the primary outcome was significantly lower on lithium than valproate semisodium (HR 0.71, 95% CI 0.51 to 1.00, p=0.05). The proportional hazards assumption held in all the analyses and the results were essentially unchanged after adjustment for minimization factors (Figure 2).

Pre-specified subgroup analyses taking into account baseline severity of disorder (measured as number of previous admissions) and nature of most recent mood episode did not find materially different results (Figure 3). Sensitivity analyses restricted to those participants taking adequate doses of drugs and to those treated

per protocol (observations censored at the point when the trial medication was stopped) confirmed the robustness of the results (Figure 3). Excluding events occurring within the first 3 months post-randomization found broadly similar results to the primary analysis (Figure 3).

Secondary outcomes

Separate analyses were conducted for the two components of the primary outcome and were consistent with the primary analysis (Table 2 and Figure 2). Notably, the adjusted risk of hospital admission in participants allocated to combination therapy was significantly lower than in patients allocated to valproate semisodium (HR 0.51, 95% CI 0.27 to 0.96, p=0.04), replicating the finding on the primary outcome. The superiority of combination therapy over valproate semisodium was most apparent on manic relapses (HR 0.51, 95% CI 0.32 to 0.80, p=0.003) whereas the superiority of lithium over valproate semisodium was most apparent on depressive relapses (HR 0.63, 95% CI 0.41 to 0.96, p=0.03). There were no significant differences between the groups in terms of discontinuation of allocated treatment, self-harm, quality of life or global functioning (Table 2).

Safety analyses

Serious adverse events occurred in 5 participants in the run-in. Following randomisation, 16 participants experienced serious adverse events: valproate semisodium monotherapy 7 (4 deaths – stroke, peritonitis, pneumonia, carcinoma bronchus), lithium monotherapy 5 (2 deaths – respiratory failure, bronchopneumonia) and combination therapy 4 (1 death, respiratory failure). One event (polycystic ovaries) was considered to have been revealed by the trial medication. There were no suicides. Five women became pregnant during the trial and stopped trial medicines (2 in the run-in phase and 3 in the randomised phase). No obstetric complications or congenital abnormalities were reported. The majority of participants (lithium 95%, valproate semisodium 92%, combination 100%) reported at least one non-serious adverse event by 24 months.

DISCUSSION

The results of BALANCE demonstrate that, for people with bipolar I disorder for whom long-term therapy is clinically indicated, combination therapy with lithium plus valproate semisodium is statistically significantly more likely to prevent relapse than monotherapy with valproate semisodium. The 41% relative benefit appears to be irrespective of baseline severity of illness, maintained for up to two years and most apparent in the prevention of manic relapse. BALANCE could neither confirm nor refute a benefit of combination therapy compared with lithium monotherapy. Since the trial was designed primarily to compare combination therapy with monotherapy, conclusions about the comparative efficacy of the two agents should be cautious. Nevertheless, lithium monotherapy was modestly more effective than valproate semisodium. The smaller margin of difference than that for combination therapy is compatible with an additive effect when the two drugs are used in combination. Previous trials have not shown unequivocal differences between lithium and valproate [14,29, 30].

In absolute terms, there was a 15.5% difference in risk between combination therapy and valproate semisodium monotherapy over 24 months (number need to treat [NNT] = 7[31]), a 10% difference between valproate semisodium and lithium monotherapies (NNT= 10) and a statistically non-significant 5.5% difference between combination therapy and lithium monotherapy (NNT= 19). The observed unequivocal and substantial effect of adding lithium to valproate semisodium is striking and may be even larger in highly adherent patients with optimised therapy. There is one previous randomised trial comparing lithium monotherapy with combination lithium plus valproate semisodium in patients with rapid-cycling disorder and comorbid substance abuse[17]. Although this trial was quite small and so of limited power, the estimate of the HR (0.72, 95% confidence interval 0.32 to 1.65) was compatible with that observed in BALANCE.

Although BALANCE did not have a no-treatment or placebo group, an approximate indirect estimate of the relative benefit of combination therapy compared to no treatment can be obtained from the product of the BALANCE combination:monotherapy hazard ratios and the relative risk estimated in previous trials of monotherapy versus placebo[6,14]. This yields a relative risk reduction for combination therapy compared to placebo in the range of 45-64%.

