# Synopsis – Study 10206

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| **Title of Study**<br>A 40-week open, flexible-dose, extension study of bifeprunox in patients with schizophrenia |
| **Investigators**<br>57 investigators in 11 countries<br>*Signatory investigator* – Dieter Naber, Professor, MD, Universitätsklinik Eppendorf, Hamburg, Germany |
| **Study Centres**<br>56 centres – 3 in Austria, 6 in the Czech Republic, 7 in Germany, 12 in France, 6 in Hungary, 2 in India, 4 in Israel, 3 in Italy, 1 in Norway, 6 in Poland, 6 in Russia |
| **Publications**<br>None (as of the date of this report) |
| **Study Period**<br>*First patient first visit* – 9 June 2004<br>*Last patient last visit* – 30 May 2006 |
| **Objectives**<br>• *Primary objective*:<br>– to evaluate the long-term safety and tolerability of flexible doses of bifeprunox over a period of 40 weeks in patients with schizophrenia, having completed Study 10207<br>• *Secondary objective*:<br>– to evaluate the maintenance of therapeutic effect of flexible doses of bifeprunox over a period of 40 weeks in patients with schizophrenia, having completed Study 10207 |
| **Methodology**<br>• Multinational, multi-centre, open-label, flexible-dose, 40-week extension study in patients with schizophrenia who had completed 12 weeks of double-blind treatment with a daily dose of 30 mg bifeprunox, 40 mg bifeprunox, or 15 mg olanzapine in lead-in Study 10207.<br>• The first week of treatment was double-blind. During that week, patients who had received olanzapine in the lead-in study (BX(OLZ)) were abruptly switched to bifeprunox and up-titrated to 30 mg/day in 8 days. Patients who had received 30 mg/day bifeprunox in the lead-in study (BX(BX)) continued their treatment. Patients who had received 40 mg/day bifeprunox in the lead-in study ((BX(BX)) were switched to 30 mg/day bifeprunox.<br>• After the first week, the dose was flexible (20, 30, or 40 mg/day bifeprunox) on the basis of response and tolerability, as judged by the investigator.<br>• Patients were evaluated after 1 week of double-blind treatment and at 4 weeks intervals during the open-label, flexible-dose treatment period.<br>• A safety follow-up visit was scheduled for 1 week after completion of the study (Week 40) or after withdrawal from the study. |

**Number of Patients Planned and Analysed**

- 200 patients were expected to be enrolled; 223 patients completed the lead-in study and were eligible for enrolment. A total of 166 patients were included and 165 patients were analysed.
- Patient disposition is tabulated below:

| | BX(OLZ) | | BX(BX) | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Patients included | 84 | | 82 | | 166 | |
| **Patients treated (all-patients-treated set (APTS)):** | 83 | | 82 | | 165 | |
| Patients completed | 17 | 20 | 39 | 48 | 56 | 34 |
| Patients withdrawn | 66 | 80 | 43 | 52 | 109 | 66 |
| **Primary reason for withdrawal[1]:** | | | | | | |
| Adverse event(s) | 38 | 46 | 29 | 35 | 67 | 41 |
| Lack of efficacy | 9 | 11 | 4 | 5 | 13 | 8 |
| **Analysis sets:** | | | | | | |
| APTS | 83 | | 82 | | 165 | |
| Full-analysis set (FAS) | 73 | | 80 | | 153 | |

BX(OLZ): patients who had received olanzapine in the lead-in study; BX(BX): patients who had received bifeprunox in the lead-in study; n = number of patients; % = percentage of patients within treatment group

1 If adverse event(s) contributed to withdrawal, they were considered the primary reason.

**Diagnosis and Main Inclusion Criteria**

In- and outpatients, aged 18 to 75 years (extremes included) at inclusion into lead-in Study 10207, with a primary diagnosis of schizophrenia according to DSM-IV-TR criteria, who had completed 12 weeks of double-blind treatment with 30 mg/day bifeprunox, 40 mg/day bifeprunox, or 15 mg/day olanzapine in lead-in Study 10207.

