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Research report

Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: Experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I

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ABSTRACT

Background: Eslicarbazepine acetate (ESL) is an anticonvulsant approved as an adjunctive therapy in adults with partial-onset seizures.
Objective: To evaluate the efficacy, safety and tolerability of ESL in the treatment of acute mania and prevention of recurrence in bipolar disorder I.
Methods: Two 3-week multicentre, double-blind, randomised, placebo-controlled studies in acute mania (study BIA-2093-203: dose titrated by response, ESL 600–1800 mg or 800–2400 mg, once-daily; study BIA-2093-204: fixed doses of 600, 1200 and 1800 mg, once-daily) were followed by a recurrence prevention study consisting of a 2-week open-label period (900 mg, once-daily) continued by a double-blind, parallel-group, fixed dose (300, 900 and 1800 mg, once-daily) period for a minimum of 6 months. The primary endpoint was changed from baseline until the end of the 3-week treatment period in Young Mania Rating Scale (YMRS) in studies BIA-2093-203 and BIA-2093-204, and the proportion of patients showing no worsening according to the Clinical Global Impressions – Bipolar Version (CGI-BP) over Part II in study BIA-2093-205.
Results: In study BIA-2093-203 ($n=160$, ITT), neither dose group was statistically different from placebo in the primary endpoint, though the ESL 800–2400 mg showed a greater reduction in YMRS score ($p=0.0523$). CGI-BP score changes for mania and overall bipolar illness indicate a significant improvement in patient symptomatology for the ESL 800–2400 mg group (from preceding and worst phase) and for ESL 600–1800 mg group (from worst phase only) when compared to placebo. Study BIA-2093-204 ($n=38$) results were inconclusive due to premature termination caused by recruitment difficulties. In study BIA-2093-205 ($n=85$, ITT), at least 50% of patients showed no worsening in all treatment groups ($p=0.250$). ESL adverse events were mostly of mild and moderate intensities and consistent with previously reported observations for ESL.
Conclusion: ESL treatment was not significantly different from placebo in manic patients in the primary outcome, but secondary outcomes may be suggestive of efficacy. The recurrence prevention study provides preliminary support for efficacy of ESL in patients recovered from an acute manic episode.

1. Introduction

Bipolar disorder is a recurrent, severe, and often debilitating illness characterised by episodes of mania, depression and long-term psychosocial disability (Muller-Oerlinghausen et al., 2002). Patients with bipolar I disorder are characterised by having had at

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least 1 episode of mania (American Psychiatric Association, 2000). Most patients have previous depressive episodes, and subsequent episodes (that can be either manic or depressive) are common (American Psychiatric Association, 2000). The estimated life time prevalence of bipolar I disorder ranges from 0.4–1.6%; different figures are mostly due to differences in the populations analysed and the definitions employed (Judd and Akiskal, 2003; Merikangas et al., 2007; Merikangas et al., 2011; Weissman et al., 1996).

Management of bipolar disorder patients includes both the treatment of acute manic/mixed/depressive episodes and the prevention of recurrence of episodes. Lithium, valproate or atypical antipsychotics are usually first line treatment for acute mania episodes whereas haloperidol and carbamazepine are used as second line alternatives (Fountoulakis et al., 2012; Grunze et al., 2009). Maintenance treatment choice is dependent on the predominant polarity of the disorder (Colom et al., 2006). Lithium better prevents relapse to new manic episodes while lamotrigine better prevents the re-occurrence of depressive episodes (Bowden et al., 2003; Calabrese et al., 2003; Geddes et al., 2004; Licht et al., 2010). Over the past decades, several treatment options for bipolar disorder became available, particularly for the treatment of manic episodes. However, a significant proportion of patients remains refractory to these agents or cannot tolerate the adverse events (AE) (e.g., kidney and thyroid disorders associated with lithium therapy, hirsuitism and polycystic ovary syndrome (PCOS) associated with valproate or allergic skin rash in patients starting lamotrigine treatment) (Bushe and Tohen, 2010; Fountoulakis et al., 2012; Malhi et al., 2012). Therefore, the development of additional treatments for bipolar disorder with better efficacy, safety and tolerability profiles is still necessary (Malhi et al., 2012).

Eslicarbazepine acetate (ESL) is a once-daily (QD) anticonvulsant, extensively and rapidly converted to eslicarbazepine after oral administration (Almeida and Soares-da-Silva, 2007; Bialer and Soares-da-Silva, 2012). ESL was approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalisation (EMA, 2009), and was approved in 2013 by the US Food and Drug Administration (FDA) as adjunctive treatment of POS (FDA, 2013; Sperling et al., 2013). ESL is not approved for use in bipolar disorder.

