CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BREXPIPRAZOLE (REXULTI — LUNDBECK CANADA INC AND OTSUKA CANADA PHARMACEUTICAL Inc.)
Indication: Treatment of schizophrenia in adults

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that brexpiprazole be reimbursed for the treatment of adults with schizophrenia, if the following conditions are met:

Conditions:

- Reimburse in a similar manner to other oral formulations of atypical antipsychotic agents for the treatment of adults with schizophrenia.
- The drug plan cost of treatment with brexpiprazole should not exceed the drug plan cost of treatment with the least costly atypical antipsychotic agent.

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- The drug plan cost of treatment with brexpiprazole should not exceed the drug plan cost of treatment with the least costly atypical antipsychotic agent.

Reasons for the Recommendation:

1. Results from three six-week acute exacerbation trials (VECTOR [N = 636], BEACON [N = 674], and LIGHTHOUSE [N = 468]) demonstrated that brexpiprazole was associated with a statistically significant improvement compared with placebo in the primary efficacy outcome of PANSS total score (least squares mean difference [LSMD]: –8.72 [95% confidence interval [CI], –13.1 to –4.37] for the 2 mg dose, and LSMD 7.64 [95% CI, –12.0 to –3.30] for the 4 mg dose in VECTOR; LSMD −6.47 [95%, −10.6 to −2.35] for the 4 mg dose in BEACON). There was no statistically significant improvement in PANSS score for flexibly-dosed (2 to 4 mg per day) brexpiprazole compared to placebo in the LIGHTHOUSE trial. There was a statistically significant improvement in CGI-S scores compared with placebo in the VECTOR trial for both the 2 mg/day and 4 mg/day doses of brexpiprazole (LSMD: −0.33 [95% CI, −0.56 to −0.10] and −0.38 [95% CI, −0.61 to −0.15], respectively), and a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.3 [95% CI, −0.5 to −0.1]) for flexibly-dosed brexpiprazole in the LIGHTHOUSE trial.

2. Results from one 52-week maintenance therapy trial (EQUATOR [N = 202]) demonstrated that there was a statistically significant improvement in the primary endpoint, time to impending relapse, in the brexpiprazole group compared with the placebo group (HR: 0.29 [95% CI, 0.16 to 0.55]; P < 0.0001). The proportion of patients meeting the criteria for impending relapse was statistically significantly lower in the brexpiprazole group compared with the placebo group (13.5% versus 38.5% [P <0.0001]).

3. In the absence of direct evidence assessing the comparative efficacy and safety of brexpiprazole compared to other active treatment options, the manufacturer submitted two network meta-analyses (NMAs). In the acute setting, the manufacturer's NMA suggested [redacted].

4. At the submitted price of $3.50 per tablet, brexpiprazole ($1,278 per year) is marginally cost saving over select brand name atypical antipsychotics; however, it is more expensive than generic products of similar efficacy and safety such as quetiapine and risperidone. The evidence provided by the manufacturer did not suggest that brexpiprazole offers any additional clinical benefits compared with other atypical antipsychotics; therefore, the price should not exceed the least costly alternative.

Of Note:

- CDEC noted that patient group input and the clinical expert highlighted the need for additional antipsychotic treatment options for individuals with schizophrenia and that patients and clinicians are looking for more efficacious and safer options than

currently available treatments. There is no evidence to suggest that brexpiprazole has any added benefit compared to currently available treatments.

Discussion Points:

