Synopsis – Study 11051

Title of Study An open-label safety study of bifeprunox investigating flexible doses of 20, 30, or 40mg/day in patients with schizophrenia who have completed Studies 10206 or 10265
Investigators 5 investigators at 5 centres in 2 countries *Signatory investigator* – Dieter Naber, MD, PhD, Clinic for Psychiatry and Psychotherapy, University Hospital Eppendorf, Hamburg, Germany
Study Centres 5 centres – 2 in Italy and 3 in Poland
Publications None (as of the date of this report)
Study Period *First patient first visit* – 18 January 2006 *Last patient last visit* – 23 January 2008
Objectives • *Primary objective*: – to provide access to bifeprunox for patients with schizophrenia who have completed Studies 10206 or 10265, and require continued treatment with bifeprunox, other treatments not being feasible as judged by the investigator • *Secondary objective*: – to investigate the long-term safety and tolerability of bifeprunox in patients with schizophrenia
Methodology • This was a multi-national, multi-centre, open-label, flexible-dose extension study to Studies 10206 and 10265. • In this study (as in Studies 10206 and 10265), all the patients received flexible doses of bifeprunox, 20, 30, or 40 mg/day based on response and tolerability, as judged by the investigator. • Patients who continued directly to Study 11051 without interruption of bifeprunox treatment could continue at the same dose they had received in Study 10206 or 10265. Patients who did not continue directly from Study 10206 or 10265 started a 7-day up-titration to bifeprunox 20 mg/day. For patients who had been treated with an antipsychotic other than bifeprunox after they had completed Study 10206 or 10265, a washout period of at least 2 days was required before they began the 7-day up-titration period. • Efficacy and safety data were collected at Weeks 0 (baseline), 1, 4, and 9, and at 8-week intervals thereafter throughout the study. • A Safety Follow-up Visit was scheduled for 1 week after completion of the study or after withdrawal from the study. • Patients could stay in the study until the launch of bifeprunox or the discontinuation of the bifeprunox development programme. However, the study was terminated prematurely. Due to the small number of patients enrolled, the results of this study should be interpreted with caution.

Number of Patients Planned and Analysed

- The 244 patients who completed Study 10206 or 10265 were eligible for enrolment provided they met the selection criteria for this study.
- 11 patients were enrolled and treated (Table 1)
- 11 patients withdrew:
  - 1 due to an SAE
  - 2 due to withdrawal of consent
  - 8 due to *other reasons* (7 of these due to suspension of the study by sponsor; Listing 2)
- 11 patients were included in the analyses

Diagnosis and Main Inclusion Criteria

In- or outpatients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria, who had completed either of the two studies below and were in need of continued bifeprunox treatment:

- Study 10206 – extension study to Study 10207 in patients with acute schizophrenia
- Study 10265 – extension study to Study 10214 in patients with chronic schizophrenia but also including new patients with chronic schizophrenia who had not previously participated in a bifeprunox study

Investigational Medicinal Product, Doses and Mode of Administration, Batch Numbers

Bifeprunox – 20, 30, or 40 mg/day (initial up-titration over 7 days to 20 mg/day for patients who had not received bifeprunox for more than 2 days after completion of Studies 10206 or 10265); 0.25, 0.5, 1, 2, 5, 10, and 20 mg tablets, orally; batch Nos. 67205, 69726 (0.25 mg); 67207, 69755 (0.5 mg); 67210, 69756 (1 mg); 67318, 69758 (2 mg); 67324, 69759 (5 mg); 67219, 67987, 69760 (10 mg), 67224, 67999, 69761 (20 mg)

Duration of Treatment

Patients could stay in the study until the launch of bifeprunox or the discontinuation of the bifeprunox development programme; the study was terminated before either.

Efficacy Assessments

Clinical Global Impression – Severity of Illness (CGI-S) scale score

Safety Assessments

Adverse events (AEs), extrapyramidal symptoms (Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BARS], and Abnormal Involuntary Movement Scale [AIMS] scores), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical and neurological examinations

Statistical Methodology

- The analysis set used was the *all-patients-treated set* (APTS), which comprised all patients who took at least one dose of bifeprunox.
- Only descriptive statistics were used in this study.
- For age, weight, and body mass index (BMI), the baseline values were those at the Baseline Visit of Study 11051. Other demographic data were obtained from Study 10207 or 10214, or from Study 10265 for patients who had not participated in Study 10214.
- All adverse events were listed and adverse events that occurred after the first dose of IMP in this study and within 1 week after the last dose of IMP in this study were tabulated by system organ class and preferred term.
- For body weight and BMI, absolute values and changes from baseline were tabulated by visit using observed cases (OC).
- Exposure was summarised by duration (days), summary statistics (mean, standard deviation, median, minimum, and maximum), and total exposure (years).
- All other variables were listed by patient.

