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CADTH COMMON DRUG REVIEW

Clinical Review Report

BREXPIPRAZOLE (REXULTI)

(Lundbeck Canada Inc. and Otsuka Canada Pharmaceutical Inc.)

Indication: Treatment of schizophrenia in adults

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Abbreviations

AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BPRS	Brief Psychiatric Rating Scale
C-SSRS	Columbia Suicide Severity Rating Scale
CDR	CADTH Common Drug Review
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
DDD	defined daily dose
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSM-III	*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
EMA	European Medicines Agency
EPS	extrapyramidal symptom
GAF	Global Assessment of Functioning scale
HR	hazard ratio
LOCF	last observation carried forward
LSMD	least squares mean difference
MMRM	mixed model repeated measures
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PANSS	Positive and Negative Syndrome Scale
PSP	Personal and Social Performance Scale
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SAS	Simpson-Angus Scale
SD	standard deviation
S-QoL	Schizophrenia Quality of Life Scale
TEAE	treatment-emergent adverse event
XR	extended release
WDAE	withdrawal due to adverse event

Executive Summary

Introduction

Brexpiprazole is an atypical antipsychotic drug indicated for the treatment of schizophrenia in adults. The product monograph states that the efficacy of brexpiprazole is thought to be mediated through partial agonist activity at serotonergic 5-HT1A and dopaminergic D2 receptors, and antagonist activity at serotonergic 5-HT2A receptors. The recommended dosage is 2 mg to 4 mg once daily. The product monograph recommends a starting dosage of 1 mg per day on days 1 to 4, titrated to 2 mg once daily on days 5 to 7, and then to 4 mg on day 8, based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg for most patients. The manufacturer has requested that brexpiprazole be reimbursed in accordance with the Health Canada–approved indication (i.e., for the treatment of schizophrenia in adults).

Results and Interpretation

Included Studies

There were four randomized controlled trials (RCTs) that met the inclusion criteria of the systematic review conducted by the CADTH Common Drug Review (CDR). These included three 6-week acute exacerbation trials (VECTOR [N = 636], BEACON [N = 674], and LIGHTHOUSE [N = 468]) and one 52-week maintenance therapy trial (EQUATOR [N = 202]). All three acute exacerbation trials were double-blind phase III studies that enrolled patients who were experiencing an acute relapse of schizophrenia. Both the VECTOR and BEACON trials were four-arm, placebo-controlled trials that were conducted using three different fixed doses of brexpiprazole. Patients in VECTOR were randomized to brexpiprazole 4 mg per day, 2 mg per day, 0.25 mg per day, or placebo. Patients in BEACON were randomized to brexpiprazole 4 mg per day, 2 mg per day, 1 mg per day, or placebo. Patients in LIGHTHOUSE were randomized to brexpiprazole (2 mg to 4 mg per day), quetiapine (400 mg to 800 mg per day), or placebo. Patients were hospitalized for the duration of the all three studies. In all three studies, change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score was the primary end point and change from baseline in Clinical Global Impression – Severity (CGI-S) was the key secondary end point.

The EQUATOR maintenance trial consisted of the following four phases: a screening phase of up to 15 days; a conversion phase of one to four weeks for patients to convert from existing antipsychotic drugs to brexpiprazole and continue washout of prohibited medications; a single-blind stabilization phase of up to 24 weeks where patients underwent titration of brexpiprazole (1 mg to 4 mg); and a 52-week, randomized, maintenance phase. Patients who completed the stabilization phase were randomized (1:1) to continue treatment with 1 mg to 4 mg brexpiprazole or to receive matching placebo. The primary efficacy outcome was time from randomization to impending relapse, and the key secondary end point was the proportion of patients meeting impending relapse criteria. Other non-key secondary outcomes measured in the trials, and identified as important by patient groups, included positive and negative symptoms (measured using the PANSS subscales) and health-related quality of life (measured by the Schizophrenia Quality of Life Scale [S-QoL]).

Efficacy

Treatment of Acute Exacerbation

In the VECTOR trial, both the 2 mg and 4 mg doses of brexpiprazole were associated with a statistically significant improvement in PANSS total score compared with placebo (least squares mean difference [LSMD]: −8.72 [95% confidence interval [CI], −13.1 to −4.37] and −7.64 [95% CI, −12.0 to −3.30], respectively). In the BEACON study, the 4 mg dose of brexpiprazole was associated with a statistically significant improvement in PANSS compared with placebo (LSMD: −6.47 [95% CI, −10.6 to −2.35]); however, there was no statistically significant difference with the 2 mg dosage (LSMD: −3.08 [95% CI, −7.23 to 1.07). In the LIGHTHOUSE trial, there was no statistically significant difference between flexibly dosed brexpiprazole and placebo (LSMD: −4.1 [95% CI, −8.2 to 0.1]; *P* = 0.0560); however, there was a statistically significant difference favouring quetiapine compared with placebo (LSMD: −8.0 [95% CI, −12.2 to −3.9]).

In the VECTOR trial, both the 2 mg per day and 4 mg per day dosages of brexpiprazole were associated with a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.33 [95% CI, −0.56 to −0.10] and −0.38 [95% CI, −0.61 to −0.15], respectively). Failure to demonstrate a statistically significant difference between the 2 mg brexpiprazole group and the placebo group in the BEACON trial stopped the statistical testing hierarchy at the primary end point; therefore, the results of the CGI-S analyses are considered exploratory. The treatment effect favoured the 4 mg per day dosage of brexpiprazole compared with placebo (LSMD: −0.38 [95% CI, −0.62 to −0.15]). In contrast, the 2 mg per day dosage of brexpiprazole did not demonstrate a difference compared with placebo (LSMD: −0.19 [95% CI, −0.42 to 0.05]). In the LIGHTHOUSE trial, [redacted]brexpiprazole [redacted] demonstrated a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.3 [95% CI, −0.5 to −0.1] and −0.4 [redacted]).

In the VECTOR trial, both the 2 mg per day and 4 mg per day dosages of brexpiprazole were associated with statistically significant improvements in the PANSS Positive subscale, Negative subscale, and Excited Component subscale compared with placebo. In the BEACON trial, statistically significant differences were demonstrated between the 4 mg per day brexpiprazole group and placebo for the positive subscale, Negative subscale, and Excited Component subscale; however, the 2 mg per day dosage did not demonstrate a statistically significant improvement compared with placebo in these PANSS subscales. In the LIGHTHOUSE trial, brexpiprazole was associated with a statistically significant improvement in the PANSS Positive subscale compared with placebo; however, there was no statistically significant difference in either the Negative or Excited Component subscales. Quetiapine was associated with a statistically significant improvement in all three subscales relative to placebo.

In both the VECTOR and BEACON trials, there was no statistically significant difference between the 2 mg brexpiprazole and placebo groups for the proportion of patients who discontinued due to a lack of efficacy (relative risk [RR]: 0.87 [95% CI, 0.46 to 1.65] and 1.00 [95% CI, 0.55 to 1.85], respectively). There was a statistically significant difference favouring the 4 mg per day group over placebo in the VECTOR trial (RR: 0.39 [95% CI, 0.18 to 0.85]); however, there was no statistically significant difference in the BEACON trial for the 4 mg per day dosage (RR: 0.82 [95% CI, 0.44 to 1.51]). Time to discontinuation due to a lack of efficacy was a secondary end point in the LIGHTHOUSE trial. Compared with

placebo, both the brexpiprazole and quetiapine groups were associated with a [redacted] in the risk of the discontinuation due to a lack of efficacy (hazard ratio [HR]: 0.44 [redacted] and 0.45 [redacted]), respectively.

[redacted] brexpiprazole [redacted] associated with statistically significant improvements in S-QoL total score compared with placebo ([redacted]

Maintenance Treatment

Time to impending relapse was statistically significantly delayed in the brexpiprazole group compared with the placebo group in both the interim (HR: 0.34 [95% CI, 0.17 to 0.66]) and final analyses (HR: 0.29 [95% CI, 0.16 to 0.55]). The median time to impending relapse in the interim and final analyses was [redacted] and 169.0 days in the brexpiprazole group and [redacted] and 111.0 days in the placebo group, respectively. In both the interim and final analyses, the proportion of patients meeting the criteria for impending relapse was statistically significantly lower in the brexpiprazole group compared with the placebo group ([redacted] versus [redacted] and 13.5% versus 38.5% [*P* < 0.0001], respectively).

Harms

The CDR review included data from two of the populations specified in the manufacturer's safety evaluation plan: pooled adverse event data from the acute treatment trials; and data from the single maintenance treatment trial. The pooled data set consists of adverse event data from VECTOR (N = 636), BEACON (N = 674), LIGHTHOUSE (N = 468), and one phase II study (331-07-203; N = 459). The phase II study was a six-arm trial that allocated patients to placebo, aripiprazole 15 mg per day, or one of four starting regimens of brexpiprazole (i.e., 0.25 mg, 1 mg, 2.5 mg, or 5 mg per day).

Treatment of Acute Exacerbation

The proportion of patients who experienced at least one treatment-emergent adverse event was similar in the pooled brexpiprazole group (2 to 4 mg per day) and placebo group [redacted].

[redacted]

[redacted]

The proportion of patients who experienced at least one serious adverse event was [redacted] than in the quetiapine group (1.3%). The proportion of patients who withdrew as a result of one or more adverse events was lower in the brexpiprazole group compared with the placebo group (7.8% versus 12.2%) and greater than in the quetiapine group (2.6%). Schizophrenia was the most commonly cited adverse event leading to discontinuation in the groups (4.0% with brexpiprazole, 7.4% with placebo, and 2.0% with quetiapine).

Maintenance Treatment

In the stabilization phase, [redacted] of brexpiprazole-treated patients experienced at least one adverse event, 7.3% of patients experienced at least one serious adverse event, 8.8% withdrew as a result of adverse events, and 14.2% experienced at least one extrapyramidal symptom (EPS)-related adverse event. In the maintenance phase, the proportion of patients who experienced at least one serious adverse event or withdrew as a result of adverse events was greater in the placebo group compared with the brexpiprazole group (10.6% versus 3.1% and 11.5% versus 5.2%, respectively). The proportion of patients who experienced at least one EPS-related adverse event was similar in the brexpiprazole group (6.2%) and the placebo group (4.8%). There were no statistically significant differences between the brexpiprazole and placebo groups in the Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS). In the stabilization phase of EQUATOR, [redacted] of patients demonstrated an increase in body weight of at least 7% after initiating treatment with brexpiprazole. In the maintenance phase, the proportion of patients with an increase of at least 7% in body weight was 5.2% in the brexpiprazole group, and 1.0% in the placebo group.

Indirect Comparisons

The manufacturer submitted two unpublished network meta-analyses (NMA) investigating the comparative efficacy and safety of brexpiprazole versus other atypical antipsychotic drugs used in Canada for use in the short-term and long-term treatment of schizophrenia.

Treatment of Acute Exacerbation

For patients experiencing an acute exacerbation of schizophrenia, the manufacturer's NMA suggested that [redacted]. There was likely considerable heterogeneity across studies; however, poor reporting of study and patient characteristics made it challenging to accurately evaluate the similarities and differences across the studies that were pooled. The manufacturer's NMA excluded all flexibly dosed regimens and a number of fixed-dose regimens from the reference case analyses and all sensitivity analyses with the exception of the extended treatment network. The clinical expert consulted by CADTH indicated that the more commonly used regimens were included in the analyses and that the exclusion of the alternative dosage regimens was not a significant clinical concern. However, it should be noted that the brexpiprazole estimate of effect is based on the most favourable dosage regimen for change from baseline in PANSS (i.e.,

4 mg per day). The analysis of safety end points was limited to a single aggregate outcome (i.e., withdrawals due to adverse events) and suggested that withdrawals from short-term clinical trials as a result of adverse events were similar across the atypical antipsychotic drugs included in their analysis, when adjusted for differences in withdrawal from the placebo groups. Such an aggregate end point cannot be used to evaluate the unique safety profiles of different atypical antipsychotic drugs on outcomes important to patients, such as weight gain and EPS-related events.

Maintenance Treatment

The results of the manufacturer's maintenance treatment NMA suggested that [redacted] In addition, [redacted] (which was demonstrated in the direct estimate from the EQUATOR trials). Given the high degree of the clinical and methodological heterogeneity of the NMA, the results were too uncertain to make any inference regarding the comparative efficacy and safety of brexpiprazole as a maintenance treatment for schizophrenia. Similar to the acute exacerbation NMA, the analysis of safety end points in the maintenance treatment NMA was limited to a single aggregate outcome (i.e., withdrawals due to adverse events).

Other Considerations

Brexpiprazole is also approved for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in the US, but is not currently approved for that indication in Canada.

Conclusions

The CDR systematic review included four double-blind RCTs that investigated the safety and efficacy of brexpiprazole for the treatment of patients with schizophrenia. One double-blind maintenance therapy study (EQUATOR) demonstrated that patients who were stabilized on brexpiprazole and subsequently randomized to continue treatment with brexpiprazole were less likely to experience a relapse than those who were randomized to placebo. Three double-blind acute exacerbation studies demonstrated that treatment with 4 mg per day brexpiprazole resulted in statistically significant and clinically meaningful improvements in PANSS total score and CGI-S for patients experiencing an acute exacerbation of schizophrenia (VECTOR, BEACON, and LIGHTHOUSE). When administered at a lower dosage (2 mg per day) brexpiprazole failed to consistently demonstrate statistically significant improvements in the primary or secondary end points in each study compared with placebo; however, a significant difference was observed in the pooled estimate from the manufacturer's NMA. Flexibly dosed brexpiprazole (2 to 4 mg per day) failed to demonstrate a statistically significant improvement in PANSS total score; however, improvements were observed in secondary end points such as CGI-S and in the proportion of patients achieving pre-specified response criteria. The clinical expert consulted by CADTH suggested that the lower dosage regimens of brexpiprazole would likely be effective for a subset of patients with schizophrenia; however, the majority would likely receive a dosage of 4 mg per day.

Overall, the manufacturer's assumption of similar efficacy with other atypical antipsychotic drugs used in Canada is supported by the NMA and clinical expert opinion for the treatment of acute exacerbations. However, the assumption regarding similar efficacy when used as maintenance treatment remains uncertain due to challenges and limitations of the indirect comparison reviewed.

Treatment with brexpiprazole is associated with an increased risk of weight gain and akathisia relative to placebo. Regulatory authorities and the clinical expert consulted by CADTH suggested that the adverse event profile of brexpiprazole is similar to that of other atypical antipsychotic drugs. The manufacturer's indirect comparisons of safety end points was limited to the aggregate end points of withdrawals due to adverse events and suggested that withdrawals from short-term clinical trials as a result of adverse events were similar across the atypical antipsychotic drugs included in their analysis, when adjusted for differences in withdrawal from the placebo groups.

Table 1: Summary of Efficacy Results From the Acute Exacerbation Trials

Study	Comparison	PANSS Total LSMD (95% CI)	PANSS Positive LSMD (95% CI)	PANSS Negative LSMD (95% CI)	PANSS Response RR (95% CI)	CGI-S LSMD (95% CI)	CGI-I LSMD (95% CI)
VECTOR	BREX 2 mg vs. PLC	−8.72 (−13.1 to −4.37)	−2.22 (−3.67 to −0.77)	−1.78 (−2.81 to −0.76)	1.51 (1.19 to 1.90)	−0.33 (−0.56 to −0.10)	−0.54 (−0.82 to −0.26)
	BREX 4 mg vs. PLC	−7.64 (−12.0 to −3.30)	−2.44 (−3.88 to −0.99)	−1.41 (−2.44 to −0.39)	1.51 (1.21 to 1.90)	−0.38 (−0.61 to −0.15)	−0.50 (−0.77 to −0.22)
BEACON	BREX 2 mg vs. PLC	−3.08 (−7.23 to 1.07)	−0.47 (−1.86 to 0.93)	−0.77 (−1.83 to 0.29)	1.14 (0.89 to 1.45)	−0.19 (−0.42 to 0.05)	−0.30 (−0.60 to −0.01)
	BREX 4 mg vs. PLC	−6.47 (−10.6 to −2.35)	−1.70 (−3.08 to −0.31)	−1.22 (−2.28 to −0.17)	1.33 (1.06 to 1.66)	−0.38 (−0.62 to −0.15)	−0.49 (−0.78 to −0.20)
LIGHTHOUSE	BREX 2 mg to 4 mg vs. PLC	−4.1 (−8.2 to 0.1)	−1.6 [redacted]	−0.6 [redacted]	NA	−0.3 (−0.5 to −0.1)	−0.3 (−0.6 to −0.0)
	QUET vs. PLC	−8.0 (−12.2 to −3.9)	−2.7 [redacted]	−1.4 [redacted]	NA	−0.4 [redacted]	−0.6 [redacted]

BREX = brexpiprazole; CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; CI = confidence interval; LSMD = least squares mean difference; mg = milligrams; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PLC = placebo; QUET = quetiapine; RR = relative risk; vs. = versus.
Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] and LIGHTHOUSE[3]

Table 2: Summary of Efficacy Results From the Maintenance Trial

Study	End Point	BREX 2-4 mg Versus PLC	
		Effect Estimate (95% CI)	*P* Value
EQUATOR	Time to impending relapse	HR: [redacted]	< 0.0001
	PANSS total	LSMD: −6.31 (−18.1 to 5.46)	0.2800
	PANSS positive	LSMD: −2.71 (−5.20 to −0.22)	0.0339
	PANSS negative	LSMD: 0.43 (−4.14 to 5.00)	0.8470
	CGI-S	LSMD: −0.51 (−1.09 to 0.06)	0.0002

BREX = brexpiprazole; CGI-S = Clinical Global Impression - Severity; CI = confidence interval; HR = hazard ratio; LSMD = least squares mean difference; mg = milligrams; PANSS = Positive and Negative Syndrome Scale; PLC = placebo.
Source: Clinical Study Report for EQUATOR[4]

Table 3: Summary of Adverse Events

Adverse Events n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX 2-4 mg (N = 972)	Placebo (N = 624)	ARI[a] (N = 50)	QUET (N = 153)	BREX (N = 97)	Placebo (N = 104)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	42 (43.3)	58 (55.8)
SAE	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.1)	11 (10.6)
WDAE	[redacted]	[redacted]	[redacted]	[redacted]	5 (5.2)	12 (11.5)
Any EPS-related AE	[redacted]	[redacted]	[redacted]	[redacted]	6 (6.2)	5 (4.8)
Increase in weight ≥ 7%	[redacted]	[redacted]	[redacted]	[redacted]	5 (5.21)	1 (0.96)

AE = adverse event; ARI = aripiprazole; BREX = brexpiprazole; EPS = extrapyramidal symptom; mg = milligram; n = number of patients with events; N = total number of patients; PLC = placebo; QUET = quetiapine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Aripiprazole was a study treatment in a single phase II study that was included in the manufacturer's safety analysis.

Source: Common Technical Document Section 2.7.4.[5]

Introduction

Disease Prevalence and Incidence

Schizophrenia is a mental illness that is associated with hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[6] The prevalence of schizophrenia in Canada has been estimated to be approximately 1% of the population.[6,7] Schizophrenia is a chronic or recurrent illness. Patients are at an increased risk for numerous other medical illnesses, suicide and substance abuse, homelessness, and unemployment.[8]Schizophrenia symptoms are often categorized as being either positive or negative in nature,[9] with positive symptoms reflecting a distortion or abundance of normal functions and negative symptoms reflecting a loss or restriction of normal functioning (Table 4).[10] The underlying principles for the administration of pharmacotherapy include the individualization of medication (including patient preferences), simple medication regimens, appropriate dosages, attention to side effect profiles, regular evaluation of responses (including adverse events),[8] and short- and long-term clinical efficacy, safety, and tolerability.[11]

Table 4: Examples of Schizophrenia Symptoms

Positive Symptoms	Negative Symptoms	General Psychopathology Symptoms
Delusion Conceptual disorganization Hallucinatory behaviour Excitement Grandiosity Suspiciousness/persecution Hostility	Blunted affect Emotional withdrawal Poor rapport Apathetic social withdrawal Difficulty in abstract thinking Lack of spontaneity and flow of conversations Stereotyped thinking	Mannerism and posturing Motor retardation Uncooperativeness Unusual thought content Disorientation Poor attention Lack of judgment and insight Disturbance of volition Poor impulse control Preoccupation Active social avoidance

Source: Kay et al., 1988.[12]

Standards of Therapy

Antipsychotic medications form the cornerstone of treatment for schizophrenia[6] as they target the characteristic symptoms of the disease.[13] Existing antipsychotic therapies fall into one of two classes. The typical antipsychotic drugs (also known as conventional antipsychotic drugs or neuroleptics) are of the first-generation antipsychotic class. These drugs have antagonistic activity at dopamine D2 receptors,[14] and are associated with an increased incidence of extrapyramidal side effects.[11] The atypical, or second-generation antipsychotic drugs have activity at D2 receptors, histamine 1 (H1) receptors, alpha-receptors, and serotonin (5-HT2A) receptors. Table 5 provides a summary of the orally administered atypical antipsychotic drugs that are currently marketed in Canada. The risk of extrapyramidal symptoms (EPS) incidence appears reduced with atypical antipsychotic drugs, however, differences between typical and atypical drugs can be variable in this respect.[15,16] Both classes of drug are considered to be equally effective in the treatment of positive symptoms. Atypical antipsychotic drugs appear to be more effective in the

treatment of negative symptoms;[11] however, they also have an increased risk of weight gain and metabolic side effects associated with their use.[8]

Treatment of schizophrenia is typically divided into three phases: acute, stabilization, and maintenance. In the acute phase, the patient is routinely experiencing psychotic or positive symptoms, with pharmacotherapy being initiated or adjusted as soon as possible.[17,18] Oral medications represent first-line treatment, although the formulations administered may differ under certain circumstances (e.g., in the case of non-adherence, or the need for rapid control of symptoms). Examples of alternative formulations that may be used in these situations include intramuscular, short-acting injectable treatments.

Non-emergent acute presentations still have a degree of urgency as a delay in treatment may lead to patient distress and/or harm to self or others. Moreover, a longer time to treatment has been linked to a less favourable outcome.[19-21] Current guidelines favour the use of an atypical antipsychotic in patients experiencing a first episode of psychosis, as these individuals are more sensitive to side effects such as EPS,[22,23] which can be uncomfortable, potentially life-threatening (e.g., acute laryngeal-pharyngeal dystonia), and contribute to non-adherence. Patients who experience multiple episodes are, as a rule, offered a trial of another antipsychotic.[17,18,24] Atypical antipsychotic drugs are again the treatment of choice unless the patient prefers a typical antipsychotic or has had a prior good response to a typical antipsychotic.

Table 5: Key Characteristics of Orally Administered Atypical Antipsychotic Drugs Available in Canada

Drug	Schizophrenia Indication(s)	Oral Recommended Dosage
Brexpiprazole[25]	Treatment of schizophrenia	2 mg to 4 mg q.d.
Lurasidone[26]	Management of manifestations of schizophrenia	40 mg or 80 mg q.d.
Aripiprazole[27]	Treatment of schizophrenia and related psychotic disorders in adults	10 mg or 15 mg q.d.
Ziprasidone[28]	Treatment of schizophrenia and related psychotic disorders	40 mg b.i.d.
Asenapine[29]	Treatment of schizophrenia	5 mg or 10 mg b.i.d.
Olanzapine[30]	Acute and maintenance treatment of schizophrenia and related psychotic disorders	10 mg q.d.
Risperidone[31]	Management of manifestations of schizophrenia	4 mg to 6 mg/day (q.d. or b.i.d.)
Quetiapine[32]	Management of manifestations of schizophrenia	300 mg/day (150 mg b.i.d.)
Clozapine[33]	Management of symptoms of treatment-resistant schizophrenia	300 mg to 600 mg/day
Paliperidone[34]	Treatment of schizophrenia and related psychotic disorders	6 mg q.d.

b.i.d. = twice daily; mg = milligram; q.d. = once daily.

Drug

Brexpiprazole is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. The manufacturer has requested that brexpiprazole be recommended for reimbursement in accordance with the Health Canada–approved indication. The product monograph states that efficacy of brexpiprazole in the treatment of schizophrenia may be mediated through partial agonist activity at serotonergic 5-HT1A and dopaminergic D2 receptors with antagonist activity at serotonergic 5-HT2A receptors.[25]

Brexpiprazole is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets. The recommended dosage for the treatment of schizophrenia is 2 mg to 4 mg once daily. The

product monograph recommends a starting dosage of 1 mg per day on days 1 to 4, titrated to 2 mg once daily on days 5 to 7, then to 4 mg on day 8, based on the patient's clinical response and tolerability.[25] The maximum recommended daily dosage is 4 mg for most patients.[25] The maximum recommended dosage is reduced to 3 mg per day for patients with moderate to severe hepatic impairment (Child-Pugh score greater than and equal to 7) or those with moderate, severe, or end-stage renal impairment (creatinine clearance less than 60 mL per minute.[25] Dosage adjustments are recommended in patients who are known to be CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors, or strong CYP3A4 inducers.[25]

Indication under review
Treatment of schizophrenia in adults
Reimbursement criteria requested by the applicant
As per indication

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of brexpiprazole for the treatment of schizophrenia in adults.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 6.

Table 6: Inclusion Criteria for the Systematic Review

Patient Population	Adults with schizophrenia **Subgroups** • Resistance to other atypical antipsychotic drugs • Drug naive • Prior exposure to one or more atypical antipsychotic drugs
Intervention	Brexpiprazole (oral) at recommended dosages
Comparators	Atypical antipsychotic drugs: • Risperidone • Paliperidone • Aripiprazole • Asenapine • Lurasidone • Ziprasidone • Olanzapine • Quetiapine
Outcomes	**Efficacy Outcomes** • Global symptoms[a] • Functional capacity (e.g., employment) • Mortality (including suicide)[a] • Clinical remission • Relapse[a] • Positive symptoms[a] • Hospitalization • Negative symptoms[a] • Suicidality • Cognition • Health-related quality of life[a] • Persistence with therapy • Withdrawals due to lack of efficacy
	Harms Outcomes • Serious AEs • Weight gain • Non-serious AEs • EPS-related AEs • WDAEs • Cardiovascular AEs
Study Design	Published and unpublished RCTs

AE = adverse event; EPS = extrapyramidal symptoms; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients, as described in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, in-process records and daily updates via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Rexulti and brexpiprazole.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 6, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 19, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 8; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of 86 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7, Table 8, and Table 9 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

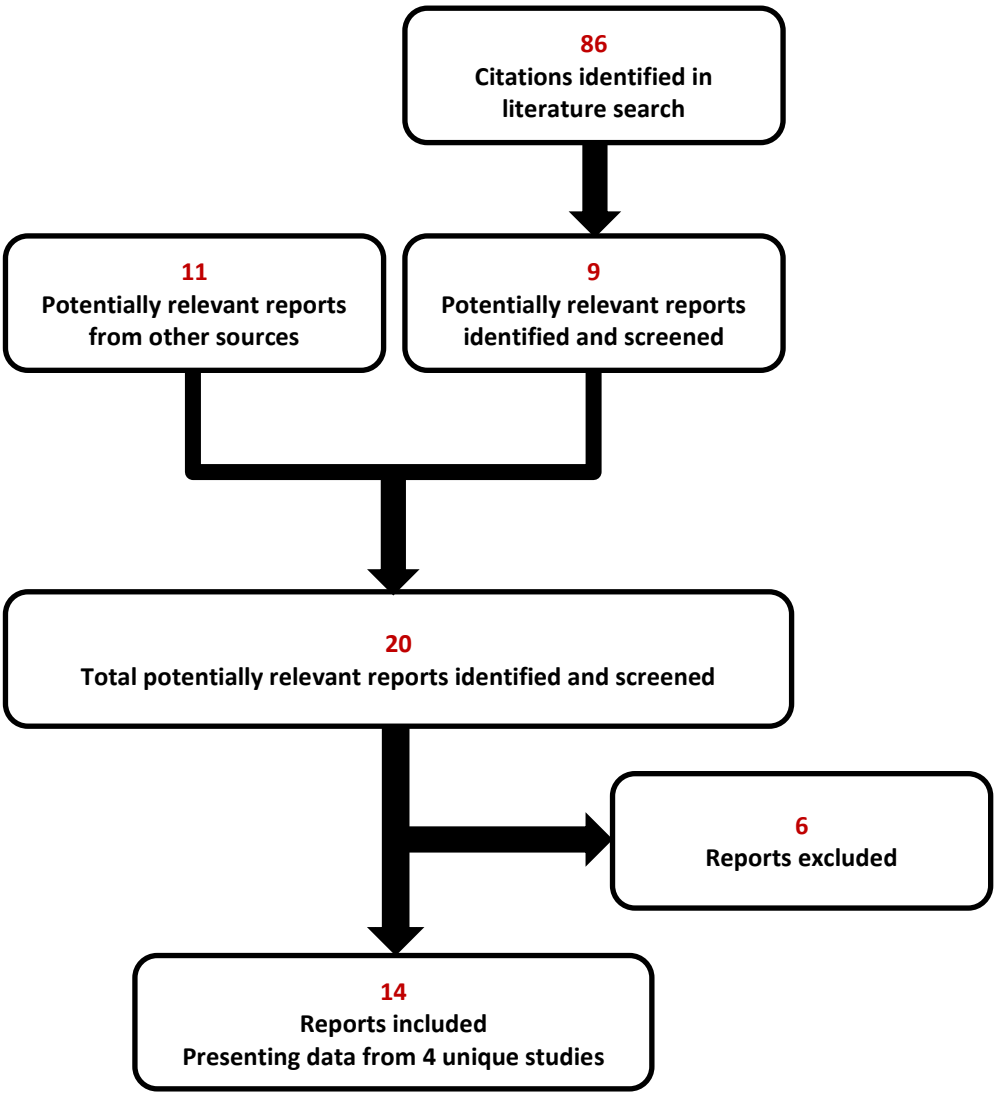


Table 7: Details of Included Fixed-Dose Acute Exacerbation Studies

		VECTOR (231)	BEACON (230)
Designs & Populations	**Study Design**	Phase III, four-arm, multinational, double-blind, placebo-controlled, RCT	Phase III, four-arm, multinational, double-blind, placebo-controlled, RCT
	Locations	65 sites in 10 countries (Canada, Japan, South Korea, Latvia, Malaysia, Poland, Romania, Serbia, Ukraine, and US)	68 sites in 8 countries (Colombia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan, and US)
	Randomized	636 (2:2:1:2)	674 (3:3:2:3)
	Inclusion Criteria	• SCZ (DSM-IV-TR criteria confirmed by MINI) • All of the following: BPRS score > 40; score of ≥ 4 on at least 2 of the following BPRS items: hallucinatory behaviour, unusual thought content, conceptual disorganization, or suspiciousness; score of ≥ 4 on the CGI-S • Would benefit from hospitalization for current acute relapse of SCZ • Previous outpatient AP treatment (other than clozapine) for ≥ 6 weeks with a good response within 12 months	
	Exclusion Criteria	• SCZ that is resistant/refractory to AP treatment • Patients with a first episode of schizophrenia [redacted] • > 30% improvement in BPRS score between screening and baseline [redacted]	
Drugs	**Intervention**	• Brexpiprazole 0.25 mg/day • Brexpiprazole 2 mg/day • Brexpiprazole 4 mg/day	• Brexpiprazole 1 mg/day • Brexpiprazole 2 mg/day • Brexpiprazole 4 mg/day
	Comparator	• Placebo	• Placebo
Duration	Run-In	Up to 2 weeks	Up to 2 weeks
	Double-Blind	6 weeks	6 weeks
	Follow-Up	30 days	30 days or entry into ZENITH
Outcomes	**Primary End Point**	PANSS total score at 6 weeks	PANSS total score at 6 weeks
	Other End Points	• CGI-S Score (key secondary end point) • Personal and Social Performance Scale • PANSS subscales • CGI-I scale score • Response • Discontinuations due to lack of efficacy • PANSS Excited Component score • PANSS Marder Factor scores	• CGI-S Score (key secondary end point) • Personal and Social Performance Scale • PANSS subscales • CGI-I scale score • Response • Discontinuations due to lack of efficacy • PANSS Excited Component score • PANSS Marder Factor scores
Notes	**Publications**	• Correll et al., 2015[35] • Clinicaltrials.gov[36] • Clinical Study Report[1] • FDA review reports[37-39]	• Kane et al., 2015[40] • Clinicaltrials.gov[41] • Clinical Study Report[2] • FDA review reports[37-39]

AP = antipsychotic; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision*; MINI = Mini International Neuropsychiatric Interview; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SCZ = schizophrenia.
Source: Clinical Study Reports for VECTOR[1] and BEACON.[2]

Table 8: Details of Included Flexible-Dose Acute Exacerbation Study

		LIGHTHOUSE (14644A)
Designs & Populations	**Study Design**	Phase III, multinational, double-blind, placebo-controlled, active-reference, RCT
	Locations	62 sites in 9 countries (Estonia, France, Poland, Romania, Russia, Serbia, Slovakia, Ukraine, and US)
	Randomized	468
	Inclusion Criteria	• SCZ (DSM-IV-TR criteria confirmed by MINI) • All of the following: PANSS total score ≥ 80, PANSS single item score ≥ 4 for at least two of the following items: hallucinatory behaviour, unusual thought content, conceptual disorganization, or suspiciousness/persecution, and a CGI-S score ≥ 4 at screening. • Would benefit from hospitalization for current acute relapse of SCZ • Previous outpatient AP treatment (other than clozapine) for ≥ 6 weeks with a good response within 12 months
	Exclusion Criteria	• SCZ that is resistant/refractory to AP treatment • Patients with a first episode [redacted] • Clinically significant tardive dyskinesia or severe akathisia • [redacted]
Drugs	**Intervention**	• Brexpiprazole 2 mg to 4 mg/day
	Comparators	• Quetiapine 400 mg to 800 mg/day • Placebo
Duration	Run-In	Up to 2 weeks
	Double-Blind	6 weeks
	Follow-Up	30 days
Outcomes	**Primary End Point**	PANSS total score at 6 weeks
	Other End Points	• PANSS subscales • Clinical Global Impression – Severity (key secondary end point) • Clinical Global Impression – Global Improvement • Personal and Social Performance Scale • Readiness to Discharge Questionnaire • Drug Attitude Inventory – 10 Item • Cogstate Cognitive Test Battery • Schizophrenia Quality of Life Scale • Karolinska Sleepiness Scale • Adverse events, serious adverse events, withdrawal due to adverse events • Columbia Suicide Severity Rating Scale • Simpson-Angus Scale • Barnes Akathisia Scale • Abnormal Involuntary Movement Scale
Notes	**Publications**	• Clinicaltrials.gov[42] • Clinical Study Report[3]

AP = antipsychotic; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; MINI = Mini International Neuropsychiatric Interview; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SCZ = schizophrenia.

Source: Clinical Study Report for LIGHTHOUSE.[3]

Table 9: Details of Included Maintenance Study

		EQUATOR (232)
Designs & Populations	**Study Design**	Phase III, multicenter, double-blind, placebo-controlled, maintenance RCT
	Locations	49 sites in 7 countries (US, Malaysia, Colombia, Romania, Ukraine, Serbia, and Turkey)
	Randomized	• 464 enrolled in stabilization phase • 202 randomized into maintenance phase
	Inclusion Criteria	**Stabilization Phase** • SCZ (DSM-IV-TR criteria confirmed by MINI) • Previous response to AP (other than clozapine) • Acute exacerbation of psychotic symptoms requiring stabilization (PANSS > 80 at screening) • Completed washout of all prohibited medications **Maintenance Phase** • Receiving monotherapy with brexpiprazole (1 mg to 4 mg/day) at a stable dose for ≥ 4 weeks • All of the following criteria for 12 weeks: (1) outpatient status; (2) PANSS ≤ 70; (3) score of ≤ 4 on each of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content; (4) CGI-S score ≤ 4; (5) no current suicidal behaviour as assessed by the C-SSRS; (6) no evidence of aggressive or violent behaviour
	Exclusion Criteria	• SCZ that is resistant/refractory to AP treatment • Patients with a first episode • Experienced acute depressive symptoms within the past 30 days • Clinically significant tardive dyskinesia or severe akathisia [redacted]
Drugs	**Intervention**	Brexpiprazole (1 mg to 4 mg per day)
	Comparator	Placebo
Duration	Screening	2 weeks
	Run-in	1 to 4 weeks
	Stabilization	12 to 36 weeks
	Follow-up	52 weeks
Outcomes	**Primary End Point**	Time to exacerbation of psychotic symptoms/impending relapse
	Other End Points	• Proportion meeting impending relapse criteria (key secondary end point) • Proportion meeting stability criteria • PANSS total score • PANSS subscales (positive, negative, Excited Component, Marder Factors) • CGI-S and CGI-I scales • Personal and Social Performance Scale • Global Assessment of Functioning scale • Time to discontinuation due to all causes
Notes	**Publications**	• Clinical Study Report[3] • Fleischhacker et al. 2016[43] • Clinicaltrials.gov[44]

AP = antipsychotic; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; mg = milligram; MINI = Mini International Neuropsychiatric Interview; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SCZ = schizophrenia.
Source: Clinical Study Report for EQUATOR[4]

Included Studies

Description of Studies

There were four RCTs that met the inclusion criteria of the CDR systematic review. These included three six-week acute exacerbation trials (VECTOR [N = 636], BEACON [N = 674], and LIGHTHOUSE [N = 468]) and one 52-week maintenance therapy trial (EQUATOR [N = 202]).[1-4]

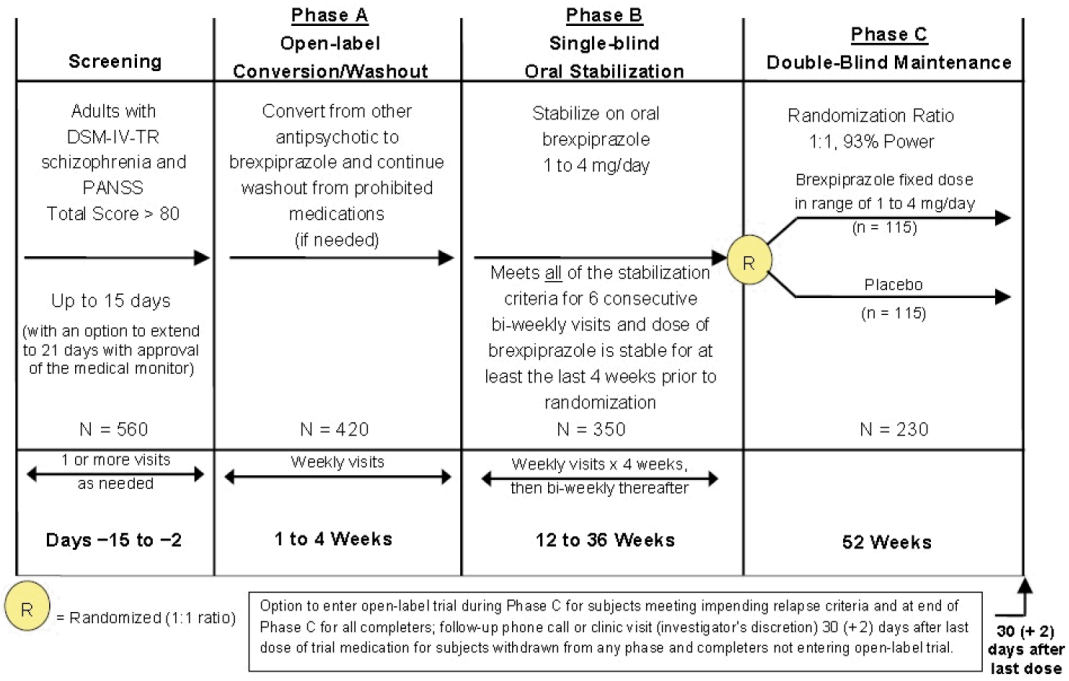
Acute Exacerbation Trials

All three acute exacerbation trials were multi-centre, multinational, double-blind, phase III studies. Both the VECTOR and BEACON trials were four-arm, placebo-controlled trials that were conducted using three different fixed doses of brexpiprazole. Patients in VECTOR were randomized (3:3:2:3) to brexpiprazole 4 mg per day (n = 180), brexpiprazole 2 mg per day (n = 182), brexpiprazole 0.25 mg per day (n = 90), or placebo (n = 184). Patients in BEACON were randomized (3:3:2:3) to brexpiprazole 4 mg per day (n = 184), brexpiprazole 2 mg per day (n = 186), brexpiprazole 1 mg per day (n = 120), or placebo (n = 184). LIGHTHOUSE was a three-arm study that included both a placebo group and an active comparator group (i.e., quetiapine). Patients in LIGHTHOUSE were randomized to flexibly dosed brexpiprazole (2 mg to 4 mg per day; n = 151), flexibly dosed quetiapine (400 mg to 800 mg per day; n = 154), or placebo (n = 163). All three acute treatment trials consisted of a screening phase of up to two weeks, a double-blind treatment phase of six weeks, and a follow-up period of 30 days. Patients were hospitalized for the duration of the all three studies. Diagrams showing the design of the acute exacerbation trials are provided in Figure 19 and Figure 20 (page 82)

Maintenance Treatment Trial

The EQUATOR trial consisted of the following four phases: a screening phase of up to 15 days; a conversion phase of 1 week to 4 weeks for patients to convert from existing antipsychotic drugs to brexpiprazole and continue washout of prohibited medications; a single-blind stabilization phase of up to 24 weeks where patients underwent titration of brexpiprazole (1 mg to 4 mg); and a 52-week, randomized, maintenance phase (summarized in Figure 2). Patients who completed the stabilization phase were randomized (1:1) to continue treatment with 1 mg to 4 mg brexpiprazole (n = 97) or to receive matching placebo (n = 105).

Figure 2: Schematic Showing the Design of the EQUATOR Trial



DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; mg = milligrams; N = total number of patients; n = number of patients in subgroup; PANSS = Positive and Negative Syndrome Scale; R = randomization.

