Synopsis – Study 11915A

Title of Study A one-year multi-national, multi-centre, randomised, double-blind, parallel-group, fixed-dose bifeprunox study combining a 12-week placebo-controlled, quetiapine-referenced phase with a 12-month quetiapine-controlled phase in patients with schizophrenia
Investigators 34 investigators at 34 centres in 7 countries *Signatory investigator* – Michel Bourin, MD, PharmD, PhD, Neurobiology of Anxiety and Depression, University of Nantes, France
Study Centres 34 centres – 2 in Bulgaria, 2 in China, 9 in Romania, 12 in Russian Federation, 4 in Thailand, 2 in Taiwan, and 3 in Ukraine
Publications None (as of the date of this report)
Study Period *First patient first visit* – 21 March 2008 *Last patient last visit* – 18 August 2009 *Study terminated* – 14 June 2009
Objectives • *Primary objective:* – to show superior efficacy of fixed doses of bifeprunox (20 mg/day) *versus* placebo following 12 weeks of treatment in patients with schizophrenia inadequately controlled in the maintenance phase • *Secondary objectives:* – Key secondary objective: • to show non-inferior efficacy of fixed doses of bifeprunox (20 mg/day) *versus* fixed doses of quetiapine (600 mg/day) following 12 months of treatment in patients with schizophrenia inadequately controlled in the maintenance phase – Other secondary objectives: • to compare the safety and tolerability of 12 weeks of treatment with fixed doses of bifeprunox (20 mg/day) to that of placebo and quetiapine (600 mg/day) • to compare the safety and tolerability of 12 months of treatment with fixed doses of bifeprunox (20 mg/day) to that of quetiapine (600 mg/day) • to determine and compare the effect on functional outcomes, quality of life, and treatment compliance of 12 weeks of treatment with fixed doses of bifeprunox (20 mg/day) to that of placebo and quetiapine (600 mg/day) • to determine and compare the effect on functional outcomes, quality of life, and treatment compliance of 12 months of treatment with fixed doses of bifeprunox (20 mg/day) to that of quetiapine (600 mg/day) • to investigate any correlations between genotype and treatment response to bifeprunox • to explore biological parameters (messenger ribonucleic acid [mRNA], endogenous metabolites, and proteins) that may be associated with schizophrenia, the effect of treatment, or the treatment response

Methodology

- This was a one-year, multi-national, multi-centre, randomised, double-blind, parallel-group, fixed-dose study in patients with a primary diagnosis of schizophrenia. The study consisted of a 4-week lead-in period, a 12-week placebo-controlled, quetiapine-referenced period, followed by a 9-month quetiapine-controlled period.
- During the lead-in period, the patients' current antipsychotic medication was kept constant. After the lead-in period, the patients were randomised (1:1:1) to receive one of three treatments: bifeprunox 20 mg/day (BX), quetiapine 600 mg/day (QUE) or placebo (PBO-BX), and entered a cross-titration double-blind treatment period. Current antipsychotic medication was down-tapered over the first 21 days while bifeprunox and quetiapine were up-titrated until the target dose was reached on Day 22. Patients in the active treatment groups who completed the 12-week placebo-controlled period continued with the same treatment for an additional 9 months while patients in the placebo group were switched to bifeprunox and up-titrated to 20 mg/day in 28 days. A safety follow-up visit was scheduled for 7 days after completion of the study or after withdrawal from the study, and 30 days after intake of last dose of the investigational medicinal product (IMP).
- Efficacy data were collected at weekly intervals for the first 4 weeks and at 2-week intervals for the next 12 weeks, and thereafter at 4-week intervals. Safety data were collected throughout the study.
- This study was terminated following a statistical interim analysis of pooled data (Studies 11915A and 11916A) that was conducted to investigate whether patients were benefitting adequately from treatment with bifeprunox to justify continuation of the study. The interim analysis results did not support a continuation of the study as it was improbable that bifeprunox could be shown to be non-inferior to quetiapine at the end of the study.