The wide range of patients enrolled from a variety of locations and clinical situations ensure that the findings from BALANCE are broadly applicable to patients with bipolar disorder. The proportion of participants with substance misuse comorbidity (8%) was lower than that reported in population surveys[32]. This probably reflects differences in case ascertainment: in BALANCE the investigator was simply asked to record if they considered substance/alcohol use to be a clinically significant problem, whereas in population surveys, evidence of substance misuse is sought through structured interview. The use of an active run-in means that the randomised sample was a selected group and hence the results are most applicable to patients who can tolerate treatment with lithium and valproate semisodium and are largely adherent to therapy [21,33]. Nonetheless, the active run-in would tend to increase the clinical applicability of the results in a real-world clinical setting where people who are prescribed long-term treatments are usually selected from those who have been able to tolerate the medication in the short-term[33].

It is important to consider several possible weaknesses in the study design. First, treatment allocation was not masked from the investigators or participants. Therefore, performance and ascertainment biases could have arisen if clinicians and/or participants had behaved systematically differently depending on the treatment allocation, and influenced the recorded outcome. Our prospective strategy to avoid these biases was to limit trial entry to patients for whom there was explicit uncertainty about which treatment was likely to be best. Patients who had, or developed, a strong preference for an investigational therapy were excluded either at screening or prior to randomisation. Second, although the eligibility criteria required that participants were not acutely unwell, symptomatic status was not systematically assessed and it is possible that there was some pre-randomisation selection on the basis of response to treatment. Third, although intervention for a new mood episode is, we believe, a meaningful clinical endpoint, it could also be subverted by, for example, the very early introduction of additional medication into monotherapy arms. This does not appear to have occurred because the difference between treatments was constant up to two years and exclusion of events occurring in the first 3 months did not materially change the results. Most importantly, the magnitude of the reduction in the risk of admission to hospital on combination therapy was similar to that found on the primary outcome. Admission to hospital would be very unlikely to involve the trial physician acting alone. It is unlikely, therefore, that lack of equipoise and consequent bias could explain the observed difference in admissions between the study treatments. Finally, although

around 21% of patients withdrew from the trial before 24 months there were no clear differences in the reasons for withdrawal between arms.

BALANCE was designed to reflect the routine use of the agents in clinical practice. Hence, the lithium levels at randomisation were possibly suboptimal in a proportion of patients. This did not prevent the trial from detecting a substantial effect of adding lithium to valproate semisodium. Similarly, the dose of valproate semisodium used in the trial was lower than recommended in acute mania and higher doses might have improved its putative effectiveness. However, it was agreed by the manufacturer and independent experts and was determined during piloting to optimize tolerability. Moreover, patients in the run-in phase dropped out more often because of intolerance than for any other reason, so using a higher dose would likely have decreased tolerability and overall effectiveness. There was no clear difference between the treatments in terms of adverse events or tolerability in the randomised phase.

Although BALANCE has provided reliable evidence to inform the treatment of people with bipolar disorder, it is important to emphasise that over half of the participants treated with combination therapy required additional treatment over the two year follow-up period. Depressive episodes in bipolar disorder are both prevalent and disabling, and currently available therapies show only limited effectiveness in treating and preventing them[6,34,35]. Each depressive relapse leads to disability that can jeopardize a person's ability to function at home or in work and contributes to the burden on caregivers[36]. Other monotherapies, both pharmacotherapies and psychotherapies, now exist that may reduce relapse and further study is needed of other possible combinations[8,37].

Quantification of the risk of specific adverse effects of both drugs including the possibility of renal toxicity with lithium and congenital abnormalities with valproate semisodium[38] was beyond the scope of BALANCE but should also be considered in clinical application of the results.

The main BALANCE findings have important implications for clinical decisions about long-term therapy in bipolar disorder. First, valproate monotherapy is recommended by current clinical practice guidelines as a first line option for long-term therapy[3-5]. BALANCE indicates that patients should be advised that a better outcome would be likely with combination therapy with lithium plus valproate semisodium or lithium alone. Second, current guidelines suggest that switching to valproate monotherapy is an

option for patients who continue to get frequent relapses on lithium monotherapy[5]: BALANCE suggests that patients would do better changing to combination therapy.

ACKNOWLEDGEMENTS

Most importantly, we acknowledge the participants in the study and the clinical and administrative staff in all four countries who assisted with the trial. BALANCE was funded by the Stanley Medical Research Institute, with French centres funded by Sanofi-Aventis. All study drugs for the UK and France were donated by Sanofi-Aventis, the manufacturers of lithium carbonate (Priadel) and valproate semisodium (Depakote). In the UK, the study was adopted by the Mental Health Research Network in February 2005 to facilitate recruitment in some sites.