Source: Clinical Study Report for EQUATOR.[4]

Populations

Inclusion and Exclusion Criteria

Acute Exacerbation Trials

All three of the acute exacerbation trials enrolled patients who were experiencing an acute relapse of schizophrenia. Patients who were experiencing a first episode of schizophrenia were excluded from the studies. All three studies specified that patients were to have schizophrenia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria that was subsequently confirmed by the *Mini International Neuropsychiatric Interview (MINI) for Schizophrenia and Psychotic Disorders Studies.*

Both the VECTOR and BEACON studies used the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression – Severity (CGI-S) scales to establish the minimum threshold for disease severity at screening.[1,2] Specifically, both studies required patients to have a BPRS score above 40, with a score of at least 4 on at least two of the following items: hallucinatory behaviour, unusual thought content, conceptual disorganization, or suspiciousness; and a score of at least 4 on the CGI-S. The LIGHTHOUSE study used the Positive and Negative Syndrome Scale (PANSS) and CGI-S to evaluate the minimum threshold for disease severity at screening. Specifically, PANSS total score greater than and equal to 80, with a score greater than and equal to 4 for at least two of the following items:

hallucinatory behaviour, unusual thought content, conceptual disorganization, or suspiciousness/persecution, and a CGI-S score greater than and equal to 4 at screening.[3] In VECTOR and BEACON, any patients who demonstrated an improvement of at least 30% in BPRS score between the screening and baseline evaluations were excluded.[1,2]

In all three trials, enrolment was limited to patients who had undergone previous treatment with an antipsychotic other than clozapine for at least six weeks. This prior exposure to an antipsychotic had to be on an outpatient basis and the patient was required to have demonstrated a good response within 12 months of initiating treatment. Any patients with a history of schizophrenia that was resistant or refractory to antipsychotic treatment were excluded from the trials. All three studies excluded patients with clinically significant tardive dyskinesia (i.e., a score of greater than and equal to 3 on item 8 of the Abnormal Involuntary Movement Scale) or severe akathisia (i.e., a score of 5 on the Barnes Akathisia Rating Scale). [redacted].[1-3]

All three trials were conducted in hospitalized patients and the inclusion criteria stated that in order to eligible for the trial, investigators were required to confirm that patients would benefit from hospitalization for their current acute relapse of schizophrenia. [redacted].[1-3]

Maintenance Treatment Trial

The EQUATOR trial had separate eligibility criteria for the stabilization and maintenance phases.4 Similar to the acute treatment trials, patients were required to have a diagnosis of schizophrenia using the DSM-IV-TR criteria with confirmation using the MINI for Schizophrenia and Psychotic Disorders Studies. Patients were eligible if they were experiencing an acute exacerbation of psychotic symptoms with a PANSS greater than 80 at screening. Patients experiencing a first episode of schizophrenia or those with a history of schizophrenia that was resistant or refractory to treatment with antipsychotic drugs were excluded. Patients were required to have undergone previous treatment with an antipsychotic other than clozapine for at least six weeks and demonstrated a good response. Exclusion criteria for the EQUATOR trial were similar to those that were used in the acute exacerbation trials. Patients were also excluded if they had clinically significant tardive dyskinesia, [redacted] Table 9. Patients who had experienced acute depressive symptoms within the past 30 days that required treatment with an antidepressant were excluded.4

To be eligible for the maintenance phase of EQUATOR, patients were required to have been receiving monotherapy with brexpiprazole at a dosage of 1 mg to 4 mg per day, with a stable dose for at least four weeks.4 Over the screening period, patients were required to demonstrate the following for at least 12 weeks: (1) outpatient status; (2) a PANSS total score of ≤ 70; (3) a score of ≤ 4 on each of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content; (4) CGI-S score ≤ 4; (5) no current suicidal behaviour as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS); and (6) no evidence of aggressive or violent behaviour.4

Baseline Characteristics

Acute Exacerbation Trials

Key baseline and demographic characteristics for the VECTOR, BEACON, and LIGHTHOUSE trials are summarized in Table 10. Across all three acute exacerbation trials, the majority of study participants were male (range: 56.9% to 63.1%) and Caucasian (range: 60.4% to 75.2%).[1-3] In BEACON and VECTOR, approximately one-third of the study participants were from centres in the US (not reported for LIGHTHOUSE).[1-3] There were seven Canadian patients enrolled in VECTOR, but none in the other studies. Mean body mass index at baseline was similar across the acute exacerbation trials (range: 26.3 to 27.3 kg/m^2). PANSS total scores at baseline were as follows: brexpiprazole 2 mg/day (range: 95.9 to 96.3), brexpiprazole 4 mg/day (range: 94.9 to 95.1), brexpiprazole 2 mg to 4 mg/day (97.8), placebo (range: 94.8 to 98.4), and quetiapine (98.8).[1-3]

Maintenance Treatment Trial

Key baseline and demographic characteristics for the EQUATOR trial are summarized in Table 11. The mean age of participants in the randomized, maintenance phase of the trial was slightly lower in the brexpiprazole group (38.8 years) compared with the placebo group (41.6 years). The majority of patients in both the brexpiprazole and placebo groups were male (59.8% and 61.9%, respectively), white (63.9% and 61.9%, respectively), and non-Hispanic (82.5% and 81.0%, respectively). At the time of enrolment in the stabilization phase of the EQUATOR trial, the mean (standard deviation [SD]) PANSS total score was 84.5 (12.1) and the mean (SD) CGI-S was 4.3 (0.8). For those who were randomized into the maintenance phase of the trial, mean (SD) total PANSS scores had improved to 56.5 (8.7) and 58.1 (8.1) in the brexpiprazole and placebo groups, respectively. Mean (SD) CGI-S scores had improved to 3.0 (0.6) and 3.1 (0.6) for those in the brexpiprazole and placebo groups, respectively.

Table 10: Summary of Baseline Characteristics From Acute Exacerbation Trials

Characteristic	Scale	BEACON			VECTOR			LIGHTHOUSE		
		BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	BREX 2 mg (N = 182)	BREX 4 mg (N = 180)	Placebo (N = 184)	Placebo (N = 161)	BREX 2-4 mg (N = 150)	QUET (N = 153)
Age	Mean (SD)	36.9 (10.9)	38.6 (11.0)	39.3 (10.8)	39.6 (10.2)	40.8 (11.0)	39.7 (10.8)	40.9 (10.56)	39.7 (10.87)	41.1 (10.91)
Sex	Male (%)	122 (65.6)	113 (61.4)	111 (60.3)	111 (61)	111 (61.7)	118 (64.1)	91 (56.5)	84 (56.0)	89 (58.2)
	Female (%)	64 (34.4)	71 (38.6)	73 (39.7)	71 (39)	69 (38.3)	66 (35.9)	70 (43.5)	66 (44.0)	64 (41.8)
Race	Caucasian (%)	118 (63.4)	104 (56.5)	110 (59.8)	120 (65.9)	119 (66.1)	121 (65.8)	123 (76.4)	113 (75.3)	113 (73.9)
	Asian (%)	7 (3.8)	12 (6.5)	10 (5.4)	19 (10.4)	16 (8.9)	16 (8.7)	2 (1.2)	1 (0.7)	0
	African-Am. (%)	41 (22)	50 (27.2)	45 (24.5)	43 (23.6)	42 (23.3)	45 (24.5)	35 (21.7)	33 (22.0)	38 (24.8)
	Native Am. (%)	8 (4.3)	6 (3.3)	5 (2.7)	0 (0)	0 (0)	1 (0.5)	0	1 (0.7)	0
	Native Hawaiian	NR	NR	NR	0 (0)	1 (0.6)	1 (0)	1 (0.6)	0	1 (0.7)
	Other (%)	12 (6.5)	12 (6.5)	14 (7.6)	0 (0)	2 (1.1)	0 (0)	0	2 (1.3)	1 (0.7)
Ethnicity	Hispanic (%)	31 (16.7)	32 (17.4)	31 (16.8)	3 (1.6)	10 (5.6)	9 (4.9)	NR	NR	NR
	Non-Hispanic (%)	155 (83.3)	150 (81.5)	151 (82.1)	179 (98.4)	170 (94.4)	175 (95.1)	NR	NR	NR
	Unknown (%)	0 (0)	2 (1.1)	2 (1.1)	NR	NR	NR	NR	NR	NR
Location	US	66 (35.5)	66 (35 9)	67 (36.4)	63 (34.6)	65 (36.1)	67 (36.4)	NR	NR	NR
	Non-US	120 (64.5)	118 (64.1)	117 (63.6)	119 (65.4)	115 (63 9)	117 (63.6)	NR	NR	NR
Weight (kg)	Mean (SD)	[redacted]	[redacted]	[redacted]	80.0 (19.7)	80.1 (18.3)	77.8 (18.3)	NR	NR	NR
BMI (kg/m^2)	Mean (SD)	26.3 (6.1)	27.1 (6.6)	26.6 (5.6)	27.3 (5.9)	27.1 (5.8)	26.5 (5.4)	NR	NR	NR
Current episode (weeks)	Mean (SD)	2.7 (3.0)	2.3 (2.2)	2.6 (2.8)	2.8 (2.3)	2.4 (1.6)	2.7 (2.6)	NR	NR	NR
PANSS	Total Score	96.3 (12.8)	95.1 (12.5)	94.8 (13.0)	95.9 (13.7)	94.9 (12.2)	95.9 (11.5)	98.4 (10.30)	97.8 (10.25)	98.8 (10.83)
	Positive Subscale	24.9 (4.3)	24.9 (4.4)	25 (4.6)	25.6 (4.4)	25 (4 5)	25.2 (4.1)	NR	NR	NR
	Negative Subscale	24.1 (5.2)	23.9 (5.0)	24 (5.3)	23.2 (4.60	23.3 (4.7)	23.5 (4.4)	NR	NR	NR
CGI-S Score	Mean (SD)	5.0 (0.7)	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)	4.8 (0.6)	4.8 (0.7)	4.94 (0.57)	4.96 (0.59)	4.98 (0.57)
PSP Score	Mean (SD)	43.7 (11.4)	44.7 (11.1)	43.7 (10.8)	45.4 (10.5)	45.3 (10.9)	45.1 (9.5)	43.9 (10.67)	42.8 (10.35)	[redacted]
BPRS Total Score	Mean (SD)	55.5 (7.5)	55.2 (7.5)	55.1 (8.0)	56.4 (8.6)	55.3 (7.4)	55.7 (7.1)	NR	NR	NR
S-QoL	Mean (SD)	NA	NA	NA	NA	NA	NA	44.7 (17.82)	43.7 (18.90)	[redacted]

Am. = American; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; BREX = brexpiprazole; CGI-S = Clinical Global Impression - Severity; kg = kilogram; m^2 = square metres; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; QUET = quetiapine; SD = standard deviation; S-QoL = Schizophrenia Quality of Life Scale.

Source: FDA Medical Review[37] and Clinical Study Report for LIGHTHOUSE.[3]

Table 11: Summary of Baseline Characteristics From EQUATOR

Characteristics		Scale	Stabilization	Maintenance	
			BREX (1–4 mg) (N = 464)	BREX (1–4 mg) (N = 97)	Placebo (N = 105)
Age (years)	Baseline	Mean (SD)	39.2 (11.2)	38.8 (10.7)	41.6 (10.6)
	At diagnosis	Mean (SD)	25.0 (8.5)	26.5 (8.2)	27.9 (8.3)
Gender	Male	n (%)	278 (59.9)	58 (59.8)	65 (61.9)
	Female	n (%)	186 (40.1)	39 (40.2)	40 (38.1)
Race	White	n (%)	277 (59.7)	62 (63.9)	65 (61.9)
	African American	n (%)	[redacted]	[redacted]	[redacted]
	Asian	n (%)	[redacted]	[redacted]	[redacted]
	Other	n (%)	[redacted]	[redacted]	[redacted]
Ethnicity	Hispanic/Latino	n (%)	[redacted]	[redacted]	[redacted]
	Not Hispanic/Latino	n (%)	[redacted]	[redacted]	[redacted]
	Unknown	n (%)	[redacted]	[redacted]	[redacted]
Body composition	Weight (kg)	Mean (SD)	[redacted]	[redacted]	[redacted]
	BMI (kg/m^2)	Mean (SD)	27.8 (6.4)	28.2 (6.7)	29.1 (6.9)
PANSS	Total score	Mean (SD)	84.4 (12.3)	56.5 (8.7)	58.1 (8.1)
	Conceptual disorganization	Mean (SD)	[redacted]	[redacted]	[redacted]
	Suspiciousness	Mean (SD)	[redacted]	[redacted]	[redacted]
	Hallucinatory	Mean (SD)	[redacted]	[redacted]	[redacted]
	Unusual thought content	Mean (SD)	[redacted]	[redacted]	[redacted]
	Positive subscale	Mean (SD)	[redacted]	[redacted]	[redacted]
	Negative subscale	Mean (SD)	[redacted]	[redacted]	[redacted]
	Excited Component	Mean (SD)	[redacted]	[redacted]	[redacted]
PANSS Marder	Positive symptoms	Mean (SD)	[redacted]	[redacted]	[redacted]
	Negative symptoms	Mean (SD)	[redacted]	[redacted]	[redacted]
	Disorganized thought	Mean (SD)	[redacted]	[redacted]	[redacted]
	Uncontrolled hostility/excitement	Mean (SD)	[redacted]	[redacted]	[redacted]
	Anxiety/depression	Mean (SD)	[redacted]	[redacted]	[redacted]
Other end points	CGI-S score	Mean (SD)	4.3 (0.8)	3.0 (0.6)	3.1 (0.6)
	GAF score	Mean (SD)	45.8 (10.4)	64.3 (9.2)	63.1 (8.4)
	PSP total score	Mean (SD)	48.0 (11.6)	50.1 (12.4)	48.7 (11.7)

BMI = body mass index; BREX = brexpiprazole; CGI-S = Clinical Global Impression - Severity; GAF = Global Assessment of Functioning; kg = kilogram; m^2 = square metres; N = total number of patients; n = number of patients in subgroup; mg = milligrams; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; SD = standard deviation.

Source: Clinical Study Report for EQUATOR.[4]

Interventions

Acute Exacerbation Trials

The first dose of the study drug (brexpiprazole or matching placebo) was administered on the day of randomization. The dose titration schemes that were used in the acute exacerbation trials are summarized in Table 12. In the VECTOR and BEACON trials, all patients in the 2 mg and 4 mg brexpiprazole groups initiated treatment with a dosage of 1 mg per day (or matching placebo) for the first four days. The dosage was subsequently increased to 2 mg per day on day 5 in both groups. For those randomized to 4 mg per day,

the dosage was increased from 2 mg per day to 4 mg per day beginning at week 2.[1,2] In the LIGHTHOUSE study, brexpiprazole was titrated at 1 mg increments for the first three days of the trial (i.e., 1 mg, 2 mg, and 3 mg doses on days 1, 2, and 3, respectively).[3] After day 4, the dose of brexpiprazole could be adjusted in 1 mg increments between 2 and 4 mg per day based on efficacy and tolerability. The patients in the quetiapine group received 300 mg on day 1 and 600 mg on days 2 and 3. After day 4, the dose of quetiapine could be adjusted in 200 mg increments between 400 mg per day and 800 mg per day, based on efficacy and tolerability.[3]

Table 12: Summary of Dose Titration in the Acute Exacerbation Trials

Study	Schedule	Fixed-Dose Regimen		Flexible-Dose Regimen	
		BREX 2 mg	BREX 4 mg	BREX 2-4 mg	QUET
VECTOR and BEACON	Days 1 to 4	1 mg	1 mg	NA	
	Days 5 to 7	2 mg	2 mg		
	Weeks 2 to 6	2 mg	4 mg		
LIGHTHOUSE	Day 1	NA		1 mg	300 mg
	Day 2			2 mg	600 mg
	Day 3			3 mg	600 mg
	Day 4 onwards			2 to 4 mg	400 to 800 mg

BREX = brexpiprazole; mg = milligrams; NA = not applicable; QUET = quetiapine.

Source: Clinical Study Reports for VECTOR, BEACON, and LIGHTHOUSE.[1-3]

Maintenance Treatment Trial

Patients in the EQUATOR trial who participated in the conversion phase were required to switch from their current antipsychotic regimen to monotherapy with brexpiprazole at a dosage of 1 mg per day to 4 mg per day.[4] The initial dosage of brexpiprazole in the conversion phase was 1 mg per day. Failure to tolerate the 1 mg per day dosage resulted in discontinuation from the study. Dose increases proceeded gradually in the conversion phase, based on response and tolerability, in increments of 1 mg up to a maximum of 4 mg per day.[4] During the stabilization phase of the EQUATOR trial, all patients received single-blind brexpiprazole at a dosage of 1 mg per day to 4 mg per day for at least 12 weeks and up to a maximum of 36 weeks. Investigators could modify the daily dose within the range of 1 mg to 4 mg, based on response and tolerability; however, the dose must have been stable for at least the last 4 weeks before entry into the randomized, double-blind, maintenance phase.[4] Patients who were randomized to brexpiprazole in the maintenance phase were to continue treatment using the final daily dose that was achieved in the stabilization phase. The study protocol permitted one increase or decrease in the dosage of brexpiprazole (or matching placebo) from the stabilization dosage, and, for those who underwent dose modification, one opportunity to return to the original dosage.[4] Compliance with the study treatments was high during both the stabilization and maintenance phases, with nearly all patients receiving at least 80% of study drug doses.[45]

Outcomes

Acute Exacerbation Trials

Table 13 summarizes the primary, secondary, and exploratory efficacy end points from each of the included studies. In all three studies, change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score was the primary end point and change from baseline in Clinical Global Impression - Severity (CGI-S) was the key secondary end

point.[1-3] All three studies included the following secondary end points: PANSS subscales, PANSS Marder Factors, PSP, CGI-I, and response rates.[1-3] The proportion of patients who discontinued from the study due to a lack of efficacy was a secondary end point in the VECTOR and BEACON studies;[1,2] while time to discontinuation due to lack of efficacy was a secondary end point in LIGHTHOUSE.[3] As shown in Table 13, the LIGHTHOUSE study included a number of additional exploratory end points, including the Readiness to Discharge Questionnaire, Drug Attitude Inventory-10 Item, Cogstate, Schizophrenia Quality of Life Scale, and the Karolinska Sleepiness Scale.[3]

Table 13: End Points Evaluated in the Six-Week Acute Treatment Trials

End Point	VECTOR	BEACON	LIGHTHOUSE
PANSS total score	**Primary**	**Primary**	**Primary**
CGI-S	Key secondary	Key secondary	Key secondary
PANSS Positive subscale	Secondary	Secondary	Secondary
PANSS Negative subscale	Secondary	Secondary	Secondary
PANSS Excited Component	Secondary	Secondary	Secondary
PANSS General Psychopathology subscale	NA	NA	Secondary
PANSS Marder Factors	Secondary	Secondary	Secondary
PSP score	Secondary	Secondary	Secondary
CGI-I score	Secondary	Secondary	Secondary
Response rate	Secondary	Secondary	Secondary
Discontinuation due to lack of efficacy	Secondary	Secondary	NA
Time to discontinuation due to lack of efficacy	NA	NA	Secondary
RDQ scores	NA	NA	Exploratory
DAI-10 total	NA	NA	Exploratory
DAI-10 response	NA	NA	Exploratory
Cogstate	NA	NA	Exploratory
Cogstate subscales	NA	NA	Exploratory
S-QoL total	NA	NA	Exploratory
S-QoL subscales	NA	NA	Exploratory
KSS total	NA	NA	Exploratory

CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; DAI-10 = Drug Attitude Inventory-10 Item; KSS = Karolinska Sleepiness Scale; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; RDQ = Readiness to Discharge Questionnaire; S-QoL = Schizophrenia Quality of Life Scale.

Source: Clinical Study Reports for VECTOR, BEACON, and LIGHTHOUSE.[1-3]

Maintenance Treatment Trial

Table 14 summarizes the primary, secondary, and exploratory efficacy end points from the EQUATOR maintenance trial. The primary efficacy outcome was time from randomization to impending relapse and the key secondary end point was the proportion of patients meeting impending relapse criteria.[4] The EQUATOR trial included a number of pre-specified secondary end points, including PANSS total score, CGI-S, PANSS subscales and Marder Factors, PSP, GAF, CGI-I, and time to discontinuation due to all causes.[4]

Table 14: End Points Evaluated in the Maintenance Treatment Trial

End Point	Time Points	Classification
Time from randomization to impending relapse	Across 52 weeks	**Primary**
Proportion meeting impending relapse criteria	Weeks 6, 12, 24, 36, 52, last visit	Key secondary
Proportion meeting stability criteria at end point	Weeks 6, 12, 24, 36, 52, last visit	Secondary
PANSS Total score	Weeks 6, 12, 24, 36, 52, across visits	Secondary
CGI-S score	Weeks 6, 12, 24, 36, 52, across visits	Secondary
PANSS Positive subscale score	Weeks 6, 12, 24, 36, 52, across visits	Secondary
PANSS Negative subscale score	Weeks 6, 12, 24, 36, 52, across visits	Secondary
PSP	Weeks 24, 52, across visits	Secondary
GAF	Weeks 12, 24, 36, 52, across visits	Secondary
CGI-I score	Weeks 6, 12, 24, 36, 52, last visit	Secondary
Time to discontinuation due to all causes	Across 52 weeks, across visits	Secondary
PANSS Marder Factor scores	Week 52, across visits	Secondary
PANSS Excited Component score	Week 52, across visits	Secondary
Cogstate composite score	Last visit	Other outcome
Proportion of patients with remission	Weeks 28, 32, 36, 40, 44, 48, 52	Exploratory

CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; GAF = Global Assessment of Functioning scale; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale.

Source: Clinical Study Reports for EQUATOR.[4]

Positive and Negative Syndrome Scale (PANSS)

The primary efficacy outcome variable in the acute treatment trials was change from baseline to week 6 in PANSS total score. PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and consists of the following three subscales:

- Positive subscale (7 items): delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility.
- Negative subscale (7 items): blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking.
- General Psychopathology subscale (16 items): somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.[37]

PANSS Marder Factors refer to five specific categories of PANSS items: positive symptoms (eight items), negative symptoms (seven items), disorganized thought (seven items), uncontrolled hostility/excitement (four items), and anxiety/depression (four items).[46] Additional details regarding the PANSS scale are provided in Appendix 6.

Clinical Global Impression – Severity Scale

The Clinical Global Impression – Severity (CGI-S) scale was the key secondary end point of both the BEACON and VECTOR studies. The CGI-S is a 7-point scale that measures the clinician's impression about the severity of the patient's illness at the time of assessment

based on the following categories: (1) normal, not at all ill, (2) borderline mentally ill, (3) mildly ill, (4) moderately ill, (5) markedly ill, (6) severely ill, or (7) extremely ill.

The Clinical Global Impression – Improvement Scale

The Clinical Global Impressions – Improvement scale (CGI-I) was a secondary end point in both the BEACON and VECTOR studies. The CGI-I is a 7-point scale that measures the clinician's impression about how much the patient's illness has improved or worsened relative to baseline according to the following: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse.

Time to Impending Relapse

The primary efficacy end point of the EQUATOR trial was the time from randomization to exacerbation of psychotic symptoms / impending relapse, which was defined as any of the following four criteria:

1. CGI-I score greater than and equal to 5 (minimally worse, much worse, or very much worse) and:
   - An increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of greater than 4 with an absolute increase of greater than and equal to 2 on that specific item since randomization; or
   - An increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of greater than 4 and an absolute increase of greater than and equal to 4 on the combined four PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content)
2. Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons (e.g., homelessness or need for shelter that is unrelated to the patient's underlying psychiatric condition).
3. Current suicidal behaviour as assessed by the C-SSRS (i.e., an answer of "yes" to any of the questions on the Suicidal Behaviour section of the C-SSRS).
4. Violent or aggressive behaviour resulting in clinically significant self-injury, injury to another person, or property damage.

Responder Analyses

In the acute exacerbation trials, response rate was a pre-specified secondary end point and was defined as follows: a reduction (i.e., improvement) of greater than and equal to 30% from baseline in PANSS total score at week 6; or a CGI-I score of 1 (very much improved) or 2 (much improved) at week 6.

In addition to this pre-specified responder analysis, the publications for VECTOR (Correll et al., 2015)[35] and BEACON (Kane et al., 2015)[40] reported responder analyses based on improvement from baseline in PANSS of greater than and equal to 20%, greater than and equal to 40%, and greater than and equal to 50%; or a CGI-I score of 1 (very much improved) or 2 (much improved) at week 6. These analyses appear to have been conducted in a post hoc manner.

Remission

Remission was an exploratory end point in the EQUATOR maintenance treatment trial and was defined as a score of 3 or less, maintained for a period of six months, on each of the following PANSS items: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms/posturing, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation).[47]

Extrapyramidal Symptoms

Extrapyramidal symptom (EPS) assessments were performed by a physician, a nurse practitioner, or a physician's assistant. The ratings were done by the same rater at each session between two and ten hours after the morning dose of the study treatment. The assessments included: the Barnes Akathisia Rating Scale (BARS), the Simpson-Angus Scale (SAS), and the Abnormal Involuntary Movement Scale (AIMS). Higher scores on these scales indicate a greater degree of akathisia.

Statistical Analysis

Analysis Populations

The analysis populations from the included studies are summarized in Table 15.

Table 15: Data Sets From the Acute Exacerbation and Maintenance Studies

Data Set	Description
Acute Exacerbation Trials (VECTOR, BEACON, LIGHTHOUSE)	
Randomized data set	All patients who were randomized (referred to as the 'all patients randomized' set in LIGHTHOUSE).
Safety data set	All patients who received at least one dose of study treatments (referred to as the 'all patients treated' set in LIGHTHOUSE).
Efficacy data set	All patients who were randomized, received at least one dose of study treatments, and have a baseline and at least one post-baseline PANSS total score evaluation (referred to as the 'full analysis' set in LIGHTHOUSE).
Maintenance Trial (EQUATOR)	
Enrolled sample	All patients who signed the informed consent form for the trial and entered the conversion phase or the stabilization phase.
Stabilization phase efficacy sample	All patients who entered the stabilization phase and received at least one dose of brexpiprazole and had at least one post-baseline efficacy evaluation in the stabilization phase.
Double-blind maintenance phase efficacy sample	All patients randomized to double-blind study treatment who took at least one dose of the study treatments in the double-blind maintenance phase and who had at least one post-randomization efficacy evaluation in the double-blind maintenance phase.

PANSS = Positive and Negative Syndrome Scale.

Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] LIGHTHOUSE,[3] and EQUATOR.[4]

Multiple Comparisons

Acute Exacerbation Trials

In the primary efficacy analyses for the BEACON and VECTOR trials, the average effect method was used to control the type I error rate. This method involved first testing the difference between the average effect of brexpiprazole 4 mg per day and brexpiprazole 2 mg per day versus placebo, at an alpha level of 0.05. If this average effect test was statistically significant, then subsequent comparisons were conducted for each of the brexpiprazole groups (i.e., 4 mg per day and 2 mg per day) versus placebo, also using a significance level of 0.05 for both comparisons. In the LIGHTHOUSE trial, the primary statistical comparison of interest for all efficacy analyses was the difference between brexpiprazole 2 mg per day to 4 mg per day and placebo. The manufacturer reported that quetiapine was included in the trial to confirm assay sensitivity; therefore, no adjustments for multiple comparisons were performed for comparisons of quetiapine versus placebo.

For the key secondary end point (i.e., CGI-S), a hierarchical statistical testing procedure was applied to maintain a type I error rate of 0.05. In VECTOR, BEACON, and LIGHTHOUSE, statistical significance for CGI-S was only tested if statistical significance had been demonstrated for the primary end point. For the VECTOR and BEACON studies, an average effect method was used for the CGI-S in a manner similar to the primary analysis. Statistical significance for the analysis of non-key secondary end points was evaluated at a nominal level of 0.05.[47]

Maintenance Treatment Trial

The statistical analysis plan for the primary end point of the EQUATOR trial (i.e., time from randomization to impending relapse) included two pre-planned interim analyses (at accrual of approximately 50% and 75% of impending relapse events), and a final analysis using 100% of relapse events (i.e., approximately 90). The O'Brien-Fleming boundary was used to account for multiplicity in the interim analysis, with a boundary *P* value for the first interim analysis of 0.003051 (two-sided). Results of the first interim analysis were positive and the trial was terminated for having achieved the primary end point. A hierarchical testing procedure was used to handle the multiplicity for testing the primary and key secondary efficacy end points of EQUATOR. To control the overall type I error rate at 0.05, statistical significance of the key secondary end point (i.e., the proportion of patients meeting impending relapse criteria) was only tested if there was a statistically significant difference with the primary end point.[47] Statistical significance for the analysis of non-key secondary end points was evaluated at a nominal level of 0.05.

Handling of Missing Data

The methods that were used for imputing missing data in the primary and sensitivity analyses for the acute exacerbation trials and the maintenance trial are summarized in Table 16. In the short-term trials, the primary analyses were conducted using a mixed model repeated measures (MMRM) approach to impute missing data. In addition, the manufacturer conducted sensitivity analyses using a pattern-mixture model to investigate the impact of a departure from the missing at random assumption that was applied in the primary analysis. This involved the use of a delta-adjusted pattern imputation approach (i.e., progressive decrease in the treatment differences over the missing visits) for patients in the brexpiprazole group who: (1) withdrew due a lack of efficacy, (2) withdrew due to an adverse event (LIGHTHOUSE only), and (3) withdrew due to a lack of efficacy or adverse

event. For LIGHTHOUSE, an additional set of pattern-mixture model sensitivity analyses were performed using a placebo-based multiple imputation approach (i.e., brexpiprazole patients who withdrew were assumed to follow a trajectory similar to the placebo group). All three acute exacerbation studies also included sensitivity analyses that were conducted using a last observation carried forward (LOCF) approach.[1-3]

Patients who discontinued from the EQUATOR trial for a reason other than lack of efficacy were censored in the primary efficacy analysis (i.e., time to impending relapse) at the time when they withdrew from the trial. Sensitivity analyses were conducted to investigate the impact of censoring, including the use of multiple imputation, application of less stringent sub-impending relapse criteria, and by counting all early withdrawals from the brexpiprazole events as relapse events.[4]

Table 16: Handling of Missing Data

Study	End Point	Imputation Methods for Missing Data	
		Primary Analysis	Sensitivity Analyses
VECTOR BEACON	PANSS	MMRM (assumes MAR)	• LOCF • Pattern-mixture models (MNAR) ○ Delta-adjusted pattern imputation

LIGHTHOUSE	PANSS	MMRM (assumes MAR)	• LOCF
			• Pattern-mixture models (MNAR)
			  ○ Placebo-based multiple imputation
			  ○ Delta-adjusted pattern imputation

EQUATOR	Relapse	Withdrawals censored unless due to lack of efficacy	• Multiple imputation of discontinued censored observations • Discontinued patients who met sub-impending relapse criteria counted as relapsed • Discontinuations counted as events for brexpiprazole group

LOCF = last observation carried forward; MAR = missing at random; MNAR; missing not at random; MMRM = mixed model repeated measures; PANSS = Positive and Negative Syndrome Scale.

Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] LIGHTHOUSE,[3] and EQUATOR.[4]

Power Calculations

The sample size calculations for the VECTOR and BEACON trials were based on comparing the 2 mg per day and 4 mg per day dosages of brexpiprazole against placebo.[1,2] The manufacturer reported that 180 patients would be required to detect a difference of −7.5 points in change from baseline in PANSS at week 6 with 90% power at an alpha level of 0.025.[1,2] The sample size calculation for LIGHTHOUSE was based on the comparison of brexpiprazole and placebo (quetiapine was included for assay sensitivity).[3] The manufacturer report that 150 patients would be required per treatment group (i.e., N = 450) to detect a difference of −7.5 points in change from baseline in PANSS at week 6 with 90% power at an alpha level of 0.05.[3] All three acute exacerbation trials assumed a standard deviation of 20 for the primary end point in the sample size calculations.[1-3] The EQUATOR maintenance trial was planned to have 93% power to detect a difference between brexpiprazole and placebo, based on 90 impending relapse events.[4]

Patient Disposition

Acute Exacerbation Trials

A summary of patient disposition from the three acute exacerbation trials is provided in Table 17. The proportion of screening failures was similar across the trials, ranging from [redacted] in LIGHTHOUSE to 33.0% in BEACON.[2,3] Reasons for screening failure were not reported. The proportion of patients who discontinued from the studies was greater in the placebo groups than in the brexpiprazole groups and the quetiapine group. The most common reasons for discontinuation across the studies were withdrawn consent, adverse events, and lack of efficacy. In the brexpiprazole groups the most common reason for discontinuation was withdrawn consent in the BEACON and VECTOR trials (range: 13.2% to 13.4% and 12.5% to 17.2% for the 2 mg per day and 4 mg per day doses, respectively) and adverse events in the LIGHTHOUSE trial (9.3%).[1-3] Within the placebo groups, adverse events were the most common reason for withdrawal in BEACON and VECTOR (12.0% and 17.4%, respectively) and lack of efficacy was the most common reason in LIGHTHOUSE (14.9%).[1-3]

Table 17: Patient Disposition in the Acute Exacerbation Trials

Disposition, n (%)	BEACON			VECTOR			LIGHTHOUSE		
	BREX 2 mg	BREX 4 mg	Placebo	BREX 2 mg	BREX 4 mg	Placebo	Placebo	BREX 2 mg to 4 mg	QUET
Screened	1005			949			[redacted]		
Randomized (total)	674[a]			636[a]			468		
Randomized	186 (100)	184 (100)	184 (100)	182 (100)	180 (100)	184 (100)	163 (100)	151 (100)	154 (100)
All patients treated set	186 (100)	184 (100)	184 (100)	182 (100)	180 (100)	184 (100)	161 (98.8)	150 (99.3)	153 (99.4)
Analyzed for efficacy	179 (96.2)	181 (98.4)	180 (97.8)	180 (98.9)	178 (98.9)	178 (96.7)	159 (97.6)	150 (99.3)	150 (97.4)
Completed	129 (69.4)	130 (70.7)	118 (64.1)	124 (68.1)	121 (67.2)	109 (59.2)	108 (67.1)	113 (75.3)	122 (79.7)
Discontinued	57 (30.6)	54 (29.3)	66 (35.9)	58 (31.9)	59 (32.8)	75 (40.8)	53 (32.9)	37 (24.7)	31 (20.3)
Lost to follow-up	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	NR	NR	NR
Adverse events	11 (5.9)	13 (7.1)	22 (12.0)	15 (8.2)	17 (9.4)	32 (17.4)	11 (6.8)	14 (9.3)	4 (2.6)
Met withdrawal criteria	0 (0)	2 (1.1)	1 (0.5)	0 (0)	1 (0.6)	0 (0)	NR	NR	NR
Investigator withdrew consent	0 (0)	0 (0)	1 (0.5)	1 (0.5)	1 (0.6)	3 (1.6)	NR	NR	NR
Patient withdrew consent	25 (13.4)	23 (12.5)	21 (11.4)	24 (13.2)	31 (17.2)	21 (11.4)	6 (3.7)	0	6 (3.9)
Protocol deviation	1 (0.5)	0 (0)	0 (0)	1 (0.5)	2 (1.1)	0 (0)	1 (0.6)	0	1 (0.7)
Lack of efficacy	20 (10.8)	16 (8.7)	21 (11.4)	17 (9.3)	7 (3.9)	18 (9.8)	24 (14.9)	10 (6.7)	11 (7.2)
Administrative or other	NR	NR	NR	NR	NR	NR	11 (6.8)	13 (8.7)	9 (5.9)

BREX = brexpiprazole; mg = milligrams; n = number of patients in subgroup; NR = not reported; QUET = quetiapine.

[a] Totals include patients who were randomized to 1 mg brexpiprazole (n = 120) or 0.25 brexpiprazole (n = 90) in BEACON and VECTOR, respectively.

Source: FDA Statistical Report[38] and Clinical Study Report for LIGHTHOUSE.[3]

Maintenance Treatment Trial

In the EQUATOR trial, a total of 753 patients were screened and 229 were reported as screening failures (30.4%). A total of 464 patients entered the stabilization phase (118 patients entered directly and the remaining patients completed the medication conversation phase). Following the stabilization phase, 202 patients were randomized into the double-blind maintenance phase. Reasons for discontinuation from the stabilization phase are summarized in Table 18. During the double-blind maintenance phase, the most common reason for discontinuation was lack of efficacy (impending relapse) without an adverse event (11.3% and 28.6% in the brexpiprazole and placebo groups, respectively).[4]

Table 18: Patient Disposition in the Maintenance Trial

Disposition, n (%)	Stabilization Phase	Maintenance Phase	
		BREX (1 mg to 4 mg)	Placebo
Screened	753		
Entered stabilization phase	464	NA	
Entered maintenance phase	NA	202	
Randomized	NA	97 (100.0)	105 (100.0)
Completed	202 (43.5)	14 (14.4)	9 (8.6)
Discontinued	262 (56.5)	83 (85.6)	96 (91.4)
Lost to follow-up	16 (3.4)	4 (4.1)	6 (5.7)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn consent	60 (12.9)	3 (3.1)	5 (4.8)
[redacted]	[redacted]	[redacted]	[redacted]
Adverse event without impending relapse	43 (9.3)	4 (4.1)	2 (1.9)
Lack of efficacy	21 (4.5)	NA	NA
Lack of efficacy (impending relapse) with AE	NA	2 (2.1)	10 (9.5)
Lack of efficacy (impending relapse) without AE	NA	11 (11.3)	30 (28.6)
Study terminated based on interim analysis or reached conclusion	86 (18.5)	49 (50.5)	38 (36.2)

AE = Adverse Event; BREX = brexpiprazole; mg = milligrams; N = total number of patients, n = number of patients with event; NA = not applicable.

Source: Clinical Study Report for EQUATOR[4]

Exposure to Study Treatments

Study Treatments

A summary of exposure to the study treatments in the acute treatment trials (VECTOR, BEACON, and LIGHTHOUSE) and in the maintenance trial (EQUATOR) is provided in Table 19. Across all of the acute treatment trials, mean (SD) exposure to 2 mg, 4 mg, or 2 mg to 4 mg brexpiprazole was [redacted] days. This is similar to the mean exposure in the placebo groups ([redacted]). Results were similar among the different brexpiprazole dosage regimens: [redacted]. The mean dosage of brexpiprazole in the LIGHTHOUSE study was 3.53 mg per day (standard deviation [SD] 0.43) and the mean dosage of quetiapine was 674.44 mg per day (SD 113.58). A greater proportion of brexpiprazole-treated patients received the maximum dosage of the study treatments (i.e., 4 mg per day) compared with the quetiapine group (i.e., 800 mg per day) ([redacted]). The mean dosage of brexpiprazole in the EQUATOR trial was 3.56 mg per day. At the last study visit, the proportion of patients using 1 mg, 2 mg, 3 mg, and 4 mg dosages of brexpiprazole were [redacted].[4]

Table 19: Exposure in the Acute and Maintenance Treatment Trials

Study	Time Point	BREX 2 mg	BREX 4 mg	Placebo
VECTOR	N	184	180	184
	1-7 days	[redacted]	[redacted]	[redacted]
	8–14 days	[redacted]	[redacted]	[redacted]
	15–21 days	[redacted]	[redacted]	[redacted]
	22–28 days	[redacted]	[redacted]	[redacted]
	29–35 days	[redacted]	[redacted]	[redacted]
	36–42 days	[redacted]	[redacted]	[redacted]
	> 42 days	[redacted]	[redacted]	[redacted]
BEACON	**Time Point**	[redacted]	[redacted]	[redacted]
	N	[redacted]	[redacted]	[redacted]
	1–7 days	[redacted]	[redacted]	[redacted]
	8–14 days	[redacted]	[redacted]	[redacted]
	15–21 days	[redacted]	[redacted]	[redacted]
	22–28 days	[redacted]	[redacted]	[redacted]
	29–35 days	[redacted]	[redacted]	[redacted]
	36–42 days	[redacted]	[redacted]	[redacted]
	> 42 days	[redacted]	[redacted]	[redacted]
LIGHTHOUSE	**Time Point**	[redacted]	[redacted]	[redacted]
	N	[redacted]	[redacted]	[redacted]
	1–7 days	[redacted]	[redacted]	[redacted]
	8–14 days	[redacted]	[redacted]	[redacted]
	15–28 days	[redacted]	[redacted]	[redacted]
	29–50 days	[redacted]	[redacted]	[redacted]
EQUATOR	**Time Point**	[redacted]	[redacted]	
	2 weeks	[redacted]	[redacted]	
	4 weeks	[redacted]	[redacted]	
	6 weeks	[redacted]	[redacted]	
	8 weeks	[redacted]	[redacted]	

Study	Time Point	BREX 2 mg	BREX 4 mg	Placebo
	12 weeks	[redacted]	[redacted]	
	16 weeks	[redacted]	[redacted]	
	20 weeks	[redacted]	[redacted]	
	24 weeks	[redacted]	[redacted]	
	28 weeks	[redacted]	[redacted]	
	32 weeks	[redacted]	[redacted]	
	36 weeks	[redacted]	[redacted]	
	40 weeks	[redacted]	[redacted]	
	44 weeks	[redacted]	[redacted]	
	48 weeks	[redacted]	[redacted]	
	52 weeks	[redacted]	[redacted]	
	> 52 weeks	[redacted]	[redacted]	

BREX = brexpiprazole; mg = milligrams; N = total number of patients; QUET = quetiapine.

Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] LIGHTHOUSE,[3] and EQUATOR.[4]

Concomitant Treatments

All of the included studies prohibited the use of antipsychotic drugs (other than the investigational products), antidepressants, mood stabilizers, varenicline, CYP2D6 inhibitors, and CYP3A4 inhibitors and inducers (details provided on Table 30 on page 82). Limited use of specific oral benzodiazepines was allowed as a rescue medication for the control of agitation and/or insomnia. Non-benzodiazepine sleep aids were permitted as a rescue medication for the treatment of insomnia, but were not to be administered on the same day as a benzodiazepine. All prohibited medications were to be discontinued during the screening and washout period.[37] In the fixed-dose acute exacerbation trials, protocol violations for the use of concomitant medications were reported as follows: [redacted].[1,2] Violations for concomitant medications were not reported by treatment group in the LIGHTHOUSE trial.[3] In the maintenance trial, violations for concomitant medications were reported for [redacted] of patients in the brexpiprazole and placebo groups, respectively.[4]

Table 20 provides a summary of selected concomitant medications that were initiated during the acute and maintenance trials (i.e., anticholinergics, beta-blockers, psycholeptics, and psychoanaleptics).

Across all three acute exacerbation trials, psycholeptics were the most commonly used concomitant class of medication (i.e., greater than 60% of patients in all treatment groups were receiving at least one psycholeptic medication). In all of the studies, benzodiazepines and non-benzodiazepine hypnotics were the most commonly used psycholeptics. The use of concomitant psycholeptic medications was generally balanced across the treatment groups, with the exception of the BEACON trial [redacted].

In the two fixed-dose acute exacerbation trials (BEACON and VECTOR), usage of at least one anticholinergic medication [redacted]. In the flexibly dosed LIGHTHOUSE

study, the proportion of patients who initiated treatment with an anticholinergic drug during the study [redacted].[4] The proportion of patients who initiated treatment with a beta-blocker ranged from [redacted].[1-3]

Table 20: Concomitant Medications in the Acute and Maintenance Treatment Trials

Study	Treatment	Concomitant Medications, n (%)			
		Anticholinergics	Beta-Blockers	Psycholeptics[a]	Psychoanaleptics[b]
BEACON	BREX 2 mg	[redacted]	[redacted]	[redacted]	[redacted]
	BREX 4 mg	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
VECTOR	BREX 2 mg	[redacted]	[redacted]	[redacted]	[redacted]
	BREX 4 mg	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
LIGHTHOUSE	BREX 2-4 mg	[redacted]	[redacted]	[redacted]	[redacted]
	QUET	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
EQUATOR	BREX 2-4 mg	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]

BREX = brexpiprazole; mg = milligrams; n = number of patients in subgroup; QUET = quetiapine.