Number of Patients Planned and Analysed

- 450 patients were planned for enrolment: 150 in the BX group, 150 in the QUE group, and 150 in the PBO-BX group.
- Patient disposition is tabulated below:

	BX		QUE		PBO-BX		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	82		76		68		226	
Patients treated (all-patients-treated set [APTS]):	80		76		68		224	
Patients completed	0	(0)	1	(1)	0	(0)	1	(0)
Patients withdrawn	80	(100)	75	(99)	68	(100)	223	(100)
Primary reason for withdrawal:								
Adverse events	16	(20)	11	(14)	15	(22)	42	(19)
Lack of efficacy	4	(5)	6	(8)	9	(13)	19	(9)
Early termination	47	(59)	48	(63)	37	(54)	132	(59)
Other	13	(16)	10	(13)	7	(10)	30	(13)
Analysis sets:								
APTS	80		76		68		224	
Full-analysis set (FAS)	79		76		68		223	

Cross-reference: Tables 1 and 4
Withdrawals from the study by all reasons are summarised in Table 5.

- Patients mainly withdrew due to termination of the study. Withdrawal due to adverse events was lowest in the QUE group (14%) and comparable in the BX and PBO-BX groups (20% and 22%, respectively).
- Only one patient (QUE group) completed the 12-month study. The mean exposure to IMP was 124 days in the BX group, 160 days in the QUE group, and 125 days in the PBO-BX group (Table 17). The total IMP exposure was 26 patient-years in the BX group, 32 patient-years in the QUE group, and 23 patient-years in the PBO-BX group. The proportion of patients who completed 12 weeks of treatment was comparable in the BX and PBO-BX groups (55% and 56%, respectively) and highest (67%) in the QUE group (Table 3).

Diagnosis and Main Inclusion Criteria

Inpatients, partially hospitalised patients, or outpatients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria, who:

- were ≥18 and ≤65 years of age
- had a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 (*moderately ill*) at screening and at baseline
- had a Positive and Negative Syndrome Scale (PANSS) total score ≥60 at screening and at baseline
- had a score of ≤4 on the following PANSS items at screening and at baseline: P2 (*conceptual disorganisation*), P7 (*hostility*) and G8 (*uncooperativeness*)
- were in the maintenance phase and did not have an acute exacerbation within 8 weeks prior to screening or 4 weeks prior to baseline
- did not have their antipsychotic medications changed within 8 weeks prior to screening (agent) or between screening and baseline (agent and dose)

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

Bifeprunox – 20 mg/day (patients randomised to bifeprunox at baseline were up-titrated over 21 days during the 12-week double-blind, placebo-controlled treatment period; patients randomised to placebo at baseline were up-titrated over 28 days after completion of the 12-week double-blind, placebo-controlled treatment period); encapsulated tablets, orally; batch Nos. 0.125 mg (E05249-001E, E05211-023E, E05211-070E), 0.25 mg (E05249-002E, E05211-024E, E05211-071E), 0.5 mg (E05249-003E, E05211-025E, E05211-072E), 1 mg (E05249-004E, E05211-026E, E05211-073E), 2 mg (E05249-005E, E05211-027E, E05211-074E), 5 mg (E05249-006E, E05211-028E, E05211-075E), 10 mg (E05249-007E, E05211-029E, E05211-076E), 20 mg (E05249-008E, E05249-041E, E05211-030E, E05211-077E, E05211-145E)

Duration of Treatment

12 months: a 12-week placebo-controlled, quetiapine-referenced treatment period (including a 3-week cross-titration period) and a 9-month quetiapine-controlled treatment period

Reference Therapies, Doses and Mode of Administration, Batch Numbers

Quetiapine (Seroquel®) – 600 mg/day (up-titrated over 21 days); encapsulated tablets, orally; batch Nos. 25 mg (E05249-010E, E05211-032E, E05211-078E), 50 mg (05249-011E, E05211-033E, E05211-079E), 75 mg (E05249-012E, E05211-034E, E05211-080E), 100 mg (E05249-013E, E05211-035E, E05211-081E), 150 mg (E05249-014E, E05211-036E, E05211-082E), 200 mg (E05249-015E, E05211-037E, E05211-083E), 250 mg (E05249-016E, E05211-038E, E05211-084E), 300 mg (E05249-017E, E05249-042E, E05211-039E, E05211-085E)