CONFLICT OF INTEREST OF WRITING COMMITTEE

John Geddes has received research funding from MRC, ESRC, NIHR, Stanley Medical Research Institute and has received donations of drugs supplies for trials from Sanofi-Aventis and GSK. He has acted as an expert witness for Dr Reddys but otherwise has received no payment from drug companies in the past three years.

Guy Goodwin has received research grants from Bailly Thomas, MRC, Sanofi-Aventis, Servier, honoraria from AstraZeneca, BMS, Eisai, Lundbeck, Sanofi-Aventis, Servier,; is a shareholder in P1vital, has a paid position at University of Oxford and has been a member of advisory boards with AstraZeneca, BMS, Lilly, Janssen Cilag, Lundbeck, P1Vital, Sanofi-Aventis, Servier, Wyeth. He has acted as an expert witness for Lilly and Servier.

Jennifer Rendell – none

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Richard Morriss has received honoraria from Lilly, Janssen, Astra-Zeneca and Bristol-Myers-Squibb and travel grants from Lilly and Janssen

Jean-Michel Azorin has undertaken consultancy work for Lilly, Janssen, Sanofi-Aventis, Lundbeck, Astra-Zeneca and Bristol-Myers-Squibb; he has received honoraria fdrom Lilly, Janssen, Lundbeck, Sanofi-Aventis, Bristol-Myers-Squibb, Pfizer and Novartis in relation to conference presentations.

Michael Ostacher has acted as consultant for Pfizer, received travel grants from Bristol-Myers-Squibb and honoraria from Lilly, Janssen, Sanofi-Aventis, GSK Pfizer, Reed Education, France foundations, SciMed, Concordant Rater Systems, Astra-Zeneca and Bristol-Myers-Squibb

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Table 1. Patient characteristics at screening and randomisation

Characteristic	At screening (n=459)	At randomisation Lithium (n=110)	Valproate (n=110)	Combination (n=110)
Number in region (%)				
England				
Central	43 (9)	7 (6)	10 (9)	9 (8)
East	19 (4)	4 (4)	2 (1)	4 (4)
London	14 (3)	3 (3)	3 (3)	5 (5)
North East	7 (2)	2 (2)	1 (1)	2 (2)
North West	59 (13)	13 (12)	14 (13)	9 (8)
South	216 (47)	55 (50)	53 (48)	58 (53)
South West	33 (7)	9 (8)	9 (8)	9 (8)
Northern Ireland	5 (1)	2 (2)	1 (1)	1 (1)
Scotland	18 (4)	5 (5)	6 (6)	3 (3)
France	17 (4)	5 (5)	5 (5)	5 (5)
USA	17 (4)	3 (3)	4 (4)	3 (3)
Italy	11 (2)	2 (2)	2 (2)	2 (2)
Number male (%)	219 (48)	57 (52)	55 (50)	56 (51)
Mean age (sd)	43.1 (13)	43.0 (12)	44.0 (13)	41.5 (13)
Median number of previous psychiatric admissions (range)	2 (0 to 30)	2 (0 to 20)	2 (0 to 30)	1.5 (0 to 20)
Nature of most recent episode Number (%)				
Mania	223 (49)	58 (53)	57 (52)	57 (52)
Depression	170 (37)	32 (29)	40 (36)	39 (36)
Mixed	49 (11)	15 (14)	12 (11)	11 (10)
Cycling	17 (4)	5 (5)	1 (1)	3 (3)
Number with previous maintenance treatment with mood stabilisers (%)	340 (74)	82 (75)	84 (76)	81 (74)
Number on current medication in addition to BALANCE medication (%)				
Other mood stabilisers	80 (17)	3 (3)	6 (6)	9 (8)
Missing	0	1 (1)	0	0
Antipsychotics	208 (45)	29 (26)	33 (30)	23 (21)
Missing	0	1 (1)	0	0
Antidepressants	177 (39)	36 (33)	29 (26)	32 (29)
Missing	2 (0.4)	0	0	0