[a] Psycholeptics includes antipsychotic drugs, anxiolytics, hypnotics, and sedatives

[b] All of the psychoanaleptics reported in the studies were antidepressants, with the exception of one patient receiving a psychostimulant in the EQUATOR trial.[1-4]

Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] LIGHTHOUSE,[3] and EQUATOR.[4]

Critical Appraisal

Internal Validity

Randomization in the acute exacerbation studies (VECTOR, BEACON, and LIGHTHOUSE) and maintenance treatment study (EQUATOR) was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., interactive voice response system [IVRS] or interactive Web response system [IWRS]).[1-4] Although randomization was conducted without stratification for any patient characteristics, key baseline and demographic characteristics were generally balanced between the placebo and brexpiprazole groups in both the acute and maintenance trials.[45]

All treatments were administered in a double-blind manner. A double-dummy design was used in the LIGHTHOUSE trial due to differences in the dosage form of quetiapine (capsules) and brexpiprazole (tablets). The manufacturer reported that the adverse event profile of quetiapine may have compromised blinding in the LIGHTHOUSE trial,[48] particularly the increases in somnolence (22.2% versus [redacted] in the pooled analysis) and weight gain (13.1% versus [redacted]).[5] Health Canada also noted the potential for unblinding due to the sedation and somnolence associated with quetiapine, particularly since it was administered during the day in LIGHTHOUSE rather than in the evening, as is typically the case in routine Canadian practice.[45] Although a strength in terms of internal validity, it is possible that the use of a double-dummy design in the LIGHTHOUSE study may have contributed to the high rate of withdrawals due to high pill burden.

The study characteristics of the acute exacerbation trials are aligned with recommendations from the European Medicines Agency (EMA) regarding the appropriate primary and secondary end points for short-term schizophrenia trials (PANSS and CGI-S, respectively), the duration of the studies (six weeks), the inclusion of a placebo group, and the diagnostic criteria for screening patients (two-stage diagnosis based on DSM criteria with confirmation using a structured interview and with a well-defined severity threshold based on PANSS).[49] The use of in-patient treatment is aligned with guidance from the EMA on the conduct of placebo-controlled trials involving patients with schizophrenia, where it is recommended that the setting should be highly controlled to avoid unnecessary risks for patients and others.[49]

The design of the EQUATOR trial (randomized withdrawal study following at least 12 weeks of stable treatment with the investigational product) is also aligned with EMA guidance for maintenance treatment trials.[49] This trial pre-dated the FDA's initial review of brexpiprazole; however, it was specified as a required post-market study to establish long-term efficacy of treatment with brexpiprazole.[37] The clinical expert consulted by CADTH suggested that the definition of relapse used in the EQUATOR trial was likely more robust than the definition that would be applied in clinical practice.

All of the acute exacerbation trials demonstrated a high proportion of early withdrawals (greater than 20% in all trials), which is generally consistent with schizophrenia trials. Since withdrawal is unlikely to occur randomly, it is possible that the high proportion of discontinuations may have compromised randomization, and that the characteristics (measured and unmeasured) of the treatment groups may not have remained similar over time. Furthermore, many of the end point measurements reported in these trials had to be estimated by imputation. The primary analyses used MMRM for imputing missing data, which is often considered to be associated with a reduced risk of bias in schizophrenia trials, compared with alternative methodologies, such as LOCF.[49]

The use of concomitant anticholinergic medications varied between the 4 mg brexpiprazole groups ([redacted]) and the placebo groups ([redacted]). It is possible that the use of these drugs may have affected the tolerability of brexpiprazole and should be considered simultaneously with the EPS-related adverse event data. The clinical expert consulted by CADTH suggested that in routine clinical practice, EPS-related adverse events would typically be managed through dose reduction or by switching to an alternative drug, as opposed to prescribing additional medication to manage these events.

[redacted][45]. [redacted][45]. [redacted][45].

External Validity

Enrolment in the acute exacerbation trials was restricted to patients who met a minimum threshold for disease severity (e.g., PANSS greater than and equal to 80) and who would benefit from hospitalization. This results in a patient population that is more severe than typical Canadian patients, who would often have mild to moderate disease. The trials excluded patients who were deemed to be at risk of self-harm or harm to others, or who had a history of substance abuse. Although common in clinical trials, the exclusion of these

patients may limit the generalizability of the results to clinical practice. It is possible that this patient population would have different responses in terms of efficacy and treatment adherence. The trials also excluded patients with a diagnosis of residual-type schizophrenia; therefore, the efficacy of brexpiprazole in this population is uncertain. In all three trials, enrolment was limited to patients who had undergone previous treatment with an antipsychotic other than clozapine for at least six weeks on an outpatient basis, and who had demonstrated good response to treatment.

Two of the three acute treatment trials (VECTOR and BEACON) were conducted without an active comparator group. Although the LIGHTHOUSE study included a quetiapine treatment group, the manufacturer indicated that this group was only included to ensure assay sensitivity, and that the trial was not powered to conduct statistical comparisons of efficacy between brexpiprazole and quetiapine. This limits the ability to draw conclusions regarding the comparative efficacy of brexpiprazole versus quetiapine.

The titration regimen that was used in the brexpiprazole group of the LIGHTHOUSE study was more aggressive than what is currently recommended in the Canadian product monograph. Patients randomized to brexpiprazole received 1 mg, 2 mg, and 3 mg doses on days 1, 2, and 3, (respectively), followed by flexibly dosed 2 mg to 4 mg brexpiprazole thereafter. In contrast, the product monograph recommends a slower titration scheme, starting with 1 mg for the first four days, 2 mg on days 5 to 7, followed by up to 4 mg on day 8. The initial titration procedure for quetiapine used in the LIGHTHOUSE trial was generally similar to the usual titration regimen that is recommended in the Canadian product monograph. The only minor difference was that the product monograph recommends that the maximum dose of 800 mg could be reached as early as day 3, whereas the dose was held below 800 mg until at least day 4 in the LIGHTHOUSE trial. The range of dosages used in the LIGHTHOUSE trial (i.e., 2 mg to 4 mg for brexpiprazole and 400 mg to 800 mg for quetiapine) were reflective of the dosage ranges recommended in the Canadian product monographs for brexpiprazole and quetiapine XR. The clinical expert consulted by CADTH indicated that the dosage of quetiapine XR used in the LIGHTHOUSE study was reflective of Canadian clinical practice.

All of the trials involved extensive patient contact with health care professionals, which may not be reflective of routine clinical practice in Canada. In addition, the acute exacerbation trials were conducted exclusively on an in-patient basis. This may reduce the generalizability of the results to the Canadian setting. The clinical expert consulted during this review indicated that the majority of patients in Canada with an acute exacerbation of schizophrenia would not receive six weeks of in-patient treatment. Limitations in available resources can restrict in-patient treatment to only the most severely ill patients (e.g., those considered to be at risk of self-harm or harm to others). It is possible that the in-patient treatment phase could have reduced the number of early discontinuations. The clinical expert consulted during this review also suggested that the prolonged in-patient phase could have increased the placebo response in the trial.

Efficacy for Acute Exacerbations

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 6). See Appendix 1 for detailed efficacy data.

Positive and Negative Syndrome Scale

PANSS Total Score

Changes from baseline in PANSS total score are summarized in Figure 3 for the VECTOR, BEACON, and LIGHTHOUSE studies. In all three studies, PANSS total scores improved from baseline in both the brexpiprazole and placebo groups. In the VECTOR study, both the 2 mg and 4 mg doses of brexpiprazole were associated with a statistically significant improvement compared with placebo (least squares mean difference [LSMD]: –8.72 [95% CI, –13.1 to –4.37] and –7.64 [95% CI, –12.0 to –3.30], respectively). In the BEACON study, the 4 mg dose of brexpiprazole was associated with a statistically significant improvement compared with placebo (LSMD: −6.47 [95%, −10.6 to −2.35]); however, the 2 mg dosage was not associated with a statistically significant improvement compared with placebo (LSMD: −3.08 [95% CI, −7.23 to 1.07]; *P* = 0.1448). Failure to demonstrate a statistically significant difference between the 2 mg brexpiprazole group and the placebo group stopped the statistical testing hierarchy at the primary end point in the BEACON trial. In the LIGHTHOUSE trial, there was no statistically significantly difference between flexibly dosed brexpiprazole and placebo (LSMD: −4.1 [95% CI, −8.2 to 0.1]; *P* = 0.0560); however, there was a statistically significant difference favouring quetiapine over placebo (LSMD: −8.0 [redacted]).[3] There was no analysis conducted comparing brexpiprazole against quetiapine in the LIGHTHOUSE study.[3]

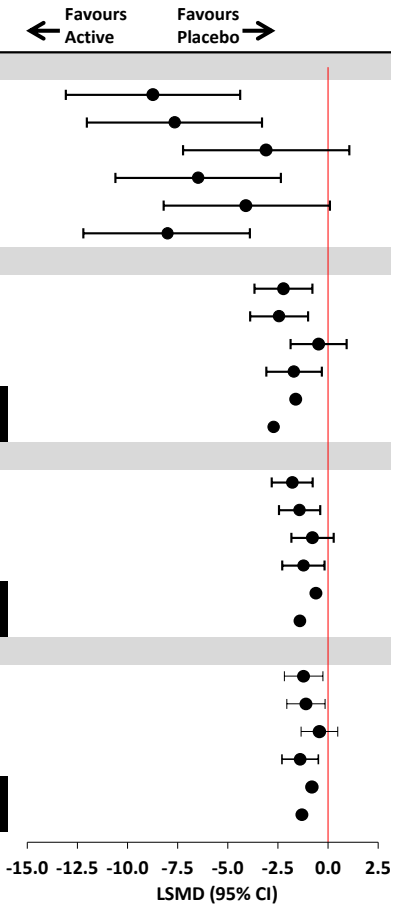
PANSS Subscales

Change from baseline in the PANSS Positive subscale, Negative subscale, and the Excited Component subscale are summarized in Figure 3. In the VECTOR trial, both 2 mg per day and 4 mg per day dosages of brexpiprazole were associated with statistically significant improvements in the PANSS Positive subscale, Negative subscale, and Excited Component subscale compared with placebo (all *P* < 0.05). In the BEACON trial, statistically significant differences were demonstrated between the 4 mg per day brexpiprazole group and placebo for the positive subscale (*P* = 0.0166), Negative subscale (*P* = 0.0231), and Excited Component subscale (*P* = 0.0029); however, the 2 mg per day dosage did not demonstrate a statistically significant improvement compared with placebo in the positive subscale (*P* = 0.5101), Negative subscale (*P* = 0.1547), or Excited Component subscale (*P* = 0.3559).

In the LIGHTHOUSE trial, [redacted]. The LIGHTHOUSE study also included change in PANSS General Psychopathology subscale as a secondary end point. The brexpiprazole group did [redacted] compared with placebo (LSMD: −1.7 [redacted]); however, the quetiapine group [redacted] compared with placebo (−3.4 [redacted]).

Figure 3: Change From Baseline in PANSS Total Score

Study	Comparison	LSM (SE) Active	LSM (SE) Placebo	Active vs. Placebo LSMD (95% CI)	P value
PANSS Total Score					
VECTOR	BREX 2 mg vs. PLC	-20.73 (1.55)	-12.01 (1.60)	-8.72 (-13.1, -4.37)	0.0001
	BREX 4 mg vs. PLC	-19.65 (1.54)	-12.01 (1.60)	-7.64 (-12.0, -3.30)	0.0006
BEACON	BREX 2 mg vs. PLC	-16.61 (1.49)	-13.53 (1.52)	-3.08 (-7.23, 1.07)	0.1448
	BREX 4 mg vs. PLC	-20.00 (1.48)	-13.53 (1.52)	-6.47 (-10.6, -2.35)	0.0022
LIGHTHOUSE	BREX 2-4 mg vs. PLC	-20.0 (1.5)	-15.9 (1.5)	-4.1 (-8.2, 0.1)	0.0560
	QUET vs. PLC	-24.0 (1.5)	-15.9 (1.5)	-8.0 (-12.2, -3.9)	0.0002
PANSS Positive Subscale					
VECTOR	BREX 2 mg vs. PLC	-6.57 (0.52)	-4.35 (0.54)	-2.22 (-3.67, -0.77)	0.003
	BREX 4 mg vs. PLC	-6.78 (0.51)	-4.35 (0.54)	-2.44 (-3.88, -0.99)	0.001
BEACON	BREX 2 mg vs. PLC	-5.42 (0.50)	-4.95 (0.51)	-0.47 (-1.86, 0.93)	0.5101
	BREX 4 mg vs. PLC	-6.65 (0.50)	-4.95 (0.51)	-1.70 (-3.08, -0.31)	0.0166
LIGHTHOUSE	BREX 2-4 mg vs. PLC	-7.0 (0.5)	-5.4 (0.5)	-1.6	[redacted]
	QUET vs. PLC	-8.1 (0.5)	-5.4 (0.5)	-2.7	
PANSS Negative Subscale					
VECTOR	BREX 2 mg vs. PLC	-4.02 (0.36)	-2.24 (0.38)	-1.78 (-2.81, -0.76)	0.0007
	BREX 4 mg vs. PLC	-3.65 (0.36)	-2.24 (0.38)	-1.41 (-2.44, -0.39)	0.007
BEACON	BREX 2 mg vs. PLC	-2.91 (0.38)	-2.14 (0.39)	-0.77 (-1.83, 0.29)	0.1547
	BREX 4 mg vs. PLC	-3.36 (0.39)	-2.14 (0.39)	-1.22 (-2.28, -0.17)	0.0231
LIGHTHOUSE	BREX 2-4 mg vs. PLC	-3.7 (0.4)	-3.1 (0.4)	-0.6	[redacted]
	QUET vs. PLC	-4.5 (0.4)	-3.1 (0.4)	-1.4	
PANSS Excited Component					
VECTOR	BREX 2 mg vs. PLC	-2.87 (0.34)	-1.64 (0.36)	-1.22 (-2.19, -0.26)	0.01
	BREX 4 mg vs. PLC	-2.75 (0.34)	-1.64 (0.36)	-1.10 (-2.06, -0.14)	0.02
BEACON	BREX 2 mg vs. PLC	-1.90	-1.47	-0.43 (-1.34, 0.48)	0.3559
	BREX 4 mg vs. PLC	-2.86	-1.47	-1.39 (-2.30, -0.48)	0.0029
LIGHTHOUSE	BREX 2-4 mg vs. PLC	-3.3 (0.3)	-2.5 (0.3)	-0.8	[redacted]
	QUET vs. PLC	-3.9 (0.3)	-2.5 (0.3)	-1.3	



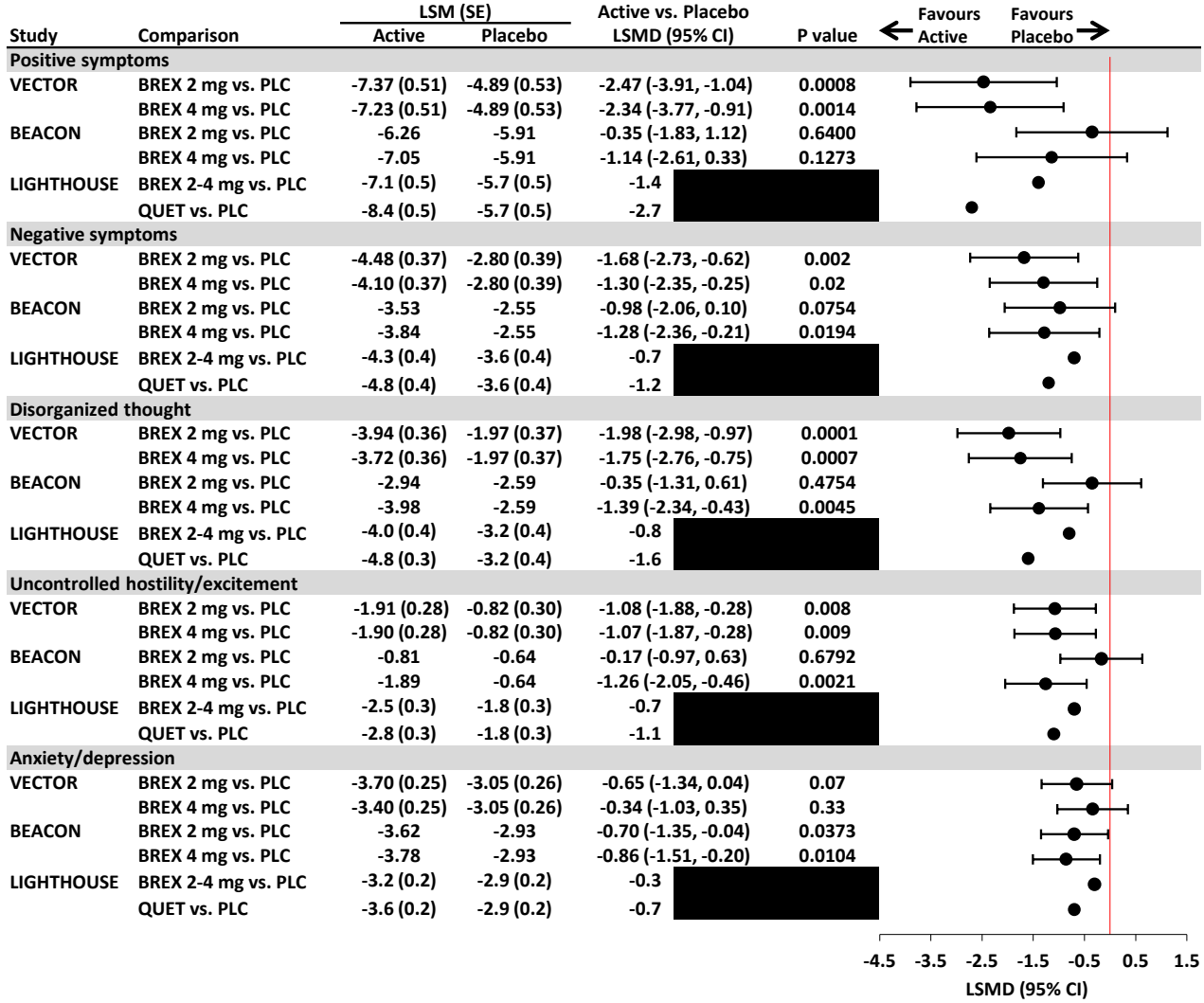
BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; PLC = placebo; QUET = quetiapine; SE = standard error; vs. = versus.

Source: Data from Correll et al. 2015,[35] Kane et al. 2015,[40] and Clinical Study Report for LIGHTHOUSE.[3]

PANSS Marder Factors

Change from baseline in PANSS Marder Factors is summarized in Figure 4. In the VECTOR trial, both the 2 mg per day and 4 mg per day brexpiprazole groups were associated with statistically significant improvements in the following PANSS Marder Factors: positive symptoms; negative symptoms, disorganized thought, and uncontrolled hostility/excitement. There was no statistically significant difference between the brexpiprazole groups and placebo for anxiety/depression. In the BEACON trial, the 2 mg per day brexpiprazole group did not demonstrate a statistically significant difference compared with placebo for positive symptoms, negative symptoms, disorganized thought, or uncontrolled hostility/excitement, but did demonstrate a statistically significant difference in the anxiety/depression subscale. The 4 mg per day brexpiprazole group demonstrated a statistically significant difference in each of the Marder Factor subscales, with the exception of positive symptoms (P = 0.1273). In the LIGHTHOUSE trial, [redacted]

Figure 4: Change from Baseline in PANSS Marder Factors



BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; mg = milligrams; PLC = placebo; SE = standard error; QUET = quetiapine; vs. = versus.

Source: Data from Correll et al. 2015,[35] Kane et al. 2015,[40] and Clinical Study Report for LIGHTHOUSE.[3]

Clinical Global Impression of Severity and Improvement

Clinical Global Impression of Severity

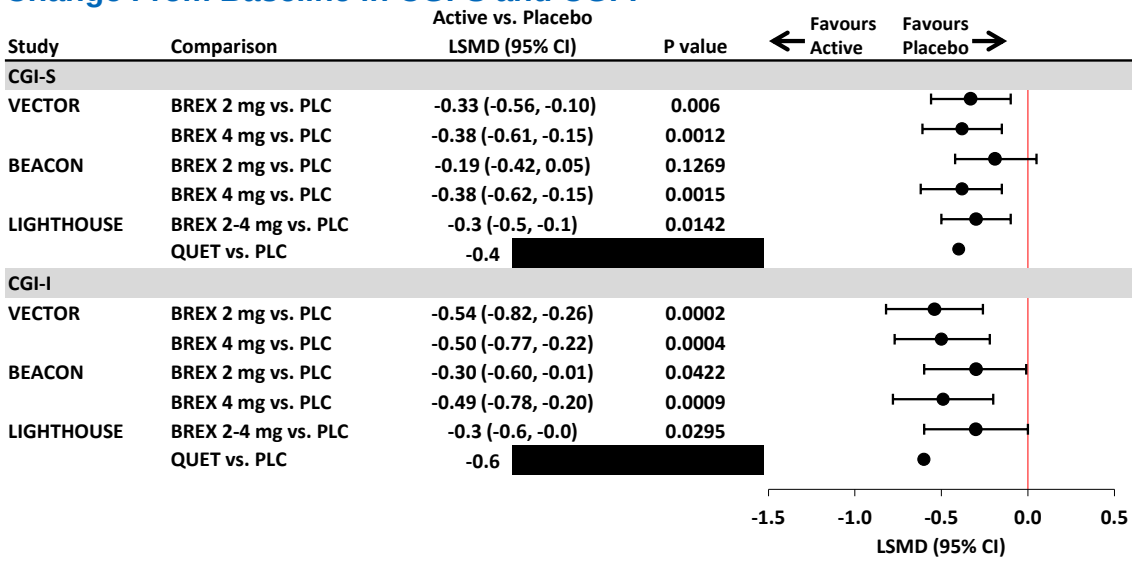
Results for change from baseline in the CGI-S are summarized in Figure 5. CGI-S was a key secondary end point of both the VECTOR and BEACON trials. In the VECTOR trial, both the 2 mg per day and 4 mg per day dosages of brexpiprazole were associated with a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.33 [95% CI, −0.56 to −0.10] and −0.38 [95% CI, −0.61 to −0.15], respectively). Failure to demonstrate a statistically significant difference between the 2 mg brexpiprazole and placebo group in the BEACON trial stopped the statistical testing hierarchy at the primary end point; therefore, the results of CGI-S analyses are considered exploratory. The LSMD favoured the 4 mg per day dosage of brexpiprazole compared with placebo (LSMD: −0.38

[95% CI, −0.62 to −0.15]). In contrast, the 2 mg per day dosage of brexpiprazole did not demonstrate a difference compared with placebo (LSMD: −0.19 [95% CI −0.42 to 0.05]). In the LIGHTHOUSE trial, [redacted] brexpiprazole [redacted] demonstrated a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.3 [95% CI, −0.5 to −0.1] and −0.4 [redacted]).

Clinical Global Impression of Improvement

Results for change from baseline in the CGI-I are summarized in Figure 5. Change from baseline in CGI-I was a secondary end point in all three of the acute exacerbation trials. In both the VECTOR and BEACON trials, both the 2 mg per day and 4 mg per day dosages of brexpiprazole were associated with a statistically significant improvement in CGI-I compared with placebo. In the LIGHTHOUSE trial, [redacted] brexpiprazole [redacted] demonstrated a statistically significant improvement in CGI-S compared with placebo.

Figure 5: Change From Baseline in CGI-S and CGI-I



BREX = brexpiprazole; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; LSMD = least squares mean difference; mg = milligrams; PLC = placebo; QUET = quetiapine; vs. = versus.

Source: Data from Correll et al. 2015,[35] Kane et al. 2015,[40] and Clinical Study Report for LIGHTHOUSE.[3]

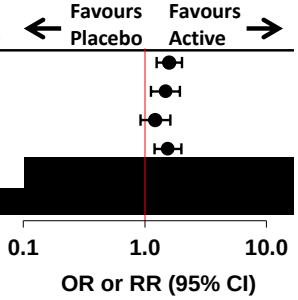
Responder Analyses

Response was defined as a reduction of greater than and equal to 30% from baseline in PANSS total score at week 6 or a CGI-I score of 1 (very much improved) or 2 (much improved) at week 6. Results for the responder analyses are summarized in Figure 6. In both the VECTOR and BEACON trials, the 4 mg per day dosages of brexpiprazole were associated with a statistically significantly greater proportion of responders compared with placebo (RR: 1.48 [95% CI, 1.14 to 1.91] and 1.54 [95% CI, 1.20 to 2.00]).[1,2] The 2 mg per day dosage was superior to placebo in the VECTOR trial (RR: 1.59 [95% CI, 1.23 to 2.05]), but not in the BEACON trial (RR: 1.22 [95% CI, 0.92 to 1.62]).[1,2] In the LIGHTHOUSE trial, [redacted] brexpiprazole [redacted] demonstrated a statistically significantly greater proportion of responders compared with placebo ([redacted] and 3.56 [redacted]).[3]

The proportion of patients who achieved an improvement in PANSS total score from baseline of at least 20%, 40%, or 50% were post hoc exploratory end points in the VECTOR and BEACON trials. The results for each analysis were similar to those based on the 30% improvement in PANSS and are summarized in Figure 21 (84).

Figure 6: Proportion of Patients Meeting Criteria for Response

Study	Comparison	Response, n (%) Active	Response, n (%) Placebo	Active vs. Placebo RR or OR (95% CI)	P value
VECTOR	BREX 2 mg vs. PLC	86 (47.78)	54 (30.34)	RR: 1.59 (1.23, 2.05)	0.0004
	BREX 4 mg vs. PLC	82 (46.07)	54 (30.34)	RR: 1.48 (1.14, 1.91)	0.0032
BEACON	BREX 2 mg vs. PLC	69 (38.55)	57 (31.67)	RR: 1.22 (0.92, 1.62)	0.1680
	BREX 4 mg vs. PLC	90 (49.72)	57 (31.67)	RR: 1.54 (1.20, 2.00)	0.0006
LIGHTHOUSE	BREX 2-4 mg vs. PLC	73 (48.7)	51 (32.1)	[redacted]	0.0032
	QUET vs. PLC	[redacted]			



BREX = brexpiprazole; CI = confidence interval; mg = milligrams; n = number of responders; OR = odds ratio; PLC = placebo; QUET = quetiapine; RR = relative risk; vs. = versus.

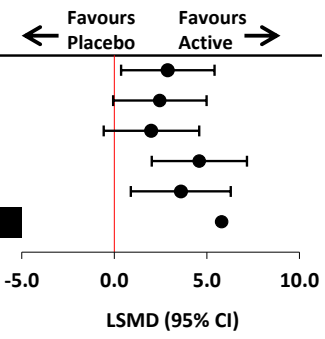
Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] and LIGHTHOUSE.[3]

Personal and Social Performance Scale

Change from baseline in the Personal and Social Performance Scale (PSP) score are summarized in Figure 7. In the two fixed-dose trials, results for the 2 mg per day and 4 mg per day brexpiprazole were conflicting. In the VECTOR trial, the 2 mg per day brexpiprazole was associated with a statistically significant difference in PSP compared with placebo (LSMD: 2.89 [95% CI, 0.37 to 5.42]); however, the 4 mg per day group was not associated with a statistically significant difference (LSMD: 2.46 [95% CI, −0.06 to 4.98]).[1] In the BEACON trial, the 2 mg per day brexpiprazole was not associated with a statistically significant difference compared with placebo (LSMD: 2.00 [95% CI, −0.58 to 4.59]); however, there was a statistically significant difference favouring the 4 mg per day group over placebo (LSMD: 4.59 [95% CI, 2.02 to 7.17]).[2] [redacted] brexpiprazole [redacted] were associated with statistically significant difference compared with placebo in the LIGHTHOUSE trial (LSMD: 3.6 [95% CI, 0.9 to 6.3] and 5.8 [redacted]).[3]

Figure 7: Change From Baseline in Personal and Social Performance Scale

Study	Comparison	LSM (SE) Active	LSM (SE) Placebo	Active vs. Placebo LSMD (95% CI)	P value
VECTOR	BREX 2 mg vs. PLC	13.15 (0.93)	10.26 (0.98)	2.89 (0.37, 5.42)	0.03
	BREX 4 mg vs. PLC	12.72 (0.93)	10.26 (0.98)	2.46 (-0.06, 4.98)	0.06
BEACON	BREX 2 mg vs. PLC	10.52 (0.95)	8.52 (0.97)	2.00 (-0.58, 4.59)	0.1286
	BREX 4 mg vs. PLC	13.11 (0.94)	8.52 (0.97)	4.59 (2.02, 7.17)	0.0005
LIGHTHOUSE	BREX 2-4 mg vs. PLC	13.0 (1.0)	9.4 (1.0)	3.6 (0.9, 6.3)	0.0101
	QUET vs. PLC	[redacted]		5.8 [redacted]	



BREX = brexpiprazole; CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; mg = milligrams; PLC = placebo; QUET = quetiapine; SE = standard error; vs. = versus.

Source: Data from Correll et al. 2015,[35] Kane et al. 2015,[40] and Clinical Study Report for LIGHTHOUSE.[3]

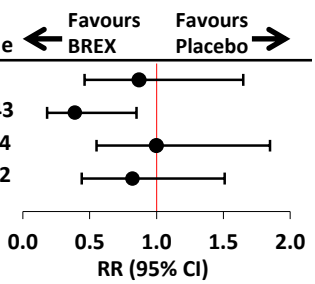
Discontinuation Due to a Lack of Efficacy

The proportion of patients who discontinued due to a lack of efficacy is summarized in Figure 8. In both the VECTOR and BEACON trials, there was no statistically significant difference between the 2 mg brexpiprazole and placebo groups for the proportion of patients who discontinued due to a lack of efficacy (RR: 0.87 [95% CI, 0.46 to 1.65] and 1.00 [95% CI, 0.55 to 1.85], respectively).[1,2] There was a statistically significant difference favouring the 4 mg per day group over placebo in the VECTOR trial (RR: 0.39 [95% CI, 0.18 to 0.85]); however, there was no statistically significant difference in the BEACON trial (RR: 0.82 [95% CI, 0.44 to 1.51]).[1,2]

Time to discontinuation due to a lack of efficacy was a secondary end point in the LIGHTHOUSE trial. Compared with placebo, [redacted].[3]

FIGURE 8: DISCONTINUATIONS DUE TO LACK OF EFFICACY

Study	Comparison	Events, n (%) BREX	Events, n (%) Placebo	BREX vs. Placebo RR (95% CI)	P value
VECTOR	BREX 2 mg vs. PLC	17 (9.4)	18 (10.1)	0.87 (0.46, 1.65)	0.66
	BREX 4 mg vs. PLC	7 (3.9)	18 (10.1)	0.39 (0.18, 0.85)	0.0143
BEACON	BREX 2 mg vs. PLC	20 (11.17)	21 (11.67)	1.00 (0.55, 1.85)	0.9894
	BREX 4 mg vs. PLC	16 (8.84)	21 (11.67)	0.82 (0.44, 1.51)	0.5202



BREX = brexpiprazole; CI = confidence interval; mg = milligrams; PLC = placebo; RR = relative risk; vs. = versus.

Source: Data from Correll et al. 2015[35] and Kane et al. 2015.[40]

Schizophrenia Quality of Life

Change from baseline in the S-QoL total score and subscales were secondary end points in the LIGHTHOUSE trial and the results are summarized in Figure 9. [redacted] brexpiprazole [redacted] associated with statistically significant improvements in S-QoL total score compared with placebo [redacted]

Figure 9: Results for Schizophrenia Quality of Life

Confidential data removed at manfuacturer's request.

BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; PLC = placebo; QUET = quetiapine; SE = standard error.

Source: Clinical Study Report for LIGHTHOUSE.[3]

Efficacy for Maintenance Treatment

Impending Relapse

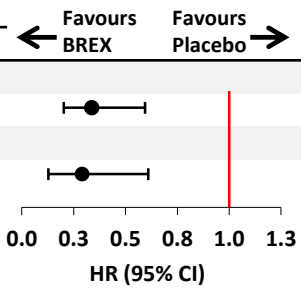
Time to Impending Relapse

Time to impending relapse was the primary end point of the EQUATOR maintenance study. Figure 10 shows the results for time to impending relapse in the interim and final analyses. Time to impending relapse was statistically significantly delayed in the brexpiprazole group compared with the placebo group in both the interim (HR: 0.34 [95% CI, 0.17 to 0.66]; $P = 0.0008$) and final analyses (HR: 0.29 [95% CI, 0.16 to 0.55]; $P < 0.0001$).[4] The median time to impending relapse in the interim and final analyses was [redacted] and 169.0 days in the brexpiprazole group and [redacted] and 111.0 days in the placebo group.[4] Kaplan-Meier curves for risk of impending relapse are shown in Figure 11.

The following sensitivity analyses were conducted and demonstrated results which were consistent with the primary analysis (i.e., all favoured brexpiprazole compared with placebo): multiple imputation of discontinued censored observations; sub-impending relapse criteria (CGI-I score greater than and equal to 5 AND an increase on any of the individual PANSS items of conceptual disorganization, hallucinatory behaviour, suspiciousness, or unusual thought content to a score greater than 4); handling 20% of randomly selected discontinued patients only from the brexpiprazole groups as events (Table 31 on page 85).[4]

Figure 10: Time to Impending Relapse

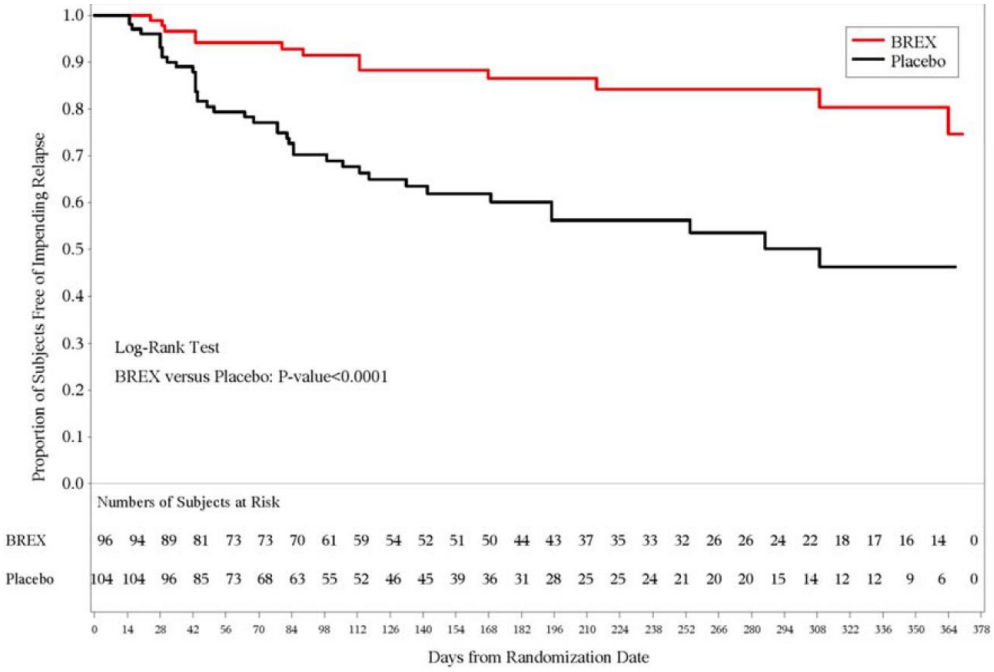
Comparison	Impending Relapse, n/N (%) BREX	PLC	BREX 2-4 mg vs. PLC HR (95% CI)	P value
Interim Analysis				
BREX 2-4 mg vs. PLC	12/78 (15.38)	33/89 (37.08)	0.338 (0.174, 0.655)	0.0008
Final Analysis				
BREX 2-4 mg vs. PLC	13/96 (13.54)	40/104 (38.46)	0.292 (0.156, 0.548)	<0.0001



BREX = brexpiprazole; CI = confidence interval; HR = hazard ratio; mg = milligrams; N = total number of patients; n = number of patients in subgroup; PLC = placebo; vs. = versus.

Source: Clinical Study Report for EQUATOR.[4]

Figure 11: Kaplan-Meier Curves of Time to Impending Relapse



BREX = brexpiprazole.

Source: Clinical Study Report for EQUATOR.[4]

Proportion of Patients with Impending Relapse

The proportion of patients who met the criteria for impending relapse was the key secondary end point of the EQUATOR trial. In both the interim and final analyses, the proportion of patients meeting the criteria for impending relapse was statistically significantly lower in the brexpiprazole group compared with the placebo group ([redacted] and 13.5% versus 38.5% [$P < 0.0001$], respectively).[4] The most common criteria for impending relapse in both the brexpiprazole and placebo groups were the CGI-I and PANSS scores criteria, as described in section 0.[4]

Proportion of Patients Meeting Stability Criteria

The proportion of patients who met the criteria for stability was a secondary end point of the EQUATOR trial. As shown in Table 21, there were no statistically significant differences between brexpiprazole and placebo for the individual time point evaluations (i.e., weeks 6, 12, 24, 36, and 52).[4] However, there was a statistically significant difference favouring brexpiprazole in the evaluation that was conducted using the patient's last visit (i.e., before completion of the study or discontinuation).[4]

Table 21: Exposure in the Acute and Maintenance Treatment Trials

Time Point	Stability Criteria, n/N (%)		*P* Value
	BREX	Placebo	
Week 6	75/81 (92.59)	73/84 (86.90)	0.2296
Week 12	68/73 (93.15)	59/68 (86.76)	0.2051
Week 24	48/50 (96.00)	34/36 (94.44)	0.7354
Week 36	31/33 (93.94)	20/24 (83.33)	0.1977
Week 52	13/15 (86.67)	8/9 (88.89)	0.8734
Last visit	76/96 (79.17)	59/104 (56.73)	0.0007

BREX = brexpiprazole; n = number of patients meeting stability criteria; N = total number of patients in analysis.

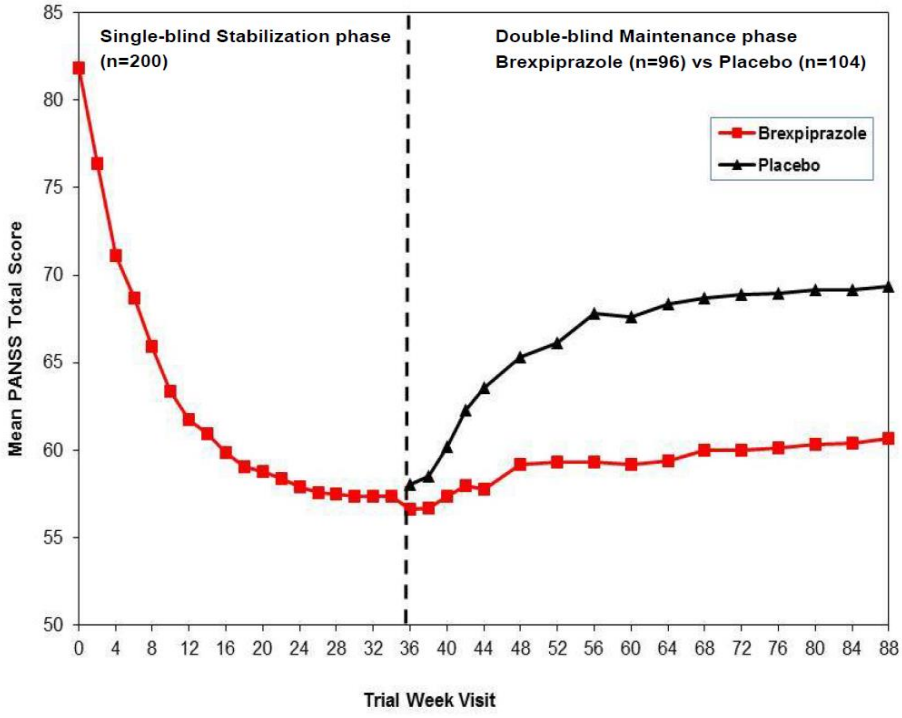
Source: Clinical Study Report for EQUATOR.[4]

Positive and Negative Syndrome Scale

PANSS Total Score

Mean PANSS total scores in the stabilization and maintenance phases of EQUATOR are summarized in Figure 12. Change from baseline in PANSS total score was a secondary end point of the EQUATOR trial and the results are summarized in Figure 13 for the MMRM analyses and Figure 22 (page 84) for the LOCF analyses. There was a statistically significant difference favouring brexpiprazole at weeks 12, 24, and 36 in the MMRM analyses and at all time points in the LOCF analyses.

Figure 12: Change From Baseline PANSS Total Score in Stabilization and Maintenance Phases



n = number of patients in subgroup; PANSS = Positive and Negative Syndrome Scale.