- CDEC noted that there was no direct evidence available to assess the safety and efficacy of brexpiprazole against other antipsychotic agents. The committee discussed one six-week, open-label, exploratory, Phase 3B RCT (Study 008, [N = 97]) where patients were randomized in a 2:1 ratio to receive either open-label brexpiprazole (titration of 1 to 4 mg per day; N = 64) or open-label aripiprazole (10 to 20 mg per day; N = 33). Aripiprazole was included in this study to establish assay sensitivity and there were no statistical comparisons made between brexpiprazole and aripiprazole. Given the limitations of the study, the committee could not draw any conclusions regarding the comparative efficacy and safety of brexpiprazole compared to aripiprazole.
- CDEC noted that evidence from the network meta-analysis submitted by the manufacturer for the long-term treatment of schizophrenia was limited by the heterogeneity in the study designs and patient populations across the included studies and by the considerable uncertainty in the indirect estimates of effect. Given these limitations, the results were too uncertain to make any inference regarding the comparative efficacy and safety of brexpiprazole as a maintenance treatment for schizophrenia.
- CDEC discussed the implications of the flat-pricing of brexpiprazole (i.e., $3.50 per tablet regardless of strength), noting that the cost of treatment could be two- to three-fold higher per day if multiple tablets are required to achieve optimal clinical response and tolerability.
- CDEC noted that the 2 mg per day fixed-dosage of brexpiprazole failed to consistently demonstrate a statistically significant improvement in PANSS compared with placebo. It was noted that regulatory authorities granted approval for this dosage based on additional considerations, including 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. The clinical expert consulted by CADTH suggested that the 2 mg per day dosage would likely only be used in a subset of patients, with the majority of patients receiving treatment with an increased dosage.

Background:

Brexpiprazole is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. The recommended dosage for the treatment of schizophrenia is 2 mg to 4 mg orally once daily. The product monograph recommends a starting dosage of 1 mg per day on days 1 to 4, with titration 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. The maximum recommended daily dosage is 4 mg for most patients and 3 mg per day for patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) or those with moderate, severe or end-stage renal impairment (creatinine clearance < 60 mL/minute). Brexpiprazole is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of brexpiprazole, two indirect comparisons submitted by the manufacturer, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience treating patients with schizophrenia, and patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by schizophrenia.

Patient Input Information

Three patient groups responded to the call for patient input for this CDR review: the Schizophrenia Society of Canada (SSC), the Schizophrenia Society of Ontario (SSO), and the British Columbia Schizophrenia Society (BCSS). Information was primarily gathered through the lived experiences of patients, one-on-one conversations and online surveys, from people living with schizophrenia and

other persistent mental illnesses (e.g., schizoaffective disorder) and their families and caregivers. The following is a summary of key input from the perspective of patient groups:

- Patient groups reported that schizophrenia often strikes young people at a critical stage of life and significantly interferes with the daily activities of employment, education, socialization, and maintenance of relationships with family and friends. Caregivers for those living with schizophrenia can be faced with considerable emotional and financial burdens.
- Schizophrenia is 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. 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.
- Patient groups reported that many of the available treatments are limited by significant side effects, such as inability to concentrate, fatigue, sleep problems, weight gain, sexual dysfunction, restlessness, and muscle spasms.

Patients indicated that there is a need for additional antipsychotic treatment options for individuals with schizophrenia. Many antipsychotic medications have similar efficacy across a patient population; however, there is variability in individual patient response, such that a particular drug may not be effective in some patients but may be in others.

Clinical Trials

There were four RCTs that met the inclusion criteria of the systematic review conducted by CDR. 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]). All three acute exacerbation trials were double-blind phase 3 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/day, 2 mg/day, 0.25 mg/day, or placebo. Patients in BEACON were randomized to brexpiprazole 4 mg/day, 2 mg/day, 1 mg/day, or placebo. Patients in LIGHTHOUSE were randomized to brexpiprazole (2 to 4 mg per day), quetiapine (400 to 800 mg per day), or placebo. In accordance with the Health Canada–approved dosage regimen for brexpiprazole, the CDR systematic review focused on the results for of the 2 mg/day, 4 mg/day, and 2 to 4 mg/day (flexible) dosages of brexpiprazole in the acute treatment trials. Patients were hospitalized for the duration of all three acute exacerbation studies.