Placebo – encapsulated tablets, orally; batch Nos. E05249-009E, E05211-031E, and E05211-063E

Efficacy Assessments

- *Primary variable* – PANSS total score
- *Secondary variables* – PANSS positive symptoms score, PANSS negative symptoms score, PANSS general psychopathology score, CGI-S score, Clinical Global Impression – Global Improvement (CGI-I) score, and Calgary Depression Scale for Schizophrenia (CDSS)

Pharmacoeconomic Assessments

Schizophrenia Quality of Life (S-QoL) scale, Drug Attitude Inventory (DAI-30), Global Assessment of Functioning (GAF), Personal and Social Performance (PSP) scale, and Client Service Receipt Inventory (CSRI). CSRI will be reported separately.

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, body mass index (BMI), waist circumference, electrocardiograms (ECGs), physical and neurological examinations, abnormal movement scores obtained from the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BARS), and Simpson-Angus Scale (SAS)

Pharmacokinetic/Pharmacodynamic Assessments

Blood samples were collected for the determination of serum/plasma levels of bifeprunox (results not included in this report).

Pharmacogenetic/Biomarker Assessments

Blood samples were collected for genotyping and for exploratory biomarker assessments (results not included in this report).

Statistical Methodology

- The following analysis sets were defined:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the PANSS total score
  - *per-protocol set* (PPS) – all patients in the FAS who did not violate inclusion criterion 6 (diagnosis of schizophrenia), 7 (CGI-S score ≥4 at screening and baseline), or 8 (PANSS total score ≥60 at screening and baseline); exclusion criterion 1 (Axis I primary psychiatric diagnosis) or 5 (treated with clozapine within 60 days prior to screening); or any other protocol criteria that would interfere with a reasonable opportunity for the treatment to produce its expected response
- The efficacy analyses were performed on the FAS. Unless otherwise stated, all statistical tests on efficacy variables were two-sided at the 5% level of significance for main effects and at the 10% level of significance for interaction terms. The primary analysis was to be repeated for the PPS but was not performed due to termination of the study. All safety analyses were conducted on the APTS.
- The primary analysis was a test for superiority of bifeprunox to placebo at Week 12 based on the change from baseline in PANSS total score at Week 12, using the last observation carried forward (LOCF). The bifeprunox and placebo groups were compared using an analysis of covariance (ANCOVA), with pooled centre and treatment as factors, and the baseline PANSS total score as a covariate. The primary analysis was repeated using observed cases (OC).
- The key secondary endpoint, non-inferiority of bifeprunox *versus* quetiapine based on the change from baseline in PANSS total score after 12 months of treatment, was not performed due to termination of the study.
- Exploratory analyses of the change from baseline in S-QoL total score, PSP global score, and DAI-30 total score at Week 12 were performed on the FAS, OC data using an ANCOVA. Study, treatment group, and grouped centre were fixed factors and baseline values were covariates in the model.
- The incidences of treatment-emergent adverse events (TEAEs) were tabulated by system organ class and preferred term.
- Absolute values and changes from baseline to each assessment in clinical safety laboratory tests, vital signs, weight, BMI, waist circumference, and ECG parameters were summarised using descriptive statistics. Potentially clinically significant (PCS) values were flagged and tabulated.
- Changes from baseline in AIMS, BARS, SAS scores, and CDSS were summarised using descriptive statistics.