The objective of these phase II studies was to evaluate the efficacy, safety and tolerability of ESL in phase II clinical studies in acute mania and recurrence prevention of bipolar disorder I.

2. Patients and methods

2.1. Study design

Study BIA-2093-203 (EudraCT no. 2005-002131-27) followed a multicentre, double-blind, randomised, parallel-group, placebo-controlled, dose-titration design. This study was conducted at 23 centres across Europe. Patients were randomised in a 3:3:2 ratio to one of the following treatment groups: (1) ESL starting with 800 mg QD and up-titrated in 800 mg steps until 2400 mg QD (maximum dose) according to clinical response, (2) ESL starting with 600 mg QD and up-titrated in 600 mg steps until 1800 mg QD (maximum dose) according to clinical response, and (3) Placebo QD. Patients were followed for up to 3 weeks. The study schedule consisted of a screening visit (V1), randomisation visit (V2, Day 1), and subsequent visits to evaluate clinical response (V3, Day 4; V4, Day 7; V5, Day 10; V6, Day 14 and V7, Day 21). In patients showing no improvement of symptoms, the dose of study medication was increased every 3 days until the maximum doses were reached. If maximum doses showed no effect for 3 days, the patient was tapered off and switched to an open-label escape therapy with an established antimanic drug. At the end of the 3-week treatment period, patients who responded to treatment had the option of entering the recurrence prevention study (Study BIA-2093-205).

Study BIA-2093-204 (EudraCT no. 2005-002133-13) followed a multicentre, double-blind, randomised, parallel-group, placebo-controlled, fixed multiple dose design. This study was conducted at 25 study centres in Europe, South Africa and South America. Patients were randomised in a 1:1:1:1 ratio to one of the following treatment groups: (1) ESL 1800 mg QD, (2) ESL 1200 mg QD, (3) ESL 600 mg QD, and (4) Placebo QD. The visit schedule in study BIA-2093-204 was identical to that of study BIA-2093-203. Patients who showed no improvement of symptoms by Day 10 were switched to open-label escape therapy with an established antimanic drug. Patients responding to treatment had the option of entering study BIA-2093-205. Response to treatment in both studies was defined as $\geq 50\%$ improvement in the Young Mania Rating Scale (YMRS) total score or a YMRS total score < 12.

Study BIA-2093-205 (EudraCT no. 2005-002134-35) was a recurrence prevention study designed as a continuation of studies BIA-2093-203 and BIA-2093-204, and comprised two sequential parts. Part I followed an open-label design in which all participants received treatment with ESL 900 mg QD for 2 weeks. Part II followed a double-blind, parallel-group, fixed multiple dose design in which participants were randomly assigned in a 1:1:1 ratio to one of the following treatment groups: (1) ESL 1800 mg QD, (2) ESL 900 mg QD, and (3) ESL 300 mg QD. The evaluations at the end of the 3-week treatment period in studies BIA-2093-203 and BIA-2093-204 served as admission procedure (V1) for study BIA-2093-205. Patients stable in remission continued double-blind therapy until approximately 6 months after the last patient entered Part II of study BIA-2093-205. The occurrence of a new manic/mixed/depressive episode requiring medication was considered a treatment failure, and the patient was discontinued from the study.

All the studies were conducted in accordance with local regulations, the ethical principles derived from the Helsinki Declaration and the Good Clinical Practice recommendations. The pertinent Ethics Committees and regulatory authorities approved the study protocol. The subjects provided their written informed consent prior to entering the study.

2.2. Sample size calculation design

Assuming a common standard deviation (SD) of 11 for change from baseline in YMRS total score, it was estimated that a sample size of 160 patients (60 patients in each ESL group and 40 in the placebo group in study BIA-2093-203; 40 patients per group in study BIA-2093-204) would be required to detect a difference of 6.4 points in the primary endpoint in comparison to placebo using a 2-sided t-test with a power of 80% and an alpha level of 0.05. Assuming a response rate (secondary efficacy endpoint) of 30% for the placebo group, it was also estimated that with 160 patients the test would be able to detect a difference of approximately 30% between the response rates of the ESL groups versus the placebo group (Vieta et al., 2005). Since study BIA-2093-205 was an extension of studies BIA-2093-203 and BIA-2093-204, the number of patients who would enter the study could not be predicted and no sample size was formally calculated.

2.3. Study population

Studies BIA-2093-203 and BIA-2093-204 enroled patients with ages ≥ 18 years, currently displaying an acute manic (including mixed) episode and with a documented diagnosis of bipolar I disorder according to the DSM-IV criteria (American Psychiatric Association, 2000). Eligible patients should have a YMRS total score ≥ 20, with symptoms of the current manic episode starting within two weeks prior to randomisation. Patients were excluded