Source: Clinical Study Report for EQUATOR.[4]

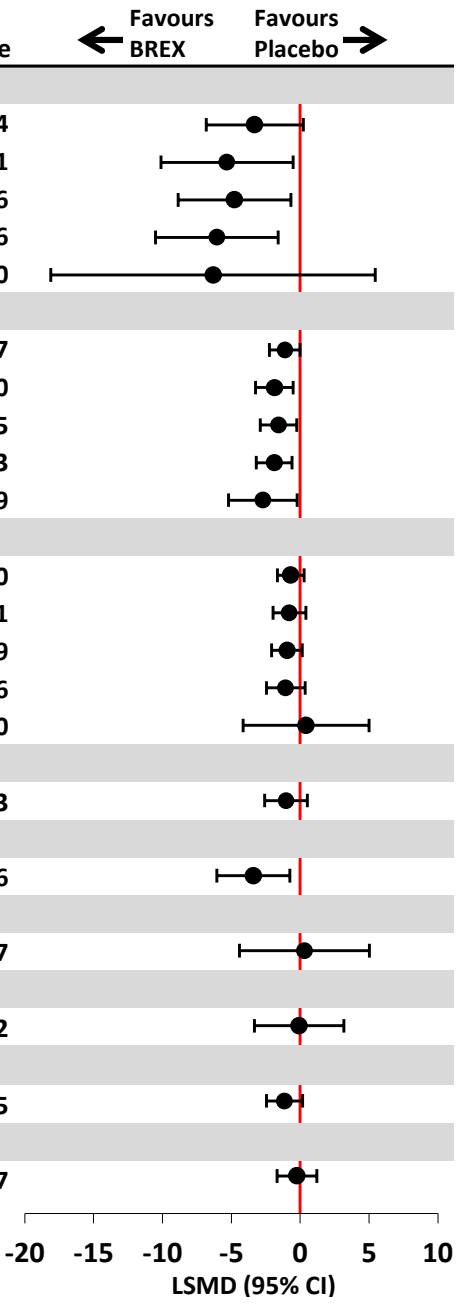
PANSS Subscales and Marder Factors

For the positive PANSS subscale, brexpiprazole demonstrated a statistically significant improvement compared with placebo at all time points with the exception of week 6 in both the MMRM and LOCF analyses. For the PANSS Negative subscale, there were no statistically significant differences between brexpiprazole and placebo at any time points in the MMRM analyses; however, there was a statistically significant difference in the LOCF analyses at weeks 12, 24, and 36.[4] The PANSS Excited Component subscale was only evaluated at 52 weeks and there was a statistically significant difference favouring brexpiprazole over placebo in the LOCF analysis. There was no statistically significant difference in the MMRM analysis.[4]

Change from baseline in PANSS Marder Factors was also only evaluated at 52 weeks. In the MMRM analysis, there was a statistically significant difference in the positive symptoms score and no significant difference for the other four Marder Factors. In the LOCF analyses, there was also a statistically significant improvement in the positive symptom score as well as the disorganized thought score and uncontrolled hostility/excitement score.[4]

Figure 13: Summary of PANSS End Points in Maintenance Trial (MMRM)

Time point	LS Mean Change (N) BREX	PLC	LSMD (95% CI)	P value
PANSS Total				
Week 6	0.79 (81)	4.09 (84)	-3.30 (-6.82, 0.23)	0.0664
Week 12	0.84 (73)	6.15 (68)	-5.31 (-10.1, -0.52)	0.0301
Week 24	-1.88 (50)	2.89 (36)	-4.77 (-8.86, -0.68)	0.0226
Week 36	-2.71 (33)	3.33 (24)	-6.03 (-10.5, -1.59)	0.0086
Week 52	0.61 (15)	6.92 (9)	-6.31 (-18.1, 5.46)	0.2800
PANSS Positive				
Week 6	0.17 (81)	1.28 (84)	-1.11 (-2.23, 0.00)	0.0507
Week 12	-0.06 (73)	1.81 (68)	-1.87 (-3.24, -0.50)	0.0080
Week 24	-0.84 (50)	0.72 (36)	-1.56 (-2.89, -0.24)	0.0215
Week 36	-0.97 (33)	0.91 (24)	-1.88 (-3.19, -0.58)	0.0053
Week 52	-1.21 (15)	1.50 (9)	-2.71 (-5.20, -0.22)	0.0339
PANSS Negative				
Week 6	-0.04 (81)	0.65 (84)	-0.69 (-1.66, 0.29)	0.1650
Week 12	-0.22 (73)	0.55 (68)	-0.78 (-1.97, 0.42)	0.2001
Week 24	-0.78 (50)	0.18 (36)	-0.95 (-2.07, 0.16)	0.0939
Week 36	-1.03 (33)	0.02 (24)	-1.05 (-2.44, 0.35)	0.1396
Week 52	1.30 (15)	0.87 (9)	0.43 (-4.14, 5.00)	0.8470
PANSS PEC				
Week 52	-0.04 (15)	1.00 (9)	-1.03 (-2.58, 0.51)	0.1803
Marder Positive Symptoms Score				
Week 52	-1.62 (15)	1.78 (9)	-3.40 (-6.05, -0.75)	0.0136
Marder Negative Symptoms Score				
Week 52	1.37 (15)	1.06 (9)	0.31 (-4.40, 5.02)	0.8927
Marder Disorganized Thought Score				
Week 52	-0.37 (15)	-0.30 (9)	-0.07 (-3.32, 3.17)	0.9632
Marder Uncontrolled Hostility/Excitement				
Week 52	-0.20 (15)	0.94 (9)	-1.14 (-2.46, 0.18)	0.0875
Marder Anxiety/Depression Score				
Week 52	0.04 (15)	0.28 (9)	-0.23 (-1.68, 1.21)	0.7437



BREX = brexpiprazole; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed model repeated measures; N = total number of patients; PANSS = Positive and Negative Syndrome Scale; PEC = PANSS Excited Component; PLC = placebo.

Source: Clinical Study Report for EQUATOR.[4]

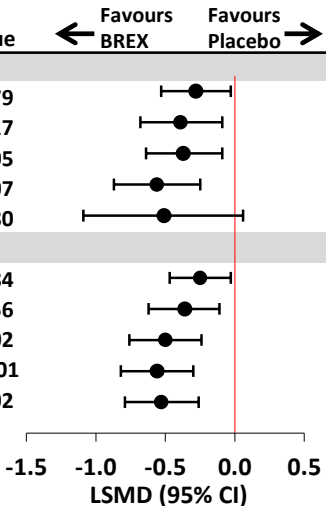
Clinical Global Impression of Severity and Improvement

Clinical Global Impression of Severity

Change from baseline in CGI-S score was a secondary end point of the EQUATOR trial and the results are summarized in Figure 14. There was a statistically significant difference favouring brexpiprazole at weeks 12, 24, and 36 in the MMRM analyses and at all time points in the LOCF analyses.[4]

Figure 14: Summary of Change From Baseline in CGI-S in Maintenance Trial

Time point	LS Mean Change (N) BREX	PLC	LSMD (95% CI)	P value
MMRM				
Week 6	-0.01 (81)	0.26 (84)	-0.28 (-0.53, -0.03)	0.0279
Week 12	-0.01 (73)	0.37 (68)	-0.39 (-0.68, -0.09)	0.0117
Week 24	-0.16 (50)	0.21 (36)	-0.37 (-0.64, -0.09)	0.0105
Week 36	-0.31 (33)	0.25 (24)	-0.56 (-0.87, -0.25)	0.0007
Week 52	-0.23 (15)	0.28 (9)	-0.51 (-1.09, 0.06)	0.0780
LOCF				
Week 6	-0.08 (96)	0.17 (104)	-0.25 (-0.47, -0.03)	0.0284
Week 12	-0.04 (96)	0.32 (104)	-0.36 (-0.62, -0.11)	0.0056
Week 24	-0.03 (96)	0.47 (104)	-0.50 (-0.76, -0.24)	0.0002
Week 36	-0.00 (96)	0.56 (104)	-0.56 (-0.82, -0.30)	<0.0001
Week 52	0.02 (96)	0.55 (104)	-0.53 (-0.79, -0.26)	0.0002



BREX = brexpiprazole; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed model repeated measures; N = total number of patients; PLC = placebo; SD = standard deviation.

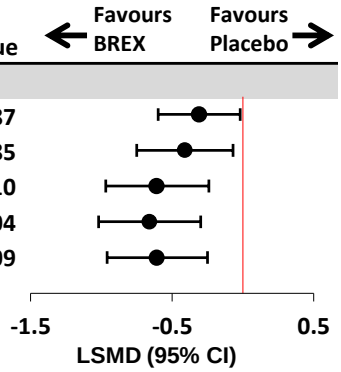
Source: Clinical Study Report for EQUATOR.[4]

Clinical Global Impression of Improvement

Change from baseline in CGI-I score was a secondary end point of the EQUATOR trial and the results are summarized in Figure 15. When analyzed using LOCF, there were statistically significant differences favouring brexpiprazole over placebo at all time points. There were no MMRM analyses conducted for the CGI-I end point.[4]

Figure 15: Summary of Change From Baseline in CGI-I in Maintenance Trial (LOCF)

Time point	Mean (SD) BREX (N = 96)	Mean (SD) PLC (N = 104)	LSMD (95% CI)	P value
CGI-I				
Week 6	3.68 (0.98)	4.00 (1.14)	-0.31 (-0.60, -0.02)	0.0387
Week 12	3.66 (1.19)	4.10 (1.30)	-0.41 (-0.75, -0.07)	0.0185
Week 24	3.67 (1.27)	4.30 (1.32)	-0.61 (-0.97, -0.24)	0.0010
Week 36	3.71 (1.27)	4.39 (1.30)	-0.66 (-1.02, -0.30)	0.0004
Week 52	3.77 (1.26)	4.40 (1.32)	-0.61 (-0.96, -0.25)	0.0009



BREX = brexpiprazole; CGI-I = Clinical Global Impression – Improvement; CI = confidence interval; LOCF = last observation carried forward; LSMD = least squares mean difference; N = total number of patients; PLC = placebo; SD = standard deviation.

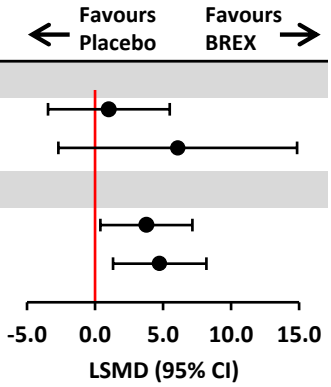
Source: Clinical Study Report for EQUATOR.[4]

Personal and Social Performance Scale

Change from baseline in the PSP was a secondary end point of the EQUATOR trial and the results are summarized in Figure 16. There was no statistically significant difference between the brexpiprazole and placebo groups at 24 and 52 weeks when analyzed using MMRM; however, there was a statistically significant difference when analyzed using LOCF.[4]

Figure 16: Summary of Change From Baseline in PSP in Maintenance Trial (MMRM)

Time point	LS Mean Change (N) BREX	LS Mean Change (N) PLC	LSMD (95% CI)	P value
MMRM				
Week 24	18.85 (50)	17.84 (36)	1.01 (-3.47, 5.49)	0.6525
Week 52	18.63 (15)	12.55 (9)	6.08 (-2.71, 14.87)	0.1677
LOCF				
Week 24	15.20 (94)	11.41 (100)	3.79 (0.40, 7.17)	0.0285
Week 52	15.06 (94)	10.31 (100)	4.75 (1.31, 8.18)	0.0071



BREX = brexpiprazole; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MMRM = mixed model repeated measures; N = total number of patients; PLC = placebo; PSP = Personal and Social Performance Scale; SD = standard deviation.

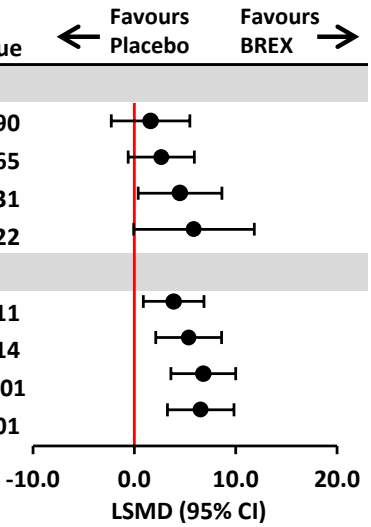
Source: Clinical Study Report for EQUATOR.[4]

Global Assessment of Functioning

Change from baseline in the GAF scale was a secondary end point of the EQUATOR trial and the results are summarized in Figure 17. When analyzed using MMRM, there was a statistically significant difference between brexpiprazole and placebo at 36 weeks, but not at 12, 24, or 52 weeks. In contrast, there was a statistically significant difference favouring brexpiprazole over placebo at all time points in the LOCF analysis.[4]

Figure 17: Summary of Change From Baseline in GAF in Maintenance Trial (MMRM)

Time point	LS Mean Change (N) BREX	PLC	LSMD (95% CI)	P value
MMRM				
Week 12	1.59 (73)	-0.03 (68)	1.61 (-1.65, 4.88)	0.3290
Week 24	3.74 (50)	1.09 (36)	2.66 (-1.22, 6.54)	0.1765
Week 36	4.71 (33)	0.21 (24)	4.50 (0.38, 8.63)	0.0331
Week 52	5.72 (15)	-0.16 (9)	5.88 (-0.06, 11.82)	0.0522
LOCF				
Week 12	0.44 (95)	-3.44 (102)	3.88 (0.90, 6.86)	0.0111
Week 24	0.85 (95)	-4.51 (102)	5.36 (2.10, 8.62)	0.0014
Week 36	0.97 (95)	-5.84 (102)	6.81 (3.61, 10.00)	<0.0001
Week 52	0.55 (95)	-6.01 (102)	6.55 (3.28, 9.83)	0.0001



BREX = brexpiprazole; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MMRM = mixed model repeated measures; N = total number of patients; PLC = placebo; PSP = Personal and Social Performance Scale; SD = standard deviation.

Source: Clinical Study Report for EQUATOR.[4]

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). In accordance with the manufacturer's safety analysis plan,[5] this section of the report summarizes adverse event data from the single 52-week maintenance treatment trial (EQUATOR [N = 202]) and pooled adverse event data for the brexpiprazole and placebo groups from the acute treatment trials. The pooled data set consists of adverse event data from the six-week VECTOR (N = 636), BEACON (N = 674), and LIGHTHOUSE (N = 468) studies, and one six-week phase II study (331-07-203; N = 459). As noted earlier, the CDR systematic review is focused only on the Health Canada–approved dosage of brexpiprazole; therefore, data for brexpiprazole dosage groups below 2 mg and above 4 mg are not summarized. The active treatments from the LIGHTHOUSE trial (quetiapine) and the phase II study (aripiprazole) are included in the summary tables. Table 22 provides a summary of adverse events from both the maintenance trial population and the pooled acute exacerbation trial populations.

Table 22: Summary of Adverse Events

Adverse Events n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX (N = 1406)	Placebo (N = 624)	ARI (N = 50)	QUET (N = 153)	BREX (N = 97)	Placebo (N = 104)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	42 (43.3)	58 (55.8)
Any severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.1)	11 (10.6)
WDAE	[redacted]	[redacted]	[redacted]	[redacted]	5 (5.2)	12 (11.6)

ARI = aripiprazole; BREX = brexpiprazole; n = number of patients with events; N = total number of patients; n = number of patients in subgroup; PLC = placebo; QUET = quetiapine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Source: Common Technical Document Section 2.7.4.[5]

Adverse Events

[redacted]. Table 23 [redacted]

Table 24 summarizes the adverse events that were for reported for at least 5% of patients in the brexpiprazole group (stabilization or maintenance), or the placebo group. In the stabilization phase of EQUATOR, [redacted] of brexpiprazole-treated patients experienced at least one adverse event. The treatment-emergent adverse events that were reported in at least 5% of brexpiprazole-treated patients were insomnia (12.1%), akathisia (9.1%), agitation (6.5%), schizophrenia (6.0%), weight increased (5.2%), and headache (5.0%). In the maintenance phase of EQUATOR, the most frequently occurring TEAEs in the brexpiprazole group were headache (6.2%) and insomnia (5.2%), both of which occurred at a higher incidence in the placebo group (7.7% and 9.6%, respectively). Adverse events that were reported in at least 2% of patients in the brexpiprazole group with a greater incidence compared with the placebo were: tremor (3.1% versus 0.0%), pruritus (2.1% versus 0.0%), decreased appetite (2.1% versus 0.0%), musculoskeletal pain (2.1% versus 1.0%), muscle spasm (2.1% versus 0.0%), and toothache (3.1% versus 1.0%).

Table 23: Adverse Events in at Least 2% of Patients in Acute Treatment Trials

Adverse Events n (%)	Acute Treatment Trials			
	BREX 2–4 mg (N = 972)	Placebo	ARI (N = 50)	QUET (N = 153)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders				
Tachycardia	[redacted]	[redacted]	1 (2.0)	3 (2.0)
Supraventricular extrasystoles	[redacted]	[redacted]	1 (2.0)	0 (0.0)
Gastrointestinal disorders				
Constipation	[redacted]	[redacted]	1 (2.0)	7 (4.6)
Diarrhea	[redacted]	[redacted]	4 (8.0)	2 (1.3)
Nausea	[redacted]	[redacted]	1 (2.0)	4 (2.6)
Dyspepsia	[redacted]	[redacted]	1 (2.0)	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	0 (0.0)	13 (8.5)
Abdominal discomfort	[redacted]	[redacted]	1 (2.0)	[redacted]

Adverse Events n (%)	Acute Treatment Trials			
	BREX 2–4 mg (N = 972)	Placebo	ARI (N = 50)	QUET (N = 153)
Abdominal pain	[redacted]	[redacted]	1 (2.0)	[redacted]
Eructation	[redacted]	[redacted]	1 (2.0)	[redacted]
General disorders and administration site				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Periodontitis	[redacted]	[redacted]	[redacted]	[redacted]
Tinea pedis	[redacted]	[redacted]	[redacted]	[redacted]
Abscess oral	[redacted]	[redacted]	[redacted]	[redacted]
Investigations				
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Prothrombin level increased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders				
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Increased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and CTD				
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]	[redacted]	[redacted]
Muscle rigidity	[redacted]	[redacted]	[redacted]	[redacted]
Rhabdomyolysis	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders				
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Sedation	[redacted]	[redacted]	[redacted]	[redacted]
Extrapyramidal disorder	[redacted]	[redacted]	[redacted]	[redacted]
Complex partial seizures	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders				
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]	[redacted]
Schizophrenia	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
Restlessness	[redacted]	[redacted]	[redacted]	[redacted]
Tension	[redacted]	[redacted]	[redacted]	[redacted]
Libido increased	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events n (%)	Acute Treatment Trials			
	BREX 2–4 mg (N = 972)	Placebo	ARI (N = 50)	QUET (N = 153)
Reproductive and breast disorders				
Prostatitis	[redacted]	[redacted]	[redacted]	[redacted]
RTM disorders				
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]
Skin and SC tissue disorders				
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Rash generalized	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders				
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; ARI = aripiprazole; BREX = brexpiprazole; CPK = creatine phosphokinase; CTD = connective tissue disorders; ECG = electrocardiogram; n = number of patients with events; N = total number of patients; n = number of patients in subgroup; NR = none reported; QUET = quetiapine; RTM = respiratory, thoracic, and mediastinal; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Source: Common Technical Document Section 2.7.4.[5]

Table 24: Adverse Events in at Least 5% of Patients in Maintenance Trial

Adverse Events n (%)	Stabilization Phase	Maintenance Phase	
	BREX 2-4 mg (N = 464)	BREX 2-4 mg (N = 97)	Placebo (N = 104)
Headache	23 (5.0)	6 (6.2)	10 (9.6)
Insomnia	56 (12.1)	5 (5.2)	8 (7.7)
Nasopharyngitis	16 (3.4)	3 (3.1)	7 (6.7)
Schizophrenia	28 (6.0)	3 (3.1)	7 (6.7)
Psychotic disorder	5 (1.1)	1 (1.0)	6 (5.8)
Agitation	30 (6.5)	1 (1.0)	3 (2.9)
Akathisia	42 (9.1)	1 (1.0)	1 (1.0)
Weight increased	24 (5.2)	1 (1.0)	0 (0.0)

BREX = brexpiprazole; mg = milligrams; n = number of patients with events; N = total number of patients.

Source: Fleischhacker et al. 2016.[43]

Serious Adverse Events

Table 25 provides a summary of the adverse events in the acute exacerbation and maintenance trials. In the acute exacerbation studies, the proportion of patients who experienced at least one serious adverse event [redacted] aripiprazole (2/50 [4.0%]), [redacted] quetiapine group (2/153 [1.3%]). [redacted].

In the stabilization phase of the EQUATOR trial, serious adverse events were reported for 7.3% of patients, with schizophrenia (4.7%), psychotic disorder (0.6%), and suicidal ideation (0.6%) being the only events that occurred in more than one patient. In the maintenance

phase of EQUATOR, the proportion of patients who experienced at least one serious adverse event was greater in the placebo group compared with the brexpiprazole group (10.6% versus 3.1%). Similar to the stabilization phase, schizophrenia and psychotic disorder were the most commonly reported events in both the placebo and brexpiprazole groups (4.8% versus 1.0%, and 3.8% versus 1.0%, respectively).

Table 25: Serious Adverse Events in Acute and Maintenance Treatment Trials

SAEs, n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX 2–4 mg (N = 972)	Placebo (N = 624)	ARI (N = 50)	QUET (N = 153)	BREX 2–4 mg (N = 97)	Placebo (N = 104)
SAEs	[redacted]	[redacted]	2 (4.0)	2 (1.3)	3 (3.1)	11 (10.6)
Gastrointestinal disorders	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Gastric ulcer	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Metabolism/nutrition disorders	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Hypoglycemia	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Type 2 diabetes mellitus	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Musculoskeletal and CTD	[redacted]	[redacted]	1 (2.0)	0 (0.0)	NR	NR
Rhabdomyolysis	[redacted]	[redacted]	1 (2.0)	0 (0.0)	NR	NR
Nervous system disorders	[redacted]	[redacted]	1 (2.0)	0 (0.0)	NR	NR
Dizziness	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Grand mal convulsion	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Complex partial seizures	[redacted]	[redacted]	1 (2.0)	0 (0.0)	NR	NR
Psychiatric disorders	[redacted]	[redacted]	0 (0.0)	2 (1.3)	2 (2.1)	10 (9.6)
Schizophrenia	[redacted]	[redacted]	0 (0.0)	1 (0.7)	1 (1.0)	5 (4.8)
Psychotic disorder	[redacted]	[redacted]	0 (0.0)	1 (0.7)	1 (1.0)	4 (3.8)
Schizophrenia (paranoid)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Suicidal ideation	[redacted]	[redacted]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Suicide attempt	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Acute psychosis	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Anxiety	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Irritability	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Skin and SC tissue disorders	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Angioedema	[redacted]	[redacted]	0 (0.0)	0 (0.0)	NR	NR
Cardiac disorders	NR	NR	NR	NR	0 (0.0)	2 (2.0)
Angina unstable	NR	NR	NR	NR	0 (0.0)	1 (1.0)
Arrhythmia	NR	NR	NR	NR	0 (0.0)	1 (1.0)
Investigations	NR	NR	NR	NR	1 (1.0)	0 (0.0)
Hepatic enzyme increased	NR	NR	NR	NR	1 (1.0)	0 (0.0)
Vascular disorders	NR	NR	NR	NR	0 (0.0)	1 (1.0)
Hypertension	NR	NR	NR	NR	0 (0.0)	1 (1.0)

ARI = aripiprazole; BREX = brexpiprazole; CTD = connective tissue disorders; n = number of patients with events; N = total number of patients; NR = not reported; QUET = quetiapine; SAE = serious adverse event; SC = subcutaneous.

Source: Common Technical Document Section 2.7.4.[5]

Withdrawal Due to Adverse Events

Table 26 provides a summary of the withdrawal due to adverse events (WDAEs) that occurred [redacted] than in the quetiapine group (2.6% [4/153]). [redacted].

In the stabilization phase of the EQUATOR trial, WDAEs were reported for 8.8% (41/464) of brexpiprazole-treated patients. The most commonly cited events leading to discontinuation were schizophrenia (5.2%), psychotic disorder (0.9%), suicidal ideation (0.6%), somnolence (0.4%) and hepatic enzyme increased (0.4%). In the maintenance phase, WDAEs were less common in the brexpiprazole group compared with the placebo group (5.2% versus 11.5%). The manufacturer reported that this was due to a lower incidence of discontinuations due to schizophrenia, psychotic disorder, and/or suicidal ideation.

Table 26: Withdrawal Due to Adverse Events in the Acute and Maintenance Trials

WDAEs, n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX 2–4 mg (N = 972)	Placebo (N = 624)	ARI (N = 50)	QUET (N = 153)	BREX 2–4 mg (N = 97)	Placebo (N = 104)
WDAEs	[redacted]	[redacted]	[redacted]	[redacted]	5 (5.2)	12 (11.5)
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
GERD	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Gastric ulcer	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
General and admin. site	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Peripheral edema	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Drug-induced liver injury	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Non-alcoholic steatohepatitis	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hepatitis C	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Blood CPK increased	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Blood triglycerides increased	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
ECG QRS complex prolonged	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
ECG QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
ECG T-wave inversion	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Liver function test abnormal	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

WDAEs, n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX 2–4 mg (N = 972)	Placebo (N = 624)	ARI (N = 50)	QUET (N = 153)	BREX 2–4 mg (N = 97)	Placebo (N = 104)
Metabolism/nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Musculoskeletal and CTD	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Rhabdomyolysis	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Musculoskeletal stiffness	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Psychomotor hyperactivity	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Convulsion	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Grand mal convulsion	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Complex partial seizures	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Extrapyramidal disorder	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Headache	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	4 (4.1)	12 (11.5)
Schizophrenia	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	6 (5.8)
Psychotic disorder	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	5 (4.8)
Agitation	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Irritability	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hallucination	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hostility	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Schizophrenia (paranoid)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Suicide attempt	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Suicidal Ideation	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	1 (1.0)
Acute psychosis	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Mental disorder	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Skin and SC disorders	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Rash	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

admin. = administration; ALT = alanine aminotransferase; ARI = aripiprazole; BREX = brexpiprazole; CPK = creatine phosphokinase; CTD = connective tissue disorders; ECG = electrocardiogram; GERD = gastroesophageal reflux disease; n = number of patients with events; N = total number of patients; n = number of patients in subgroup; NR = not reported; QUET = quetiapine; SC = subcutaneous; WDAE = withdrawal due to adverse event.

Source: Common Technical Document Section 2.7.4.[5]

Extrapyramidal Symptoms

The safety evaluation plan for brexpiprazole involved analyses of EPS-related adverse events and the use of EPS scales (i.e., Simpson-Angus Scale, Barnes Akathisia Rating Scale, and the Abnormal Involuntary Movement Scale).

EPS-Related Adverse Events

Table 27 [redacted]

[redacted]

In the stabilization phase of the EQUATOR trial, at least one EPS-related adverse event was reported in [redacted] of brexpiprazole-treated patients. The most commonly reported EPS-related adverse events were akathisia (9.1%) and parkinsonian events (4.1%). In the maintenance phase of the EQUATOR trial, the proportion of patients who experienced at least one EPS-related adverse event was similar in the brexpiprazole group ([redacted]) and placebo group ([redacted]). Tremor (3.1%) and muscle spasm (2.1%) were the only EPS-related adverse events that were reported for more than one brexpiprazole-treated patient. There were no serious EPS-related adverse events in EQUATOR.

Table 27: Summary of EPS-Related Adverse Events

EPS-related AEs, n (%)	Acute Treatment Trials				Maintenance Trial	
	BREX 2-4 mg (N = 972)	Placebo (N = 624)	ARI (N = 50)	QUET (N = 153)	BREX 2-4 mg (N = 97)	Placebo (N = 104)
Any EPS-related AE	[redacted]	[redacted]	6 (12.0)	[redacted]	[redacted]	[redacted]
Total Akathisia Events	[redacted]	[redacted]	2 (4.0)	[redacted]	1 (1.0)	1 (1.0)
Akathisia	[redacted]	[redacted]	2 (4.0)	6 (3.9)	1 (1.0)	1 (1.0)
Psychomotor hyperactivity	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Total Dyskinetic Events	[redacted]	[redacted]	0 (0.0)	[redacted]	1 (1.0)	[redacted]
Choreoathetosis	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	1 (1.0)
Tardive dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	1 (1.0)
Total Dystonic Events	[redacted]	[redacted]	2 (4.0)	[redacted]	2 (2.1)	1 (1.0)
Dystonia	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	1 (1.0)
Muscle rigidity	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.1)	0 (0.0)
Total Parkinsonian Events	[redacted]	[redacted]	3 (6.0)	[redacted]	[redacted]	2 (1.9)
Bradykinesia	[redacted]	[redacted]	0 (0.0)	[redacted]	NR	NR
Extrapyramidal disorder	[redacted]	[redacted]	2 (4.0)	[redacted]	1 (1.0)	2 (1.9)
Parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.1)	0 (0.0)
Total Residual Events	[redacted]	[redacted]	0 (0.0)	[redacted]	NR	NR
Muscle twitching	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Myoclonus	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

AE = adverse event; ARI = aripiprazole; BREX = brexpiprazole; EPS = extrapyramidal symptoms; n = number of patients with events; N = total number of patients; NR = not reported; QUET = quetiapine.

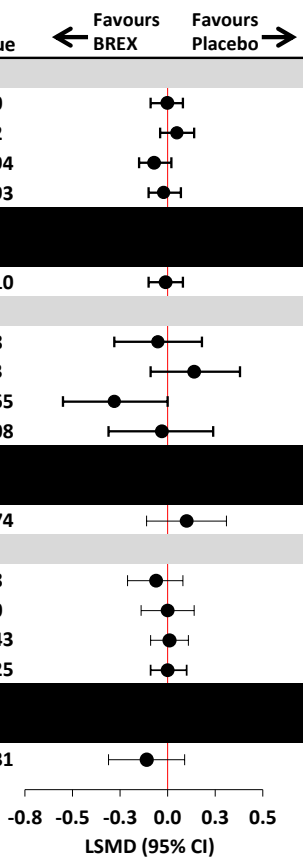
Source: Common Technical Document Section 2.7.4.[5]

EPS Rating Scales

Results for change from baseline in the BARS, SAS, and AIMS are summarized in Figure 18 for the acute exacerbation trials (VECTOR, BEACON, and LIGHTHOUSE) and the maintenance trial (EQUATOR). There were no statistically significant differences between brexpiprazole and placebo in any of the EPS rating scales in either the acute or maintenance trials.

Figure 18: Summary of Change from Baseline BARS, SAS, and AIMS

Study	Comparison	LSM (SE) BREX	LSM (SE) Placebo	BREX vs. Placebo LSMD (95% CI)	P value
Barnes Akathisia Rating Scale					
VECTOR	BREX 2 mg vs. PLC	0.01 (0.03)	0.01 (0.03)	0.00 (-0.09, 0.09)	1.00
	BREX 4 mg vs. PLC	0.05 (0.03)	0.01 (0.03)	0.05 (-0.04, 0.13)	0.32
BEACON	BREX 2 mg vs. PLC	-0.01 (0.03)	0.06 (0.03)	-0.07 (-0.15, 0.02)	0.1294
	BREX 4 mg vs. PLC	0.04 (0.03)	0.06 (0.03)	-0.02 (-0.10, 0.07)	0.6793
LIGHTHOUSE	BREX 2-4 mg vs. PLC	[redacted]			
	QUET vs. PLC				
EQUATOR	BREX 2-4 mg vs. PLC	-0.08 (0.03)	-0.07 (0.03)	-0.01 (-0.10, 0.08)	0.7610
Simpson-Angus Scale					
VECTOR	BREX 2 mg vs. PLC	-0.07 (0.08)	-0.02 (0.08)	-0.05 (-0.28, 0.18)	0.68
	BREX 4 mg vs. PLC	0.12 (0.08)	-0.02 (0.08)	0.14 (-0.09, 0.38)	0.23
BEACON	BREX 2 mg vs. PLC	-0.25 (0.10)	0.03 (0.10)	-0.28 (-0.55, -0.00)	0.0465
	BREX 4 mg vs. PLC	-0.00 (0.10)	0.03 (0.10)	-0.03 (-0.31, 0.24)	0.8108
LIGHTHOUSE	BREX 2-4 mg vs. PLC	[redacted]			
	QUET vs. PLC				
EQUATOR	BREX 2-4 mg vs. PLC	-0.02 (0.08)	-0.12 (0.07)	0.10 (-0.11, 0.31)	0.3374
Abnormal Involuntary Movement Scale					
VECTOR	BREX 2 mg vs. PLC	-0.11 (0.05)	-0.05 (0.05)	-0.06 (-0.21, 0.08)	0.38
	BREX 4 mg vs. PLC	-0.05 (0.05)	-0.05 (0.05)	-0.00 (-0.14, 0.14)	1.00
BEACON	BREX 2 mg vs. PLC	-0.07 (0.03)	-0.08 (0.03)	0.01 (-0.09, 0.11)	0.8443
	BREX 4 mg vs. PLC	-0.08 (0.03)	-0.08 (0.03)	0.00 (-0.09, 0.10)	0.9525
LIGHTHOUSE	BREX 2-4 mg vs. PLC	[redacted]			
	QUET vs. PLC				
EQUATOR	BREX 2-4 mg vs. PLC	-0.03 (0.07)	0.08 (0.07)	-0.11 (-0.31, 0.09)	0.2931



AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; mg = milligrams; PLC = placebo; SAS = Simpson-Angus Scale; SE = standard error; vs. = versus.

Source: Data from Correll et al. 2015,[35] Kane et al. 2015,[40] and Clinical Study Reports for LIGHTHOUSE[3] and EQUATOR.[4]

Change in Body Weight

Table 28 [redacted]

[redacted]

In the EQUATOR trial, the mean change in body from baseline to last visit was 0.8 kg in the stabilization phase and [redacted]% of patients demonstrated an increase in body weight of greater than and equal to 7%. In the maintenance phase, the mean change from baseline in body weight was −0.3 kg for the brexpiprazole group compared with −2.2 kg for the placebo group. The proportion of patients with an increase of 7% in body weight was 5.2% in the brexpiprazole group and 1.0% in the placebo group.

Table 28: Summary of Change in Body Weight

Body Weight	Acute Treatment Trials				Maintenance Trial	
	BREX 2–4 mg (N = 972)	Placebo	ARI (N = 50)	QUET (N = 153)	BREX 2–4 mg (N = 97)	Placebo (N = 104)
Baseline (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change at last visit (kg)	[redacted]	[redacted]	[redacted]	[redacted]	−0.3 (4.9)	−2.2 (3.6)
Decrease ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	9 (9.38)	16 (15.38)
Increase ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	5 (5.21)	1 (0.96)

ARI = aripiprazole; BREX = brexpiprazole; kg = kilogram; n = number of patients with events; N = total number of patients; n = number of patients in subgroup; QUET = quetiapine.

Source: Common Technical Document Section 2.7.4.[5]

Changes in Prolactin Levels

The manufacturer defined potentially clinically relevant changes in prolactin as greater than 1 × upper limit of normal (ULN). Table 29 provides a summary of the proportion of patients who experienced elevated prolactin levels of at least 1, 2, or 3 × ULN in the acute exacerbation and maintenance trials. In the acute exacerbation trials, the proportion of patients with prolactin elevation of at least 1 × ULN was greater in the brexpiprazole 2 mg to 4 mg per day group compared with the placebo group for both females and males (14.6% versus 6.1% and 11.8% versus 8.6%). Elevated prolactin of greater than 1 × ULN was rare in the double-blind portion of the EQUATOR trial with four patients surpassing this threshold in both the brexpiprazole and placebo groups.

Table 29: Summary of Prolactin Elevation

Sex	Prolactin Elevation	Acute Treatment Trials n/N (%)				Maintenance Trial n/N (%)	
		BREX	Placebo	ARI	QUET	BREX	Placebo
Females	> 1 × ULN	52/355 (14.60)	14/231 (6.10)	0/16 (0.00)	5/61 (8.20)	2/38 (5.26)	1/38 (2.63)
	> 2 × ULN	14/355 (3.90)	9/231 (3.90)	0/16 (0.00)	0/61 (0.00)	2/38 (5.26)	1/38 (2.63)
	> 3 × ULN	3/355 (0.80)	3/231 (1.30)	0/16 (0.00)	1/61 (1.60)	0/38 (0.00)	2/38 (5.26)
Males	> 1 × ULN	67/569 (11.80)	30/348 (8.60)	0/34 (0.00)	11/82 (13.40)	2/55 (3.64)	3/61 (4.92)
	> 2 × ULN	8/569 (1.40)	11/348 (3.20)	0/34 (0.00)	1/82 (1.20)	0/55 (0.00)	3/61 (4.92)
	> 3 × ULN	5/569 (0.90)	8/348 (2.30)	0/34 (0.00)	2/82 (2.40)	0/55 (0.00)	2/61 (3.28)

ARI = aripiprazole; BREX = brexpiprazole; n = number of patients with events; N = total number of patients; QUET = quetiapine; ULN = upper limit of normal.

Source: Common Technical Document Section 2.7.4.[5]

Mortality

No patients died while enrolled in the VECTOR, BEACON, or LIGHTHOUSE studies, or during the 30-day follow-up periods.[1-3] In the EQUATOR trial, one patient died during the stabilization phase and no patients died during the maintenance phase.[4]

Discussion

Summary of Available Evidence

There were three six-week acute exacerbation trials (VECTOR [N = 636], BEACON [N = 674], and LIGHTHOUSE [N = 468]) that met the inclusion criteria of the CDR systematic review. All three acute treatment trials were double-blind phase III studies that enrolled patients who were experiencing an acute relapse of schizophrenia. Patients were hospitalized for the duration of the all three studies. Both the VECTOR and BEACON trials were four-arm, placebo-controlled trials that were conducted using different fixed doses of brexpiprazole (4 mg per day, 2 mg per day, 1 mg per day, 0.25 mg per day), or placebo. The CDR review focused on the Health Canada–approved dosage regimen for the treatment of schizophrenia with brexpiprazole (i.e., 2 mg to 4 mg once daily). Therefore, the efficacy and safety data for the 0.25 mg per day and 1 mg per day treatment groups from VECTOR and BEACON, respectively, are not reported. Patients in the LIGHTHOUSE trial were randomized to brexpiprazole (2 mg to 4 mg per day), quetiapine (400 mg to 800 mg per day), or placebo; however, the trial was not designed or powered for statistical comparisons between the two active treatments. As there were no studies identified that compared brexpiprazole against other active treatments for schizophrenia, CADTH also considered the results of the manufacturer's network meta-analyses (NMAs) for the treatment of acute exacerbations and maintenance treatment (appendices 8 and 9).

There was also one 52-week maintenance therapy trial (EQUATOR [N = 202]) that was conducted using a relapse prevention design. Patients were only randomized following the successful completion of a stabilization phase where they were required to demonstrate a response to brexpiprazole for a period of at least 12 weeks. Those who completed the stabilization phase were randomized into the maintenance phase where they would either continue treatment with 1 mg to 4 mg brexpiprazole or to receive matching placebo.

The controlled studies were relatively short-term, ranging from six weeks to 12 months in duration. Therefore, CADTH also summarized the available data from the manufacturer's long-term extension trial (ZENITH) which provides an additional 12 months of efficacy and safety data (Appendix 7). However, it must be noted that ZENITH was an open-label, uncontrolled extension trial; therefore, the benefits of brexpiprazole may be overestimated and the harms underestimated as the patient population was highly selected for those who were responders and able to tolerate the treatment.

Several external validity issues were identified which, although common in schizophrenia clinical trials, may limit the generalizability of the included trials to the Canadian setting. These issues included extensive patient contact with health care professionals, including six weeks of in-patient treatment in the acute exacerbation trials, as well as the exclusion of patients who had a history of substance abuse, were at risk of self-harm or harm to others, or had a diagnosis of residual-type schizophrenia.

Interpretation of Results

Efficacy

The primary efficacy outcome in the acute exacerbation trials was change from baseline to week 6 in PANSS total score. It is currently unclear what degree of improvement in the PANSS total or subscale scores represents a clinically relevant improvement. However, in a comparison of PANSS to the Clinical Global Impression (CGI) scale it was suggested that an absolute reduction of 15 in the total PANSS score corresponds to "minimally improved" on the CGI-I score, and a reduction of the CGI-S scale of one severity step.[50] The Australian Pharmaceutical Benefits Advisory Committee (PBAC) has previously cited a minimal clinically important difference (MCID) of 7 points for PANSS.[51,52] This lower threshold was surpassed in the VECTOR trial for both the 2 mg per day and 4 mg per day dosages of brexpiprazole (–8.72 and –7.64, respectively), but not in any of the other trials.

Alternatively, the EMA has stated that a relative improvement from baseline of at least 30% in PANSS total score is generally considered to be clinically relevant for short-term trials involving patients with an acute exacerbation of symptoms.[49] The responder analysis in the acute exacerbation trials for brexpiprazole was defined as either a reduction of at least 30% in PANSS total score or a CGI-I score of 1 (very much improved) or 2 (much improved). In all three studies, a greater proportion of brexpiprazole-treated patients achieved the response criteria (range: 38.5% to 49.7%) compared with placebo (range: 30.3% to 32.1%), and both were numerically lower than the proportion who achieved a response with quetiapine (62.7%). The clinical expert consulted by CADTH suggested that the results for PANSS, CGI-S, and CGI-I were clinically relevant for patients with an acute exacerbation of symptoms.

Changes from baseline in PANSS positive and negative subscales were generally consistent with those observed for the PANSS total scores. The clinical expert consulted by CADTH noted that controlling positive symptoms is particularly important for patients experiencing an acute exacerbation of schizophrenia, as these have the greatest potential to result in hospitalization for the patient. The results of the secondary CGI-S end points generally supported the findings of the PANSS analysis in all of the acute exacerbation trials.

The 2 mg per day fixed-dosage of brexpiprazole failed to consistently demonstrate a statistically significant improvement in PANSS compared with placebo (i.e., achieved in VECTOR, but not in BEACON). However, regulatory authorities granted approval for this dosage based on additional considerations, including the following: a pooled analysis of the VECTOR and BEACON studies that suggested benefit for the 2 mg per day dosage, the numerical increase in the proportion of responders with the 2 mg per day dosage relative to placebo, and the belief that patients should be treated with the lowest effective dose in clinical practice.[37] The clinical expert consulted by CADTH suggested that the 2 mg per day dosage is likely to be effective for a subset of patients, with the majority of patients receiving treatment with an increased dosage.

The EMA has stated that both short-term treatment and longer-term maintenance studies are required in order to obtain an indication for the treatment of schizophrenia. Although their review pre-dated the EQUATOR trial, the FDA has specified that such a study is a post-market requirement for brexpiprazole.[37,49] In the EQUATOR trial, the median time to impending relapse in the interim and final analyses was [redacted] and 169.0 days in the brexpiprazole group and [redacted] and 111.0 days in the placebo group.[4] The EQUATOR trial

demonstrated that people who received brexpiprazole were statistically significantly less likely to relapse over time compared with those who switched to placebo (HR: 0.292 [95% CI, 0.156 to 0.548]).[4] The clinical expert consulted by CADTH suggested that the results for the EQUATOR trial were clinically relevant.

There were no adequately designed trials identified that directly compared brexpiprazole against other atypical antipsychotic drugs for either the short-term treatment of acute exacerbations or longer-term maintenance treatment. Therefore, the manufacturer submitted two unpublished NMAs investigating the comparative efficacy and safety of brexpiprazole for use in the short-term and long-term treatment of schizophrenia. The manufacturer reported that brexpiprazole was associated with similar efficacy compared with other atypical antipsychotic drugs for the treatment of acute exacerbations and maintenance treatment. There is considerable clinical and methodological heterogeneity across the various studies included in the manufacturer's analyses, including substantial differences in the treatment effects reported for the placebo groups. The manufacturer conducted sensitivity analyses to adjust for these differences in placebo rates of withdrawal and withdrawals due to adverse events.