Demography of Study Population

- There was an approximately similar proportion of men (54%) and women (46%), and most of the patients were Caucasian (88%; Table 6). The mean age was similar in all three treatment groups (approximately 39 years), and there were no clinically relevant differences in height, weight, or BMI between the three treatment groups (Table 7). The mean baseline PANSS total score was 79 in the BX group and 80 in both the QUE and PBO-BX groups, indicating that the patients had moderately severe symptoms of schizophrenia (Table 18). Patient disposition by centre is shown in Table 2.
- In all three treatment groups, the results of the physical and neurological examinations at baseline were normal in all or the majority of the patients (Tables 13 and 14).
- The majority of the patients were outpatients (88%; Table 16). Slightly more than half of the patients in the BX and PBO-BX groups had had <5 prior episodes of schizophrenia compared with 45% in the QUE group (Table 15). However, more patients in the BX group (12%) had had >15 episodes of schizophrenia than in the QUE group (5%) or in the PBO-BX group (3%). The majority of the patients (88%) were diagnosed with paranoid schizophrenia and patients had had schizophrenia for ≤10 years (46%) or between 11 and 20 years (32%) in all treatment groups (Table 15). Medical history is listed in Listing 2.
- The proportion of patients who discontinued concomitant medication at baseline was largely similar in the three treatment groups (between 43% and 50%; Table 12). The proportion of patients who continued taking concomitant medication at baseline (between 74% and 82%), as well as the proportion of patients who started taking concomitant medication at or after baseline (approximately 95%) were also largely similar in the three treatment groups. According to the protocol, the patients were to have their concomitant antipsychotic medication down-tapered over 21 days so that the last dose was taken on Day 21. However, a number of patients either continued taking concomitant antipsychotic medication after Day 21 or started a new antipsychotic after Day 21 while receiving IMP: 8 patients (10%) in the BX group, 2 patients (3%) in the QUE group, and 3 patients (4%) in the PBO-BX group (Listing 1).
- The proportion of patients who smoked cigarettes was comparable: 43% in the BX group, 41% in the QUE group, and 38% in the PBO-BX group (Table 11). Very few patients drank alcohol: 5% in the BX group, 4% in the QUE group, and 4% in the PBO-BX group.
  - Among patients who smoked cigarettes, the mean number of cigarettes that they smoked per week at baseline and at Week 12 was – BX: 108 and 94; QUE: 105 and 111; PBO-BX: 90 and 131 (Table 9). Only one patient in the BX group smoked cigars at baseline (14 per week; Table 10). Among patients who consumed alcohol, the mean alcohol units that they consumed per week at baseline and at Week 12 was – BX: 2.5 and 0.7; QUE: 0.5 and 3.3; PBO-BX: 1.5 and 1.4 (Table 8).

Efficacy Results

- The PANSS and CGI-S results (FAS, LOCF) are summarised below:

	Treatment	Baseline	Week 12	Change at Week 12
		n	Mean±SD	Mean±SD	Mean±SD
PANSS total score	BX	79	78.9±12.4	73.4±15.3	-5.6±12.0
	QUE	76	80.4±12.9	71.3±18.1	-9.2±14.7
	PBO-BX	68	79.9±12.2	79.6±17.4	-0.3±13.9
PANSS positive symptoms score	BX	79	17.3±5.2	15.3±5.8	-2.0±5.0
	QUE	76	17.3±5.0	14.9±5.9	-2.4±5.2
	PBO-BX	68	16.8±4.7	16.8±5.5	0.01±5.1
PANSS negative symptoms score	BX	79	22.8±4.6	20.8±4.7	-2.0±3.2
	QUE	76	23.6±4.9	21.0±5.5	-2.5±4.4
	PBO-BX	68	23.8±4.3	22.9±5.1	-0.9±4.0
PANSS general psychopathology score	BX	79	38.9±6.3	37.3±7.8	-1.5±6.2
	QUE	76	39.5±7.0	35.3±9.0	-4.2±7.0
	PBO-BX	68	39.3±7.0	39.9±9.4	0.7±6.4
CGI-S score	BX	79	4.2±0.4	4.0±0.7	-0.2±0.6
	QUE	76	4.2±0.4	3.8±0.9	-0.4±0.9
	PBO-BX	68	4.3±0.4	4.2±0.8	-0.03±0.8