**Investigational Product, Dose and Mode of Administration, Batch Number**

*Bifeprunox* – flexible doses of 20, 30, or 40 mg/day (initial up-titration over 8 days to 30 mg for patients treated with olanzapine in the lead-in study); 0.25, 0.5, 1, 2, 5, 10, and 20 mg tablets, orally; batch Nos. E02499-011E, -451E (0.25 mg); E02499-012E, -452E (0.5 mg); E02499-013E, -453E (1 mg); E02499-014E, -454E (2 mg); E02499-015E, -455E (5 mg); E02499-016E, -412E, 64973, 65504, 67987 (10 mg); E02499-021E, -022E, -414E, 64975, 65072, 66561, 66562, 66563, 66568, 68000 (20 mg); placebo (for blinding during the first week of the extension study) – capsule batch Nos. E02499-027E, -458E

**Duration of Treatment**

- For patients who had received bifeprunox in lead-in Study 10207: 40 weeks of open-label treatment with bifeprunox (20 to 40 mg/day) after the 12 weeks of double-blind treatment with 30 or 40 mg/day bifeprunox in the lead-in study
- For patients who had received olanzapine in lead-in Study 10207: 40 weeks of open-label treatment with bifeprunox (20 to 40 mg/day)

**Reference Therapy**

None

**Criteria for Evaluation – Efficacy**

Positive and Negative Syndrome Scale (PANSS) total and positive and negative subscale scores, Clinical Global Impression – Severity of Illness (CGI-S) score, Calgary Depression Scale for Schizophrenia (CDSS) total score

**Criteria for Evaluation – Safety**

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

**Statistical Methods**

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who completed the lead-in study and who took at least one dose of IMP in the extension study
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of efficacy in the extension study
- The efficacy variables are presented for the FAS. All safety analyses were conducted on the APTS.
- The following groups were defined:
  - BX(BX) – those who had received bifeprunox in the lead-in study; the patients were exposed to bifeprunox for a minimum of 12 weeks (the duration of the lead-in study) and up to 1 year (12 weeks plus the 40 weeks in the extension study)
  - BX(OLZ) – those who had received olanzapine in the lead-in study; the patients were exposed to bifeprunox for up to 40 weeks (the duration of the extension study)
  - BX-Total – all patients who took at least one dose of IMP in the extension study (equals the APTS)
- Unless otherwise stated, baseline was defined as the time of first exposure to bifeprunox: for the patients who had received bifeprunox (30 or 40 mg/day) in the lead-in study (BX(BX)), baseline was equal to the lead-in study baseline; for the patients who had received olanzapine in the lead-in study (BX(OLZ)), baseline was equal to baseline in extension Study 10206.
- Due to the open-label design of the study, all efficacy measures are considered exploratory and are presented using descriptive statistics.
- The incidences of all adverse events were tabulated by primary system organ class (SOC) and preferred term by previous treatment group and overall. In addition, all adverse events were tabulated by preferred term and intensity categories by previous treatment group and overall. All adverse events that were considered *related* to IMP by the investigators were tabulated by preferred term and intensity categories by previous treatment group.
- The prevalence and incidence of adverse events by preferred term were also tabulated in 3-month intervals (first 3 months (Days 1 to 90); Months 4 to 6 (Days 91 to 180); Months 7 to 9 (Days 181 to 270); Months 10 to 12 (After Day 270)) from first exposure to bifeprunox for all patients (BX-Total). In each 3-month interval, the prevalence was calculated as the number of patients with an adverse event ongoing in that period.
- For the patients who had received bifeprunox in the lead-in study (BX(BX)) and for the patients who had received olanzapine in the lead-in study (BX(OLZ)), the incidences of adverse events during the first week (Titration Week) were tabulated by preferred term.
- The incidences of withdrawals due to adverse events were tabulated in 1-month (first, second, and third month) and 3-month (Months 4 to 6, Months 7 to 9, and Months 10 to 12) intervals for all patients (BX-Total). For the patients who had received olanzapine in the lead-in study (BX(OLZ)), the incidences of withdrawals due to adverse events during the first week (Titration Week) were tabulated by preferred term.
- The changes from baseline to each assessment in EPS, based on the SAS, BAS, and AIMS, were summarised for each group using descriptive techniques.
- Absolute values and changes from baseline to the last assessment in clinical safety laboratory tests, vital signs, weight, and ECG parameters were summarised using descriptive techniques. Values that were potentially clinically significant (PCS) were flagged and tabulated, as were clinical safety laboratory values that were outside the reference range.
- Observations from the physical and neurological examinations performed at screening (for the patients who had received bifeprunox in the lead-in study) and at baseline of the extension study (for the patients who had received olanzapine in the lead-in study) and at the Termination Visit were summarised.