Overall, the manufacturer's assumption of similar efficacy with other atypical antipsychotic drugs used in Canada is supported by the NMA and clinical expert opinion for the treatment of acute exacerbations. Although the assumption regarding similar efficacy when used as maintenance treatment remains uncertain due to challenges and limitations of the indirect comparison reviewed, the clinical expert consulted by CADTH suggested that it appears to be similar to the other available drugs. Similarly, PBAC recently issued a positive recommendation for brexpiprazole based on comparative efficacy with lurasidone.[53] The manufacturer reported that PBAC's decision was supported by the advice of four clinical experts who suggested that brexpiprazole and lurasidone were similarly efficacious.[54]

In their input to CADTH, patient groups emphasized that not all individuals living with schizophrenia will respond to antipsychotic medications in the same manner. Patients have reported that they often have to try several different treatments before finding one that adequately controls their symptoms; hence, they believe that multiple treatment options should be available.

Harms

The majority of the serious adverse events reported in the included studies were attributable to worsening of the patients' underlying disease (e.g., schizophrenia and psychotic disorder). The most commonly reported adverse events for patients receiving treatment with brexpiprazole were weight gain ([redacted]) and akathisia ([redacted]). Reviewers for the FDA and Health Canada concluded that the adverse event data for brexpiprazole did not demonstrate unexpected safety issues for an atypical antipsychotic drug.[37,45] The clinical expert consulted by CADTH concurred with the FDA reviewers, suggesting that the adverse event profile is comparable with that of other atypical antipsychotic drugs.

Although there were no statistically significant differences between brexpiprazole and placebo in any of the EPS rating scales in either the acute or maintenance trials, EPS-related adverse events were slightly more common in the brexpiprazole groups of acute exacerbation trials compared with the placebo group ([redacted]).[5] Reviewers for the FDA noted that brexpiprazole was also associated with an increase in EPS-related adverse events compared with placebo in the major depressive disorder portion of the clinical development program (approximately 15% versus 6%).[37] In the fixed-dose treatment

groups, the 4 mg per day brexpiprazole dosage was associated with an increased need for concomitant anticholinergic medication to manage EPS-related adverse events ([redacted]) compared with the 2 mg per day dosage ([redacted]) and the placebo group ([redacted]). The clinical expert consulted by CADTH suggested that in routine clinical practice, EPS-related adverse events would typically be managed through dose reduction or by switching to an alternative drug, as opposed to prescribing additional medication to manage these events.

None of the EPS-related adverse events in the included studies were considered to be serious and few led to discontinuation. Although there were no events of tardive dyskinesia reported in the clinical development program for brexpiprazole,[37] the Canadian product monograph includes a warning regarding the potential risk of tardive dyskinesia, particularly for those patients requiring long-term treatment.[25] This is due to the serious and irreversible nature of the condition and the fact that it has been associated with other atypical antipsychotic drugs.[37] This warning is consistent with the product monographs of other atypical antipsychotic drugs marketed in Canada.[26-34]

The weight gain associated with second-generation antipsychotic drugs has been cited as a risk factor for diabetes and cardiovascular disease.[17] Statistical testing was not performed in the short-term trials; however, brexpiprazole was associated with a numerical increase in body weight relative to [redacted]. Body weight increased in the stabilization phase of the EQUATOR trial (0.8 kg), but was relatively unchanged in the maintenance phase (−0.3 kg), suggesting that weight gain was more likely to occur within the first few months of initiating treatment. The product monograph recommends that body weight be monitored clinically for those undergoing treatment with brexpiprazole;[25] though recommendations are not provided regarding the frequency of monitoring or the course of action if weight gain is observed. The clinical expert agreed that change in body weight of 7% or more would be clinically important and that body weight would typically be monitored on a monthly basis for patients initiating a new antipsychotic treatment.

The manufacturer's NMA of safety end points was limited to the aggregate end point of withdrawals due to adverse events. The manufacturer's NMA suggested that withdrawals from short-term clinical trials as a result of adverse events were similar across the atypical antipsychotic drugs included in their analysis, when adjusted for differences in the rate of withdrawal from the placebo groups. This indirect comparison was conducted with relatively short-term trials (with unspecified durations) that were not individually powered to evaluate safety end points and were limited by substantial heterogeneity across the studies; therefore, the results may not be reflective of the comparative safety profile that would be observed in larger patient populations exposed to brexpiprazole for a greater duration of treatment. In addition, aggregate adverse event end points cannot fully capture the unique safety data that may be associated with each individual drug. Previous NMAs that have been conducted for atypical antipsychotic drugs have included additional comparisons of adverse events (e.g., weight gain, EPS-related events, prolactin increase, QTc prolongation, sedation).[55]

Similar to the other atypical antipsychotic drugs approved for use in Canada, the product monograph for brexpiprazole contains a black box warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[25] The monograph states that brexpiprazole is not indicated for the treatment of patients with dementia.

Other Considerations

Brexpiprazole is also approved for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in the US, but is not currently approved for that indication in Canada.

Potential Place in Therapy[a]

Antipsychotic drugs continue to occupy a central place in the treatment of schizophrenia, ameliorating symptom severity in the acute phase of the illness, facilitating participation in rehabilitation during the stabilization and chronic phases, and preventing relapse into acute episodes.[56] Optimizing antipsychotic treatment response and minimizing side effects are the twin goals of therapy. No single antipsychotic drug achieves these goals for all patients, nor are combination or high-dose antipsychotic treatment strategies recommended.[57] There are no predictive tests to match patients and medication treatments. Access to multiple therapeutically effective medications allows the best possibility of personalizing treatment through matching an individual patient's treatment response, with the side effect sensitivity profile.

Compared with placebo, brexpiprazole demonstrates effectiveness in the acute phase of illness, and in preventing relapses. Brexpiprazole has a half-life of 91 hours, and requires 10 to 12 days at the target dose to reach a plateau plasma level, a factor that may need consideration in evaluating dosing and response to treatment in the acute phase, as well as the possible emergence of side effects. Patients with moderate or more severe compromise in hepatic or renal function should receive lower doses of brexpiprazole.

Direct head-to-head comparisons with other antipsychotic drugs are limited. As a result, specific advantages or disadvantages of brexpiprazole compared with other antipsychotic drugs are uncertain. Similar to other second-generation antipsychotic drugs, side effects that may be apparent in clinical practice include extrapyramidal symptoms (particularly akathisia) and weight gain. Possibly relevant differences in mechanism of action compared with most other drugs include partial agonist effects at the serotonin 5-HT1a and dopamine D2 receptors.[58] Unpublished material from the manufacturer suggests that like aripiprazole (and unlike other second-generation antipsychotic drugs), brexpiprazole has a very high occupancy of dopamine D2 receptors, but relatively low extrapyramidal symptoms. This unique profile provides a pharmacological rationale that may differentiate response and side effect profiles with brexpiprazole within the heterogeneous group of patients with schizophrenia.

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

The CDR systematic review included four double-blind RCTs that investigated the safety and efficacy of brexpiprazole for the treatment of patients with schizophrenia. One double-blind relapse prevention study (EQUATOR) demonstrated that patients who were stabilized on brexpiprazole and subsequently randomized to continue treatment with brexpiprazole were less likely to experience a relapse over time than those who were randomized to placebo. Three studies demonstrated that treatment with 4 mg per day brexpiprazole resulted in statistically significant and clinically meaningful improvements in PANSS total score and CGI-S for patients experiencing an acute exacerbation of schizophrenia (VECTOR, BEACON, and LIGHTHOUSE). When administered at a lower dosage (2 mg per day) brexpiprazole failed to consistently demonstrate statistically significant improvements in the primary or secondary end points of the pivotal studies; however, a significant difference was observed in the pooled treatment effect derived from the manufacturer's NMA. Flexibly dosed brexpiprazole (2 mg to 4 mg per day) failed to demonstrate a statistically significant improvement in PANSS total score; however, improvements were observed in secondary end points such as CGI-S and in the proportion of patients achieving pre-specified response criteria. The clinical expert consulted by CADTH suggested that the lower dosage regimens of brexpiprazole would likely be effective for a subset of schizophrenia patients; however, the majority would likely receive a dosage of 4 mg per day.

The manufacturer's NMAs reported that brexpiprazole was associated with similar efficacy compared with other atypical antipsychotic drugs used in Canada. Overall, the manufacturer's assumption of similar efficacy with other atypical antipsychotic drugs is supported by the NMA and clinical expert opinion for the treatment of acute exacerbations. However, the assumption regarding similar efficacy when used as maintenance treatment remains uncertain, due to challenges and limitations in the conduct of indirect comparisons involving those studies.

Treatment with brexpiprazole is associated with an increased risk of weight gain and akathisia relative to placebo. Regulatory authorities and the clinical expert consulted by CADTH suggested that the adverse event profile of brexpiprazole is comparable with that of other atypical antipsychotic drugs. The manufacturer's indirect comparisons of safety end points was limited to the aggregate end points of withdrawals due to adverse events and suggested that withdrawals from short-term clinical trials as a result of adverse events were similar across the atypical antipsychotic drugs included in their analysis, when adjusted for differences in withdrawal from the placebo groups.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Three patients groups responded to the call for patient input for this CADTH Common Drug Review submission.

- The Schizophrenia Society of Canada (SSC) is a non-profit incorporated charity serving people living with schizophrenia and their families. Their mission is to improve the quality of life of those affected by schizophrenia and psychosis through public education, support programs, public policy, and research. The SSC declared joint working, sponsorship, and/or funding arrangements with Janssen, Lundbeck Canada, and Otsuka Canada Pharmaceutical. The SSC also received a grant from Otsuka to conduct patient surveys for this submission.
- The Schizophrenia Society of Ontario (SSO) is a non-profit charitable organization dedicated to making a positive difference in the lives of people, families, caregivers, and communities affected by schizophrenia and psychotic illnesses across the province by building supportive communities, through services and education, advocating for system change, and conducting research into the psychosocial factors that directly affect mental illness. The SSO receives funding from Janssen Canada Inc., Novartis Pharmaceuticals Canada Inc., Otsuka-Lundbeck Alliance, Eli Lilly Canada Inc., Pfizer Canada Inc., Hoffmann-La Roche Limited, Bristol-Myers Squibb Canada Co., and Sunovion Pharmaceuticals Canada Inc. The SSO declared no conflict of interest in the preparation of this submission.
- The British Columbia Schizophrenia Society (BCSS) is a registered charity dedicated to providing support and education to families/caregivers and their ill relatives. The BCSS offers programs, services, education, support, public policy, and research, to families, caregivers, schools, communities, health agencies, front-line support personnel, and police agencies to improve the quality of life for those affected by schizophrenia and psychosis. BCSS receives sponsorship from the Otsuka-Lundbeck Alliance and Janssen Inc. and has declared no conflicts of interest in the preparation of this submission.

2. Condition-Related Information

Information was primarily gathered through lived experiences, one-on-one conversations, and online surveys from people living with schizophrenia and other persistent mental illness (e.g., schizoaffective disorder) and their family and caregivers.

One patient group described schizophrenia as the cruellest of illnesses, often striking young people at a critical stage of life. According to the BCSS, approximately one-third of patients suffering from schizophrenia can resume their daily lives with antipsychotic therapies and other types of therapeutic supports. Another one- third recover fairly well after onset; however, they find it difficult or impossible to pursue education or careers, and hobbies or activities of interest before the onset of illness. Despite some limitations, these patients are able to recover to a level that allows them to live reasonably full lives when treated. The remaining one-third of patients with schizophrenia cannot resume their original activities, nor can they fully function as a part of the community. These patients are typically drug-treatment resistant and find themselves in a perpetual state of psychosis, trapped in cyclical admissions to hospital which can lead to permanent cognitive impairment. Consequently, they are unable to secure their basic needs such as food, clothing, shelter, hygiene, healthy

relationships, and meaningful community engagement. New therapy options for this population are imperative to ensure the potential for recovery.

According to patient groups, schizophrenia is primarily associated with hallucinations and delusions as well as symptoms such as anxiety, paranoia, irritability or anger, depression, fatigue, difficulty with concentration, difficulty with social interactions, and insomnia. Some patients also experience workload stress, challenges with memory, changes in appetite, and confused or racing thoughts. The manifestations of schizophrenia can lead to self-harm or harm to others, self-stigma or public stigma, lack of meaningful community engagement, and cognitive problems limiting executive skills and memory and verbalization skills, socialization, and integration with society. Furthermore, schizophrenia was also reported to interfere with identity formation resulting in delayed maturation due to psychosis. Public stigma and self-stigma are difficult to live with. Consequently, patients with schizophrenia find it difficult or nearly impossible to maintain relationships, careers, or education without effective treatments.

One patient group suggested that patients who are inadequately treated with current therapies resort to substances other than prescribed medications to help them cope with the symptoms of mental illness (e.g., recreational alcohol, marijuana, or cocaine).

3. Current Therapy-Related Information

Patient groups most commonly identified antipsychotic medication as the typical treatment for schizophrenia and indicated inadequately controlled symptoms, varying degrees of efficacy from one patient to another, and relapse despite treatment with currently available therapies. Because the response to medication is unique for each patient, most have tried many medications, trying to find an effective drug for their symptoms which is convenient and has minimal side effects in hopes of improving their quality of life. Other therapies for the management of schizophrenia include antidepressants, benzodiazepines, cognitive behavioural therapy (CBT), and dialectical behaviour therapy (DBT) for psychosis, psychiatric rehabilitation, and recovery-oriented services as well as counselling, self-help, spirituality, and family support. Patients treated with therapies for the management of schizophrenia reported many side effects such as dry mouth, constipation, drowsiness, lethargy, fatigue, inability to concentrate, cognitive impairment, tiredness, insomnia, weight gain, sexual dysfunction, restlessness, dizziness, and muscle spasms, while others reported relatively few side effects. One family member/caregiver stated that "*Antipsychotic drugs have pulled my son out of his psychoses several times, and he is compliant with his drug protocol. I'm thankful for the [medications], but resent the strong side effects. He has had heart 'episodes;' has spent several months sleeping 18 hrs/day…he's had akathisia, tardive dyskinesia, black/green tongue, skin rashes....and still, his depression and suicidal ideation persist."* Another patient noted concerns with the sedation associated with antipsychotic drugs stating, *"…could not function in any way while on any kind of antipsychotic drugs."* Patient groups identified the plethora of side effects as the most common reason for treatment discontinuation. They also indicated that psychosocial treatments may be more effective than pharmacological treatments and that a combination of both is most effective. One family member/caregiver stated that, *"[Antipsychotic medication] could be improved if it was used as an adjunct to talk therapy. this has been the key piece that has been missing in his treatment … We cannot expect a pill to cure everything. We are still on a waiting list for therapy/CBT. This, in my opinion, is how antipsychotic medication can be improved."*

Respondents noted that current medication options are restricted by provincial drug plans and by the lack of training by general practitioners to prescribe. In addition, patients who

suffer from schizophrenia and their caregivers reported serious concerns regarding the cost of treatment. One patient stated that, *"Antipsychotic drugs should be covered by OHIP because those using it are often on ODSP and in financial difficulty."* Patients also reported barriers with accessing psychiatrists and professional help in terms of availability and costs, especially in rural areas. In addition, patient groups also highlighted barriers to compliance and adherence with currently available treatments (e.g., treatment regimens that require multiple pills per day). Furthermore, patient groups indicated that both CBT and DBT are virtually unavailable in many places as they are also not covered by provincial health care plans. Overall, patient groups suggested that no perfect medication is currently available on the market.

Family are the primary caregivers of those living with schizophrenia and describe it as "24/7 care" carrying a significant burden and stigma. Caregivers indicated that they help with patients' self-care (e.g., laundry, cleaning, and meals), assisting with managing appointments and other schedules (e.g., work, hospitalizations and medical appointments), shelter, and providing emotional support. Some caregiver responsibilities require time off work creating financial burden. According to the patient groups, there is no respite for caregivers. They have to help with the patients' medication adherence, hospital admission, and help reduce the risk of patients self-harming, sometimes against patients' wishes. They feel frustrated by the difficulty in accessing treatment and information and in navigating the mental health system. Persistence of symptoms leads to feelings of hopelessness, stress, and depression. The burden of care can leave caregivers feeling burned out and may create tension between family members. Families worry about side effects and note the need for adherence. Families are looking for better medication to improve patients' quality of life.

4. Expectations About the Drug Being Reviewed

None of the patient groups were able to gather information from patients who have experience with brexpiprazole; however, those without experience indicated that new therapies are expected to improve quality of life by treating all symptoms (negative and positive) associated with schizophrenia with minimal side effects and should be affordable and easy and convenient to administer. Other important factors in novel treatments include better control over hallucinations, false beliefs, reduced facial expression or emotions, and lack of motivation. New treatments are also expected to reduce hospitalizations due to relapse of disease symptoms and cognitive and memory impairment.

In addition, new therapies are expected to be associated with fewer cases of weight gain, sexual problems (sex drive, intimacy, sexual functioning), akathisia, sedation, fatigue, drowsiness, insomnia, dizziness, anxiety, worry, stress, agitation, depression, involuntary movements (tremors or muscle contraction), dental issues, diabetes, elevated cholesterol, and heart disease. Some patients also indicated that new therapies should also address the risk of growing breasts in men and reduce menstrual cycle problems in women.

According to the input provided for this submission, most patients indicated that they were not prepared to accept increased or serious side effects for additional treatment efficacy, with the exception of a minority of patients (especially those with treatment-resistant schizophrenia).

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Epub Ahead of Print PsycINFO 1967 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 6, 2017
Alerts:	Bi-weekly search updates until July 19, 2017 (date of CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number (CAS, UNII)
.nm	Name of substance word
.id	Key concepts (PsycINFO)
.mh	MeSH (PsycINFO)
ppez	Ovid database code; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present, updated weekly

MULTI-DATABASE STRATEGY

Line #	Searches
1	(Rexulti* or brexpiprazole* or OPC-34712 or OPC34712).ti,ab,kf,ot,hw,rn,nm.
2	(913611-97-9 or 2J3YBM1K8C).rn,nm.
3	or/1-2
4	3 use ppez
5	*brexpiprazole/
6	(Rexulti* or brexpiprazole* or OPC-34712 or OPC34712).ti,ab,kw.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
7	or/5-6
8	7 not conference abstract.pt.
9	8 use oemezd
10	(Rexulti* or brexpiprazole* or OPC-34712 or OPC34712).ti,ab,ot,hw,nm,id,mh.
11	10 use psyb
12	4 or 9 or 11
13	remove duplicates from 12

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February-March 2017
Keywords:	Rexulti, brexpiprazole, schizophrenia
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

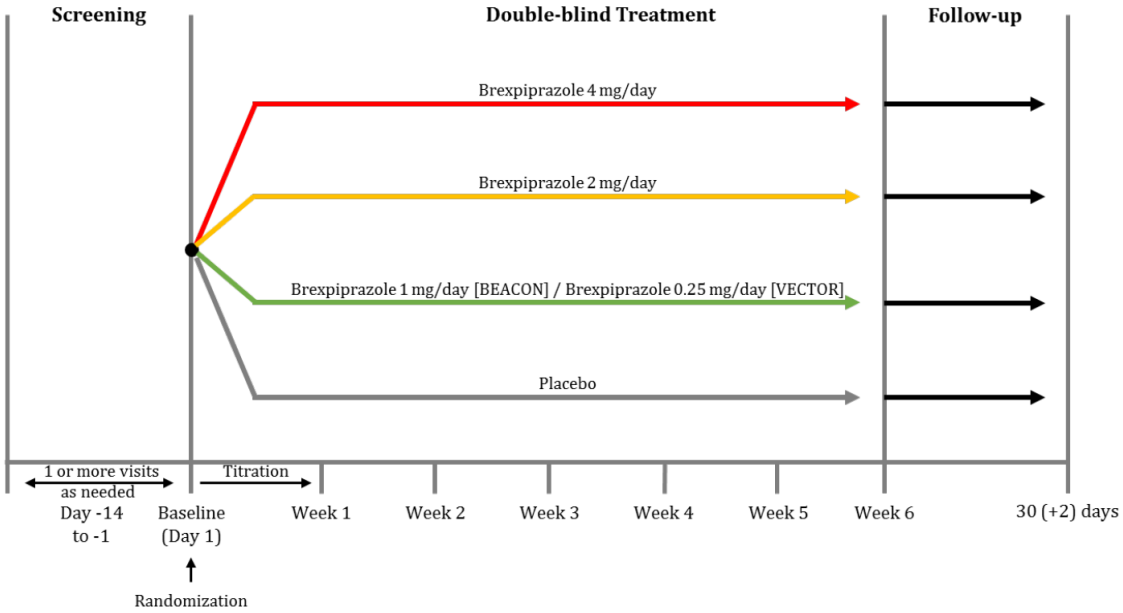
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Eaves S, Rey JA. Brexpiprazole (Rexulti): a new monotherapy for schizophrenia and adjunctive therapy for major depressive disorder. P t. 2016 Jul;41(7):418-22.[59]	Review article
Hussar DA, Shatynski R. Brexpiprazole, cariprazine hydrochloride, and flibanserin. J Am Pharm Assoc (2003). 2016 Mar;56(2):211-4.[60]	Review article
Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA. The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomized, exploratory study. Int Clin Psychopharmacol. 2016 Jul;31(4):192-201.[61]	Exploratory study; not designed to compare brexpiprazole with at least one of the comparators included in the systematic review protocol
Malla A, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA. The effect of brexpiprazole in adult outpatients with early-episode schizophrenia: an exploratory study. Int Clin Psychopharmacol. 2016 Nov;31(6):307-14.[62]	This study is not an RCT and lacks a comparator group
Angersbach D. Schizophrenia: brexpiprazole relieves positive and negative symptoms. Psychopharmakotherapie: PPT. 2016;23(1):35-7.[63]	Review article
Zagaria MAE. Brexpiprazole: a newly approved atypical antipsychotic agent. US Pharm. 2015;2015(10):13-5.[64]	Review article

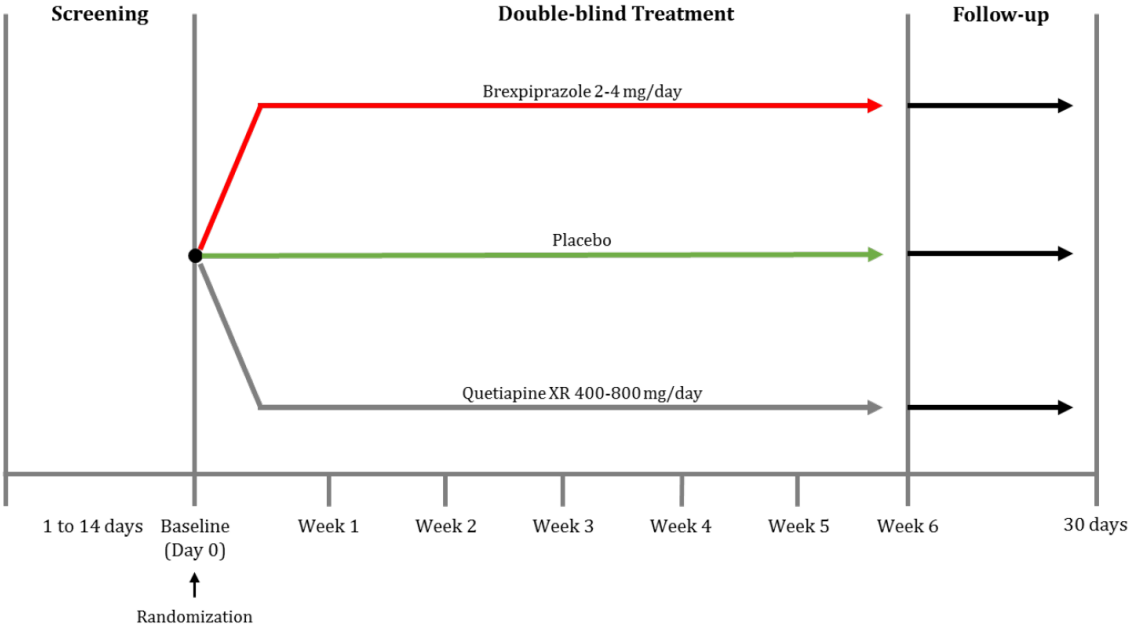
Appendix 4: Detailed Trial Characteristics

Figure 19: Design of the VECTOR and BEACON Studies



Source: Manufacturer's Clinical Summary.[48]

Figure 20: Design of the LIGHTHOUSE Study



Source: Manufacturer's Clinical Summary.[48]

Table 30: List of Prohibited Concomitant Medications

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

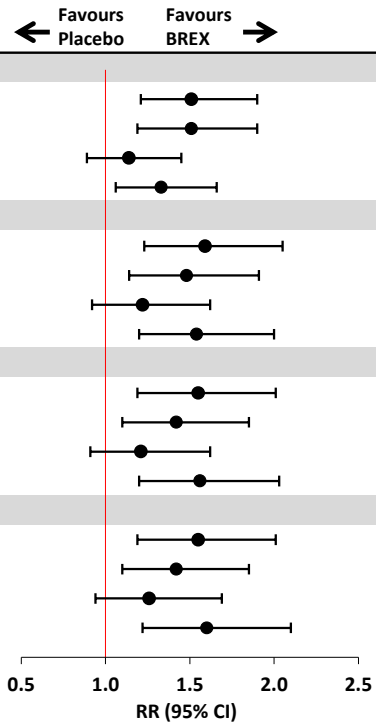
BL = baseline; IM = intramuscular; LAI = long-acting injectable; MAOI = monoamine oxidase inhibitors

Source: Clinical Study Report for LIGHTHOUSE[3]

Appendix 5: Detailed Outcome Data

Figure 21: PANSS Responder Analysis

Study	Comparison	PANSS Response, n (%) BREX	PANSS Response, n (%) Placebo	BREX vs. Placebo RR (95% CI)	P value
≥20% Improvement					
VECTOR	BREX 2 mg vs. PLC	94 (52.2)	62 (34.8)	1.51 (1.19, 1.90)	0.0005
	BREX 4 mg vs. PLC	96 (53.9)	62 (34.8)	1.51 (1.21, 1.90)	0.0003
BEACON	BREX 2 mg vs. PLC	44.7	40.0	1.14 (0.89, 1.45)	0.3036
	BREX 4 mg vs. PLC	53.6	40.0	1.33 (1.06, 1.66)	0.0114
≥30% Improvement					
VECTOR	BREX 2 mg vs. PLC	86 (47.8)	54 (30.3)	1.59 (1.23, 2.05)	0.0004
	BREX 4 mg vs. PLC	82 (46.1)	54 (30.3)	1.48 (1.14, 1.91)	0.004
BEACON	BREX 2 mg vs. PLC	38.6	31.7	1.22 (0.92, 1.62)	0.1680
	BREX 4 mg vs. PLC	49.7	31.7	1.54 (1.20, 2.00)	0.0006
≥40% Improvement					
VECTOR	BREX 2 mg vs. PLC	84 (46.7)	54 (30.3)	1.55 (1.19, 2.01)	0.0009
	BREX 4 mg vs. PLC	79 (44.4)	54 (30.3)	1.42 (1.10, 1.85)	0.009
BEACON	BREX 2 mg vs. PLC	36.9	30.6	1.21 (0.91,1.62)	0.1881
	BREX 4 mg vs. PLC	48.6	30.6	1.56 (1.20, 2.03)	0.0006
≥50% Improvement					
VECTOR	BREX 2 mg vs. PLC	84 (46.7)	54 (30.3)	1.55 (1.19, 2.01)	0.0009
	BREX 4 mg vs. PLC	79 (44.4)	54 (30.3)	1.42 (1.10, 1.85)	0.009
BEACON	BREX 2 mg vs. PLC	36.9	29.4	1.26 (0.94, 1.69)	0.1265
	BREX 4 mg vs. PLC	48.1	29.4	1.60 (1.22, 2.10)	0.0004



BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; mg = milligrams; PLC = placebo; RR = relative risk; vs. = versus.

Source: Data from Correll et al., 2015[35] and Kane et al., 2015.[40]

Figure 22: Summary of PANSS End Points in Maintenance Trial (LOCF)

Confidential data removed at manufacturer's request.

BREX = brexpiprazole; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; PEC = PANSS Excited Component subscale; PLC = placebo.

Source: Data from Clinical Study Report for EQUATOR.[4]

Table 31: Sensitivity Analyses for Impending Relapse

Sensitivity Analyses		Interim Analysis		Final Analysis	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sub-impending relapse criteria		0.338 (0.174 to 0.655)	0.0008	0.292 (0.156 to 0.548)	< 0.0001
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BREX = brexpiprazole; CI = confidence interval; HR = hazard ratio.

Source: Clinical Study Report for EQUATOR.[4]

Table 32: Summary of Serious Adverse Events From Individual Studies

Serious Adverse Events n (%)	VECTOR			BEACON			LIGHTHOUSE			EQUATOR	
	BREX 2 mg (N = 184)	BREX 4 mg (N = 180)	Placebo (N = 184)	BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	Placebo (N = 161)	BREX 2–4 mg (N = 150)	QUET (N = 153)	BREX 1–4 mg (N = 97)	Placebo (N = 105)
SAEs	4 (2.2)	2 (1.1)	7 (3.8)	4 (2.2)	4 (2.2)	10 (5.4)	6 (3.7)	7 (4.7)	2 (1.3)	3 (3.1)	11 (10.6)
Gastrointestinal disorders											
Gastric ulcer	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	NR	NR	NR	NR	NR
General disorders											
Irritability	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	NR	NR
Musculoskeletal and CTD											
Rhabdomyolysis	1 (0.6)	0 (0.0)	0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR
Nervous system disorders											
Grand mal convulsion	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	0	1 (0.7)	0	NR	NR
Psychiatric disorders											
Psychotic disorder	1 (0.6)	0 (0.0)	2 (1.1)	2 (1.1)	1 (0.5)	1 (0.5)	1 (0.6)	0	1 (0.7)	1 (1.0)	4 (3.8)
Schizophrenia	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	3 (1.6)	8 (4.4)	4 (2.5)	3 (2.0)	1 (0.7)	1 (1.0)	5 (4.8)
Schizophrenia (paranoid)	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	1 (0.6)	0	0	NR	NR
Acute psychosis	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	NR	NR
Aggression	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR	NR	NR	NR
Suicidal ideation	NR	NR	NR	0 (0.0)	1 (0.5)	0 (0.0)	NR	NR	NR	0 (0.0)	1 (1.0)
Suicide attempt	NR	NR	NR	NR	NR	NR	0	1 (0.7)	0	NR	NR
Anxiety	NR	NR	NR	NR	NR	NR	1 (0.6)	0	0	NR	NR
Vascular disorders											
Hypertension	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	1 (1.0)
Investigations											
Hepatic enzyme increased	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (1.0)	0 (0.0)
Cardiac disorders											
Angina, unstable	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	1 (1.0)
Arrhythmia	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	1 (1.0)

Serious Adverse Events n (%)	VECTOR			BEACON			LIGHTHOUSE			EQUATOR	
	BREX 2 mg (N = 184)	BREX 4 mg (N = 180)	Placebo (N = 184)	BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	Placebo (N = 161)	BREX 2–4 mg (N = 150)	QUET (N = 153)	BREX 1–4 mg (N = 97)	Placebo (N = 105)
Metabolic disorders											
Type 2 diabetes	NR	NR	NR	NR	NR	NR	0	1 (0.7)	0	NR	NR
Skin and SC disorders											
Angioedema	NR	NR	NR	NR	NR	NR	0	1 (0.7)	0	NR	NR

BREX = brexpiprazole; CTD = connective tissue disorders; n = number of patients with events; N = total number of patients; NR = none reported; QUET = quetiapine; SAE = serious adverse event; SC = subcutaneous; vs. = versus.

Source: clinicaltrials.gov entries for VECTOR[36] and BEACON,[41] Clinical Study Report for LIGHTOUSE,[3] and Clinical Study Report for EQUATOR.[4]

Table 33: Summary of Withdrawals Due to Adverse Events From Individual Studies

WDAEs n (%)	VECTOR			BEACON			LIGHTHOUSE			EQUATOR	
	BREX 2 mg (N = 184)	BREX 4 mg (N = 180)	Placebo (N = 184)	BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	Placebo (N = 161)	BREX 2–4 mg (N = 150)	QUET (N = 153)	BREX 1–4 mg (N = 97)	Placebo (N = 105)
WDAE	15 (8.2)	17 (9.4)	32 (17.4)	11 (5.9)	13 (7.1)	22 (12.0)	[redacted]	[redacted]	4 (2.6)	5 (5.2)	12 (11.5)
Cardiac disorders											
Acute MI	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Coronary artery disease	1 (0.5)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Gastrointestinal disorders											
Gastric ulcer	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Diarrhea	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	NR	NR
GERD	NR	NR	NR	0 (0.0)	1 (0.5)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
General and admin. site											
Irritability	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	NR	NR
Hepatobiliary disorders											
Drug-induced liver injury	1 (0.5)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Steatohepatitis	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Investigations											
ECG QT prolonged	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR

WDAEs n (%)	VECTOR			BEACON			LIGHTHOUSE			EQUATOR	
	BREX 2 mg (N = 184)	BREX 4 mg (N = 180)	Placebo (N = 184)	BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	Placebo (N = 161)	BREX 2–4 mg (N = 150)	QUET (N = 153)	BREX 1–4 mg (N = 97)	Placebo (N = 105)
Hepatic enzyme increased	1 (0.5)	2 (1.1)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
LFT abnormal	0 (0.0)	0 (0.0)	2 (1.1)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
AST increased	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
CPK increased	NR	NR	NR	0 (0.0)	1 (0.5)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
Triglycerides increased	NR	NR	NR	1 (0.5)	0 (0.0)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
ECG QRS prolonged	NR	NR	NR	0 (0.0)	1 (0.5)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
ECG T wave inversion	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	NR	NR
Musculoskeletal and CTD											
Rhabdomyolysis	1 (0.5)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Musculoskeletal stiffness	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Nervous system disorders											
Convulsion	0 (0.0)	1 (0.6)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Extrapyramidal disorder	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Grand mal convulsion	0 (0.0)	0 (0.0)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Headache	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	NR	NR
Psychomotor hyperactivity	0 (0.0)	1 (0.6)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Tremor	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Psychiatric disorders											
Agitation	0 (0.0)	1 (0.6)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Hostility	1 (0.5)	0 (0.0)	0 (0.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Psychotic disorder	2 (1.1)	1 (0.6)	2 (1.1)	4 (2.2)	1 (0.5)	2 (1.1)	[redacted]	[redacted]	[redacted]	1 (1.0)	5 (4.8)
Schizophrenia	7 (3.8)	10 (5.6)	19 (10.3)	5 (2.7)	9 (4.9)	14 (7.6)	[redacted]	[redacted]	[redacted]	2 (2.1)	6 (5.8)
Schizophrenia (paranoid)	1 (0.5)	0 (0.0)	1 (0.5)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Insomnia	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	1 (1.0)	0 (0.0)
Acute psychosis	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	0 (0.0)	1 (1.0)
Aggression	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
Hallucination	NR	NR	NR	1 (0.5)	0 (0.0)	0 (0.0)	[redacted]	[redacted]	[redacted]	NR	NR
Mental disorder	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR

WDAEs n (%)	VECTOR			BEACON			LIGHTHOUSE			EQUATOR	
	BREX 2 mg (N = 184)	BREX 4 mg (N = 180)	Placebo (N = 184)	BREX 2 mg (N = 186)	BREX 4 mg (N = 184)	Placebo (N = 184)	Placebo (N = 161)	BREX 2–4 mg (N = 150)	QUET (N = 153)	BREX 1–4 mg (N = 97)	Placebo (N = 105)
Anxiety	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Suicide attempt	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Skin/SC tissue disorders											
Rash	NR	NR	NR	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]	[redacted]	NR	NR
Angioedema	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR
Infections/infestations											
Hepatitis C	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR

AST = aspartate aminotransferase; BREX = brexpiprazole; CPK = creatine phosphokinase; CTD = connective tissue disorders; ECG = Electrocardiogram; GERD = gastroesophageal reflux disease; LFT = liver function test; MI = myocardial infarction; n = number of patients with events; N = total number of patients; NR = none reported; SC = subcutaneous; vs. = versus; WDAE = withdrawal due to adverse event.

Source: Clinical Study Reports for VECTOR,[1] BEACON,[2] LIGHTOUSE,[3] and EQUATOR[4]

Appendix 6: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Positive and Negative Syndrome Scale (PANSS)
- Clinical Global Impression - Severity of illness (CGI-S), and Clinical Global Impression – Improvement (CGI-I)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)
- Simpson-Angus Scale (SAS)
- Personal and Social Performance Scale (PSP)
- Schizophrenia Quality of Life Scale (S-QoL)

Findings

The scales used for main and secondary outcome measures are briefly summarized in Table 34.

Table 34: Validity and MCID of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
PANSS	30-item rating scale (3 subscales; a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms): positive symptoms, negative symptoms, and general psychopathology.	Yes	Unclear, depends on baseline severity	12,50,65-69
CGI	3-item scale: severity of illness (-S), global improvement (-I) and efficacy index (-E). CGI-S and CGI-I are rated from 1 (normal or very much improved) to 7 (extremely ill or very much worse) scale and are considered separately.	Yes	1 point	70-72
BARS	4-item scale (lower scores such as 0 represent absence of symptoms; higher scores such as 3 or 5 represent severe akathisia): observation, awareness, distress, and global clinical assessment.	Yes	Unknown	73-75
AIMS	12-item scale (lower scores such as 0 represent absence of symptoms; higher scores such as 4 represent severe condition): seven items specific to abnormal movements, three specific to global assessment, and two items specific to dentition.	Yes	Unknown	76-81
SAS	10-item scale (lower scores such as 0 represent absence of symptoms; higher scores such as 4 represent severe condition): one measuring gait, six measuring rigidity, and three measuring glabellar tap, tremor, and salivation.	Yes	0.3-0.65	82,83
PSP	4-item scale (higher scores indicate higher functioning): socially useful activities including work, personal and social relationships, self-care, and disturbing and aggressive behaviours.	Yes	10 points	84-86
S-QoL	41-item scale (8 subscales; lower scores such as 0 represent least favourable quality of life and higher scores such as 100 represent most favourable quality of life): psychological well-being (10 items), self-esteem (6 items), family relationships (5 items), relationships	Yes	Unknown	87

Instrument	Type	Evidence of Validity	MCID	References
	with friends (5 items), resilience (5 items), physical well-being (4 items), autonomy (4 items), and sentimental life (2 items).			

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI = Clinical Global Impression; MCID = minimal clinically important difference; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; SAS = Simpson-Angus Scale; S-QoL = Schizophrenia Quality of Life Scale.

Psychotic Disorder Scales

Positive and Negative Syndrome Scale (PANSS)

The PANSS was developed as a 30-item rating scale, which adapted 18 items from the Brief Psychiatric Rating Scale (BPRS) and 12 items from the Psychopathology Rating Schedule.[66] The PANSS requires a 30- to 40-minute patient interview to gather information on which to assess the patient with regard to the presence and severity of psychopathology in the previous week. The PANSS instrument provides a complete definition of each item as well as detailed anchoring criteria for each of seven rating points; 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, 7 = extreme. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. In the 30-item scale, seven items are related to positive symptoms, seven items are related to negative symptoms, and sixteen items are related to general psychopathology (as shown below). The General Psychopathology scale is considered an adjunct to the positive and negative syndrome assessment since it provides a separate but parallel measure of schizophrenia severity that can serve as a point of reference for interpreting the positive and negative scores.[66] Finally, a composite scale may be derived by subtracting the negative from the positive score. This scale expresses the direction and magnitude of difference between positive and negative syndromes. This score may reflect the degree of predominance of one syndrome over the other based on the score (positive or negative).

Table 35: Thirty Items of the Positive and Negative Syndrome Scale (PANSS)

Positive Scale	General Psychopathology Scale
P1. Delusions	G1. Somatic concern
P2. Conceptual disorganization	G2. Anxiety
P3. Hallucinatory behaviour	G3. Guilt feelings
P4. Excitement	G4. Tension
P5. Grandiosity	G5. Mannerisms & posturing
P6. Suspiciousness	G6. Depression
P7. Hostility	G7. Motor retardation
	G8. Uncooperativeness
Negative Scale	G9. Unusual thought content
N1. Blunted affect	G10. Disorientation
N2. Emotional withdrawal	G11. Poor attention
N3. Poor rapport	G12. Lack of judgment & insight
N4. Passive/apathetic social withdrawal	G13. Disturbance of volition
NS. Difficulty in abstract thinking	G14. Poor impulse control
N6. Lack of spontaneity & flow of conversation	G15. Preoccupation
N7. Stereotyped thinking	G16. Active social avoidance

Source: Kay et al., 1988[12]

In clinical trials, changes from baseline in the PANSS total score, as well those for the Positive and Negative subscales, are typically used as study end points. The PANSS total is scored by summing ratings across items. The potential ranges are 7 to 49 for the Positive and Negative scales and 16 to 112 for the General Psychopathology scale. Thus, the range of possible scores is from 30 to 210. The General Psychopathology scale is usually not rated individually, but it is captured in the total score. The range of scores for the composite scale is from –42 to +42, which may be used for characterization of whether positive or negative symptoms predominate and is not a part of the PANSS total score.

Kay et al. reported on psychometric testing of the PANSS in 101 in-patients with schizophrenia.[66] Scores on all subscales were reported to exhibit a normal distribution, suggesting suitability for parametric statistical analysis. Further, the range of scores was less than the potential range, suggesting a lack of ceiling effect. Internal consistency was demonstrated for the positive (alpha = 0.73), negative (alpha = 0.83) and the General Psychopathology (alpha = 0.79) subscales. Test-retest reliability was assessed three to six months later on a cohort of 15 patients who remained hospitalized. Pearson correlation coefficients were 0.80, 0.68, and 0.60 for the positive, Negative, and General Psychopathology subscales, respectively.[66] Peralta and Cuesta reported on the interrater reliability of the PANSS from a sample of 100 consecutively admitted patients with schizophrenia.[68] Positive and Negative scales showed good interrater reliability, and interclass correlation coefficients of 0.72 and 0.80, respectively. Interrater reliability was moderate for the General Psychopathology scale, and interclass correlation coefficient was 0.56.