Cross-reference: Tables 18, 19, 21, 22, 23, 24, 25, 26, 27, and 28

- In the active treatment groups, the mean PANSS total score decreased during the 12-week treatment period but remained relatively unchanged in the PBO-BX group (Table 18 and Figure 1). The decrease in mean PANSS total score at Week 12 was statistically significantly greater in both the BX group (-5.9±1.5; 95% CI: -9.85 to -1.24; $p<0.05$) and the QUE group (-8.9±1.5; 95% CI: -12.88 to -4.32; $p<0.05$; Table 20) than in the PBO-BX group. The OC results for PANSS, CGI-S and CGI-I are summarised in Tables 34 to 47.
- Improvement in the three PANSS subscale scores was observed after 12 weeks of treatment in the active treatment groups but remained relatively unchanged in the PBO-BX group (Figures 2 to 4).
- The mean CGI-S score improved slightly after 12 weeks in the active treatment groups but remained relatively unchanged in the PBO-BX group. The proportion of patients who were *markedly* or *severely ill* at Week 12 was 18%, 14%, and 35% in the BX, QUE, and PBO-BX groups, respectively (from 20%, 24%, and 26%, respectively at baseline; [LOCF] Table 29).
- The mean CGI-I score at Week 12 was lower in the BX and QUE groups than in the PBO-BX group (LOCF: 3.7 and 3.2, respectively, *versus* 4.2; Table 30). The proportion of patients with a score of 1 (*very much improved*) or 2 (*much improved*) on the CGI-I at Week 12 was higher in the BX and QUE groups than in the PBO-BX group (LOCF: 13% and 24%, respectively, *versus* 9%; Table 31).
- The results of the CDSS score are shown in Tables 32 and 33 (LOCF) and in Tables 48 and 49 (OC). The mean CDSS total score improved in the BX and QUE groups but deteriorated slightly in the PBO-BX group after 12 weeks of treatment.

Pharmacoeconomic Results

- The S-QoL total score, DAI-30 score, GAF total score, and PSP global score (FAS, OC) are summarised below:

		BX		QUE		PBO-BX	
Variable	Visit	n	Mean±SD	n	Mean±SD	n	Mean±SD
S-QoL total score	Baseline	79	49±18	76	47±20	68	43±18
	Week 12	48	57±16	52	50±19	42	48±17
DAI-30 score	Baseline	79	1±8	76	2±6	68	2±6
	Week 12	48	-0.5±6	52	1±7	42	2±6
GAF total score	Baseline	79	55±10	76	55±10	68	55±11
	Week 12	48	59±13	52	63±9	42	56±14
PSP global score	Baseline	79	52±17	76	54±15	68	52±16
	Week 12	48	59±16	52	62±14	42	53±16

Cross-reference: Tables 50, 60, 62, and 63

- Only the mean change in PSP global score from baseline to Week 12 was statistically significantly higher for both the BX group (6.7±2.3; 95% CI: 2.14 to 11.31; $p<0.05$) and the QUE group (6.7±2.2; 95% CI: 2.34 to 11.09; $p<0.05$) than in the PBO-BX group (Table 64).
- The mean change in S-QoL total score or in DAI-30 score from baseline to Week 12 was not statistically significantly different between the BX or QUE group and PBO-BX group (Table 51 and Table 61).
- The S-QoL dimension scores (FAS, OC) are summarised below:

		BX		QUE		PBO-BX	
Variable	Visit	n	Mean±SD	n	Mean±SD	n	Mean±SD
Psychological well-being	Baseline	79	60±27	76	57±26	68	54±23
	Week 12	48	71±22	52	64±26	42	61±25
Self esteem	Baseline	79	45±20	76	44±24	68	40±21
	Week 12	48	53±20	52	48±20	42	45±23
Family relationships	Baseline	79	59±20	76	54±25	68	59±22
	Week 12	48	63±21	52	56±23	42	59±23
Relationship with friends	Baseline	79	47±21	76	45±25	68	38±26
	Week 12	48	53±22	52	49±23	42	42±27
Resilience	Baseline	79	45±23	76	45±24	68	41±24
	Week 12	48	54±21	52	47±21	42	41±22
Physical well-being	Baseline	79	40±20	76	41±24	68	32±22
	Week 12	48	46±21	52	42±21	42	42±24
Autonomy	Baseline	79	50±22	76	49±23	68	44±21
	Week 12	48	56±19	52	49±22	42	47±23
Sentimental life	Baseline	79	43±26	76	42±25	68	39±25
	Week 12	48	56±21	52	47±21	42	47±23

