Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Brexpiprazole

Proprietary Product Name: Rexulti

Sponsor: Lundbeck Australia Pty Ltd

First round CER: October 2016

Second round CER: January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
5-HT	Serotonin
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of covariance
AUC_{0-24}	Area under the concentration-time curve from time zero to 24 hours
AUC_t	Area under the concentration-time curve during a dosing interval at steady state
AUC∞	Area under the concentration-time curve from time zero to infinity
BARS	Barnes Akathisia Rating Scale
BRCP	Breast cancer resistance protein
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity of Illness Scale
CI	Confidence interval
CLcr	Creatinine clearance
CL/F	Apparent oral clearance
C_{max}	Maximum (peak) plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450 (isoenzyme subtypes)
D	Dopamine
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
Emax	Maximum effect
EC_{50}	Concentration of a drug that gives half maximal response

Abbreviation	Meaning
ECG	Electrocardiogram
EM	Extensive metaboliser
EMA	European Medicines Agency
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration (US)
IMP	Investigational Medicinal Product
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
K_i	Inhibitory constant
LOCF	Last Observation Carried Forward
MDD	Major depressive disorder
MDR1	Multiple drug resistance 1
MMRM	Mixed model repeated measures
MTD	Maximum tolerated dose
OAT	Organic anion transporter
OCT	Organic cation transporter
PANSS	Positive and Negative Syndrome Scale
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PM	Poor metaboliser
PTSD	Post Traumatic Stress Disorder
QT	The time between the QRS complex and the end of the T-wave
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcI	Individually corrected QT interval

Abbreviation	Meaning
RCT	Randomised Controlled Trial
SAS	Simpson Angus Scale
SD	Standard deviation
Vc/F	Apparent volume of distribution in the central compartment
Vd	Volume of distribution

1. Introduction

1.1. Submission type

This is a submission to register Rexulti, a new chemical entity (NCE) in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets.

1.2. Drug class and therapeutic indication

Atypical antipsychotic medication indicated for the treatment of adult patients with schizophrenia.

1.3. Dosage forms and strengths

Film coated immediate release tablets of strengths 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg.

1.4. Dosage and administration

The recommended starting dose for Rexulti in the treatment of patients with schizophrenia is 1 mg once daily on Days 1 to 4. The recommended target dose range is 2 mg to 4 mg once daily. Doses should be titrated to 2 mg once daily on Day 5, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

Maintenance treatment: The recommended maintenance dose range is 2 mg/day to 4 mg/day.

2. Clinical rationale

2.1. Background

Schizophrenia is a severely debilitating mental illness characterised by delusions, hallucinations, and disordered cognition that affects approximately 1% of the world population. It has been estimated that, globally, schizophrenia reduces life expectancy by an average of 10 years.[1] The illness, typically emerging between the late teens and mid-thirties, is characterised by the presence of positive symptoms (for example, hallucinations and delusions) as well as negative symptoms (for example, social withdrawal and lack of emotion, energy, and motivation) and cognitive impairments.[2] While there are several currently marketed drugs for the treatment of schizophrenia, both efficacy and their side effect profiles limit their use in some patients and there remains an unmet need for further treatment options.[3]

The course of schizophrenia is highly variable, but often characterised by acute episodes of psychosis, characterised by the positive symptoms (all considered 'relapses' after the first occurrence), repeating themselves at varying intervals between periods of relative symptomatic stability. Negative symptoms and cognitive disturbance can persist between episodes and

[1] Rössler W, et al. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol. 2005;15(4): 399-409.

[2] Karasu T, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. Second ed. American Psychiatric Association. 2000.

[3] Lublin H, et al. Current therapy issues and unmet clinical needs in the treatment of schizophrenia: a review of the new generation antipsychotics. Int Clin Psychopharmacol. 2005; 20: 183-198.

contribute significantly to disability. They also tend to be less responsive to currently available treatments. After relapsing, patients with schizophrenia rarely return to their 'pre-relapse' state and this erosion can increase the patient's sense of isolation and difficulty in finding and sustaining employment and meaningful relationships. Thus, prevention of future exacerbations and relapses is a crucial goal of schizophrenia management, and providing adequate treatment as early as possible in the course of the illness is a logical therapeutic goal.[1,2,3,4,5]