The EQUATOR maintenance trial consisted of four phases: a screening phase of up to 15 days; a conversion phase of 1 to 4 weeks for patients to convert from existing antipsychotics to brexpiprazole and continue washout of prohibited medications; a single-blind stabilization phase of 12 to 36 weeks where patients underwent titration of brexpiprazole (1 mg to 4 mg); and a 52-week, randomized, maintenance phase. Patients who met stabilization criteria were randomized (1:1) to continue treatment with 1 to 4 mg brexpiprazole or to receive matching placebo.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- PANSS — a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia that consists of three subscales (positive, negative, and general psychopathology).
- PANSS Marder factors — five specific categories of PANSS subscale items: positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression.
- Clinical Global Impressions – Severity of Illness (CGI-S) — a 7-point scale that measures the clinician's impression about the severity of the patient's illness at the time of assessment , ranging from 1 (normal) to 7 (extremely ill).
- Clinical Global Impressions – Improvement scale (CGI-I) — a 7-point scale that measures the clinician's impression about how much the patient's illness has improved or worsened relative to baseline, ranging from 1 (very much improved) to 7 (very much worse).
- Time to impending relapse — time from randomization to exacerbation of psychotic symptoms/impending relapse, which was defined as any of the following four criteria:

1. CGI-I score ≥ 5 and: an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score of > 4 with an absolute increase of ≥ 2 on that specific item since randomization; or an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score of > 4 and an absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content)
2. Hospitalization due to worsening of psychotic symptoms
3. Current suicidal behavior as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
4. Violent or aggressive behavior resulting in clinically significant self-injury, injury to another person, or property damage.

- Response rate — proportion of patients with a reduction of ≥30% from baseline in PANSS total score at week 6; or, a CGI-I score of 1 or 2 at week 6.
- Schizophrenia Quality of Life (S-QoL) scale — a patient-rated scale consisting of 41 items in 8 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).
- Extrapyramidal symptom (EPS) assessments — 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: Barnes-Akathisia Rating Scale (BARS); Simpson-Angus Rating Scale (SARS); Abnormal Involuntary Movement Scale (AIMS). Higher scores on these scales indicate a greater degree of akathisia.

In all three acute exacerbation studies, change from baseline to week 6 in PANSS total score was the primary endpoint and change from baseline in CGI-S was the key secondary endpoint. The primary efficacy outcome in the EQUATOR study was time from randomization to impending relapse and the key secondary endpoint was the proportion of patients meeting impending relapse criteria.

Efficacy

Treatment of Acute Exacerbations

In VECTOR, 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 BEACON, the 4 mg dose of brexpiprazole was associated with a statistically significant improvement in PANSS compared with placebo (LSMD: −6.47 [95%, −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 LIGHTHOUSE, there was no statistically significantly difference between flexibly-dosed brexpiprazole and placebo (LSMD: −4.1 [95% CI, −8.2 to 0.1]); however, there was a statistically significant difference favouring quetiapine over placebo (LSMD: −8.0 [redacted]).

In VECTOR, both the 2 mg and 4 mg doses 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 endpoint; therefore, the results of the CGI-S analyses are considered exploratory. The treatment effect favoured the 4 mg/day dose of brexpiprazole compared with placebo (LSMD: −0.38 [95% CI, −0.62 to −0.15]). In contrast, the 2 mg/day dose of brexpiprazole did not demonstrate a difference compared with placebo (LSMD: −0.19 [95% CI −0.42 to 0.05]). In LIGHTHOUSE, both the brexpiprazole and quetiapine groups demonstrated a statistically significant improvement in CGI-S compared with placebo (LSMD: −0.3 [95% CI, −0.5 to −0.1] and −0.4 [95% CI, [redacted], respectively).

In VECTOR, both the 2 mg and 4 mg doses of brexpiprazole were associated with statistically significant improvements in the PANSS positive subscale, negative subscale, and excited component subscale compared with placebo. In BEACON, statistically significant differences were demonstrated between the 4 mg/day brexpiprazole group and placebo for the positive subscale, negative subscale, and excited component subscale; however, the 2 mg/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 group over placebo in VECTOR (RR: 0.39 [95% CI, 0.18 to 0.85]); however, there was no statistically significant difference in BEACON for the 4 mg dose (RR: 0.82 [95% CI, 0.44 to 1.51]). Time to discontinuation due to a lack of efficacy was a secondary endpoint in the LIGHTHOUSE trial. Compared with placebo, both the brexpiprazole and quetiapine groups were associated with a statistically significant reduction in the risk of the discontinuation due to a lack of efficacy (hazard ratio [HR]: 0.44 [ ] and 0.45 [ ]), respectively.