More recently, a number of investigators have conducted a principal component analysis to expand the identification of discrete dimensions of schizophrenia beyond the focus on positive and negative symptoms. A number of similar five-factor models including most or all of the original PANSS items have been proposed and tested for reliability and validity.[67,88-91] One such model was proposed by Marder et al. and categorizes all original PANSS items into five dimensions; positive symptoms (eight items), negative symptoms (seven items), disorganized thought (seven items), uncontrolled hostility/excitement (four items), and anxiety/depression (four items).[67]

It is unclear what degree of improvement in the PANSS total or subscale scores are clinically important. However, in a comparison of PANSS to the Clinical Global Impression (CGI) scale, it was suggested that an absolute reduction of 15 in the total PANSS score corresponds to “minimally improved” on the CGI-Improvement Score, and a reduction on the CGI-Severity Score of one severity step.[50] In comparison, a reduction of 33 in the total PANSS score corresponds to “much improved” on the CGI-Improvement Score. However, the above estimates were sensitive to baseline severity of illness to the extent that participants with a lower baseline severity of illness required smaller reductions in the PANSS to produce a particular improvement in the CGI. For this reason, it has been suggested that change in PANSS score has limited usefulness as a primary outcome, due to variability in baseline symptom intensity.[65,69] Rather, a standardized remission criteria, which may be suitable for use in clinical practice and clinical trials, has been proposed. Specifically, a score of greater than and equal to 3 on eight PANSS items (P1, P2, P3, N1, N4, N6, G5 and G9) for a period of at least six months is considered to represent remission of disease.[65,69]

Mental Health Status and Functioning

Clinical Global Impression (CGI)

The CGI scale is a 3-item scale used to assess overall severity and response to treatment of mental disorders.[72] It is not specific to schizophrenia, although efforts to adapt the scale to this disorder have been undertaken.[70] The usual CGI scale items include **severity of illness** (CGI-S) at the time of the assessment on a 7-point scale (1 = normal; 7 = extremely ill), global **improvement** (CGI-I) relative to baseline on a 7-point scale (1 = very much improved; 7=very much worse), and an **efficacy index** which incorporates the clinician's assessment of therapeutic effect in relation to adverse effects in a 4 point × 4 point grid rating scale (0 = marked improvement and no adverse events; 4 = unchanged or worse, and adverse events outweigh the therapeutic events).[72] The difficulty of combining the two concepts of efficacy and adverse events has led to criticism of this last item.[70] However, there is no total score for the CGI; rather, scores on the individual items are considered separately.

As the CGI is quick to administer, it is suited to clinical settings; however, there is little information regarding its reliability or validity. Rabinowitz et al. sought to validate the CGI-S via a comparison of PANSS and CGI-S scores from seven trials of risperidone in schizophrenia.[71] CGI-S scores from the pooled trials corresponded to the following mean PANSS scores: 1 (normal) = PANSS 55.5, 2 (borderline ill) = PANSS 67.0, 3 (mildly ill) = PANSS 79.6, 4 (moderately ill) = PANSS 92.4, and 5 (markedly ill) = PANSS 99.7. Predefined measures of clinical improvement were: a 20% reduction in the PANSS score and a 1-point decrease on the CGI-S. The sensitivities and specificities for the CGI-S to detect this level of improvement in the seven trials ranged from 64.5% to 89.6% and 65.7% to 82.8%, respectively. From this assessment it appears that the CGI-S and PANSS are correlated and exhibit substantial agreement in detecting change.

Adverse Events: Extrapyramidal Symptoms

Barnes Akathisia Rating Scale (BARS)

The BARS is the most commonly used scale to measure antipsychotic-induced akathisia in clinical trials.[74] The BARS is a four-item scale which scores patients' akathisia based on brief observation by the clinician (ranked 0 to 3); patient report of awareness of restlessness (ranked 0 to 3); patient report of distress related to restlessness (ranked 0 to 3), which produces the fourth item, a global clinical assessment of akathisia.[73] A score of 0 represents absence of symptoms, and a score of 3 represents a severe condition. The global clinical assessment contains five well-defined severity categories, which are considered clinically relevant; 0 = absent, 1 = questionable, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.[74] The global clinical evaluation is made on a 6-point scale, where 0 represents absence of symptoms and a score of 5 represents severe akathisia. Interrater reliability for all four items, based on duplicate rating of 42 chronic in-patients and measured by Cohen's kappa were: observation (0.74), awareness (0.83), distress (0.90), and global clinical assessment (0.96).[73] The BARS has been reported to correlate only weakly with motor activity measured by actometry, potentially due to the fact that actometry measures only actual movement, while the BARS also measures the patient's experience of awareness and distress.[75]

Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a 12-item scale for assessing dyskinesias, to be completed by clinician or researcher. The first seven items pertain to abnormal movements in three specific anatomical sites: facial and oral movements (four items), extremity movements (two items), and trunk movements (1 item).[76] The remaining items are global assessments (three items, including global severity, incapacitation, and patient awareness), and two items specific to dentition. Except items related to dentition, items are scored on a 5-point scale: none (0), minimal (1), mild (2), moderate (3), or severe (4). A score of 0 (none) represents absence of symptoms, and a score of 4 (severe) indicates a severe condition. Interrater reliability in a sample of 38 outpatients with a history of dyskinesia was reported to be high; Pearson correlation coefficient was 0.87 for all items excepting those related to dentition.[77] However, interrater reliability was reported to be higher among experienced raters.[81] The validity of the AIMS has been established via comparisons to other similar instruments; the Extrapyramidal Symptom Rating Scale (ESRS) and the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD).[78,79] Gharabawi et al. examined associations between individually related and overall severity scores from the AIMS and ESRS via logistic regression.[78] R^2 values ranged from 0.30 (trunk movements) to 0.67 (lips and perioral area); R^2 value was 0.56 for global severity. Loonen examined associations between the total AIMS scores, total items excluding global and dental items, and four facial and oral movement items.[79] Spearman's correlation coefficients between the active global dyskinesia subscale of the SADIMoD and the above AIMS scores were, 0.76, 0.82, and 0.83 respectively. It is unclear what would constitute a meaningful change in the AIMS. However, the presence of tardive dyskinesia is accepted as meaningful, based on a rating of mild in two or more anatomical areas, or moderate or greater symptoms in one or more anatomical areas.[78,80]

Simpson-Angus Scale (SAS)

The SAS was developed in the 1960s to identify neuroleptic-induced Parkinsonism. The scale contains 10 items; one measuring gait, six measuring rigidity, and three measuring glabellar tap, tremor, and salivation.[82] Each item is scored on a 5-point scale from 0 (complete absence) to 4 (extreme condition) and a total score is obtained by adding all item scores and dividing by 10 (the total number of items). Scores of up to 0.3 were considered to be within the normal range, however recently it has been suggested that the upper limit of normal be raised to 0.65.[82] Interrater reliability of the SAS between two physicians in a trial of haloperidol containing 14 participants was determined to have a correlation coefficient of 0.87.[83] In this same trial, SAS scores were significantly higher for participants treated with haloperidol compared with placebo, supporting the discriminant validity of the SAS.

Personal and Social Performance Scale (PSP)

A relatively recent development to assess social functioning in schizophrenia,[85] the PSP assesses the existence and level of difficulties in function over the previous month in four main areas: (a) socially useful activities including work; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviours. A single score of from 0 to 100 is assigned by the clinician, with a higher score indicating higher functioning. Explicit criteria for scoring based on observed or reported functioning within each of the four areas above are used to assign patients to a percentile rank. The level of functioning in other areas is used to adjust the rating inside the decimal level, e.g., between 61 and 70.

The reliability and validity of the PSP has been tested in patients in both the acute and stable phases of schizophrenia.[84,86] Reported intraclass correlation coefficients were greater than 0.70 in stable patients and greater than 0.80 for acute patients, and in both instances the PSP was able to discriminate between different levels of the CGI-S scale and was sensitive to changes in the PANSS score. Based on comparisons to the CGI-S, it has been suggested that a 10-point increase in the PSP is clinically meaningful for patients in both the acute and stable phases of schizophrenia.[84,86]

Health-Related Quality of Life

Schizophrenia Quality of Life (S-QoL) Scale

The S-QoL is a patient-rated scale designed and validated to assess the health-related quality of life of patients with schizophrenia. The S-QoL consists of 41 items in eight subscales: psychological well-being (10 items), self-esteem (6 items), family relationships (5 items), relationships with friends (5 items), resilience (5 items), physical well-being (4 items), autonomy (4 items) and sentimental life (2 items). Individual items are rated on a 5-point Likert scale, where positively phrased items are scored from 1 (much less than I would like) to 5 (more than I would like), and negatively phrased items are scored from 1 (much more than expected) to 5 (less than expected). Subscale scores are obtained from the mean of the individual item scores in the respective domain. Subscale scores are then linearly rescaled to between 0 and 100. The mean of the subscale scores results in a total score ranging from 0 (least favourable quality of life) to 100 (most favourable quality of life).[87]

Auquier et al. developed and validated the S-QoL in adults diagnosed with schizophrenia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria.[87] Initially 97 items were developed based on 20 interviews with in- and outpatients with differing levels of severity of schizophrenia. The questionnaire was subsequently administered to subsets of patients (ranging from 40 to 152 participants) and reduced to 41 items and eight dimensions. The validity, consistency, reliability, reproducibility, and sensitivity were then assessed in 207 patients with schizophrenia. Factor analysis with varimax rotation was conducted to test the underlying dimensions of the questionnaire and suggested an eight-factor structure accounting for 52% of the variance, therefore supporting the initial eight subscale structure. Item-level analyses demonstrated homogenous item response levels and relatively infrequent (less than 15%) missing data, indicating feasibility and acceptability of the questionnaire. Internal consistency of domain scores was assessed using Cronbach's alpha with a threshold of 0.7 for patient group comparisons and a threshold of 0.90 for individual comparisons. All domains achieved a Cronbach's alpha of greater than and equal to 0.7 (range from 0.72 to 0.92) and the deletion of any of the 41 items did not increase the internal consistency of any of the eight domains. S-QoL dimension scales were moderately correlated one to another ($0.24 \leq r \leq 0.60$, $P < 0.001$) with the exception of two pairs (psychological well-being versus self-esteem [r = 0.66] and family relationships versus resilience [r = 0.11]). Internal item consistency was also assessed and demonstrated greater item correlation with the domain it was hypothesized to represent than other domains based on an item-domain correlation threshold of 0.40 (range from 0.63 to 0.90). Precision was recognized by considering floor and ceiling effects, which demonstrated minor ceiling effect (maximum of 6.3% in the psychological well-being domain) and minor floor effect (maximum 7% in the physical well-being domain) with the exception of the sentimental life domain (8.8% ceiling effect and 18.7% floor effect). Validity was also tested by assessing the correlation of S-QoL domains with scores of the same dimensions in the Short Form (36) Health Survey (SF-36), Quality of Life Inventory (QoLI),

and European Quality of Life Scale (EuroQol), as well as the association of the S-QoL scores with the severity of disease (indicated by PANSS, CGI, the Calgary Depression Scale for Schizophrenia [CDSS], or Global Assessment of Functioning [GAF]), course of disease, number of hospitalizations, age of first treatment with neuroleptics, duration of hospitalization since first episode, duration of illness, age, education level, clinical setting (in or outpatient) and gender. Overall, the quality of life summary score of the S-QoL showed mild levels of correlation with the general health or satisfaction summary scores of the SF-36 (0.42), QoLI (0.54) and EuroQol (0.48). Furthermore, S-QoL domain scores were generally negatively correlated with PANSS total score (S-QoL total summary score –0.23), CDSS summary score (S-QoL total summary score –0.39) and CGI summary score (S-QoL total summary score –0.32). Contrarily, scores were positively correlated to the GAF (S-QoL total summary score 0.27). Overall, S-QoL total summary scores were not significantly associated with course of disease, number of hospitalizations, age of first treatment with neuroleptics, duration of hospitalization since first episode, duration of illness, age, education level, or gender, with the exception of clinical setting. Test-retest reliability was assessed in 53 patients with unchanged status and indicated high correlation between tests (range from 0.64 to 0.79) and paired test indicated no significant differences between both assessments, suggesting good reproducibility. Sensitivity of the S-QoL was assessed in 46 improved patients and suggested significant differences in three of the eight dimensions (five with effect sizes greater than 0.2), in addition to the S-QoL total summary score. Contrarily, no significant differences were observed with the QoLI (seven domains with effect size lower than 0.2) or the EuroQol. Auquier et al. concluded that the S-QoL was a valid questionnaire in clinical trials and other forms of evaluation of health care and can potentially more directly measure the impact of schizophrenia than other instruments; however, the S-QoL is not intended to replace conventional outcome measures.

Conclusion

A majority of the scales used in the present submission for main outcomes measures are accepted and are validated (PANSS, BARS, AIMS, SAS, PSP, S-QoL), with the exception of the CGI scale, which has limited evidence of validity. The minimal clinically important difference for these scales remains unclear, except for CGI, SAS, and PSP.

Appendix 7: Summary of Study 008

Objective

To summarize the efficacy and safety results from a six-week, open-label, exploratory, phase III B, study that investigated the use of brexpiprazole in the treatment of patients with acute exacerbations of schizophrenia. Aripiprazole was included in this study to establish assay sensitivity and there were no statistical comparisons made between brexpiprazole and aripiprazole. The following summary is based on published data from Citrome et al., 2016[61] and clinicaltrials.gov.[92]

Study Design

Study 008 was a six-week, open-label, exploratory, phase III B RCT. The study consisted of a screening period (2 to 14 days), a six-week open-label treatment period; and 30-day follow-up period. All participants were hospitalized up to at least the week 2 study visit after the initiation of active treatment. Ninety-seven patients were randomized (2:1) to receive either open-label brexpiprazole (1 mg to 4 mg per day; n = 64) or open-label aripiprazole (10 mg to 20 mg per day; n = 33). Randomization in study 008 was conducted using an interactive voice response system or interactive Web response system and was stratified by baseline cognitive function scores (≤-0.5 versus >-0.5).

Interventions

Patients who were randomized to the brexpiprazole group received 1 mg per day for the first four days of the study, followed by 2 mg per day for next three days, and then titrated to the target dose of 3 mg per day at the week 1 study visit. After the first week, the investigator could increase or decrease the dose in increments of 1 mg per day within the range of 1 mg to 4 mg per day. Patients who were randomized to the aripiprazole group received 10 mg per day for the first week of the study which was increase to 15 mg per day at the week 1 study visit. After the first week, the dose of aripiprazole could be increased or decreased in increments of 5 mg per day within the range of 10 mg to 20 mg per day at the discretion of the investigator.

Outcomes

All of the efficacy end points were assessed within each of the treatment groups individually (i.e., there were no statistical comparisons between brexpiprazole and aripiprazole). The primary efficacy end point of study 008 was within-group change from baseline in PANSS at 6 weeks (i.e., whether or not there was an improvement from baseline in the brexpiprazole group). Secondary end points including the following within-group assessments: change from baseline in cognitive test battery at 6 weeks; change from baseline in CGI-S at 6 weeks; CGI-I at 6 weeks; and response rate at six weeks (i.e., a reduction from baseline of at least 30% in PANSS total score or a CGI-I score of 1 or 2); change from baseline in Specific Levels of Functioning Scale (SLOF); and change from baseline in the Barratt Impulsiveness Scale 11-item (BIS-11). In addition to adverse events, the safety evaluations included the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Table 36: Characteristics of Study 008

		331-13-008 (Study 008)
Designs & Populations	**Study Design**	6-week, open-label, exploratory, phase III B, randomized trial
	Locations	US (19 sites)
	Randomized (N)	97 patients (2:1) • 64 brexpiprazole • 33 aripiprazole
	Inclusion Criteria	• Schizophrenia (DSM-IV-TR criteria confirmed by MINI) • All of the following: PANSS total score of ≥ 80; score of ≥ 4 on at least two of the following PANSS items: unusual thought content, conceptual disorganization, hallucinatory behaviour, or suspiciousness • Clinical Global of Impression - Severity score of at least 4 (moderately ill) • Would benefit from hospitalization for current acute relapse of schizophrenia
	Exclusion Criteria	• First episode of schizophrenia • Hospitalized for > 21 days for current acute episode • Diagnosis other than schizophrenia • Improvement of ≥ 20% in total PANSS score between screening and baseline
Drugs	**Intervention**	• Brexpiprazole (flexibly dosed at 1, 2, 3 or 4 mg/day – target dose of 3 mg/day)
	Positive control	• Aripiprazole (flexibly dosed at 10 mg to 20 mg/day) included for assay sensitivity
Duration	**Phase**	
	Screening	2 to 14 days
	Double-blind	6 weeks
	Follow-up	30 days
Outcomes	**Primary End Point**	Within-group change from baseline in PANSS at 6 weeks
	Other End Points	Within-group assessments of the following: • Change from baseline in Cognitive test battery at 6 weeks • Change from baseline in Clinical Global of Impression - Severity at 6 weeks • Change from baseline in Clinical Global of Impression - Improvement at 6 weeks • Within-group response rate at 6 weeks • Change from baseline in Specific Levels of Functioning Scale • Change from baseline in Barratt Impulsiveness Scale 11-item • Change from baseline in Simpson-Angus Scale • Change from baseline in Abnormal Involuntary Movement Scale • Change from baseline in Barnes Akathisia Rating Scale • Change from baseline in Columbia Suicide Severity Rating Scale
Notes	**Publications**	• Citrome et al., 2016[61] • Clinicaltrials.gov[92]

PANSS = Positive and Negative Syndrome Scale.
Source: Citrome et al, 2016[61] and clinicaltrials.gov.[92]

Statistical Analysis

The manufacturer reported that two data sets were used in the analyses:

- Safety analysis set: all patients who took at least one dose of study medication
- Full analysis set: all randomized patients who underwent a baseline assessment, took at least one dose of study medication, and who underwent at least one post-baseline efficacy assessment

The manufacturer used MMRM to evaluate within-group change from baseline in PANSS, CGI-S, and cognitive battery test scores. An ANCOVA model was used to evaluate change from baseline in SLOF and BIS-II. There were no adjustments for multiple comparisons. There were no statistical tests reported for any of the following end points: CGI-I, response rate, SAS, AIMS, BARS, and CSSR.

Table 37: Statistical testing in Study 008

End Point	Analysis	Imputation Method
Positive and Negative Syndrome Scale	MMRM	From observed data
Cognitive test battery	MMRM	From observed data
Clinical Global of Impression - Severity	MMRM	From observed data
Specific Levels of Functioning Scale	ANCOVA	LOCF
Barratt Impulsiveness Scale 11-item	ANCOVA	LOCF
Clinical Global of Impression - Improvement	No statistical testing	
Response rate		
Simpson-Angus Scale		
Barnes Akathisia Rating Scale		
Abnormal Involuntary Movement Scale		
Columbia Suicide Severity Rating Scale		

ANCOVA = analysis of covariance; LOCF = last observation carried forward; MMRM = mixed model repeated measures.

Population

Inclusion criteria

Patients (18 to 65 years) with schizophrenia diagnosed using the DSM-IV-TR criteria and confirmed by MINI were eligible if they experiencing an acute exacerbation of symptoms. Patients were required to have a PANSS total score of at least 80; a score of at least four on at least two of the following PANSS items: unusual thought content, conceptual disorganization, hallucinatory behaviour, or suspiciousness. Patients were also required to have a CGI-S score of at least 4 (moderately ill) and would benefit from hospitalization for current acute relapse of schizophrenia (in the opinion of the investigator). Key exclusion criteria were: any patients experiencing a first episode of schizophrenia, any patients who had been hospitalized for more than 21 days for the current acute episode, any patients who experienced an improvement of 20% or more in the interval between screening and baseline, and patients with a DSM-IV-TR Axis I diagnosis of than schizophrenia (e.g., schizoaffective disorder, major depressive disorder, bipolar disorder, post-traumatic stress disorder, anxiety disorders, delirium, dementia, amnestic, or other cognitive disorders).

Baseline characteristics

Key baseline and demographic characteristics are summarized in **Table 38** for the brexpiprazole and aripiprazole groups. The reported characteristics were well balanced between the two groups. The majority of study participants were male (71.9% and 69.7% with brexpiprazole and aripiprazole, respectively) and African American (75.0% and 72.7% with brexpiprazole and aripiprazole, respectively). The mean age of participants was 42 years in both groups. Mean baseline PANSS scores were 94.1 in the brexpiprazole group and 93.3 in the aripiprazole group.

Table 38: Baseline and Demographic Characteristics

Baseline characteristics		Brexpiprazole (N = 64)	Aripiprazole (N = 33)
Age (years)	Mean (SD)	42.2 (10.1)	42.1 (10.4)
Weight (kg)	Mean (SD)	89.9 (19.7)	87.2 (18.3)
Height (cm)	Mean (SD)	173.1 (9.0)	173.5 (9.8)
BMI (kg/m^2)	Mean (SD)	30.2 (7.4)	29.1 (6.2)
Sex (n [%])	Male	46 (71.9)	23 (69.7)
	Female	18 (28.1)	10 (30.3)
Race n (%)	White	14 (21.9)	8 (24.2)
	African American	48 (75.0)	24 (72.7)
	Asian	1 (1.6)	0 (0.0)
	Other	1 (1.6)	1 (3.0)
Ethnicity n (%)	Hispanic/Latino	7 (10.9)	2 (6.1)
	Not Hispanic/Latino	57 (89.1)	30 (90.9)
	Other	0 (0.0)	1 (3.0)
Age at diagnosis (years)	Mean (SD)	25.6 (9.2)	22.8 (9.3)
Current episode duration (weeks)	Mean (SD)	4.1 (3.1)	4.0 (3.0)
PANSS	Mean (SD)	94.1 (10.1)	93.3 (9.6)
CGI-S	Mean (SD)	5.0 (0.7)	4.8 (0.8)

BMI = body mass index; CGI-S = Clinical Global of Impression – Severity; n = number of patients with characteristic; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation
Source: Citrome et al, 2016[61]

Patient disposition

Patient disposition is summarized in Table 39. The proportion of patients who discontinued early was high in both groups (i.e., 37.5% and 36.4% with brexpiprazole and aripiprazole, respectively). There were notable differences in the reasons for withdrawal between the two groups. Withdrawn consent was the most commonly cited reason for the brexpiprazole group (21.9%) and it occurred at a greater frequency than in the aripiprazole group (12.1%). Lost to follow-up was the most common reason in the aripiprazole group (15.2%) and was less frequently reported in the brexpiprazole group (4.7%). A greater proportion of brexpiprazole-treated patients fulfilled the withdrawal criteria compared with the aripiprazole-treated patients (6.3% versus 3.0%).

Table 39: Summary of Patient Disposition

Patient disposition, n (%)	Brexpiprazole (N = 64)	Aripiprazole (N = 33)
Randomized	64	33
Treated	64 (100.0)	33 (100.0)
Completed	40 (62.5)	21 (63.6)
Discontinued	24 (37.5)	12 (36.4)
Withdrawn consent	14 (21.9)	4 (12.1)
Lost to follow-up	3 (4.7)	5 (15.2)
Fulfilled withdrawal criteria	4 (6.3)	1 (3.0)
Adverse events	3 (4.7)	1 (3.0)
Withdrawn by investigator	0 (0.0)	1 (3.0)

n = number of patients with event.
Source: Citrome et al., 2016.[61]

Efficacy End Points

PANSS Total Score

As shown in Table 40, both brexpiprazole and aripiprazole were associated with statistically significant improvements from baseline in PANSS total score at six weeks (−22.9 and −19.4, respectively). As noted previously, there were no comparisons between brexpiprazole and aripiprazole.

Table 40: Summary of PANSS Total Score

End Point	Group	n	Baseline Mean (SD)	Change From Baseline		Brexpiprazole Versus Aripiprazole
				LSM (SE)	*P* Value	
PANSS total score	Brexpiprazole	64	94.1 (10.1)	−22.9 (1.7)	< 0.0001	Not compared
	Aripiprazole	33	93.3 (9.6)	−19.4 (2.4)	< 0.0001	

LSM = least squares mean; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = standard error.
Source: Citrome et al., 2016.[61]

Clinical Global Impression – Severity

As shown in Table 41, both brexpiprazole and aripiprazole were associated with statistically significant improvements from baseline in CGI-S score at six weeks (−1.6 and −1.3, respectively). There were no comparisons between brexpiprazole and aripiprazole.

Table 41: Summary of Clinical Global Impression — Severity

End Point	Group	n	Baseline Mean (SD)	Change From Baseline		Brexpiprazole Versus Aripiprazole
				LSM (SE)	*P* Value	
CGI-S	Brexpiprazole	64	5.0 (0.7)	−1.6 (0.1)	< 0.0001	Not compared
	Aripiprazole	33	4.8 (0.8)	−1.3 (0.2)	< 0.0001	

CGI-S = Clinical Global of Impression – Severity; LSM = least squares mean; SD = standard deviation; SE = standard error.
Source: Citrome et al., 2016.[61]

Clinical Global Impression – Improvement

The manufacturer reported that the mean CGI-I scores at six weeks were 2.5 (SD: 0.9) for brexpiprazole and 2.7 (SD: 1.0) for aripiprazole. There were no statistical tests performed for the CGI-I end point.

Response Rate

The proportion of patients who met the response criteria (i.e., a reduction of at least 30% from baseline in PANSS total score or CGI-I score of 1 or 2) was 60.9% in the brexpiprazole group and 48.5% in the aripiprazole group. There were no statistical comparisons made between the groups.

Cognitive Test Battery Scores

There were no statistically significant differences for either the brexpiprazole or aripiprazole groups for change from baseline cognitive test battery total score (Table 42).

Table 42: Summary of Results for the Cognitive Test Battery Scores

End Point	Group	n	Baseline Mean (SD)	Change From Baseline		Brexpiprazole Versus Aripiprazole
				LSM (SE)	*P* Value	
Cognitive battery test total score	Brexpiprazole	64	Not reported	0.045 (0.056)	<0.0001	Not compared
	Aripiprazole	33	Not reported	-0.024 (0.081)	<0.0001	

LSM = least squares mean; SD = standard deviation; SE = standard error.
Source: Citrome et al., 2016[61] and clinicaltrials.gov.[92]

Specific Levels of Functioning Scale

The SLOF is a 43-item instrument used to assess the current functioning and behaviour of a patient. The SLOF evaluates the following six subscales: 1) physical functioning, 2) personal care skills; 3) interpersonal relationships; 4) social acceptability; 5) activities of community living; and 5) work skills. Each question is scored used a five-point Likert scale ranging from 1 (poorest) to 5 (best). Scores range from 43 to 215, with higher scores indicating better functioning.[93,94] Patients in both the brexpiprazole group aripiprazole groups demonstrated statistically significant improvements in the Specific Levels of Functioning Scale at six weeks (Table 43). There were no statistical comparisons conducted between the brexpiprazole and aripiprazole groups.

Barratt Impulsiveness Scale 11-item

The BIS11 is a 30-item instrument used to assess impulsivity. The test consists of the following first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) as wells as three second-order factors (attentional, motor, and non-planning impulsiveness). Each item is scored using a four-point scale ranging from 1 (rarely or never) to 4 (almost always or always), with higher scores indicating greater impulsivity.[95] As shown in Table 43, patients in the brexpiprazole group demonstrated a statistically significant reduction in the BIS-11 score. There was no statistically significant difference in the aripiprazole group. There were no statistical comparisons conducted between the brexpiprazole and aripiprazole groups.

Table 43: Change from Baseline in SLOF and BIS11

End Point	Group	n	Baseline Mean (SD)	Change From Baseline		Brexpiprazole Versus Aripiprazole
				Mean (SD)	*P* Value	
Specific Levels of Functioning Scale	Brexpiprazole	64	111.9 (14.5)	7.7 (14.8)	<0.0001	Not compared
	Aripiprazole	33	112.2 (14.6)	5.5 (11.3)	0.0158	
Barratt Impulsiveness Scale 11-item	Brexpiprazole	64	70.4 (10.9)	−2.7 (10.0)	0.0392	Not compared
	Aripiprazole	33	71.3 (9.4)	0.1 (6.9)	0.9716	

SD = standard deviation.
Source: Citrome et al, 2016[61] and clinicaltrials.gov.[92]

Safety End Points

Table 44 provides a summary of the following: treatment-emergent adverse events that were reported for at least 5% of patients, the proportion of patients who experienced at least one serious adverse event, and the proportion of patients who experienced EPS-related adverse events. The proportions of patients who experienced at least one adverse event were 56.3% with brexpiprazole and 63.6% with aripiprazole. Akathisia (9.4% versus 21.2%), headache (7.8% versus 12.1%), constipation (4.7% versus 9.1%), and sedation (0% versus 6.1%) were reported less frequently in the brexpiprazole group compared with the aripiprazole group. The overall frequency of EPS-related adverse events was greater in the aripiprazole group compared with the brexpiprazole group (30.3% versus 14.1%). Serious adverse events were slightly more common in the brexpiprazole group compared with the aripiprazole group (3 [4.7%] versus 1 [3.0%]).

Table 44: Summary of Adverse Events in Study 008

Adverse events, n (%)	Brexpiprazole (N = 64)	Aripiprazole (N = 33)
TEAEs reported in ≥5% of patients		
Any adverse events	36 (56.3)	21 (63.6)
Akathisia	6 (9.4)	7 (21.2)
Weight increase	6 (9.4)	3 (9.1)
Headache	5 (7.8)	4 (12.1)
Dyspepsia	5 (7.8)	3 (9.1)
Dry mouth	5 (7.8)	2 (6.1)
Nausea	4 (6.3)	1 (3.0)
Pain in extremity	4 (6.3)	1 (3.0)
Constipation	3 (4.7)	3 (9.1)
Diarrhea	3 (4.7)	2 (6.1)
Back pain	2 (3.1)	2 (6.1)
Sedation	0 (0.0)	2 (6.1)
Muscle spasms	0 (0.0)	2 (6.1)
Toothache	0 (0.0)	2 (6.1)
EPS-related adverse events		
Any EPS-event	9 (14.1)	10 (30.3)
Akathisia events	6 (9.4)	7 (21.2)
Parkinsonian events	2 (3.1)	1 (3.0)
Dystonic events	1 (1.6)	2 (6.1)
Residual events	0 (0.0)	0 (0.0)

Adverse events, n (%)	Brexpiprazole (N = 64)	Aripiprazole (N = 33)
Dyskinetic events	0 (0.0)	0 (0.0)
Serious adverse events		
At least one SAE	3 (4.7)	1 (3.0)
Acute hepatitis B	1 (1.6)	0 (0)
Convulsion	1 (1.6)	0 (0)
Pre-syncope	0 (0)	1 (3.0)
Schizophrenia	1 (1.6)	0 (0)

EPS = extrapyramidal symptom; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Citrome et al., 2016[61] and clinicaltrials.gov.[92]

Critical Appraisal

Internal Validity

Randomization in study 008 was conducted with adequate measures to conceal treatment allocation (i.e., interactive voice response system [IVRS] or interactive Web response system [IWRS]). Randomization was stratified by baseline cognitive function scores (≤-0.5 versus >-0.5) and key baseline and demographic characteristics were generally balanced between the brexpiprazole and aripiprazole groups. Twice as many patients were randomized to the brexpiprazole group (n= 64) compared with aripiprazole group (n = 33). Unlike the VECTOR, BEACON, and LIGHTHOUSE acute treatment trials, the study treatments in study 008 were administered in an open-label manner.

All of the statistical comparisons were conducted within the individual treatment groups; however, twice as many patients were randomized to the brexpiprazole group compared with the aripiprazole group. Therefore, it is possible that the absence of a statistically significant difference in the BIS11 scale for the aripiprazole group was due to the decreased statistical power within that group.

Study 008 was an exploratory study that was not conducted with a true active comparator group; aripiprazole was only included for the purposes of establishing assay sensitivity. The study was not designed or powered for comparisons between brexpiprazole and aripiprazole; hence, there are no formal comparisons that can be evaluated with this study. This was noted by the study authors who stated that "adequately powered, head-to-head comparative studies are required to fully understand the differences between brexpiprazole and aripiprazole."[61]

Study 008 included a small number of patients (e.g., only 33 patients were randomized in the aripiprazole group). In addition, similar to the other acute treatment trials, study 008 had a high proportion of early withdrawals (> 35% in both treatment groups). This resulted in only 21 aripiprazole-treated patients completing the study. The proportion of discontinuations from the brexpiprazole (37.5%) and aripiprazole group (36.4%) in study 008 was greater than those reported for the active treatments in the other acute treatment trials (range: 20.3% to 32.8%). Since withdrawal is unlikely to occur randomly, it is possible that the high proportion of discontinuations may have compromised randomization, and that the characteristics (measured and unmeasured) of the treatment groups may not have remained similar over time.

External Validity

Enrolment in study 008 was restricted to patients who met a minimum threshold for disease severity (e.g., PANSS ≥ 80) and who would benefit from hospitalization. This results in a patient population that is more severe than typical Canadian patients, who would often have mild to moderate disease.

The initial titration regimen that was used in the brexpiprazole group of study 008 (i.e., 1 mg per day on days 1 to 4) is reflective of the Health Canada–approved product monograph. The starting and target dose of aripiprazole that is recommended in the product monograph is 10 to 15 mg per day. Therefore, the 10 mg to 20 mg per day dosage of aripiprazole that was used in study 008 exceeded the upper range of the recommended dose (i.e., 15 mg per day), but was below the 30 mg maximum dose that is stated in the product monograph). This was not a comparative study and there were no statistical comparisons; however, it is unclear if permitting only one treatment to be titrated to the maximum recommended dose could have biased the results of efficacy end points in favour of brexpiprazole and harms in favour of aripiprazole.

Similar to the other acute treatment trials, study 008 involved extensive patient contact with health care professionals which may not be reflective of routine clinical practice in Canada. The study required patients to be hospitalized until at least week 2 of the study. This may reduce the generalizability of the results to the Canadian setting.

Summary

Study 008 was a small (N = 97), six-week, open-label, exploratory study that investigated the use of flexibly dosed brexpiprazole (1 mg to 4 mg) for the treatment of patients with an acute exacerbation of schizophrenia. Aripiprazole (10 mg to 20 mg) was included in this study to establish assay sensitivity; the absence of any statistical testing between the two groups precludes any conclusions regarding the comparative effectiveness of these two agents. Key limitations of the study include the following: open-label administration of study treatments; small number of randomized patients; high proportion of discontinuations; absence of power calculations in the publication; absence of formal comparisons between the two treatments; capping the dosage of aripiprazole below the maximum dosage recommended in Canada; lack of adjustment for multiple within-group comparisons; and the large number of end points with no statistical testing reported (i.e., CGI-I, response rate, AIMS, BARS, and SAS).

Both brexpiprazole and aripiprazole were associated with statistically significant improvements from baseline in PANSS total score at six weeks, CGI-S score at six weeks, and Specific Levels of Functioning Scale at six weeks. There were no statistically significant differences for either the brexpiprazole or aripiprazole groups for change from baseline in the cognitive test battery total score. Patients in the brexpiprazole group demonstrated a statistically significant reduction in the BIS-11 score.

The percentage of patients who experienced at least one adverse event was 56.3% with brexpiprazole and 63.6% with aripiprazole. The overall frequency of EPS-related adverse events was greater in the aripiprazole group compared with the brexpiprazole group (30.3% versus 14.1%), largely due to an increase in the akathisia in the aripiprazole group.

Study 008 was not designed or powered for comparisons between brexpiprazole and aripiprazole for either efficacy or safety end points. There are no conclusions regarding the comparative efficacy of aripiprazole and brexpiprazole that can be drawn from this study.

Appendix 8: Summary of ZENITH Extension Study

Objective

To summarize the results of the ZENITH long-term safety study which evaluated the effects of brexpiprazole monotherapy in adult patients with schizophrenia on an outpatient basis.

Findings

Study Design

Study design and characteristics of the multi-centre, open-label, non-randomized, multi-dose, long-term safety study are summarized in TABLE 45 and Figure 23. The baseline characteristics at the last visit for patients who participated in prior double-blind trials (BEACON, VECTOR and EQUATOR) were considered as the baseline characteristics for the screening visit in the open-label phase. A screening visit was required for new patients who had not participated in BEACON, VECTOR or EQUATOR. Patients who were concomitantly treated with other antipsychotic drugs entered a conversion phase in which brexpiprazole was up-titrated to 2 mg per day and concomitant antipsychotic drugs were down-titrated to discontinuation. The baseline characteristics at the last visit of the conversion phase were considered as the baseline characteristics for the screening visit for the open-label phase. All patients included in the open-label phase of ZENITH were treated with an initial dose of brexpiprazole 2 mg per day with the exception of those who were treated with brexpiprazole in EQUATOR. Those patients could start treatment in the open-label phase of ZENITH using the brexpiprazole dose from the double-blind phase of the trial. Dose titration up to 4 mg per day was permitted in a step-wise approach (1 mg per week) any time during the open-label phase. Down titrations were also permitted any time during the open-label phase and followed the same step-wise approach. Patients who were not able to tolerate the initial dosage of 2 mg per day were able to down-titrate to a 1 mg per day dosage and those who remained intolerant to 1 mg were withdrawn from the study. The maximum dosage of brexpiprazole in ZENITH was 4 mg per day.

Figure 23: ZENITH Patient Enrolment

Confidential figure removed at manufacturer's request.

Source: Clinical Study Report.[96]

Table 45: Summary of the Design and Characteristics of the ZENITH Long-Term Safety Extension

		ZENITH
Designs and Populations	**Study Design**	Multi-centre, open-label, multi-dose, long-term safety
	Participants (N)	1,044
	Eligibility	• Adults ≥ 18 and ≤ 65 years of age • Any patient who participated in BEACON, VECTOR and EQUATOR and who was likely to benefit from brexpiprazole, based on investigator judgment • New outpatients (had not participated in the previous studies) satisfying DSM-IV criteria, confirmed by MINI criteria, only from select sites • Treated with at least one oral antipsychotic other than clozapine • Lapse in current treatment • No concomitant schizophrenia therapy
	Primary objective	To evaluate the long-term efficacy and safety of brexpiprazole
Drugs	**Intervention**	Brexpiprazole monotherapy 1 mg to 4 mg tablets orally once daily
	Comparators	NA
Duration	**Screening**	• Screening phase: up to four weeks • Last visit from BEACON, VECTOR, and EQUATOR for rollover patients • Screening visit for new patients only
	Conversion	• Conversion phase: up to four weeks • New patients and rollover patients treated with at least one oral antipsychotic proceeded to conversion phase. • Brexpiprazole and concomitant antipsychotic dose titration • Hospitalization optional if deemed medically necessary
	Treatment (Open-Label)	• Open-label phase: 26 weeks (before amendment) or 52 weeks • Open-label visits: Weeks 1, 2, 4, 8, 14, 20, 26, 32, 38, 44, and 52. • Patients from BEACON, VECTOR, and EQUATOR proceeded directly into open-label phase • New patients with lapse in current treatment greater than seven days proceeded to open-label phase
	Follow-Up	• Final follow-up: 30 days following last dose of open-label medication
Outcomes	**Primary End Point**	• Frequency and severity of adverse events
	Other End Points (Review Relevant Outcomes	• Change from baseline in PANSS total score • Change from baseline in CGI-S score • Change from baseline in PSP scale total score • Mean CGI-I score • Change from baseline in PANSS Positive subscale score • Change from baseline in PANSS Negative subscale score • Response rate, defined as reduction of ≥ 30% from baseline in PANSS total or CGI-I score of 1 (very much improved) or 2 (much improved) • Discontinuation rate for lack of efficacy • Change from baseline in PANSS Marder Factor scores • Change from baseline in SAS • Change from baseline in DIEPSS • Change from baseline in AIMS • Change from baseline in BARS • Change from baseline in C-SSRS

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DIEPSS = Drug-Induced Extrapyramidal Symptom Scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* MINI = Mini-International Neuropsychiatric Interview; NA = not applicable; PANSS = Positive and Negative Symptoms Scale; PSP = Personal and Social Performance; SAS =Simpson-Angus Scale.

Source: Clinical Study Report.[96]

Methods

The primary safety analysis was the frequency of adverse events in the open-label treatment phase. The incidence of treatment-emergent adverse events (TEAEs) included summaries of TEAEs by severity, potentially drug-related TEAEs, TEAEs with an outcome of death, serious TEAEs, and discontinuations due to TEAEs. Safety analyses were based on the safety population defined as participants who received at least one dose of brexpiprazole in ZENITH, and were provided for: all enrolled patients, 52-week enrolled patients, and 26-week enrolled patients. All efficacy analyses were considered as secondary end points and were evaluated as per the efficacy population defined as all patients in the safety population who had at least one post-baseline efficacy evaluation for PANSS total score, and were also provided for: all enrolled patients, 52-week enrolled patients, and 26-week enrolled patients, respectively. Data were imputed using the last observation carried forward (LOCF) method using data from the treatment phase only. No indication of any corrections to adjust for multiple statistical comparisons were applied, therefore, all end points other than the primary end point should be considered exploratory outcomes.

Patient Disposition

In the ZENITH trial, a total of 1072 patients were enrolled of which 239 (22.3%) participated in the conversion phase (28 patients discontinued the conversion phase) and 1044 (97.4%) in the open-label treatment phase. Overall, 508 (47.4%) patients completed the open-label treatment phase and 536 (50.0%) discontinued. The most common reasons for discontinuation were withdrawn consent (16.5%) and adverse events (14.8%). Detailed disposition data are presented in Table 46.

Table 46: Patient Disposition in ZENITH

Disposition, n (%)	Prior Brexpiprazole	Prior Placebo	New Patients	Total
Number of patients	611	204	257	1072
Conversion phase				
Entered	12 (2.0)	0	227 (88.3)	239 (22.3)
Completed	12 (2.0)	0	199 (77.4)	211 (19.7)
Discontinued	0 (0.0)	0	28 (10.9)	28 (2.6)
Lost to follow-up	0	0	6 (2.3)	6 (0.6)
Adverse events	0	0	8 (3.1)	8 (0.7)
Sponsor discontinued study	0	0	0 (0.0)	0 (0.0)
Protocol withdrawal criteria	0	0	7 (2.7)	7 (0.7)
Investigator discretion	0	0	1 (0.4)	1 (0.1)
Withdrew consent	0	0	5 (1.9)	5 (0.5)
Protocol deviation	0	0	0 (0.0)	0 (0.0)
Lack of efficacy	0	0	1 (0.4)	1 (0.1)
Open-Label Treatment Phase				
Entered	611 (100.0)	204 (100.0)	229 (89.1)	1044 (97.4)
Completed	308 (50.4)	109 (53.4)	91 (35.4)	508 (47.4)
Discontinued	303 (49.6)	95 (46.6)	138 (53.7)	536 (50.0)
Lost to follow-up	22 (3.6)	12 (5.9)	22 (8.6)	56 (5.2)
Adverse events	109 (17.8)	23 (11.3)	27 (10.5)	159 (14.8)
Sponsor discontinued study	0	0	0	0

Disposition, n (%)	Prior Brexpiprazole	Prior Placebo	New Patients	Total
Number of patients	611	204	257	1072
Protocol withdrawal criteria	38 (6.2)	5 (2.5)	38 (14.8)	81 (7.6)
Investigator discretion	9 (1.5)	1 (0.5)	3 (1.2)	13 (1.2)
Withdrew consent	102 (16.7)	45 (22.1)	30 (11.7)	177 (16.5)
Protocol deviation	1 (0.2)	2 (1.0)	4 (1.6)	7 (0.7)
Lack of efficacy	22 (3.6)	7 (3.4)	14 (5.4)	43 (4.0)
Safety population	605 (99.0)	202 (99.0)	224 (87.2)	1031 (96.2)
Efficacy population	591 (96.7)	198 (97.1)	223 (86.8)	1012 (94.4)

Source: Clinical Study Report.[96]

Baseline Characteristics

Key baseline and demographic characteristics for the ZENITH trial are summarized in Table 47. The mean age of participants was 40.0 years (SD 11.1). The majority of patients were male (61.8%), [redacted].