Cross-reference: Tables 52 to 59

- After 12 weeks of treatment, the mean S-QoL dimension scores generally improved slightly (or remained relatively unchanged) and the mean scores were higher in the active treatment groups than in the PBO-BX group.
- The mean scores in the four PSP domains were comparable across treatment groups at baseline (Table 65). After 12 weeks of treatment, except for the domain *disturbing and aggressive behaviour* (minimal change in mean score), the mean scores in the other three PSP domains (*socially useful activities, personal and social relationships, and self-care*) generally improved in the active treatment groups (comparable mean scores) but remained relatively unchanged in the PBO-BX group.

Safety Results

• The adverse event incidence is summarised below:

	BX		QUE		PBO-BX	
	n	(%)	n	(%)	n	(%)
Patients treated	80		76		68	
Patients who died	0	(0)	0	(0)	0	(0)
Patients with serious AEs (SAEs)	7	(8.8)	4	(5.3)	5	(7.4)
Patients with AEs	54	(67.5)	46	(60.5)	35	(51.5)
Total number of SAEs	7		4		6	
Total number of AEs	154		132		118	

Cross-reference: Table 66

• The TEAEs with an incidence ≥5% in any treatment group are summarised below:

Preferred Term	BX		QUE		PBO-BX	
(MedDRA Version 12.0)	n	(%)	n	(%)	n	(%)
Patients treated	80		76		68	
Patients with TEAEs	54	(67.5)	46	(60.5)	35	(51.5)
Nausea	18	(22.5)	3	(3.9)	7	(10.3)
Insomnia	14	(17.5)	8	(10.5)	13	(19.1)
Schizophrenia	7	(8.8)	4	(5.3)	5	(7.4)
Headache	6	(7.5)	5	(6.6)	4	(5.9)
Weight decreased	6	(7.5)	2	(2.6)	5	(7.4)
Anxiety	5	(6.3)	4	(5.3)	6	(8.8)
Dizziness	5	(6.3)	6	(7.9)	0	(0)
Tachycardia	4	(5.0)	2	(2.6)	1	(1.5)
Vomiting	4	(5.0)	4	(5.3)	5	(7.4)
Psychotic disorder	3	(3.8)	2	(2.6)	4	(5.9)
Somnolence	3	(3.8)	16	(21.1)	1	(1.5)
Extrapyramidal disorder	2	(2.5)	1	(1.3)	4	(5.9)
Nasopharyngitis	1	(1.3)	0	(0)	4	(5.9)
Weight increased	1	(1.3)	4	(5.3)	0	(0)

Cross-reference: Table 71

- No deaths occurred during the study. The incidence of SAEs was comparable in all three treatment groups: 7 patients had 7 SAEs in the BX group, 4 patients had 4 SAEs in the QUE group, and 5 patients had 6 SAEs in the PBO-BX group (Tables 72 and 73). Nine (out of 17) SAEs were considered *probably/possibly* related to IMP (Listing 4): *psychotic disorder* (2 events in the BX group, 1 event in the QUE group, 2 events in the PBO-BX group), *schizophrenia* (2 events in the BX group, 1 event in the QUE group), and *psychotic behaviour* (1 event in the PBO-BX group).
- The incidence of adverse events was comparable in both the BX and QUE groups (68% *versus* 60%) and lower in the PBO-BX group (52%; Table 66). The proportion of patients who had severe TEAEs was low in all treatment groups (≤8%); the severe TEAEs occurred mainly in the system organ class *psychiatric disorders*: 5% in the BX group, 7% in the QUE group and 7% in the PBO-BX group (Table 74). All TEAEs by system organ class and preferred term are in Table 69. All adverse events are listed in Listing 3.
- The TEAEs with the highest incidences were *nausea* and *insomnia* in both the BX (22% and 18%, respectively) and PBO-BX groups (10% and 19%, respectively) and *somnolence* in the QUE group (21%; Table 70). The incidence of TEAEs (≥10%) that were considered *probably/possibly* related to IMP were: BX group – *nausea* (23%) and *insomnia* (11%); QUE group – *somnolence* (20%); PBO-BX group – *nausea* (10%) and *insomnia* (12%; Table 75).