Exploratory analyses demonstrated that brexpiprazole and quetiapine were associated with statistically significant improvements in S-QoL total score compared with placebo (LSMD: 6.2 [95% CI, 2.9 to 9.5] and 6.7 [ ], respectively) in the LIGHTHOUSE trial.

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 and 169.0 days in the brexpiprazole group and 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 (and 13.5% versus 38.5% [P < 0.0001], respectively).

Harms (Safety and Tolerability)

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 2 study (331-07-203; N = 459). The phase 2 study was a six-arm trial that allocated patients to placebo, aripiprazole 15 mg/day, or one of four starting regimens of brexpiprazole (i.e., 0.25, 1, 2.5, or 5 mg/day).

Treatment of Acute Exacerbations

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

The proportion of patients who experienced at least one EPS-related adverse event . There were no statistically significant differences between brexpiprazole and placebo for changes in the BARS, SAS, and AIMS. The proportion of patients with an increase in body weight of at least 7% in the acute exacerbation trials was .

The proportion of patients who experienced at least one serious adverse event was , but greater 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 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 BARS, SAS, and 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.

Network Meta-Analyses

For patients experiencing an acute exacerbation of schizophrenia, the manufacturer's unpublished 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/day).

The results of the manufacturer's maintenance treatment NMA suggested that [redacted]. 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.

The analysis of safety endpoints in the NMAs 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 antipsychotics included in their analysis, when adjusted for differences in withdrawal from the placebo groups. Such an aggregate endpoint cannot be used to evaluate the unique safety profiles of different atypical antipsychotics on outcomes important to patients, such as weight gain and EPS-related events.

Cost and Cost-Effectiveness

Brexpiprazole is available as a 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablet at a flat price of $3.50 per tablet, or $3.50 per day at the recommended dose of 2 mg to 4 mg daily.

The manufacturer submitted a cost comparison of brexpiprazole with other oral atypical antipsychotics that are publicly reimbursed in Canada for the treatment of schizophrenia based on the assumption of similar clinical efficacy and safety. As such, only drug acquisition costs were considered in the analysis as other healthcare costs were assumed to be equivalent. The analysis was conducted over a one-year time horizon from the perspective of the Canadian health care payer.

CDR noted the following with the submitted cost analysis:

- The clinical similarity of brexpiprazole to other oral atypical antipsychotics was supported by two unpublished indirect comparisons submitted by the manufacturer. The assumption of clinical similarity is uncertain owing to the presence of wide credible intervals associated with the effect estimates for brexpiprazole compared to other oral atypical antipsychotics and a high degree of clinical and methodological heterogeneity.
- Brexpiprazole is a highly potent medication with a long half-life. As such, slow upward titration using multiple, smaller dosage tablets may be required to achieve optimal efficacy. Given the flat-pricing of brexpiprazole, the cost of treatment would increase uniformly with each additional tablet. Where there is a need to use multiple, identically-priced tablets per day for optimized treatment, the cost of treatment with brexpiprazole may exceed $1,278 in the first year, and cost savings resulting from the use of brexpiprazole in place of other more costly branded agents may not be realized.

At the submitted daily price, brexpiprazole ($1,278 per patient per year) is cost saving when compared to branded atypical antipsychotic drugs aripiprazole ($1,571 to $1,854 per year), lurasidone ($1,571 per year), and ziprasidone ($1,521 per year), irrespective of dose. Brexpiprazole is more costly than most generic therapies irrespective of dose, including olanzapine ($233 to $932 per year), olanzapine ODT ($235 to $939 per year), quetiapine ($254 to $508 per year), risperidone ($444 to $665 per year), and risperidone ODT ($746 to $1,116 per year). Thus, where brexpiprazole is used instead of generic oral atypical antipsychotic drugs, public drug plans would incur additional costs. A price reduction of 27% to 82% would be required for brexpiprazole to be equivalent to the lowest priced generic AAP (olanzapine; $0.64 to $2.55). Whether brexpiprazole is more or less costly than generic quetiapine XR depends on the dose considered and prices within individual public drug plans.

CDEC Members:

July 19, 2017 Meeting

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets:

None

Conflicts of Interest:

None

November 15, 2017 Meeting

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

One CDEC member did not participate due to considerations of conflict of interest.