Number in whom alcohol or substance abuse was considered to be a clinically significant problem (%)	38 (8)	8 (7)	8 (7)	10 (9)
Median GAF (range)		80 (25 to 100) (n=109)	80 (51 to 100)	80 (28 to 100)
Estimated adherence to lithium				
71-90%		11 (10)	12 (11)	7 (6)
>90%		99 (90)	98 (89)	103 (94)
Estimated adherence to valproate				
71-90%		11 (10)	14 (13)	8 (7)
>90%		98 (89)	96 (87)	102 (93)
Missing		1 (1)	0	0
Median Health state (EuroQoL (EQ-5D)) (range)		70 (5 to 99) (n=90)	70 (0 to 94) (n=94)	65 (5 to 100) (n=93)
Lithium blood levels at randomisation (Number (%))				
Unknown		19 (17)		18 (16)
<0.4		7 (6)		8 (7)
0.4-0.6		28 (26)		36 (33)
0.6-0.8		31 (28)		38 (35)
0.8-1.0		23 (21)		10 (9)
>1.0		2 (2)		0
Valproate dose (Number (%))				
Unknown			0	1 (1)
<750			3 (3)	0
750-1250			55 (50)	48 (44)
1250 (recommended dose)			41 (37)	55 (50)
>1250			11 (10)	6 (6)