Demography of Study Population

- Of the 11 patients, 4 were women, all were Caucasian, and their mean age was 46 years (range: 24 to 60 years; Table 2).
- The mean body weight and BMI at baseline were 73.3kg and 26.0kg/m^2, respectively (Table 3).
- One patient continued directly into Study 11051, 1 patient after approximately 2 months, 1 patient after approximately 5 months, and the remainder of the patients continued into Study 11051 after more than 1 year.
- Two patients took their first dose of IMP at baseline, 7 patients approximately 1 week after baseline, 1 patient 2 weeks after baseline, and 1 patient approximately 1 month after baseline.
- The median exposure to bifeprunox was 173 days (range: 14 to 531 days; Table 4).
- At the last visit, the daily bifeprunox dose was 20mg for 7 patients, 30mg for 2 patients, and 40mg for 2 patients (Listing 5).

Efficacy Results

The limited number of patients enrolled resulted in insufficient data for any meaningful analyses of efficacy (Listing 6).

Safety Results

- The adverse event incidence is summarised below and in Table 5:

	Bifeprunox 20, 30, or 40mg n
Patients treated	11
Patients who died	0
Patients with serious AEs (SAEs)	1
Patients with AEs	10
Total number of AEs	28
Total number of SAEs	1

- The adverse events that occurred in ≥2 patients were (Table 6):

Preferred Term (MedDRA Version 11.1)	Bifeprunox 20, 30, or 40mg n
Patients treated	11
Patients with AEs	10
Weight decreased	3
Blood creatine phosphokinase (CPK) increased	2
Insomnia	2
Nausea	2

- 1 patient – a [redacted] man – had a serious adverse event (Listing 8). On the first day of bifeprunox treatment, the patient received bifeprunox 20mg without being up-titrated. He had a syncope and was hospitalised [redacted]. The syncope was diagnosed as vaso-vagal. The event lasted for 1 day and the patient was discharged after 3 days. The bifeprunox treatment (20mg/day) was discontinued after 14 days and the patient recovered completely. The investigator considered the syncope possibly related to bifeprunox. The patient had completed 41 weeks of treatment with bifeprunox 30mg/day in Study 10206 in which he had had no adverse events. For more detailed information, see the narrative on page 101.
- The patient who had syncope as an SAE was the only patient who withdrew due to an adverse event (Listing 9). The adverse event was hypotension associated with the syncope.
- The mean change in body weight from baseline was -3.3kg after approximately half a year (n = 7; Table 9). During the study, 1 patient had a ≥7% increase and 4 patients had a ≥7% decrease in body weight relative to baseline (Listing 15); none of these patients had extreme BMIs at their last visit (BMI range: 20 to 24kg/m^2). For 3 of the patients, *weight decreased* was reported as an adverse event – all of which were mild (Listing 7).

Safety Results – continued

- Three patients had potentially clinically significant (PCS) laboratory values (Listing 12):
  - a 35-year-old man had a PCS high alanine transaminase (ALT) value (173 IU/L) on Day 63. At the following visits, the ALT values remained high although they were not PCS.
  - a 50-year-old man had a PCS high triglycerides value (5.1 mmol/L) on Day 118.
  - a 46-year-old woman had PCS low haemoglobin and haematocrit values (95 g/L and 0.30, respectively) on Day 11. The haemoglobin and haematocrit values had also been PCS low at baseline (92 g/L and 0.29, respectively). At the following visit (Day 31), the haemoglobin and haematocrit values had increased and from the following visit (Day 66) onwards, they were within reference ranges. The patient had a history of anaemia (Listing 3).
- Two patients had PCS vital signs:
  - a 24-year-old man (the patient who had syncope as a serious adverse event) had a PCS low supine pulse value (50 bpm) at the Termination Visit (Day 63; Listing 14).
  - a 46-year-old woman had PCS low orthostatic systolic blood pressure (-33 mmHg) on Day 66. The patient remained in the study and the orthostatic systolic blood pressure was -5 mmHg at the Termination Visit (Day 213; Listing 15).
- 5 of the 11 patients had post-baseline assessments of SAS (Listing 19), BARS (Listing 20), and AIMS (Listing 21) scores. For these patients, the scores indicated that they did not have extrapyramidal symptoms during the study.

Conclusions

This study, with a very limited number of patients and time of exposure, included treatment emergent AEs that were consistent with the known safety profile of bifeprunox. Due to the limited number of patients enrolled in the study, the results should be interpreted with caution.

Date of the Report

14 August 2009

This study was conducted in compliance with the principles of *Good Clinical Practice*.