Table 47: Baseline Characteristics in ZENITH

Characteristics	Prior Brexpiprazole (N = 611)	Prior Placebo (N = 204)	New Patients (N = 257)	Total (N = 1072)
Mean age, (SD)	38.5 (10.8)	39.6 (10.8)	44.1 (11.1)	40.0 (11.1)
Sex, n (%)				
Male	366 (59.9)	125 (61.3)	172 (66.9)	663 (61.8)
Female	245 (40.1)	79 (38.7)	85 (33.1)	409 (38.2)
Race, n (%)				
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
African American	[redacted]	[redacted]	[redacted]	[redacted]
Native American	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Mean body weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean PANSS (SD)[a]				
Total score	[redacted]	[redacted]	[redacted]	[redacted]
Positive subscale	[redacted]	[redacted]	[redacted]	[redacted]
Negative subscale	[redacted]	[redacted]	[redacted]	[redacted]
CGI-S score[a]	[redacted]	[redacted]	[redacted]	[redacted]
PSP score[a]	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; CGI-S = Clinical Global Impression-Severity; kg = kilogram; m^2 = square metres; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; SD = standard deviation.

[a] Efficacy population (n = 1031).

Source: Clinical Study Report.[96]

Exposure to Study Treatments

A summary of exposure to the study treatment in the ZENITH trial is provided in Table 48.

[redacted] Table 49 [redacted]

Table 48: Exposure in Open-Label Phase of ZENITH

Time Point	Prior Brexpiprazole	Prior Placebo	New Patients	Total
Day 1 to 28	[redacted]	[redacted]	[redacted]	[redacted]
Day 29 to 56	[redacted]	[redacted]	[redacted]	[redacted]
Day 57 to 84	[redacted]	[redacted]	[redacted]	[redacted]
Day 85 to 112	[redacted]	[redacted]	[redacted]	[redacted]
Day 113 to 140	[redacted]	[redacted]	[redacted]	[redacted]
Day 141 to 168	[redacted]	[redacted]	[redacted]	[redacted]
Day 169 to 196	[redacted]	[redacted]	[redacted]	[redacted]
Day 197 to 224	[redacted]	[redacted]	[redacted]	[redacted]
Day 225 to 252	[redacted]	[redacted]	[redacted]	[redacted]
Day 253 to 280	[redacted]	[redacted]	[redacted]	[redacted]
Day 281 to 308	[redacted]	[redacted]	[redacted]	[redacted]
Day 309 to 336	[redacted]	[redacted]	[redacted]	[redacted]
Day 337 to 364	[redacted]	[redacted]	[redacted]	[redacted]
Day > 364	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[96]

Table 49: Concomitant Medications in Open-Label Phase of ZENITH

Concomitant Medication, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Anticholinergic	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]
Psycholeptic	[redacted]	[redacted]	[redacted]	[redacted]
Psychoanaleptic	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[96]

Efficacy

Mean PANSS total score, Positive and Negative subscale scores, as well as PANSS Marder Factors during the open-label phase in ZENITH are summarized in Table 50, Table 51, and

Table 52. [redacted].

Response was defined as a reduction of at least 30% from baseline in PANSS total score or a CGI-I score of 1 (very much improved) or 2 (much improved). Results for the responder analyses are summarized in Table 53. [redacted] Table 54.

Table 50: Change From Baseline in PANSS During Open-Label Phase of ZENITH

End Point (SD)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
PANSS Total score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–6.90 (12.90)	–12.50 (14.90)	–6.60 (13.60)	–8.00 (13.60)
Mean change at week 52	–11.00 (14.40)	–18.40 (16.90)	–8.80 (12.60)	–9.00 (15.30)
Mean change at last visit	–3.80 (16.70)	–9.70 (18.70)	–3.50 (14.30)	–4.90 (16.80)
PANSS Positive Symptoms Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–2.10 (4.50)	–4.10 (5.40)	–1.70 (4.30)	–2.40 (4.70)
Mean change at week 52	–3.20 (4.60)	–5.80 (5.20)	–2.30 (4.10)	–3.60 (4.80)
Mean change at last visit	–0.90 (5.90)	–2.80 (6.40)	–1.00 (4.90)	–1.30 (5.80)
PANSS Negative Symptoms Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–1.40 (3.70)	–2.40 (4.30)	–1.30 (3.80)	–1.60 (3.90)
Mean change at week 52	–2.70 (4.50)	–3.70 (5.40)	–2.00 (3.70)	–2.80 (4.60)
Mean change at last visit	–1.00 (4.10)	–2.40 (5.00)	–0.60 (4.20)	–1.20 (4.30)
PANSS Marder Factors				
PANSS Positive Symptoms Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–2.60 (4.80)	–4.70 (5.50)	–2.00 (5.20)	–2.90 (5.10)
Mean change at week 52	–3.90 (5.20)	–6.60 (5.70)	–2.60 (4.80)	–4.20 (5.40)
Mean change at last visit	–1.60 (5.90)	–3.50 (6.50)	–1.30 (5.00)	–1.90 (5.90)
PANSS Negative Symptoms Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]

End Point (SD)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Mean change at week 26	–1.50 (3.60)	–2.20 (4.00)	–1.70 (4.10)	–1.70 (3.80)
Mean change at week 52	–2.60 (4.30)	–3.90 (5.00)	–2.20 (3.80)	–2.80 (4.40)
Mean change at last visit	–1.00 (4.10)	–2.30 (5.10)	–0.70 (4.10)	–1.20 (4.40)
Disorganized Thought Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–1.70 (3.30)	–2.60 (3.50)	–1.70 (3.50)	–1.90 (3.40)
Mean change at week 52	–2.90 (3.70)	–3.70 (4.60)	–2.30 (3.70)	–2.90 (4.00)
Mean change at last visit	–1.20 (4.20)	–2.20 (4.50)	–0.90 (4.00)	–1.40 (4.20)
Hostility/Excitement Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–0.40 (2.70)	–1.40 (3.10)	–0.60 (2.60)	–0.60 (2.80)
Mean change at week 52	–0.80 (2.70)	–1.90 (2.90)	–0.90 (2.30)	–1.10 (2.70)
Mean change at last visit	0.20 (3.40)	–0.70 (3.50)	–0.30 (3.00)	–0.10 (3.40)
Anxiety/Depression Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	–0.70 (2.60)	–1.50 (3.00)	–0.70 (3.40)	–0.90 (2.90)
Mean change at week 52	–0.90 (2.50)	–2.40 (2.90)	–0.80 (3.50)	–1.20 (2.90)
Mean change at last visit	–0.20 (3.20)	–0.90 (3.40)	–0.40 (3.80)	–0.40 (3.40)

PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

Notes:

n = 632 at week 26, n = 410 at week 52, n = 1012 at last visit.

Last visit consists of week 26 and early termination, or week 52 and early termination.

Source: Clinical Study Report.[96]

Table 51: CGI During Open-Label Phase of ZENITH

End Point (SD)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
CGI - S Score				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change at week 26	–0.35 (0.79)	–0.60 (0.98)	–0.24 (0.88)	–0.38 (0.86)
Change at week 52	–0.55 (0.86)	–0.97 (0.98)	–0.48 (0.86)	–0.63 (0.91)
Change at last visit	–0.14 (1.04)	–0.46 (1.12)	–0.17 (0.88)	–0.21 (1.03)
CGI - I Score[a]				
Week 1	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Last visit	[redacted]	[redacted]	[redacted]	[redacted]

CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; SD = standard deviation.

Notes: n = 632 at week 26, n = 410 at week 52, n = 1012 at last visit.

Last visit consists of week 26 and early termination, or week 52 and early termination.

[a] Only mean values at specified time points reported.

Source: Clinical Study Report.[96]

Table 52: Change from Baseline in PSP During Open-Label Phase of ZENITH

End Point (SD)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
PSP total score				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change at week 26	4.50 (9.70)	6.50 (11.30)	4.50 (9.00)	4.90 (10.00)
Change at week 52	7.00 (10.60)	9.60 (11.90)	7.60 (10.80)	7.70 (11.00)
Change at last visit	1.80 (12.40)	5.10 (12.80)	2.70 (11.00)	2.70 (12.20)

PSP = Personal and Social Performance Scale; SD = standard deviation.

Notes: n = 623 at week 26, n = 407 at week 52, n = 984 at last visit.

Last visit consists of week 26 and early termination, or week 52 and early termination.

Source: Clinical Study Report.[96]

Table 53: Response Rate During Open-Label Phase of ZENITH

End Point, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Responders	207 (34.2)	83 (42.6)	61 (27.2)	354 (34.3)

Source: Clinical Study Report.[96]

Table 54: Discontinuation Due to Lack of Efficacy During Open-Label Phase of ZENITH

End Point, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Discontinued due to lack of efficacy	22 (3.6)	7 (3.5)	14 (6.3)	43 (4.2)

Source: Clinical Study Report.[96]

Safety

Most participants (60.4%) experienced TEAEs during the open-label treatment phase in ZENITH. [redacted]. Generally, occurrences of serious adverse events were uncommon (12.9%), the most common being schizophrenia (8.7%). [redacted]. Detailed adverse events data are summarized in Table 55.

Extrapyramidal symptom-related adverse events and symptom rating scales data during the open-label phase of ZENITH are detailed Table 56 and Table 57. [redacted].

Table 58 summarizes change from baseline in body weight and the proportion of patients whose body weight increased or decreased by at least 7% during the open-label treatment phase of ZENITH. The manufacturer specified that a change in body weight of at least 7% was considered to be potentially clinically relevant. [redacted]

[redacted]

Table 55: Adverse Events During Open-Label Phase of ZENITH

Adverse Events, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
TEAE in ≥ 5% of patients[a]	[redacted] (60.0)	[redacted] (56.4)	[redacted] (65.2)	[redacted] (60.4)
Schizophrenia	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]
Gastric ulcer perforation	[redacted]	[redacted]	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]
Uterine cancer	[redacted]	[redacted]	[redacted]	[redacted]
Completed suicide	[redacted]	[redacted]	[redacted]	[redacted]
SAE in ≥ 5% of patients	90 (14.9)	18 (8.9)	25 (11.2)	133 (12.9)
Schizophrenia	68 (11.2)	12 (5.9)	10 (4.5)	90 (8.7)
Any WDAE	[redacted]	[redacted]	[redacted]	[redacted]
Schizophrenia	[redacted]	[redacted]	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Reported in ≥ 5% of patients in at least one group.

Source: Clinical Study Report.[96]

Table 56: Extrapyramidal-Related Adverse Events During Open-Label Phase of ZENITH

Adverse Events, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Any EPS-related AE	[redacted]	[redacted]	[redacted]	[redacted]
Total Akathisia Events	[redacted]	[redacted]	[redacted]	[redacted]
Akathisia	[redacted]	[redacted]	[redacted]	[redacted]
Total Dyskinetic Events	[redacted]	[redacted]	[redacted]	[redacted]
Dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]
Choreoathetosis	[redacted]	[redacted]	[redacted]	[redacted]
Tardive Dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]
Total Dystonic Events	[redacted]	[redacted]	[redacted]	[redacted]
Muscle Rigidity	[redacted]	[redacted]	[redacted]	[redacted]
Muscle Spasms	[redacted]	[redacted]	[redacted]	[redacted]
Dystonia	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events, n (%)	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Trismus	[redacted]	[redacted]	[redacted]	[redacted]
Total Parkinsonian Events	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Extrapyramidal Disorder	[redacted]	[redacted]	[redacted]	[redacted]
Parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]
Bradykinesia	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; EPS = extrapyramidal symptoms.

Note: Patients with multiple AEs within EPS class were counted only once in total EPS class. Patients with AEs in multiple system organ classes were counted only once toward the total.

Source: Clinical Study Report.[96]

Table 57: Change From Baseline in Extrapyramidal Symptoms Rating Scales During Open-Label Phase of ZENITH

EPS Symptom Rating Scale	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
SAS				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at last visit	[redacted]	[redacted]	[redacted]	[redacted]
BARS				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at last visit	[redacted]	[redacted]	[redacted]	[redacted]
AIMS				
Mean baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 26	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at last visit	[redacted]	[redacted]	[redacted]	[redacted]

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; EPS = extrapyramidal symptoms; SAS = Simpson-Angus Scale

Note: n = 638 at week 26, n = 410 at week 52, n = 1012 at last visit.

Last visit consists of week 26 and early termination, or week 52 and early termination.

Source: Clinical Study Report.[96]

Table 58: Change in Body Weight During Open-Label Phase of ZENITH

Weight	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Decrease ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Increase ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Decrease ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Increase ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Early termination	[redacted]	[redacted]	[redacted]	[redacted]

Weight	Prior Brexpiprazole (N = 605)	Prior Placebo (N = 202)	New Patients (N = 224)	Total (N = 1031)
Decrease ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Increase ≥ 7%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[96]

Limitations

There are several limitations to the long-term, open-label, non-randomized safety study (ZENITH). First, given that trial was uncontrolled, it remains unclear whether the changes observed in the safety profile were due to a natural course of the disease or were attributable to long-term treatment with brexpiprazole. Open-label trial designs in which both the investigators and the participants are unblinded to treatment allocation may have an impact on subjective outcomes, such as some patient-reported adverse events (AEs) and symptom scales which can bias the results. The ZENITH trial only enrolled patients who were deemed likely to benefit from brexpiprazole based on investigator judgment; therefore, the study population may be composed of patients who are more likely to tolerate and benefit from treatment with brexpiprazole compared with the general schizophrenia population. No further information was provided to clarify this inclusion criterion. It is therefore uncertain if the results of the ZENITH trial are generalizable to the Canadian patient population.

Summary

In general, treatment with brexpiprazole raised no new safety concerns relative to the previous RCTs. However, any inferences based on this long-term, open-label safety study should be made with caution given the enriched study population, lack of blinding, and non-comparative design.

Appendix 9: Summary of Indirect Comparison for Acute Exacerbation

Objective

The manufacturer conducted a network meta-analysis (NMA) based on a systematic review to evaluate the relative efficacy and safety of brexpiprazole compared with other atypical antipsychotic drugs that are approved in Canada for the short-term treatment of adult patients diagnosed with schizophrenia, with the exception of clozapine and asenapine.

The NMA was conducted as a result of a lack of head-to-head evidence comparing brexpiprazole with other atypical antipsychotic drugs. This section of the report provides a summary and critical appraisal of the methods and results of the NMA. Due to the identification of errors in the initial submission of the manufacturer's NMA for the treatment of acute exacerbations,[97] a revised data set was filed by the manufacturer. Hence, the initial submission was primarily used as the source material for describing and appraising the methodology used for the NMA and the revised data set was used as the source for the indirect estimates of effect.[98]

Methods Used for the Systematic Review and NMA

Eligibility Criteria

The interventions and comparators of interest are summarized in Table 59. The population of interest for the manufacturer's systematic review was adults with schizophrenia or schizophrenia-like psychosis. The treatments of interest included all orally administered atypical antipsychotic drugs that are approved for use in Canada, with the exception of clozapine and asenapine. The manufacturer reported that clozapine was excluded due its restricted indication (i.e., treatment-resistant schizophrenia) and asenapine was excluded due to the absence of coverage for this product by CADTH Common Drug Review-participating drug plans. There were three outcomes of interest for the NMA conducted in patients experiencing an acute exacerbation of symptoms: change from baseline to six weeks in Positive and Negative Syndrome Scale (PANSS) total score; overall withdrawals (i.e., discontinuation due to any cause), and withdrawals due to adverse events. Eligible study designs were randomized controlled trials (RCTs) that were conducted to investigate the short-term treatment of schizophrenia with at least 10 patients. Non-randomized studies, including long-term extension studies, were excluded.

Table 59: Eligibility Criteria for the Acute Exacerbation NMA

Population	• Adults with schizophrenia • Adults with schizophrenia-like psychosis	
Intervention and Comparators	**Included** • Brexpiprazole 2 mg to 4 mg • Aripiprazole 10 mg to 15 mg • Lurasidone 40 mg to 120 mg • Olanzapine 5 mg to 20 mg • Paliperidone 6 mg • Quetiapine 300 mg to 600 mg • Quetiapine XR 400 mg to 800 mg • Risperidone 4 mg to 6 mg • Ziprasidone 80 mg to 160 mg • Placebo	**Excluded** • Asenapine • Clozapine • Typical antipsychotic drugs • Long-acting injectable drugs • Drugs not licensed in Canada
Outcomes	• PANSS total score change from baseline to six weeks • Withdrawals due to any cause • Withdrawals due to adverse events	
Study Design	**Included** • RCTs for short-term treatment of schizophrenia	**Excluded** • Studies with < 10 patients • Non-randomized studies • Long-term extension studies • Review articles • Case reports • Editorials/letters

mg = milligrams; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; XR = extended release.

Source: Manufacturer's NMA for acute treatment.[97]

Network Meta-Analysis

Dosage of Comparators

The manufacturer's reference case analysis was restricted to fixed-dose treatment regimens where the target dose was within a particular dose range that was referred to by the authors as a "standard dose range." This standard dose range was derived by the authors based on the following two factors:

- The defined daily dose (DDD) for the drug (i.e., the assumed average maintenance dose per day).
- The range of dosages that was specified in CADTH's 2014 review of lurasidone for the treatment of schizophrenia.

Using the two sources noted above, the manufacturer restricted the reference case analysis (and all associated sensitivity analyses) to treatment groups where a fixed-dose regimen was used at a dosage that was greater than or equal to the DDD for the drug (i.e., the assumed average maintenance dose per day) and less than or equal to the upper range cited in CADTH's 2014 Pharmacoeconomic Review report for lurasidone (see Table 60). There is currently no DDD for brexpiprazole and this product pre-dated CADTH's 2014 review of lurasidone; therefore, different methodology was used to establish the dosage of brexpiprazole that was used in the reference case NMA. Although the dosage range recommended in the product monograph for brexpiprazole is 2 mg to 4 mg per day for the

treatment of schizophrenia, the reference case analysis for brexpiprazole was restricted to the maximum recommended dosage (i.e., 4 mg per day). The manufacturer cited the 3.5 mg per day average used in the LIGHTHOUSE trial as the rationale for assuming that 4 mg per day would be the standard dosage for brexpiprazole.

Table 60: Dosages Included in the Reference Case Analysis

Comparator	Daily Dosage		
	Range in 2014 CADTH Report	DDD	Standard Dose Range (Lower Limit ≥ DDD; Upper Limit ≤ CADTH 2014 Report)
Brexpiprazole	N/A[a]	N/A	4 mg
Aripiprazole	10 mg to 15 mg	15 mg	15 mg
Lurasidone	40 mg to 120 mg	60 mg	60 mg to 120 mg
Olanzapine	5 mg to 20 mg	10 mg	10 mg to 20 mg
Paliperidone	6 mg	6 mg	6 mg
Quetiapine	300 mg to 600 mg	400 mg	400 mg to 600 mg
Quetiapine XR	400 mg to 800 mg	400 mg	400 mg to 800 mg
Risperidone	4 mg to 6 mg	5 mg	5 mg to 6 mg
Ziprasidone	80 mg to 160 mg	80 mg	80 mg to 160 mg

DDD = defined daily dose; mg = milligrams; XR = extended release.

[a] Note: The table in the manufacturer's report cites a 2 mg to 4 mg per day dosage of brexpiprazole in the column reflecting the dosages that were included in CADTH's 2014 review of lurasidone; however, brexpiprazole was not included as a comparator in that review (pre-dated market authorization).

Source: Manufacturer's NMA for acute treatment.[97]

Reference Case and Sensitivity Analyses

The NMAs were performed using standard methodology for continuous and dichotomous end points. Copies of the WinBUGS codes were included as appendices in the manufacturer's report. Table 61 provides an overview of the analyses that were reported in the manufacturer's NMA. All of the analyses were conducted using vague prior distributions. Random-effects models were used for all analyses with the exception of fixed-effect sensitivity analyses that were conducted using the reference case networks. Meta-regression was only performed in sensitivity analyses for the overall withdrawals and withdrawals due to adverse events networks to adjust for differences in the rate of withdrawal from the placebo groups.

The manufacturer reported that two sensitivity analyses were performed based on baseline PANSS total score (i.e., PANSS greater than and equal to 80, and PANSS greater than and equal to 90). Both of these analyses were conducted using a random-effects model with a vague prior distribution. As shown in Table 61, these sensitivity analyses resulted in the exclusion of either no additional trials (PANSS greater than and equal to 90) or a single trial (PANSS greater than and equal to 80) relative to the reference case for change from baseline in PANSS total score (i.e., 23 randomized controlled trials (RCTs) versus 22 RCTs). Similarly, the PANSS greater than and equal to 80 and PANSS greater than and equal to 90 sensitivity analyses for overall withdrawals and withdrawals due to adverse events (WDAEs) resulted in the exclusion of few trials relative to the reference case analyses (range: 2 to 3 RCTs).

Extended Network

The manufacturer also conducted NMAs using an extended network that included treatment groups that used a flexible dosage regimen (e.g., the LIGHTHOUSE study for brexpiprazole)

or a regimen that was outside of the range specified using the DDD and CADTH's 2014 review of lurasidone. As noted previously, in the absence of a DDD, the manufacturer elected to use the maximum recommended dosage of brexpiprazole (i.e., 4 mg) in the reference case analyses and all sensitivity analyses with the exception of the extended network. However, the results presented in the manufacturer's initial report for the extended network were restricted to the treatment groups that were used in the reference case analyses. CADTH subsequently requested complete results for the extended network from the manufacturer.

Table 61: Overview of NMA Methods for Each End Point

End Point (Weeks)	Analysis	Sensitivity Analysis	RCTs	Scale	RE or FE	Regression	Prior
PANSS	Reference case	N/A	23	MD	RE	No	Vague
	Sensitivity analyses	Fixed-effect	23	MD	FE	No	Vague
		PANSS ≥ 80	22	MD	RE	No	Vague
		PANSS ≥ 90	23	MD	RE	No	Vague
		Extended network	38	MD	RE	No	Vague
Overall withdrawals	Reference case	Reference	35	RR	RE	No	Vague
	Sensitivity analyses	Fixed-effect	35	RR	FE	No	Vague
		PANSS ≥ 80	33	RR	RE	No	Vague
		PANSS ≥ 90	32	RR	RE	No	Vague
		Meta-regression	35	RR	RE	Rate in PLC group	Vague
		Extended network	69	RR	RE	No	Vague
WDAEs	Reference case	Reference	37	RR	RE	No	Vague
	Sensitivity analyses	Fixed-effect	37	RR	FE	No	Vague
		PANSS ≥ 80	35	RR	RE	No	Vague
		PANSS ≥ 90	35	RR	RE	No	Vague
		Meta-regression	37	RR	RE	Rate in PLC group	Vague
		Extended network	69	RR	RE	No	Vague

FE = fixed effects; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; PLC = placebo; RCTs = randomized controlled trials; RE = random effects; RR = relative risk; WDAEs = withdrawals due to adverse events.

Source: Manufacturer's NMA for acute treatment.[97]

NMA Findings

Study and Patient Characteristics

The systematic review included 74 studies for all dosage regimens and 37 studies that included "standard doses" as per the author's definition. In accordance with the inclusion of the manufacturer's systematic review, all of the included trials involved random allocation to the study treatments. The authors reported that all of the trials were described as being double-blind, though few trials specified how blinding was maintained. The majority of studies reported an intention-to-treat analysis with last observation carried forward (LOCF) used; however, the systematic review does not report the specific study level details regarding the method that was used for handling missing data. As described in Section 3.2, the pivotal trials for brexpiprazole used mixed model repeated measures (MMRM) as opposed to LOCF for the primary analyses. Several important study characteristics were not reported by the manufacturer, including: primary end point(s), trial duration, eligibility criteria, and trial setting (i.e., in-patient or outpatient).

Baseline characteristics were reported for mean age, gender, race, average disease duration, and mean PANSS total score at baseline. The authors reported that there was considerable variation in total PANSS score at baseline, ranging from 8.95 to 103.78 (median 93.6), with the majority of studies enrolling patients with a baseline PANSS total score ranging from 90 to 100. There were no details reported regarding whether or not the patients were experiencing a first episode; however, a review of the reference list demonstrates that the study involving the very low PANSS total score (i.e., 8.95) enrolled such patients. The average age of patients ranged from 23.7 years to 69.5 years (median 38.21 years) and the majority of patients were male (median 67.90%) and Caucasian (median 51.05%). Average disease duration ranged from 1.29 years to 17.85 years (median 11.3 years), though this was only reported in the publications for 20 studies. There were no details reported with respect to any of the following important patient characteristics: prior exposure to atypical antipsychotic drugs, concomitant use of medications, and whether or not the patients had demonstrated treatment-resistant schizophrenia.

Evidence Networks

The evidence networks used in the reference case and extended treatment NMAs are provided in Table 62. The reference case analyses for change from baseline in PANSS total score, overall withdrawals, and withdrawals due to adverse events consisted of 23 RCTs, 35 RCTs, and 37 RCTs, respectively. The extended network analyses for change from baseline in total PANSS score, overall withdrawals, and withdrawals due to adverse events consisted of 38 studies, 69 studies, and 69 studies, respectively.

Table 62: Evidence Networks for NMAs for the Treatment of Acute Exacerbation

[redacted]	[redacted]
[redacted]	
Confidential figure removed at manufacturer's request	Confidential figure removed at manufacturer's request
[redacted]	
Confidential figure removed at manufacturer's request	Confidential figure removed at manufacturer's request
[redacted]	
Confidential figure removed at manufacturer's request	Confidential figure removed at manufacturer's request

PANSS = Positive and Negative Syndrome Scale.

Source: Manufacturer's NMA for acute treatment.[97]

Methodological Validity Assessment of Included Studies

The authors performed a risk of bias evaluation for the included studies using the criteria recommended by the National Institute for Health and Care Excellence (NICE). This included the classification of the following characteristics as having either a low risk of bias, high risk of bias, or being unclear due to insufficient information: randomization, allocation concealment, baseline characteristics, blinding, withdrawals, outcome selection and reporting, and use of an intention-to-treat analysis. It was not reported if the risk of bias assessment was performed in duplicate. The authors reported that only a minority of studies reported the methods that were used for randomization (21 RCTs [28%]). Nearly all of the included studies were reported to have comparable patient populations at baseline (67 RCTs [91%]) All studies were described as being double-blind, though only a minority of studies reported methods for maintaining blinding (28%). Withdrawals were reported in all studies and reasons were provided in nearly all of the included studies (92%). As noted previously, the authors reported that the majority of included studies conducted an intention-to-treat analysis and used LOCF for imputing missing data.

NMA Results

Change from Baseline in Total PANSS Score

The results for the reference case and sensitivity analyses for change from baseline in PANSS total score are summarized in Table 63 (results in the table are: mean difference [MD] = brexpiprazole 4 mg per day – comparator). The reference case analysis and all of the sensitivity analyses demonstrated that [redacted]. In the sensitivity analysis using a fixed-effect model, [redacted]. However, due to the heterogeneity between the included studies, and the purpose of random-effects and fixed-effect models, the results derived from the fixed-effect model are not considered to be an accurate reflection of the comparative efficacy of the treatments and should be interpreted with caution. As shown in Table 63, there were no data for any of the following treatment groups: olanzapine 20 mg per day, quetiapine 600 mg per day (immediate-release formulation), or either of the ziprasidone dosage regimens (120 mg or 160 mg). Results were similar in the sensitivity analysis that included the 120 mg per day dosage of lurasidone (Source Manufacturer's NMA for acute treatment. [97] Table 66).

In the extended network, [redacted] (Figure 24).

Overall Withdrawals

The results for the reference case and sensitivity analyses for overall withdrawals are summarized in Source: Manufacturer's NMA for acute treatment.[97]

Table 64. The reference case analysis demonstrated [redacted]. However, in the analysis that was adjusted for differences in the rate of withdrawal from placebo groups [redacted] As shown in (Source Manufacturer's NMA for acute treatment. [97] Table 64), [redacted]. Results were similar in the sensitivity analysis that included the 120 mg per day dosage of lurasidone (Source Manufacturer's NMA for acute treatment. [97] Table 66).

Withdrawals Due to Adverse Events

The results for the reference case and sensitivity analyses for withdrawals due to adverse events are summarized in Source Manufacturer's NMA for acute treatment. [97] Table 65. [redacted]

[redacted]. Results were similar in the sensitivity analysis that included the 120 mg per day dosage of lurasidone (Source Manufacturer's NMA for acute treatment. [97] Table 66).

Figure 24: Change from Baseline in PANSS at 6 Weeks in the Extended Treatment Network

Confidential figure removed at manufacturer's request

CrI = credible interval; ER = extended release; FLEX = flexibly dosed; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; XR = extended release.
Source: Data from league table provided by the manufacturer.[97]

Table 63: NMA Results for Change From Baseline in Total PANSS Score

BREX 4 mg Versus Comparator (MD [95% CrI])	Base Case	Sensitivity Analyses				
	RE Model (23 RCTs)	FE Model (23 RCTs)	PANSS ≥ 80 (22 RCTs)	PANSS ≥ 90 (23 RCTs)	Extended Network (38 RCTs)	Exc. Studies with Large Residuals Deviance
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARI 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LURA 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PALI 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 800 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RISP 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 120 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARI = aripiprazole; BREX = brexpiprazole; CrI = credible interval; FE = fixed-effect; LURA = lurasidone; mg = milligrams; OLAN = olanzapine; PALI = paliperidone; PANSS = Positive and Negative Syndrome Scale; QUET = quetiapine; RCT = randomized controlled trial; RE = random-effects; RISP = risperidone; XR = extended release; ZIP = ziprasidone.

Source: Manufacturer's NMA for acute treatment.[97]

Table 64: NMA Results for Withdrawals Due to Any Cause

Comparator Versus BREX 4 mg (RR [95% CrI])	Base Case	Sensitivity Analyses				
	RE Model (35 RCTs)	FE Model (35 RCTs)	PANSS ≥ 80 (33 RCTs)	PANSS ≥ 90 (32 RCTs)	Meta-Regression (35 RCTs)	Extended Network (69 RCTs)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARI 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LURA 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PALI 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comparator Versus BREX 4 mg (RR [95% CrI])	Base Case	Sensitivity Analyses				
	RE Model (35 RCTs)	FE Model (35 RCTs)	PANSS ≥ 80 (33 RCTs)	PANSS ≥ 90 (32 RCTs)	Meta-Regression (35 RCTs)	Extended Network (69 RCTs)
QUET 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 800 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RISP 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 120 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARI = aripiprazole; BREX = brexpiprazole; CrI = credible interval; FE = fixed-effect; LURA = lurasidone; OLAN = olanzapine; PALI = paliperidone; QUET = quetiapine; RCT = randomized controlled trial; RE = random-effects; RISP = risperidone; ZIP = ziprasidone.

Source: Manufacturer's NMA for acute treatment.[97]

Table 65: NMA Results for Withdrawals Due to Adverse Events

Comparator Versus BREX 4 mg (RR [95% CrI])	Base Case	Sensitivity Analyses				
	RE Model (37 RCTs)	FE Model (37 RCTs)	PANSS ≥ 80 (35 RCTs)	PANSS ≥ 90 (35 RCTs)	Meta-Regression (37 RCTs)	Extended Network (69 RCTs)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARI 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LURA 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PALI 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 800 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RISP 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 120 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARI = aripiprazole; BREX = brexpiprazole; CrI = credible interval; FE = fixed-effect; LURA = lurasidone; NMA = network meta-analysis; OLAN = olanzapine; PALI = paliperidone; QUET = quetiapine; RCT = randomized controlled trial; RE = random-effects; RISP = risperidone; RR = reference range; XR = extended release; ZIP = ziprasidone.

Source: Manufacturer's NMA for acute treatment.[97]

Table 66: Sensitivity Analyses Including Lurasidone 120 mg/Day Dosage in the Reference Case

Comparator Versus BREX 4 mg	PANSS (MD [95% CrI])		WDAEs (RR [95% CrI])		Withdrawals (RR [95% CrI])	
	Without LURA 120 mg	With LURA 120 mg	Without LURA 120 mg	With LURA 120 mg	Without LURA 120 mg	With LURA 120 mg
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARI 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LURA 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LURA 120 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAN 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PALI 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QUET XR 800 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RISP 6 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 120 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZIP 160 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCTs; RD; Data Points	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARI = aripiprazole; BREX = brexpiprazole; CrI = credible interval; FE = fixed-effect; LURA = lurasidone; MD = mean difference; NA = not applicable; NR = not reported; OLAN = olanzapine; PALI = paliperidone; PANSS = Positive and Negative Syndrome Scale; QUET = quetiapine; RCT = randomized controlled trial; RD = risk difference; RE = random-effects; RISP = risperidone; RR = relative risk; WDAE = withdrawal due to adverse event; XR = extended release; ZIP = ziprasidone.

Source: Manufacturer's NMA for acute treatment.[97]

Critical Appraisal of the Manufacturer's NMA

The methodological validity of the NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons Good Research Practices, and guidance provided in CADTH's *Guidance Document on Reporting Indirect Comparisons* (October 2015).[99,100] The quality of the systematic review was appraised according to the AMSTAR criteria.

Systematic Review Methods

The research question and inclusion criteria for the systematic review were reported in the NMA; however, clarification was required to comprehend the selective inclusion of asenapine in the extended treatment network. The literature search was comprehensive, involving multiple databases (i.e., MEDLINE, Embase, the Cochrane Central trials register, PsychINFO, clinicalstudyresults.org, and clinicaltrials.gov). The search was supplemented by reviewing the reference lists from the included studies. The dates of the literature search were inconsistently reported in the initial submission of the NMA. However, the manufacturer subsequently clarified that the original systematic review was an update of an existing NICE review on schizophrenia that was published in 2008 (a reference was not provided). The authors included all relevant studies from the 2008 NICE review and conducted the following four updates of the database search: (1) Updated from 1 January 2008 to 3 September 2010 (first update); (2) up to December 2011 (second update); (3) up to January 2014 (third update); and (4) up to February 2016 (fourth update).

Study selection was performed independently by two reviewers and disagreements were resolved through discussion. The authors performed a risk of bias evaluation for the included studies using the criteria recommended by NICE. It was not reported if data extraction and the risk of bias assessment were performed in duplicate.

Reporting of the NMAs

The rationale for the NMA was clearly stated (i.e., absence of head-to-head RCTs evaluating the relative efficacy and safety of brexpiprazole compared with other atypical antipsychotic drugs). Baseline characteristics were reported for mean age, gender, race, average disease duration, and mean PANSS total score at baseline. There were no details regarding prior exposure to antipsychotic medications or use of concomitant medications (e.g., rescue medication or medications used to manage adverse events). Study characteristics were poorly reported, with no description of trial duration, primary end points, eligibility criteria, or trial setting (e.g., in-patient versus outpatient). This is in contrast to the NMA that was submitted by the manufacturer for use of brexpiprazole as maintenance treatment, where such study characteristics were reported.

The analytical method used for the NMA was well reported, including a description of the following: source code that was applied, prior distributions that were used, rationale for the use of a random-effects model, and justification for sensitivity analyses and meta-regression. Copies of the WinBUGS codes that were used were included as appendices in the manufacturer's report. The authors did not report which studies were included in each of the analyses; only the number of studies that were included in the analysis was provided. This makes it challenging to fully evaluate the appropriateness of pooling the data.

The manufacturer conducted sensitivity analyses; however, the relevance of these were not reflected on in the discussion (e.g., failure to demonstrate statistically significant differences for overall withdrawals and withdrawals due to adverse events when the analyses were adjusted for across study differences in the rates of withdrawal from the placebo groups). In addition, the report only presented and discussed a limited subset of the results for the extended treatment network (i.e., only for the treatment groups that were used in the reference case analyses).

Despite being explicitly excluded from the selection criteria of the systematic review, the results for the extended treatment network that were requested by CADTH included estimates of effect for two asenapine dosage regimens (10 mg per day and an undefined flexible dosage regimen). The manufacturer stated that the review was conducted according to "a priori eligibility criteria;" therefore, it was unclear why this drug was included in the acute exacerbation analysis. CADTH inquired regarding the inclusion of asenapine in the extended treatment network and the manufacturer stated that this particular network was developed to support Health Technology Assessment submissions in other countries and does not focus on treatments currently reimbursed in Canada.[98] The manufacturer subsequently provided the results of a sensitivity analysis including asenapine (at an unspecified dosage) in the reference case analysis. They reported the following results for brexpiprazole versus asenapine: [redacted].[98] Asenapine was included in the maintenance treatment NMA, with no explanation why this would be considered a relevant comparator in one treatment setting (i.e., maintenance) but not in the other treatment setting (i.e., acute exacerbation).

In the initial submission filed by the manufacturer, the reference case analysis for change from baseline in PANSS reported that there were no data for the olanzapine 10 mg per day in the extended treatment networks for all three end points and in the reference case for change from baseline in PANSS. CADTH inquired regarding these results and the manufacturer acknowledged the error and submitted corrected analyses that included the 10 mg per day dosage of olanzapine for all three end points. It is unclear why the manufacturer has reported that there are no data for olanzapine 20 mg per day in the sensitivity analysis including lurasidone 120 mg per day for withdrawals due to adverse events, as there are data for this treatment regimen in the more restrictive NMA network without lurasidone 120 mg per day (e.g., 37 RCTs with 83 data points versus 38 RCTs with 86 data points).

There appear to be typographical errors in Appendix 7, Appendix 8, and Appendix 9 of the manufacturer's report where there are references to results for change in total PANSS score at six "**months**;" this should likely be at six **weeks**.

NMA Methods

Analytical Methods

The NMAs were performed using standard methodology for continuous and dichotomous end points. All of the analyses were conducted using vague prior distributions (reported as normal with mean 0, and precision 0.0001). Citing the complexity of the characteristics of the evidence network and the potential clinical heterogeneity between the included studies, the authors indicated that a random-effects model was used in the reference case for all end points. Sensitivity analyses based on baseline disease severity (i.e., PANSS greater than

and equal to 80 and PANSS greater than and equal to 90) were appropriate as were meta-regressions to adjust for differences in withdrawals and WDAEs from the placebo groups.

Patient Characteristics

Sensitivity analyses were conducted using studies with a baseline total PANSS score of greater than and equal to 80, and greater than and equal to 90, to investigate the effect of variation in baseline PANSS scores. As shown in Table 10, PANSS total scores at baseline in the pivotal brexpiprazole studies were as follows: brexpiprazole 2 mg per day (range: 95.9 to 96.3), brexpiprazole 4 mg per day (range: 94.9 to 95.1), brexpiprazole 2 mg to 4 mg per day (97.8), placebo (range: 94.8 to 98.4), and quetiapine (98.8). Therefore, the analysis that was restricted to studies with a baseline PANSS total score of at least 90 is a more comparable patient population from the perspective of baseline disease severity.

There was considerable variation in the rate of withdrawals in the placebo groups across studies, ranging from 19% to 81%. Meta-regression was performed on sensitivity analyses for the overall withdrawals and for withdrawals due to adverse events networks, to adjust for differences in the rate of withdrawal from the placebo groups.

Placebo responses varied considerably within and across treatment groups (ranging from an improvement of –21.7 to a worsening of 3.8). Table 67 summarizes the range of placebo response values within and across treatment groups. Guidance from the European Medicines Agency on the development of treatments for schizophrenia noted that the difference in efficacy between active treatments and placebo has tended to be smaller than those that were observed in the past.[49] Such a confounding factor may prevent an accurate indirect estimation of comparative efficacy, though it is possible that the direction of bias could be against newer treatments such as brexpiprazole, where the effect size relative to placebo observed in the pivotal studies could be smaller than those reported for older products.

Study Characteristics

The authors reported that the included studies varied with respect to the timing of end point assessment due to differences in the duration of the trials. The NMA for change from baseline in PANSS was restricted to studies that reported this end point at six weeks. Therefore, the measurements reflected a relatively consistent duration of treatment, though this assumption would be affected by the amount of imputation that was required in each trial. In contrast, the authors elected to pool all data for withdrawals and WDAEs, irrespective of differences in the duration of studies. As the duration of a clinical trial increases, the proportion of patients who withdraw from the trial also increases. The authors of the NMA did not report the different trial durations and there were no sensitivity analyses conducted to investigate the potential impact of different trial durations. It would have been beneficial to have information regarding differences in the study protocols with respect to concomitant medications that were permitted in the included studies. For example, medications used for the management of extrapyramidal symptoms -related adverse events were permitted in the pivotal brexpiprazole studies; however, Health Canada reviewers noted that such medications are usually not to be used prophylactically during schizophrenia trials.[45]

Table 67: Appraisal of Potential Effect Modifiers in the NMA

Characteristic	Appraisal of Heterogeneity
Disease severity	The authors identified considerable heterogeneity in baseline total PANSS score across the included studies, ranging from 8.95 to 103.78 (median 93.6). Sensitivity analyses were conducted using studies with a baseline total PANSS score of ≥ 80 and ≥ 90, to investigate the effect of variation in baseline PANSS scores. PANSS total scores at baseline in pivotal brexpiprazole studies were as follows: brexpiprazole 2 mg/day (range: 95.9 to 96.3), brexpiprazole 4 mg/day (range: 94.9 to 95.1), brexpiprazole 2–4 mg/day (97.8), placebo (range: 94.8 to 98.4), and quetiapine (98.8). Therefore, the analysis restricted to baseline PANSS ≥ 90 is a more comparable patient population from the perspective of baseline disease severity.
Placebo response for PANSS	Placebo responses varied considerably within and across treatment groups (ranging from an improvement of −21.7 to a worsening of 3.8). Within the individual groups included in the NMAs, the following ranges were noted: risperidone 4 mg/day (−11.8), risperidone 6 mg/day (−5.27 to −10.93), risperidone FLEX (−3.5 to −14.4), paliperidone ER FLEX (−9.9 to −10.8), paliperidone ER 6 mg/day (−21.7 to 3.8), olanzapine 15 mg/day (−6.4 to −15.2), olanzapine 10 mg/day (−8 to 3.8), olanzapine FLEX (−9.9), lurasidone 80 mg/day (−17 to −5.5), lurasidone 40 mg/day (−17 to −6.2), quetiapine 400 mg/day (−18.8), quetiapine XR 400 mg/day (−18.8), quetiapine XR 600 mg/day (−18.8 to −5.19), quetiapine XR 800 mg/day (−18.8), aripiprazole 10 mg/day (−2.33 to −14.3), aripiprazole 15 mg/day (−2.33), brexpiprazole 2 mg/day and 4 mg/day (−12.01 to −13.53), brexpiprazole 2 mg to 4 mg (−15.9), and quetiapine XR FLEX (−15.9).
Placebo withdrawal rates	Meta-regression was performed in sensitivity analyses for the overall withdrawals and withdrawals due to adverse events networks to adjust for differences in the rate of withdrawal from the placebo groups.
Definitions and timing of end point evaluation	The timing of evaluating change from baseline in PANSS total score was not reported for the individual studies that were included in the review. The manufacturer reported that the included studies varied with respect to the duration of the trials and the timing of end-point evaluation (the extent of this heterogeneity could not be evaluated due to the failure to include this information in the report). However, the analyses for PANSS were limited to studies that reported change from baseline at six weeks. This is consistent with timing of end-point evaluation in the pivotal brexpiprazole studies for the treatment of patients with an acute exacerbation of schizophrenia (i.e., VECTOR, BEACON, and LIGHTHOUSE).
• Eligibility criteria • Trial duration • Prior-AP exposure • Clinical trial setting • Concomitant medications • First episode • Region	There were no details reported in the individual clinical trials for any of these characteristics.