**Demography of Study Population**

- Approximately two-thirds (64%) of the patients were men and the mean age was 37 years, ranging from 18 to 65 years. The majority (90%) of the patients were Caucasian; the remaining (10%) patients were Asian (BX-Total).
- The patients who had received bifeprunox in the lead-in study had a mean PANSS total score of 97 at baseline (start of bifeprunox treatment) and a CGI-S score of 4.8, indicative of markedly ill patients with moderately severe psychopathology and had schizophrenia in an acute phase at entry into the lead-in study. The patients who had received olanzapine in the lead-in study, had a mean PANSS total score of 61 at baseline (start of bifeprunox treatment) and a CGI-S score of 2.9, indicative of mildly ill patients with moderate psychopathology; they had received olanzapine for 12 weeks before starting bifeprunox treatment and were therefore considered to be stabilised; thus, the two groups of patients are not comparable.

**Efficacy Results**

- The mean PANSS total scores at baseline (start of bifeprunox treatment) and Week 40/52 are summarised below:

| | n | BX(OLZ) | n | BX(BX) |
|---|---|---|---|---|
| **PANSS total score (FAS, OC)** | | | | |
| Mean at baseline (start of bifeprunox treatment) | 73 | 61 | 80 | 97 |
| Mean at Week 40/52[1] | 17 | 53 | 39 | 52 |

BX(OLZ): patients who had received olanzapine in the lead-in study; BX(BX): patients who had received bifeprunox in the lead-in study

1 The patients who had received olanzapine in the lead-in study, received bifeprunox for 40 weeks; the patients who had received bifeprunox in the lead-in study, received bifeprunox for a total of 52 weeks.

- For the patients who continued to take bifeprunox (FAS, OC), the efficacy variable scores obtained during short-term treatment were maintained or further improved during long-term treatment. For the LOCF, the mean PANSS total score decreased from baseline to Week 12 (end of the lead-in study) after which the mean PANSS total score increased to Week 52 (only subsequent PANSS assessment).
- For the patients who had received olanzapine in the lead-in study, the efficacy variable scores were maintained or further improved during 40 weeks of treatment with bifeprunox (FAS, OC). For the LOCF, the mean PANSS total score increased from baseline (start of the extension study) to Week 40 (only subsequent PANSS assessment).
- The mean CDSS total scores remained low (FAS, OC).

**Safety Results**

- The adverse event incidence is summarised below:

| | BX(OLZ) | | BX(BX) | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Patients who died | 0 | | 1 | | 1 | |
| Patients with serious AEs (SAEs) | 23 | 28 | 27 | 33 | 50 | 30 |
| Patients with AEs | 62 | 75 | 78 | 95 | 140 | 85 |
| Total number of AEs | 237 | | 469 | | 706 | |
| Total number of SAEs | 33 | | 39 | | 72 | |

BX(OLZ): patients who had received olanzapine in the lead-in study; BX(BX): patients who had received bifeprunox in the lead-in study; n = number of patients; % = percentage of patients within treatment group