FIGURE 1. Participant flow

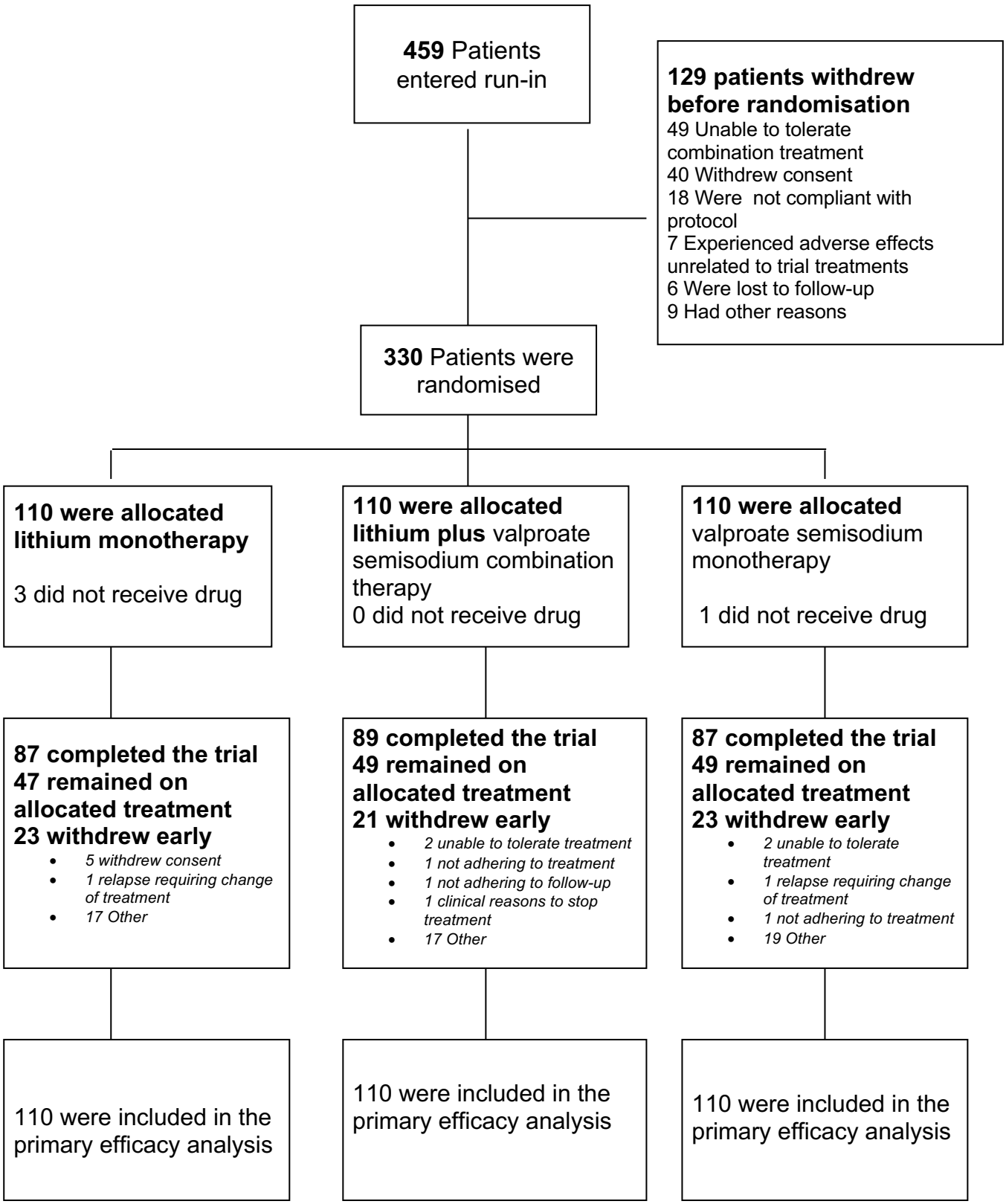


Figure 2 Time to event outcome measures