AP = antipsychotic; ER = extended release; FLEX = flexibly dosed; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; XR = extended release.

Dosage of Comparators

The manufacturer's approach to the reference case for the acute exacerbation NMA analysis involved creating a "standard dose range" that represents a range bound at the lower limit by the DDD (i.e., the assumed average maintenance dose per day)[101] and at the upper limit by the range specified in CADTH's 2014 review of lurasidone for the treatment of schizophrenia.[102] It is important to note that this does not necessarily reflect usage in Canada or the dosage recommended in Canadian product monographs for the treatment of schizophrenia. The reference case analysis for brexpiprazole was restricted to the maximum recommended dosage (i.e., 4 mg per day). The manufacturer cited the 3.5 mg per day average usage in the LIGHTHOUSE trial as the rationale for assuming that 4 mg per day would be the standard dosage for brexpiprazole. Despite using the LIGHTHOUSE study as the justification for restricting the reference case analysis to the 4 mg dosage of

brexpiprazole, this study was excluded from the reference case and all of the sensitivity analyses with the exception of the extended network NMAs. Although included in the extended treatment network, the manufacturer's report did not report the effect sizes for the 2 mg per day fixed-dose regimen or the 2 mg to 4 mg per day flexible-dose regimen. In addition, the "standard dosage regimen" approach was not used in the manufacturer's maintenance treatment NMA. There was no explanation provided regarding this discrepancy in the methodology between the acute and maintenance NMAs.

The overall result of the manufacturer's approach resulted in the exclusion of all flexibly dosed regimens and the following fixed-dose regimens from the reference case analysis and all sensitivity analyses with the exception of the extended treatment network: olanzapine (5 mg/day), aripiprazole (10 mg/day), immediate-release quetiapine (300 mg/day), risperidone (4 mg/day), lurasidone (40 mg/day), brexpiprazole (2 mg/day). Although captured within the manufacturer's "standard dose range" and included as an intervention in at least one of the pivotal trials for the product, the 120 mg per day dosage of lurasidone was not included in any of the reference case NMAs. CADTH inquired about the rationale for excluding the lurasidone 120 mg per day dosage regimen and the manufacturer reported that the systematic review was developed by a "third party" to support Health Technology Assessment submissions in other countries and they did not include data for the 120 mg per day dosage of lurasidone in the review. In response to CADTH's inquiry, the manufacturer reported that they conducted an additional literature search and identified three studies that reported data for the 120 mg per day dosage of lurasidone. Additional sensitivity analyses were subsequently submitted by the manufacturer that included the 120 mg per day dosage of lurasidone for all three outcomes (Source: Manufacturer's NMA for acute treatment.[97]

Table 66) and reported that the results did not alter the conclusions of the analysis.[98]

Table 68 provides a summary of fixed-dose treatment arms that were excluded from the manufacturer's reference case analyses. Overall, the clinical expert consulted by CADTH indicated that the exclusion of these fixed-dose regimens was not a significant concern, as the more commonly used regimens were included in the analyses.

Table 68: Exclusion of Fixed-Dose Regimens From the Reference Case NMAs

Drug	Description	Dosage Excluded
Brexpiprazole	The dose recommended in the product monograph is 2 mg to 4 mg once daily.[25] At the time of the CDR review, there was no established DDD for brexpiprazole. The reference case for brexpiprazole was restricted to the maximum recommended dosage (i.e., 4 mg per day). The manufacturer cited the 3.5 mg per day average used in the LIGHTHOUSE trial as the rationale for assuming that 4 mg per day would be the standard dosage for brexpiprazole. The 2 mg per day fixed-dose regimen was excluded from the reference case.	2 mg/day
Lurasidone	The DDD for lurasidone is 60 mg per day, which was used by the manufacturer as the lower end of the "standard dose range" for lurasidone in the reference case (i.e., 60 mg to 120 mg per day). However, 60 mg per day is not a dosage that is recommended for the treatment of schizophrenia in Canada and is not reimbursed by the CDR-participating drug plans.[103] The Canadian product monograph states that daily doses of 40 mg, 80 mg, 120 mg, and 160 mg were shown to be effective for the treatment of schizophrenia (60 mg was cited as an option for the treatment of bipolar disorder).[26] The product monograph further states that patients should be treated with the lowest effective dose that provides the optimal response, which is expected to be 40 mg or 80 mg once daily for most patients.[26] Although captured within the manufacturer's "standard dose range" and included as an intervention in several RCTs for the product, the 120 mg per day dosage of lurasidone was not included the manufacturers reference case NMAs. Following an inquiry from CADTH, the manufacturer provided sensitivity analyses including the 120 mg per day dosage.[98]	40 mg/day 120 mg/day
Risperidone	Both the product monograph and CADTH's 2014 review suggested that a relevant dosage range for risperidone is 4 mg to 6 mg per day.[31,102] However, since the DDD for risperidone is 5 mg, the manufacturer established a "standard dosage range" of 5 mg to 6 mg. Due to the absence of 5 mg per day treatment arms in the included studies, this effectively limited the NMA to a single dosage of risperidone (i.e., 6 mg).	4 mg/day
Quetiapine IR	The Canadian product monograph for immediate-release quetiapine recommends a target starting dosage of 300 mg per day and notes that the usual effective treatment dosage will be in the range of 300 mg to 600 mg per day (also reflected in the range cited in the 2014 CADTH report).[32,102] Given that the DDD for immediate-release quetiapine is 400 mg, the manufacturer's standard dose range for the reference case NMA was 400 mg to 600 mg, with data only available for the 600 mg per day group.	300 mg/day
Aripiprazole	The Canadian product monograph for aripiprazole recommends a starting and target dose in the range of 10 mg or 15 mg per day (also reflected in CADTH's 2014 report).[27,102] Since the DDD is also the upper limit of the dosage range cited in the 2014 CADTH review, the manufacturer's standard dose range for aripiprazole consisted of only a single dose (i.e., 15 mg per day).	10 mg/day
Olanzapine	The dose range specified in the Canadian product monograph for olanzapine is the same as the range stated in the CADTH 2014 report (i.e., 5 mg to 20 mg).[30,102] The DDD for olanzapine is 10 mg; therefore the manufacturer's standard dose range is 10 mg to 20 mg.	5 mg/day (all end points)
Ziprasidone	The NMA includes no estimates for change from baseline in PANSS total score for ziprasidone (at any dosage). No rationale was provided for this exclusion and the report does not discuss the potential relevance of excluding this treatment from the evaluation of PANSS. Although the NMA included one study which reported change from baseline in PANSS at six weeks (Daniel et al., 1999) for 80 mg per day (−12.6) and 160 mg per day (−17.9) dosages of ziprasidone, these were not included in the NMA. This may be due to the absence of any measure of statistical dispersion for these estimates in the publication, though this could have been imputed from the *P* values included in the FDA report of ziprasidone.	80 mg/day 160 mg/day (excluded from PANSS only)

CDR = CADTH Common Drug Review; DDD = defined daily dose; IR = immediate release; mg = milligrams; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale.

Summary and Conclusion

For patients experiencing an acute exacerbation of schizophrenia, the manufacturer's NMA suggested that [redacted]. There was likely considerable heterogeneity across studies; however, poor reporting of study and patient characteristics makes it challenging to accurately evaluate the similarities and differences across the studies that were pooled. The manufacturer's NMA resulted in the exclusion of all flexibly dosed regimens and a number of fixed-dose regimens from the reference case analyses and all sensitivity analyses with the exception of the extended treatment network. The clinical expert consulted by CADTH indicated that the more commonly used regimens were included in the analyses and that the exclusion of the alternative dosage regimens was not a significant clinical concern; however, it must be noted that the brexpiprazole estimate of effect is based on the most favourable dosage regimen for change from baseline in PANSS (i.e., 4 mg per day). The analysis of safety end points was limited to a single aggregate outcome (i.e., withdrawals due to adverse events) which cannot be used to evaluate the unique safety profiles of different atypical antipsychotic drugs on outcomes important to patients, such as weight gain and extrapyramidal symptom-related events.

Appendix 10: Summary of Indirect Comparison for Maintenance Therapy

Objective

The manufacturer conducted a network meta-analysis (NMA) based on a systematic review to evaluate the relative efficacy and safety of brexpiprazole compared with other atypical antipsychotic drugs that are approved in Canada for long-term treatment of patients diagnosed with schizophrenia, with the exception of clozapine.

The NMA was conducted as a result of a lack of head-to-head evidence comparing brexpiprazole with other atypical antipsychotic drugs. This section of the report provides a summary and critical appraisal of the methods and results of the NMA.

Methods Used for the Systematic Review and NMA

Study Eligibility and Selection Process

The interventions and comparators of interest are summarized in Table 69. The population of interest for the manufacturer's systematic review was adults with schizophrenia or schizophrenia-like psychosis. The treatments of interest included all orally administered atypical antipsychotic drugs that are approved for use in Canada, with the exception of clozapine. The manufacturer reported that clozapine was excluded due its restricted indication (i.e., treatment-resistant schizophrenia). There were only three outcomes of interest for the NMA: disease relapse (composite outcome; occurrence of event); overall withdrawals (i.e., discontinuation due to any cause), and withdrawals due to adverse events. Eligible study designs were randomized controlled trials (RCTs) that were conducted to investigate the long-term treatment of schizophrenia with at least 10 patients and six or more months of follow-up. Non-randomized studies, including long-term extension studies, were excluded.

The manufacturer reported that the NMA was based on a previous systematic literature review conducted by a research team and current to May 2014 using Embase, the Cochrane Register of Controlled Trials, PsychINFO, MEDLINE and MEDLINE In-Process, clinical trial registries (e.g., clinicaltrials.gov), abstracts, and other non-indexed citations. A subsequent literature search with overlapping dates (between January 2014 and February 2016) was conducted by the current study authors in the same databases to update the previous search and to ensure thoroughness of included articles. Only English language articles were included. Reporting satisfied the PRISMA requirements and provided a description of the methods used for the literature search, study selection, data extraction, and risk of bias assessment. The search was restricted to RCTs of orally administered second-generation antipsychotic drugs. The authors reported that long-acting injectable formulations were excluded to ensure homogeneity in patient and trial characteristics. The comparators were limited to other second-generation antipsychotic drugs or placebo. Comparisons to first-generation antipsychotic drugs were excluded to avoid the inclusion of older studies, which may compromise the exchangeability assumption. Two independent reviewers screened titles and abstracts as well as the full-text articles for inclusion in the NMA, based on the criteria in Table 69. Disagreements between reviewers were settled

through discussion and the involvement of a third reviewer. Two reviewers abstracted the data from the included studies.

Quality Assessment of Included Studies

Quality assessment of the individual included studies was performed using the Cochrane Risk of Bias Tool which assesses the risk of bias based on seven domains: random sequence generation, allocation concealment, blinding (of patients and personnel), blinding of outcome assessment, incompleteness of outcome data, selective reporting, and other biases. Bias is ranked as low risk of bias, high risk of bias, or risk of bias unclear.

Table 69: Eligibility Criteria for Long-Term NMA

Population	• Adults with schizophrenia • Adults with schizophrenia-like psychosis	
Intervention and Comparators	**Included** • Brexpiprazole • Aripiprazole • Asenapine • Lurasidone • Olanzapine • Paliperidone • Quetiapine • Risperidone • Ziprasidone • Placebo	**Excluded** • Clozapine • First-generation antipsychotic drugs • Long-acting injectable drugs • Drugs not licensed in Canada
Outcomes	• Disease relapse (defined as increase in BPRS, increase in total PANSS score or specific PANSS items such as hostility and uncooperative behaviour, increases in CGI-S score, hospitalization, and/or modification of treatment) • Withdrawals due to other causes • Withdrawals due to adverse events	
Study Design	**Included** • RCTs for long-term treatment of schizophrenia	**Excluded** • Studies with < 10 patients • Studies with < six months of follow-up • Non-randomized studies • Long-term extension studies • Review articles • Case reports • Editorials/Letters

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impressions Scale - Severity; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial.

Source: Manufacturer's NMA for long-term treatment.[104]

Network Meta-Analysis

Dosage of Comparators

Comparator dosing regimens that were included in the manufacturer's reference case analyses and the recommended defined daily dose (DDD) are presented in Table 70. There is currently no DDD for brexpiprazole; therefore, the dosage range recommended in the product monograph for brexpiprazole (2 to 4 mg per day), and the doses used in the EQUATOR trial for the treatment of schizophrenia, were used in the NMA.

Table 70: Dosages Included in the Reference Case Analysis

Comparator	Daily Dosage	
	Range in Long-Term NMA	DDD Based on Product Monographs
Brexpiprazole	1 mg to 4 mg q.d.	2 mg to 4 mg[a]
Aripiprazole	15 mg q.d.	10 mg to 15 mg q.d.
Lurasidone	40 mg to 80 mg q.d.	40 mg to 80 mg q.d.
Olanzapine	5 mg to 20 mg q.d.	10 mg q.d.
Paliperidone	5 mg to 15 mg q.d.	6 mg q.d.
Quetiapine	400 mg to 800 mg q.d.	300 mg q.d. or 150 mg b.i.d
Risperidone	4 mg to 12 mg q.d.	4 mg to 6 mg b.i.d or q.d.
Ziprasidone	40 mg to 80 mg b.i.d	40 mg b.i.d
Asenapine	5 mg to 10 mg b.i.d	5 mg to 10 mg b.i.d

b.i.d = twice daily; DDD = defined daily dose; mg = milligrams; NMA = network meta-analysis; q.d. = once daily.

[a] Dosage range as per EQUATOR and product monograph.

Source: Canadian product monographs.[17,25,26,28-32,34]

Reference Case and Sensitivity Analyses

The NMAs were performed using established code from the National Institute for Health and Care Excellence (NICE) to conduct a competing risk NMA. Copies of the WinBUGS codes that were used were included as appendices in the report. The competing risk analysis accounted for the three outcomes of interest: disease relapse, withdrawal due to adverse events, and withdrawal due to other reasons. All of the reference case analyses were conducted using random-effects models with vague prior distributions. Empirically derived informative priors for dichotomous end points based on Turner et al. were also performed as a sensitivity analysis when possible, otherwise the prior was modified from Uniform (0,5) with a precision of 0.0001 in random-effect vague analyses to Uniform (0,2) with a precision of 0.01. Random-effects models were used for all analyses with the exception of fixed-effects sensitivity analyses that were conducted using the reference case networks. Based on the clinical heterogeneity between studies (e.g., population and study methodology), the manufacturer's NMA used random-effect vague for the primary analyses (relapse, overall withdrawals, and withdrawals due to adverse events). Model fit was assessed using deviance information criterion and differences of three or more points were considered important. A three-chain model was used with burn-in and sampling durations of at least 50,000 iterations. Convergence was assessed using Gelman–Rubin plots, trace plots, and Monte Carlo standard error of parameter estimates from the Markov chain Monte Carlo analysis. All end point, point estimates (hazard ratios [HR]) were reported with corresponding 95% credible intervals. Given the nature of the networks (single-study connections with mostly open loops), no statistical heterogeneity assessments (e.g., I^2 or Cochrane Q-test) or meta-regressions were performed.

The manufacturer reported that multiple sensitivity analyses were performed. These analyses were mostly conducted using a random-effects model with a vague prior distribution. Table 71 provides an overview of the analyses that were reported in the manufacturer's NMA.

Table 71: Overview of NMA Methods for Each End Point

End Point	Analysis	Sensitivity Analysis	RCTs	Scale	Model	Prior
Relapse, overall withdrawals, and WDAEs	Reference case	NA	11	HR	RE	Vague
	Sensitivity analyses	Random-effects	11	HR	RE	Informative
		Fixed-effect	11	HR	FE	Vague
		Withdrawal studies only	6	HR	RE	Vague
		Reimbursed in Canada (brand and generic)[a]	10	HR	RE	Vague
		Reimbursed in Canada (brand only)[a]	5	HR	RE	Vague
		Lurasidone only	2	HR	RE	Vague

FE = fixed-effect; HR = hazard ratio; NA = not applicable; RE = random-effects; WDAEs = withdrawals due to adverse events.

[a] Treatments reimbursed by drug plans include: olanzapine, quetiapine, paliperidone, lurasidone, aripiprazole, ziprasidone, risperidone.

Treatments with available generics: olanzapine, quetiapine, risperidone.

Source: Manufacturer's NMA for long-term treatment.[104]

NMA Findings

Study and Patient Characteristics

The systematic review identified a total of 11 studies meeting the necessary inclusion criteria. In accordance with the inclusion of the manufacturer's systematic review, all of the included trials involved random allocation to the study treatments. The authors reported that all of the trials were described as being double-blind, though it can be inferred from the Cochrane Risk of Bias Tool that few trials specified how blinding was maintained. Only one study reported an intention-to-treat analysis. The analysis principle for all other trials was not reported, therefore the analysis principle utilized in the remainder of the studies remains unclear. The systematic review does not report the specific study level details regarding the method that was used for handling missing data.

Eligibility criteria of the individual studies included in the NMA were reported by the manufacturer and were variable across studies. Patients were generally eligible for enrolment if they were greater than and equal to 18 years of age and were diagnosed with schizophrenia, were treated or previously treated with antipsychotic drugs other than clozapine, were not treatment refractory, did not exhibit suicidal ideation or aggressive behaviour, and were not diagnosed with substance dependence or abuse. Overall, patients with concomitant psychotic disorders as per Axis I or II DSM-IV criteria were excluded from the included trials. Inclusion criteria in regards to severity varied in terms of scale (e.g., PANSS, CGI ,or GAF) and thresholds (e.g., PANSS greater than 80, PANSS less than and equal to 60) across studies included in the NMA. Schizophrenia status requirements also differed between trials; some only included patients that were stable for a minimum of two years, whereas other trials included patients who had recently experienced acute exacerbation. Trial setting was also diverse across studies (i.e., in-patient hospital setting or outpatient). Some studies also prohibited concomitant therapies such as beta-blockers, lithium, or anti-epileptics.

Study and patient baseline characteristics are detailed Table 72. Overall, PANSS scores at baseline and randomization were variable, ranging from 52.6 to 92.1 and 42.2 to 96.3, respectively. Numerous studies did not report prior antipsychotic use and duration of schizophrenia; however, of those that reported these parameters, most studies included patients with prior antipsychotic use (range: 87.5% to 100%) and the average duration of schizophrenia ranged from 8.3 and 22.9 years. The average age of patients ranged from

34.1 to 50.8 years and the majority of patients were male (range: 52.9% to 85.0%). The majority of patients were Caucasian (range: 59.1% to 100%), and the trial duration ranged from 26 weeks to 52 weeks. Most studies diagnosed schizophrenia using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria with the exception of two trials which used the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) criteria. Most trials were performed in an outpatient setting, with the exception of four studies, of which three were conducted in a combination of hospital and outpatient settings, and one study which was conducted in hospital. There were no details reported regarding either of the following important patient characteristics: concomitant use of medications, and whether or not the patients had demonstrated treatment-resistant schizophrenia.

Definitions of relapse for the individual trials are included in Table 73. Disease relapse was generally defined as a composite of events most commonly including an increase in Brief Psychiatric Rating Scale (BPRS), increase in total Positive and Negative Syndrome Scale (PANSS) score (or specific PANSS items such as hostility and uncooperative behaviour), increases in Clinical Global Impression – Severity (CGI-S) score, hospitalization, and modification of treatment. The period for assessment of relapse varied across studies. Generally, definitions and criteria for relapse across the included trials were variable. The authors indicated that withdrawals were mostly reported in patient flow diagrams as well as portions of patient disposition/safety/tolerability sections and most commonly reported lost to follow-up, withdrawal of consent, and “other” reasons. Overall, individual study withdrawals were not formally defined with pre-specified criteria for discontinuation, which can affect the classification of events and event rates and may introduce bias between studies.

Table 72: Patient and Trial Characteristics of Included Studies in Long-Term NMA

Study	Treatment Group	PANSS (Baseline)	Setting	Diagnostic Criteria	Duration (Weeks)	PANSS (Random-ization)	Mean Age (Years)	Male (%)	Caucasian (%)	Past Antipsychotic Use (%)	Average Disease Duration (Years)	Relapse Prevention Design
EQUATOR 2016	BREX (n = 97)	91.1	Hosp + OPD	DSM-IV	52	56.5	38.8	59.8	63.9	NR	NR	Yes
	PLC (n = 105)					58.1	41.6	61.9	61.9	NR	NR	
Beasley 2003	OLAN (n = 224)	54.3	OPD	DSM-IV	30	42.2	36.2	53.2	100.0	100.0	11.29	Yes
	PLC (n = 102)					43.1	35.1	52.9	100.0	100.0	10.71	
Kramer 2007	PAL (n = 105)	92.1	OPD	DSM-IV	52	51.0	39.0	55.8	59.1	93.3	NR	Yes
	PLC (n = 102)					53.4	37.5	62.4	59.8	94.1	NR	
Mackle 2009	ASEN (n = 194)	NR	OPD	DSM-IV	26	53.8	39.2	54.1	72.7	100.0	12.7	Yes
	PLC (n = 192)					53.3	38.7	60.4	72.9	100.0	12.8	
Meulien 2007	QUET (n = 94)	52.6	Unclear	DSM-IV	52	48.3	36.5	60.6	100.0	100.0	9.1	Yes
	PLC (n = 103)					48.1	34.1	63.1	100.0	100.0	8.3	
Pigott 2003	ARI (n = 155)	NR	Hosp + OPD	DSM-IV	26	81.2	42.2	54.2	90.3	100.0	NR	No
	PLC (n = 155)					83.1	41.7	58.1	91.0	100.0	NR	
Simpson 2005	ZIP (n = 55)	89.5	OPD	DSM-IV	26	Unclear	38.0	59.0	66.7	NR	NR	No
	OLAN (n = 71)					Unclear	36.3	73.0	72.7	NR	NR	
Tran 1997	RISP (n = 167)	NR	Hosp + OPD	DSM-IV	28	95.7	36.4	63.5	74.3	NR	NR	No
	OLAN (n = 172)					96.3	36.0	66.3	75.0	NR	NR	
Arato 2002	ZIP 20 mga	NR	Hosp	DSM-III	52	84.2	50.8	72.0	NR	94.4	22.9	No
	ZIP 40 mga					86.2	49.8	71.0	NR	87.5	20.7	
	ZIP 80 mga					84.2	49.6	66.0	NR	98.5	22.0	
	PLC (n = 71)					88.4	48.7	83.0	NR	91.0	21.7	

Study	Treatment Group	PANSS (Baseline)	Setting	Diagnostic Criteria	Duration (Weeks)	PANSS (Random-ization)	Mean Age (Years)	Male (%)	Caucasian (%)	Past Antipsychotic Use (%)	Average Disease Duration (Years)	Relapse Prevention Design
Tandon 2016	LURA (n = 144)	90.1	OPD	DSM-IV	28	54.0	43.0	62.5	45.1	NR	17.8	Yes
	PLC (n = 141)					54.0	42.4	62.4	50.4	NR	16.5	
Dellva-1 1997	OLAN (n = 45)	NR	OPD	DSM-III	46	NR	34.8	80.0	76.0	NR	10.9	No
	PLC (n = 13)					NR	36.4	85.0	77.0	NR	13.3	

ARI = aripiprazole; ASEN = asenapine; BREX = brexpiprazole; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Hosp = hospital; LURA = lurasidone; NMA = network meta-analysis NR = not reported; OLAN = olanzapine; OPD = outpatient diagnosis; PALI = paliperidone; PANSS = Positive and Negative Syndrome Scale; PLC = placebo; QUET = quetiapine; RIS = risperidone; ZIP = ziprasidone.

[a] n = 207 total for ziprasidone 20 mg, 40 mg, and 80 mg.

Source: Manufacturer's NMA for long-term treatment.[104]

Table 73: Definitions of Relapse of Included Studies in Long-Term NMA

Study	Definition of Relapse
EQUATOR 2016	Exacerbation of psychotic symptoms / impending relapse, defined as any of the four following items: (1) CGI-I score of ≥ 5 (minimally worse) and an increase on any of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content (a) to a score of > 4 with an absolute increase of ≥ 2 on that specific item since randomization, or (b) to a score of > 4 with an absolute increase of ≥ 4 on the combined four PANSS items since randomization; (2) hospitalization due to worsening of psychotic symptoms; (3) suicidal behaviour as assessed by the Columbia Suicide Severity Rating Scale; (4) violent or aggressive behaviour resulting in injury or property damage.
Beasley et al. 2003	A protocol-defined relapse was: (1) an increase in any BPRS positive item to > 4, and either an absolute increase of 2 on that specific item from randomization at visit 16 or an absolute increase of 4 on the BPRS positive subscale (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) from randomization at visit 16; or (2) hospitalization due to positive psychotic symptoms. An a priori secondary definition of relapse was a completed suicide or a serious suicide attempt (as determined by the investigator).
Kramer et al. 2007	Based on any one of the following criteria: (1) psychiatric hospitalization (involuntary or voluntary admission); (2) increase in PANSS total score by 25% for two consecutive days for patients who scored more than 40 at randomization, or a 10-point increase for patients who scored 40 or below at randomization; (3) increase in the CGI-S score to at least 4, for patients who scored 3 or below at randomization, or to at least 5, for patients whose CGI-S scores were 4 at randomization, for two consecutive days; (4) deliberate self-injury or aggressive behaviour, or suicidal or homicidal ideation and aggressive behaviour that was clinically significant; (5) increase in pre-specified individual PANSS item scores to at least 5, for patients whose scores were 3 or below at randomization, or to at least 6, for patients whose scores were 4 at randomization, for two consecutive days.
Mackle et al. 2009	Time to relapse or impending relapse, defined according to rating scale criteria or investigator judgment. Relapse / impending relapse considered to be a CGI-S score > 4 for two or more days within one week which was also accompanied by: a PANSS total score increase of 20% or more from double-blind baseline, a PANSS item score of 5 or more on hostility or uncooperativeness, or a PANSS item score of 5 or more on two items of "unusual thought content", "conceptual disorganization", or "hallucinatory behaviour". Relapse / impending relapse was also considered to occur if, in the investigator's opinion, schizophrenia, risk of violence to self or others, or suicide risk increased such that one or more of the following was needed: an additional 2 mg/day or more lorazepam (or equivalent) compared with the highest open-label dose for one week, addition of antipsychotic, addition or dosage increase of an antidepressant or mood stabilizer, increased psychiatric care, hospitalization or increased level of hospitalization, arrest or imprisonment, electroconvulsive therapy, or other relevant measure.
Meulien et al. 2007	Relapse was defined as at least one of the following: hospitalization due to worsening schizophrenia, increase in PANSS score of 30% from baseline, CGI-I score 6 (much worse or very much worse), or a need for additional antipsychotic medication to treat psychosis (as determined by the investigator).
Pigott et al. 2003	An impending decompensation based on one or more of the following: a CGI-I score of 5 or more; a PANSS total score of 5 or more; a PANSS score of 5 or more on the sub-score items of hostility or uncooperativeness on two successive days; or a 20% or more increase in PANSS total score. Based on this definition, patients discontinued at the earliest signs of an impending decompensation, before experiencing a complete relapse.
Simpson et al. 2005	Symptom exacerbation (a ≥ 20% worsening of PANSS total score and CGI-S score of ≥ 3).
Tran et al. 1997	Significant symptom exacerbation, considered to be a ≥ 20% worsening in PANSS total score along with a CGI-S score ≥ 3 after eight weeks of therapy.
Arato et al. 2002	Either a CGI-I score of 6 or more or a score of 6 or more on PANSS items P7 (hostility) or G8 (uncooperativeness) persisting for two successive days. Patients with a CGI-I score of 5 (minimally worse) had evaluations repeated daily for three days, and then weekly, until their condition improved (remained in the study), or deteriorated to a score Z6 (withdrawn from the study). Also, any patient who the investigator considered to be in need of additional treatment for exacerbation of symptoms was withdrawn from the study and offered appropriate treatment. Patients withdrawing under these conditions were prospectively defined as experiencing a relapse.

Study	Definition of Relapse
Tandon et al. 2016	(1) An increase of ≥ 25% from double-blind baseline in PANSS total score and CGI-S worsening of ≥ 1 point for two consecutive visits no more than ten days apart. (2) At any single visit, a PANSS item score of ≥ 5 (moderately severe) on hostility or uncooperativeness, or a PANSS item score of ≥ 5 on two or more items of unusual thought content, delusions, conceptual disorganization, or hallucinatory behaviour. (3) Initiation of supplemental treatment with an antipsychotic drug other than lurasidone, an increased dose of an antidepressant or mood stabilizer, an increase in lorazepam (or benzodiazepine equivalent) dose by ≥ 2 mg/day for at least three days, or electroconvulsive therapy. (4) Insufficient clinical response or exacerbation of underlying disease reported as an adverse event, as determined by the study investigator. (5) Deliberate self-injury or repeated aggressive behaviour, active suicidal or homicidal ideation, or attempt. (6) Psychiatric hospitalization due to worsening schizophrenia.
Dellva-1 et al. 1997	Hospitalization due to psychopathology.

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; mg = milligrams; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale.

Source: Manufacturer's NMA for long-term treatment.[104]

Evidence Network

The evidence network used in the reference case NMA is provided in Figure 25. The reference case analyses assessing relapse, overall withdrawals, and withdrawals due to adverse events consisted of 11 RCTs. Most trials compared treatments versus placebo; the network did not include any closed loops involving brexpiprazole as an intervention, therefore all active comparisons involving brexpiprazole were considered indirect. Overall, the evidence network was informed by single-study connections, with the exception of the comparison of olanzapine with placebo (two-study connection).

Figure 25: Evidence Network for Long-Term Treatment NMA

Confidential figure removed at manufacturer's request.

Source: Manufacturer's NMA for long-term treatment.[104]

Methodological Validity Assessment of Included Studies

The authors performed a risk of bias evaluation for the included studies using the Cochrane Risk of Bias Tool. This included the classification of the following characteristics as having either a low risk of bias, high risk of bias, or being unclear due to insufficient information: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, treatment of incomplete data, selective reporting, and other criteria. It was not reported if the risk of bias assessment was performed in duplicate.

Overall, the risk of bias across the included studies was variable with insufficient information. The authors reported that only a minority of studies were assessed as having a low risk of bias for randomization (3 RCTs [27%]), allocation concealment (4 RCTs [36%]), blinding of participants and personnel (3 RCTs [27%]), blinding of outcome assessment (2 RCTs [18%]), handling of incomplete data (5 RCTs [45%]), selective reporting (1 RCT [9%]). Contrarily, the majority of studies reported low risk of bias for the "other criteria" domain (9 RCTs [82%]). All studies were described as being double-blind, though only a minority of studies reported methods for maintaining blinding (27%). The authors reported that two RCTS (18%) had a high risk of bias with respect to incompleteness of data and three RCTs (27%) had a high risk of bias for selective reporting. All other bias assessments of the included studies were reported as unclear, based on the Cochrane Risk of Bias Tool. While

the brexpiprazole study was assessed to have a low risk of bias, it should be noted that the authors of the NMA had the full clinical study report only for this study, and relied on available publications for all other studies included in the NMA, therefore limiting the amount of information that could be extracted from those studies.

NMA Results

Disease Relapse

The results for the reference case and sensitivity analyses for disease relapse are summarized in Table 74. The reference case analysis and all of the sensitivity analyses demonstrated [redacted].

Withdrawals Due to Adverse Events

The results for the reference case and sensitivity analyses for withdrawals due to adverse events are summarized in Table 75. The reference case analysis and all of the sensitivity analyses demonstrated [redacted].

Withdrawals for Other Causes

The results for the reference case and sensitivity analyses for overall withdrawals are summarized in Table 76. The reference case analysis and all of the sensitivity analyses demonstrated [redacted].

Table 74: NMA Results for Disease Relapse

BREX Versus Comparator	Reference Case	Sensitivity Analyses					
	RE Vague					RE Informative	FE
	HR (95% CrI) 11 RCTs	Withdrawal Design HR (95% CrI) 6 RCTs	Reimbursed in Canada HR (95% CrI) 10 RCTs	Reimbursed in Canada (Branded Only) HR (95% CrI) 5 RCTs	Lurasidone Only HR (95% CrI) 2 RCTs	HR (95% CrI) 11 RCTs	HR (95% CrI) 11 RCTs
Olanzapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quetiapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paliperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asenapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lurasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aripiprazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ziprasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BREX = brexpiprazole; CrI = credible interval; FE = fixed effects; HR = hazard ratio; NA = not applicable; NMA = network meta-analysis; RCT = randomized controlled trial; RE = random effects.

Source: Manufacturer's NMA for long-term treatment.[104]

Table 75: NMA Results for WDAE

BREX Versus Comparator	Reference Case	Sensitivity Analyses					
	RE Vague					RE Informative	FE
	HR (95% CrI) 11 RCTs	Withdrawal Design HR (95% CrI) 6 RCTs	Reimbursed in Canada HR (95% CrI) 10 RCTs	Reimbursed in Canada (Brand Only) HR (95% CrI) 5 RCTs	Lurasidone Only HR (95% CrI) 2 RCTs	HR (95% CrI) 11 RCTs	HR (95% CrI) 11 RCTs
Olanzapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quetiapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paliperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asenapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lurasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aripiprazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ziprasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BREX = brexpiprazole; CrI = credible interval; FE = fixed effects; HR = hazard ratio; NA = not applicable; NMA = network meta-analysis; RCT = randomized controlled trial; RE = random effects; WDAE = withdrawals due to adverse event.

Source: Manufacturer's NMA for long-term treatment.[104]

Table 76: NMA Results for Withdrawals for Other Causes

BREX Versus Comparator	Reference Case	Sensitivity Analyses					
	RE Vague					RE Informative	FE
	HR (95% CrI) 11 RCTs	Withdrawal Design HR (95% CrI) 6 RCTs	Reimbursed in Canada HR (95% CrI) 10 RCTs	Reimbursed in Canada (Brand Only) HR (95% CrI) 5 RCTs	Lurasidone Only HR (95% CrI) 2 RCTs	HR (95% CrI) 11 RCTs	HR (95% CrI) 11 RCTs
Olanzapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quetiapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paliperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asenapine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lurasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aripiprazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ziprasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risperidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BREX = brexpiprazole; CrI = credible interval; FE = fixed effects; HR = hazard ratio; NA = not applicable; NMA = network meta-analysis; RCT = randomized controlled trial; RE = random effects.

Source: Manufacturer's NMA for long-term treatment.[104]

Critical Appraisal of the Manufacturer's NMA

The methodological validity of the NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and guidance provided in CADTH's *Guidance Document on Reporting Indirect Comparisons* (October 2015).[99,100] The quality of the systematic review was appraised according to the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) criteria.

Systematic Review Methods

The research question and inclusion criteria for the systematic review were clearly reported in the NMA. The literature search was comprehensive, involving multiple databases (i.e., Embase, the Cochrane Register of Controlled Trials, PsychINFO, MEDLINE and MEDLINE In-Process, clinical trial registries (e.g., clinicaltrials.gov), abstracts, and other non-indexed citations). The search was supplemented by reviewing the reference lists from the included studies. The literature search was well-reported and satisfied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement with a complete copy of the search strategy included in the report. Although the authors indicated that older first-generation antipsychotic drugs were excluded due to the age of the trials, relatively older trials including second-generation antipsychotic drugs (e.g., 1997) were included.

Study selection and data extraction was performed independently by two reviewers and disagreements were resolved through discussion and a third reviewer. The authors performed a risk of bias evaluation for the included studies using the Cochrane Risk of Bias Tool. It was not reported if the risk of bias assessments were performed in duplicate.

Reporting of the NMAs

The rationale for the NMA was clearly stated (i.e., absence of head-to-head RCTs evaluating the relative efficacy and safety of brexpiprazole compared with other atypical antipsychotic drugs). Baseline characteristics were reported for mean age, gender, race, average disease duration, prior exposure to antipsychotic medications, and mean PANSS total score at baseline. There were no details regarding use of concomitant medications (e.g., rescue medication or medications used to manage adverse events). Study characteristics were adequately reported, with description of trial duration, primary end points, eligibility criteria, and trial setting (e.g., in-patient versus outpatient). However, some patient data such as history of past therapies (either number of prior lines of treatment or history of exposure to specific treatments) and average disease duration were not reported in some studies. In regards to study end points, specifically definitions for the occurrence of withdrawals due to adverse events or other causes; outcomes were generally poorly reported across studies with no formally defined criteria.

The analytical method used for the NMA was well reported, including a description of the following: source code that was applied, prior distributions that were used, rationale for use of a random-effects model, and justification for sensitivity analyses. Copies of the WinBUGS codes that were used are included as appendices in the report. The authors adequately provided which studies were included in each of the analyses.

The manufacturer conducted several sensitivity analyses in hopes of addressing the heterogeneity between studies and provided adequate justification for each analysis to ensure more robust results.

NMA Methods

Analytical Methods

The NMAs were performed using established code from NICE to conduct a competing risk NMA. All of the reference case analyses were conducted using random-effects models with vague prior distributions (reported as normal with Uniform [0,5] with a precision of 0.0001) because of the complexity of the characteristics of the evidence network and the potential clinical heterogeneity between the included studies. In addition, based on the review of the deviance information criteria (DIC) and posterior mean residual deviance, random-effects models with vague priors were generally found to have an improved fit relative to random-effects models with informative priors, and fixed-effect models.

Evidence Network

Given the nature of the evidence network (single-study connections with mostly open loops), no statistical heterogeneity assessments (e.g., I^2 or Cochrane Q-test) or meta-regressions were performed. In addition, no tests for consistency were possible, given that there were no closed loop networks involving brexpiprazole; therefore, the robustness of the indirect comparison could not be assessed and compared with direct comparisons.

Risk of Bias

Risk of bias evaluations were performed for all included studies, however, the majority of trials mainly yielded unclear risk of bias. Therefore, the potential impact of biases across studies on study findings also is unclear.

Patient Characteristics

Overall, patient characteristics were heterogeneous across individual studies. PANSS scores at baseline and randomization, age, gender, race, prior antipsychotic drug use, and average disease duration, all varied widely between studies. Although the authors reported that sensitivity analyses were conducted in hopes of addressing the heterogeneity, the NMA did not conduct sensitivity analyses with respect to patient characteristics in an effort to address these differences; therefore, the potential for confounding due to heterogeneity based on patient characteristics is unclear.

Study Characteristics

Generally, study characteristics were heterogeneous across individual studies. Study duration, setting, and diagnostic criteria were not always comparable between studies. The authors reported that the included studies varied with respect to methodology and study design. Although the authors reported that sensitivity analyses were conducted to investigate the impact of heterogeneity (withdrawal design), the authors of the NMA did not conduct sensitivity analyses with respect to other study characteristics such as study duration, or setting. The potential for bias due to heterogeneity based on study characteristics is therefore unclear. In addition, the definitions of disease relapse and withdrawals were variable across the included studies. Given the variability in end point measures across the included studies, it is unclear whether the pooling of the results in the NMA was appropriate.

Dosage of Comparators

It is important to note that the dosage of antipsychotic drugs utilized in the included studies does not necessarily reflect usage in Canada or the dosage recommended in Canadian product monographs for the treatment of schizophrenia. Therefore, it is unclear whether the results based on the NMA are generalizable to the schizophrenia population in Canada. Table 77 provides a summary of the relevant differences in treatment between the manufacturer's analyses and the recommended doses as per the Canadian product monographs.

Table 77: Exclusion of Fixed-Dose Regimens from Manufacturer's NMA

Drug	Description	Dosage Included in NMA
Brexpiprazole	The dose recommended in the product monograph is 2 mg to 4 mg once daily.[25]	1 mg to 4 mg/day
Lurasidone	The Canadian product monograph states that daily doses of 40 mg, 80 mg, 120 mg, and 160 mg were shown to be effective for the treatment of schizophrenia (60 mg was cited as an option for the treatment of bipolar disorder).[26] The product monograph further states that patients should be treated with the lowest effective dose that provides the optimal response, which is expected to be 40 mg or 80 mg once daily for most patients.[26]	40 mg to 80 mg/day
Risperidone	The product monograph suggests that a relevant dosage range for risperidone is 4 mg to 6 mg per day.[31] It should also be noted that a combination of different dosage strengths would be required to achieve a 5 mg dosage in Canada, as there are 5 mg or 2.5 mg strength tablets available in Canada.	4 mg to 12 mg/day
Quetiapine	The Canadian product monograph for immediate-release quetiapine recommends a target starting dosage of 300 mg/day and notes that the usual effective treatment dosage will be in the range of 300 mg to 600 mg/day.[32]	400 mg to 800 mg/day
Aripiprazole	The Canadian product monograph for aripiprazole recommends a starting and target dosage in the range of 10 mg or 15 mg/day.[27]	15 mg/day
Olanzapine	The dose range specified in the Canadian product monograph for olanzapine is 5 mg to 20 mg.[30]	5 mg to 20 mg/day
Ziprasidone	The Canadian product monograph recommends that responding patients with schizophrenia be continued on ziprasidone at the lowest dose needed to maintain remission (i.e., 20 mg, 40 mg, or 80 mg).[28]	40 mg to 80 mg b.i.d.
Asenapine	The Canadian product monograph recommends a starting and target dose of 5 mg given b.i.d. and suggests no added benefit with a 10 mg b.i.d. dose.[29]	5 mg to 10 mg b.i.d.

b.i.d. = twice daily; mg = milligrams; NMA = network meta-analysis.

Source: Manufacturer's NMA for long-term treatment.[104]

Summary and Conclusion

The results of the NMA suggest that [redacted]. Given the high degree of the clinical and methodological heterogeneity of the NMA, the results were too uncertain to make any inference on the beneficial or harmful effects of brexpiprazole compared with other atypical antipsychotic drugs for the long-term treatment of adult patients diagnosed with schizophrenia.

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