- The total accrued exposure to bifeprunox from baseline was 82 patient-years; for the patients who had received bifeprunox in the lead-in study, the total accrued exposure to bifeprunox was 59 patient-years and for those who had received olanzapine in the lead-in study, the total accrued exposure to bifeprunox was 24 patient-years. During the extension study, the total accrued exposure to bifeprunox was 63 patient-years.
- Only patients who had completed the 12-week lead-in study were eligible for enrolment in the extension study. Consequently, all patients who had received bifeprunox in the lead-in study were exposed for more than 84 days, the *mean* number of days exposed was more than twice as large for the patients who had received bifeprunox in the lead-in study (264 days) than for the patients who had received olanzapine in the lead-in study (106 days), and the *median* number of days exposed was more than four times as large (332 *versus* 74 days), further demonstrating that the two groups are not comparable.
- At each scheduled visit after the first week of the extension study, approximately one-third of the patients received 40mg/day bifeprunox and between 12% and 29% of the patients received 20 mg/day bifeprunox.
- One patient died during the study: the patient, a [redacted] man, had received bifeprunox for approximately 11 months when he was found dead (*fall*) at the bottom of a rocky gully; a suicide could not be ruled out.
- A total of 85% of the patients had at least one adverse event during treatment with bifeprunox; 31% of the patients had SAEs and 41% of the patients had adverse events that led to withdrawal from the extension study.
- A total of 95% of the patients who had received bifeprunox in the lead-in study had at least one adverse event after start of bifeprunox treatment; 34% of the patients had SAEs and 35% of the patients had adverse events that led to withdrawal from the extension study. During the extension study, 80% of the patients who had received bifeprunox in the lead-in study had at least one adverse event and 32% had SAEs.
- A total of 75% of the patients who had received olanzapine in the lead-in study had at least one adverse event after start of bifeprunox treatment; 28% of the patients had SAEs and 46% of the patients had adverse events that led to withdrawal from the extension study.
- Nausea, insomnia, and anxiety were the three adverse events with the highest incidences after start of bifeprunox treatment for the patients who had received bifeprunox in the lead-in study (39%, 35%, and 34%, respectively) and for all patients during treatment with bifeprunox (30%, 28%, and 27%, respectively). During the extension study, anxiety, schizophrenia, insomnia, and weight decreased were the most common adverse events for the patients who had received bifeprunox in the lead-in study (29%, 23%, 20%, and 20%, respectively). For the patients who had received olanzapine in the lead-in study, the three adverse events with the highest incidences during the extension study were nausea, schizophrenia, and insomnia (22%, 22%, and 20%, respectively).
- The incidences of nausea and vomiting in the titration week for the patients who had received bifeprunox in the lead-in study (32% and 17%, respectively) were only slightly lower than the incidences of these adverse events in the whole study period (39% and 22%, respectively). The incidences of nausea, vomiting, and dizziness in the titration week for the patients who had received olanzapine in the lead-in study (22%, 18%, and 7%, respectively) were similar to the incidences of these adverse events in the whole study period (22%, 19%, and 7%, respectively).
- The incidences of the adverse events with an incidence ≥5% during the first 3 months after start of bifeprunox treatment (nausea, insomnia, vomiting, anxiety, weight decreased, schizophrenia, headache, tremor, agitation, and dizziness) decreased after the first 3 months of treatment. The adverse events with an incidence ≥5% after the first 6 months were anxiety (10%) and schizophrenia (8%).