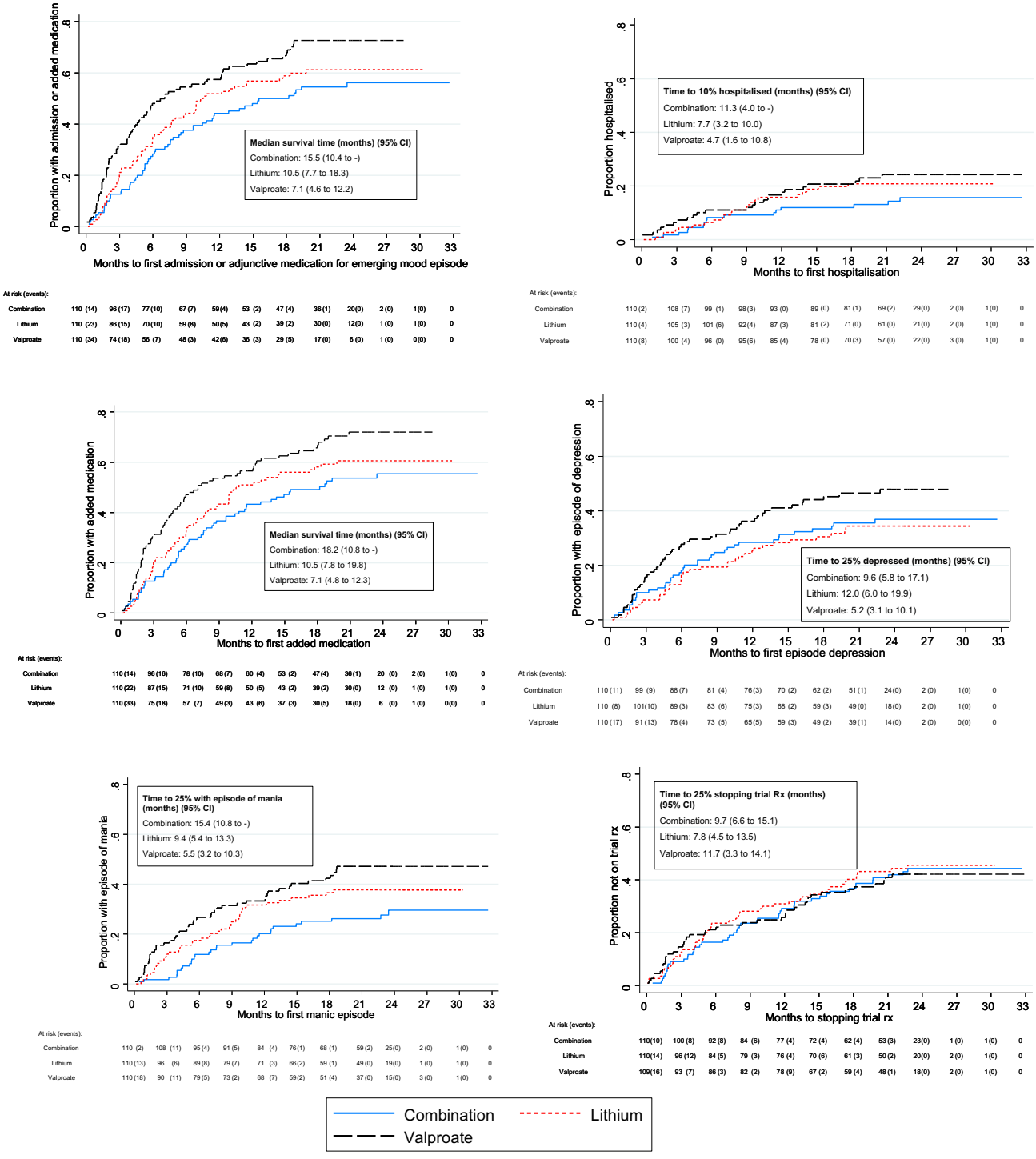
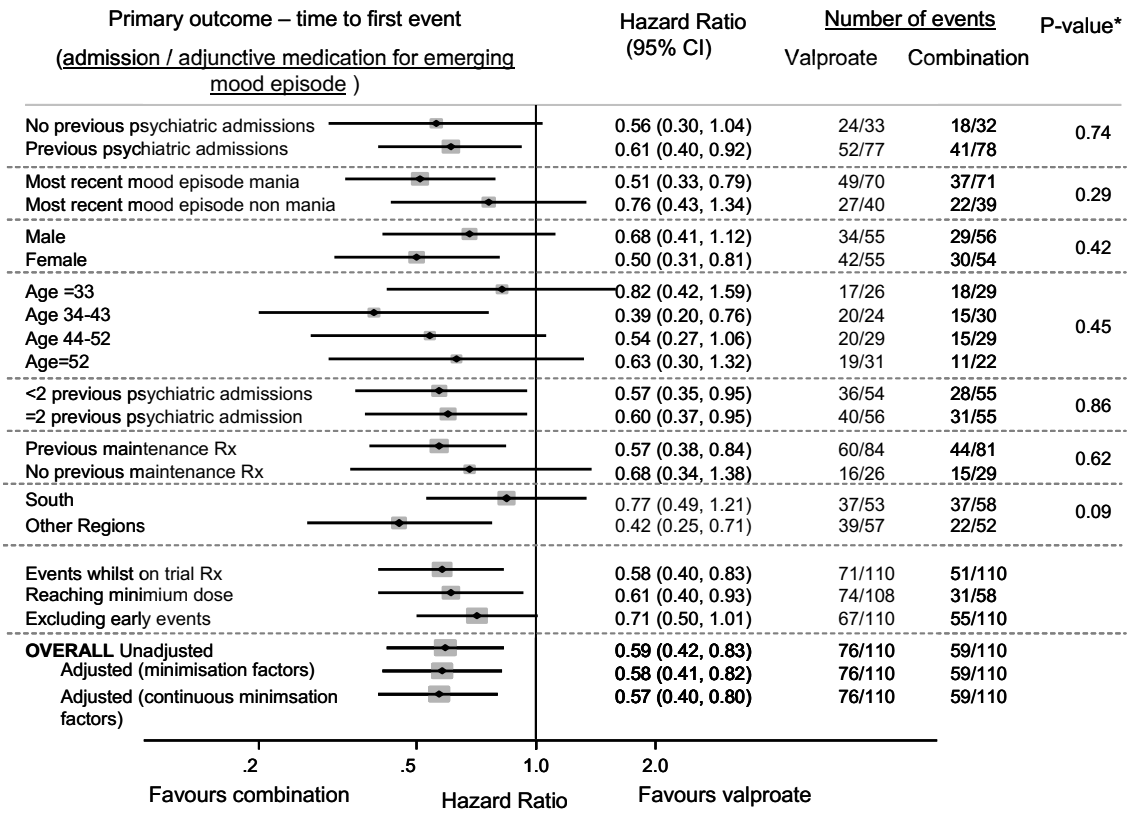
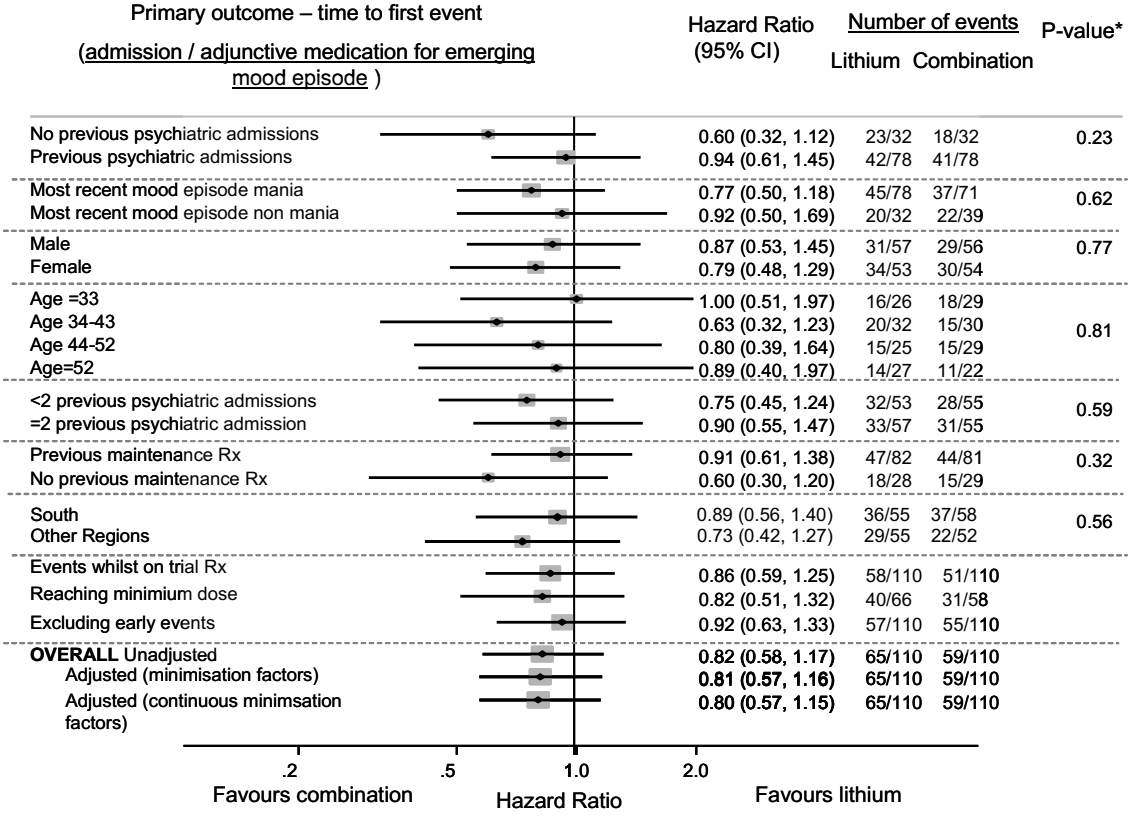