Safety Results (continued)

- The incidence of withdrawal due to adverse events was lowest in the QUE group (14%) and comparable in the BX and PBO-BX groups (20% *versus* 22%; Tables 67 and 68). In the active treatment groups, *schizophrenia* was the adverse event leading to withdrawal with the highest incidence: 9% in the BX group and 4% in the QUE group. In the PBO-BX group, *schizophrenia* and *psychotic disorder* were the two adverse events leading to withdrawal with the highest incidence (6% each; Table 68). Only patients in the BX and PBO-BX groups withdrew due to *nausea* (3.8% and 1.5%, respectively) or *vomiting* (2.5% and 2.9%, respectively; Table 68). All adverse events leading to withdrawal are listed in Listing 5.
- There were no clinically relevant changes within or between treatment groups in: vital signs (Tables 76 to 101), BMI (Tables 103 and 104), or waist circumference (Tables 105 and 106). Neither were there clinically relevant changes in any of the ECG values (Tables 109 to 122) or the clinical laboratory test values (Tables 124 to 131).
- There were no PCS vital signs (Table 102) or ECG values (Table 123) with an incidence ≥5% in any treatment group. However, post-baseline PCS laboratory values with an incidence ≥5% (Table 132) occurred for:
  - *creatine kinase* (PCS high): 11% in the BX group; 7% in the QUE group; 3% in PBO-BX group
  - *eosinophils* (PCS high): 5% in the BX group; 7% in the QUE group; 4% in the PBO-BX group
  - *fasting blood glucose* (PCS high): 4% in the BX group; 20% in the QUE group; 10% in the PBO-BX group
- The following PCS values were reported as adverse events:
  - ECG parameter:
    - *right bundle branch block*: 1 patient in the QUE group (patient was withdrawn)
    - *ECG abnormal*: 1 patient in the QUE group
  - Clinical laboratory test:
    - *alanine aminotransferase increased*: 2 patients in the BX group
    - *anaemia*: 1 patient in the BX group
    - *blood bilirubin increased*: 1 patient in the BX group (patient was withdrawn)
    - *blood creatine phosphokinase increased*: 1 patient in the QUE group
    - *blood glucose increased*: 1 patient in the BX group and 1 patient in the QUE group (patient has PCS high blood glucose value at baseline and was withdrawn at a subsequent visit)
    - *eosinophilia*: 1 patient in the BX group
    - *glutamyl transferase increased*: 1 patient in the BX group
- There was a mean weight decrease in the BX group and PBO-BX groups (0.7 *versus* 0.4 kg) and a mean weight increase in the QUE group (1.2 kg) from baseline to Week 12 (Table 108). The proportion of patients who had PCS weight increase after 12 weeks was: 4% in the BX group, 8% in the QUE group, and none in the PBO-BX group. The proportion of patients who had a PCS weight decrease after 12 weeks was: 10% in the BX group, 2% in the QUE group, and 2% in the PBO-BX group (Table 107). PCS weight changes were reported as adverse events as follows:
  - *weight decreased*: 3 patients in the BX group, 2 patients in the QUE group, and 4 patients in the PBO-BX group
  - *weight increased*: 2 patients in the QUE group
- The mean changes from baseline to Week 12 in AIMS, BARS, and SAS scores were small, with no clinically relevant differences between the treatment groups (Tables 133 to 149).

Conclusions

- The PANSS total score improved significantly after 12 weeks of treatment with bifeprunox.
- The overall incidence of adverse events with bifeprunox was higher than with placebo, but comparable to that with quetiapine. Schizophrenia or *psychotic disorder* (placebo group only) was the most common adverse event leading to withdrawal in all treatment groups. No new safety concerns were raised during the study.
- No clinically relevant changes were observed in the safety variables after 12 weeks of treatment in any of the treatment groups.
- Except for the significant improvement in the PSP global score at Week 12 in both the bifeprunox and quetiapine groups, no clinically relevant changes in functional outcome, quality of life, or treatment compliance were observed in any of the treatment groups.

Date of the Report

13 September 2010

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