**Safety Results – Continued**

- The prevalences of the majority of the adverse events with an prevalence ≥5% in the first 3 months after start of bifeprunox treatment (nausea, insomnia, vomiting, weight decreased, headache, tremor, agitation, and dizziness) decreased after the first 3 months of treatment. The prevalences of anxiety and schizophrenia fluctuated during the treatment period (between 16% and 22% for anxiety and between 7% and 14% for schizophrenia), while the prevalence of weight increased increased during the treatment period.
- After the first 3 months of bifeprunox treatment, none of the patients had dizziness.
- There were few adverse events that occurred for the first time in the 3-month intervals Months 4 to 6, Months 7 to 9, and Months 10 to 12 (18, 4, and 1 new event, respectively) and all occurred in 1 patient each.
- A total of 51 patients, including the patient who died, had 73 SAEs; 28 patients who had received bifeprunox in the lead-in study had 40 SAEs and 23 patients who had received olanzapine in the lead-in study had 33 SAEs. In addition, 1 patient had an SAE (schizophrenia) that started in the lead-in study after approximately 12 weeks of olanzapine treatment; the patient continued in the extension study, but withdrew due to schizophrenia 2 weeks later. A total of 34 patients had worsening of schizophrenia or psychotic disorder, 26 of whom withdrew from the extension study due to the event. There was no pattern in terms of the types of SAEs that were not psychiatric disorders.
- Schizophrenia was the only SAE that had an incidence ≥5% in any of the 3-month intervals and it was the only SAE that had a prevalence ≥5% in any of the 3-month intervals.
- A total of 66 patients withdrew from the extension study due to adverse events, 29 patients who had received bifeprunox in the lead-in study and 37 patients who had received olanzapine in the lead-in study. The most common adverse event leading to withdrawal was schizophrenia for the patients who had received bifeprunox in the lead-in study, for the patients who had received olanzapine in the lead-in study, and overall after start of bifeprunox treatment. The only other adverse events leading to withdrawal in ≥5% of the patients were vomiting (10%; in the patients who had received olanzapine in the lead-in study), anxiety (6%; in the patients who had received bifeprunox in the lead-in study), and nausea (6%; in the patients who had received olanzapine in the lead-in study).
- The adverse events leading to withdrawal from the extension study with the highest incidences were: vomiting (4%) and nausea (3%) during the first month after start of bifeprunox treatment (only patients who had received olanzapine in the lead-in study); schizophrenia (4%) during the second month after start of bifeprunox treatment (only patients who had received olanzapine in the lead-in study); schizophrenia (4%) and anxiety (2%) during the third month after start of bifeprunox treatment; schizophrenia (8%), anxiety (4%), and psychotic disorder (4%) during Months 4 to 6; and schizophrenia (4%) during Months 7 to 9. During Months 10 to 12, the 3 adverse events leading to withdrawal did so in 1 patient each.
- During the first week of bifeprunox treatment during which bifeprunox was up-titrated (Titration Week), the three adverse events with the highest incidences were nausea (32%), vomiting (17%), and insomnia (11%) for the patients who had received bifeprunox in the lead-in study and nausea (22%), vomiting (18%), and dizziness (7%) for the patients who had received olanzapine in the lead-in study. For the patients who had received olanzapine in the lead-in study, vomiting (7%), nausea (6%), and dizziness (2%) started during the Titration Week in ≥2 patients and led to withdrawal from the extension study. Of the 14 patients who had adverse events that started during the Titration Week and led to withdrawal, 6 patients withdrew from the extension study during the Titration Week, 3 of them due to vomiting and 1 each due to nausea, hypovolemia, and medication error with chest pain, feeling abnormal, and orthostatic hypotension.
- Four patients attempted suicide and 1 patient had suicidal ideation during bifeprunox treatment. For the patient who died, suicide could not be ruled out. Three patients had syncope during bifeprunox treatment.
- Twenty patients who had received bifeprunox in the lead-in study had EPS-related adverse events during treatment with bifeprunox, 9 of whom had EPS-related adverse events during the extension study. Eleven patients who had received olanzapine in the lead-in study had EPS-related adverse events after start of bifeprunox treatment; the most common EPS-related adverse event was tremor. There were minor fluctuations in the mean SAS, BAS, and AIMS total scores during treatment with bifeprunox, but the mean changes were not considered clinically relevant (OC and LOCF).

**Safety Results – Continued**

- There were minor fluctuations in the mean clinical safety laboratory values. The mean changes were small and not considered to be of clinical relevance. The values for the lipid profile parameters cholesterol, LDL, VLDL, and triglycerides decreased slightly during bifeprunox treatment, while those for HDL increased slightly, both for the patients who had received bifeprunox in the lead-in study and for those who had received olanzapine in the lead-in study.
- For the patients who had received bifeprunox in the lead-in study, the mean weight remained stable throughout the extension study. For the patients who had received olanzapine in the lead-in study, the mean weight decreased initially upon starting bifeprunox treatment, then increased from Week 12 to Week 24, after which it remained stable for the remainder of the extension study.
- The mean changes in weight from baseline (start of bifeprunox treatment) to last assessment were -2.5 kg for the patients who had received bifeprunox in the lead-in study and -2.8 kg for those who had received olanzapine in the lead-in study.
- There were no clinically relevant changes in vital signs, ECG parameters, or physical and neurological examinations.

**Conclusions**

- This 40-week extension study showed that bifeprunox in flexible doses was safe in the long-term treatment of schizophrenia.
- For the patients who continued to take bifeprunox, the therapeutic effect of bifeprunox was maintained during long-term treatment of schizophrenia.

**Date of the Report**

22 November 2006

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