Figure 3 Hazard ratios for the primary outcome on the basis of pre-specified subgroups according to baseline characteristics of interest.

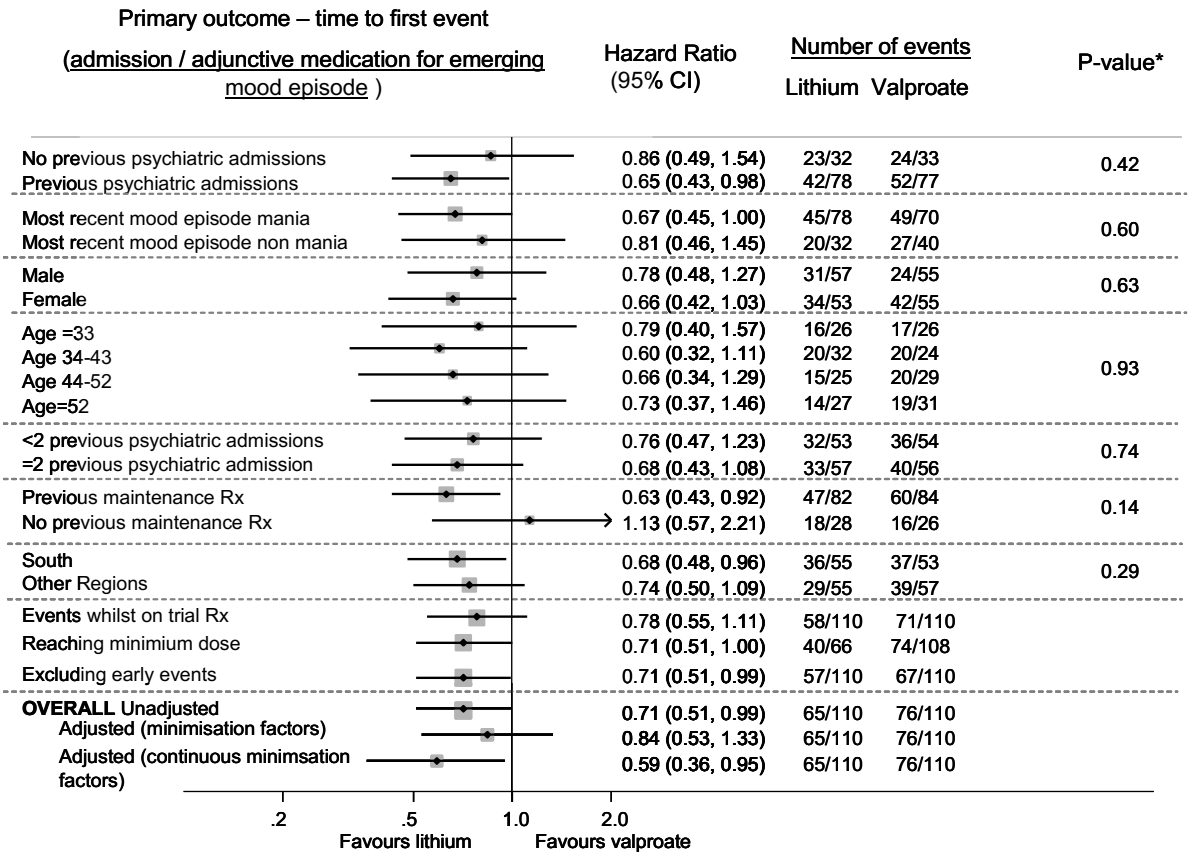
a. Combination therapy vs valproate semisodium



b. Combination therapy vs lithium carbonate



c. Lithium carbonate vs valproate semisodium



* Test for interaction

Table 2: Clinical and safety outcomes

Outcome	Combination (N=110)	Lithium (N=110)	Valproate semisodium (N=110)
New treatment for mood episode			
No. of patients with event (%)	59 (54)	65 (59)	76 (69)
Cox-model treatment comparisons			
Combination therapy			
Hazard ratio (HR, 95% CI)	1	0.82 (0.58 to 1.17)	0.59 (0.42 to 0.83)
P value		0.27	0.002
Adjusted HR* (95% CI)	1	0.80 (0.57 to 1.15)	0.57 (0.40 to 0.80)
P value		0.23	0.001
Hospital admission			
No. of patients with event (%)	16 (15)	22 (20)	25 (23)
Cox-model treatment comparisons			
Combination therapy			
HR (95% CI)	1	0.70 (0.37 to 1.33)	0.59 (0.32 to 1.11)
P value		0.28	0.10
Adjusted HR* (95% CI)	1	0.72 (0.38 to 1.38)	0.51 (0.27 to 0.96)
P value		0.32	0.04
New treatment for mood episode			
No. of patients with event (%)	58 (53)	64 (58)	75 (68)
Cox-model treatment comparisons			
Combination therapy			
HR (95% CI)	1	0.82 (0.57 to 1.17)	0.60 (0.42 to 0.84)
P value		0.27	0.003
Adjusted HR* (95% CI)	1	0.80 (0.56 to 1.14)	0.57 (0.40 to 0.80)
P value		0.21	0.001
New treatment for mania			
No. of patients with event (%)	30 (27)	40 (36)	49 (45)
Cox-model treatment comparisons			
Combination therapy			
HR (95% CI)	1	0.67 (0.42 to 1.08)	0.51 (0.32 to 0.80)
P value		0.10	0.003
Adjusted HR* (95% CI)	1	0.66 (0.41 to 1.07)	0.50 (0.31 to 0.79)
P value		0.09	0.003
New treatment for depression			
No. of patients with event (%)	39 (36)	35 (32)	50 (46)
Cox-model treatment comparisons			
Combination therapy			
HR (95% CI)	1	1.12 (0.71 to 1.76)	0.70(0.46 to 1.07)
P value		0.63	0.10
Adjusted HR* (95% CI)	1	1.06 (0.67 to 1.67)	0.71 (0.46 to 1.08)
P value		0.81	0.11
Discontinuation of allocated treatment			
No. of patients with event (%)	47 (43)	49 (45)	44 (40)

Cox-model treatment comparisons			
Combination therapy			
HR (95% CI)	1	0.93 (0.62 to 1.38)	1.02 (0.67 to 1.54)
P value		0.71	0.93
Adjusted HR* (95% CI)	1	0.89 (0.60 to 1.34)	1.01 (0.67 to 1.53)
P value		0.58	0.95
Global assessment of functioning			
No. of patients responding at 24 months (%)	79 (72)	73 (66)	72 (66)
Median at 24 months (s.d.)	79.3 (14.3)	80.2 (13.0)_	78.3 (16.2)
P value***		0.95	0.94
Deliberate self harm			
Months follow-up	2413	2299	2366
Participants with at least one episode DSH	4	2	5
Episode per month	0.0017	0.0009	0.0021
P value**		0.49	0.73
Quality of life – EQ-5D			
No. of patients responding at 24 months (%)	49 (45)	52 (47)	43 (39)
Median at 24 months (5^{th}, 95^{th} percentiles)	70 (28, 94)	65 (16, 92)	70 (35, 97)_
P value****		0.14	0.27
Serious adverse events			
No. of patients with SAE (%)	4 (4)	5 (5)	7 (6)
P value*****		1.0	0.54
No. of patients with SAE thought to be related to trial medication (%)	1 (1)	0 (0)	0 (0)

*Adjusted for sex (male, female), age at entry (continuous), number of previous admissions (continuous), nature of most recent episode (mania, non-mania), previous maintenance treatment with mood stabilisers (yes, no)
** Comparison of incidence rates
***Repeated measures analysis of variance (combination vs. monotherapy)
**** Analysis of covariance, adjusting for baseline health state (combination vs. monotherapy)
*****Fisher's exact test comparing proportions with SAE between combination therapy and monotherapy