2.1.1. Current treatment options

The first antipsychotics developed for the treatment of schizophrenia were dopamine D_2 receptor antagonists, following the incidental discovery of the antipsychotic potential of chlorpromazine. These agents were effective against positive symptoms (for example, hallucinations and delusions), but showed low efficacy for negative symptoms (such as social withdrawal and lack of emotion, energy, and motivation) and were also associated with a high incidence of hyperprolactinemia and extrapyramidal symptom (EPS) related side effects (including tardive dyskinesia), and other side effects including sedation, seizure, agranulocytosis, and neuroleptic malignant syndrome.[6,7] Second generation antipsychotics, commonly referred to as 'atypical antipsychotics' represent a significant advancement in the treatment of psychotic disorders because they are efficacious on positive symptoms; appear to have some effect, although not satisfactory, on negative symptoms; and at the same time exhibit a reduced tendency to promote EPS, especially tardive dyskinesia, relative to typical antipsychotics.

The tolerability with second-generation antipsychotics remains an important cause of medication discontinuation due to side effects of somnolence, sedation, akathisia, hyperprolactinemia, and weight gain.[8] Some agents are associated with high rates of weight gain (for example, olanzapine and quetiapine), while others have high rates of hyperprolactinemia and associated sexual dysfunction or sedation. Therapeutic options for patients with schizophrenia that offer improved tolerability also have the potential of providing significant direct and indirect benefits. That is, improved tolerability may lead to better medication adherence thus diminishing the risk of relapse and re-hospitalisation, and consequently reducing overall public health burden.

Amongst the atypical antipsychotics, aripiprazole was the first D_2 partial agonist to be approved for treatment of schizophrenia. Whilst it has a particularly favourable metabolic profile, it has been associated with high rates of activating side effects (such as akathisia and insomnia) particularly when used in higher or rapidly up titrated dose.

2.2. Clinical rationale

Brexpiprazole is thus described as being pharmacologically designed to address these liabilities by balancing activities on dopaminergic (D_2 partial agonist activity), serotonergic (potent 5-HT_{2A} antagonism and partial agonist activity at 5-HT_{1A}), and adrenergic (α_{1B} receptors antagonism) monoamine systems.

[4] Messias E, et al. Epidemiology of schizophrenia: Review of findings and myths. Psychiatr Clin North Am. 2007;30:323-338.
[5] McGrath J, et al. Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.
[6] Novick D, et al. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010;176:109-13.
[7] Thornicroft G, et al. for the INDIGO Study Group. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet. 2009;373:408-15.
[8] van Os J, Kapur S. Schizophrenia. Lancet. 2009;374:635-45.

2.3. Formulation development

Formulation development occurred in an appropriate fashion through the development program.

In Phase I trials, 0.05, 0.25, 1, and 5 mg tablets were used. A few trials utilised other dose strengths, such as the 2 mg tablet (a dose strength that was developed for the Phase III safety and efficacy trials). For the Phase II safety and efficacy trials, the initial 0.25 mg, 1 mg and 5 mg tablet strengths were used. In addition to 0.25 and 1 mg tablets, 0.5, 2, 3 and 4 mg tablets were used in Phase III trials.

All dose strengths of clinical Phase III tablets were the same as the dose strengths of the commercial tablets, and for each dose strength the composition of these tablets (except for the coating material) was exactly the same as the commercial tablets. The manufacturing methods and scale for the clinical Phase III tablets were the same as for the commercial tablets and the manufacturing process parameters were similar between the two formulations. Comparability of brexpiprazole clinical Phase III tablets to the Commercial tablets was demonstrated via comparative dissolution testing for 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 4 mg dose strengths at 3 media pH (1.2, 4.5, and 6.8). The bioequivalence of the 3 mg brexpiprazole clinical Phase III tablets to the 3 mg brexpiprazole commercial tablets was established in a clinical trial.

The planned brexpiprazole tablets for marketing are 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg dose strengths. Dose strengths of 0.25 mg and 0.5 mg were developed to allow for dose titration or dose reductions as needed due to side effects or drug-drug interactions. Brexpiprazole tablets used in clinical trials (clinical tablets) are coated immediate release tablets identical to the tablets intended for commercial use with the exception of the composition of the coating material. Both clinical and commercial tablets were film coated to protect the drug substance from light. Long term stability studies (LTSS)/commercial brexpiprazole tablets were developed as film coated tablets with different colours for each tablet dose strength: 0.25 mg tablets were brown; 0.5 mg tablets, orange; 1 mg tablets, yellow; 2 mg tablets, green; 3 mg tablets, purple and 4 mg tablets, white. All clinical tablets were the same red colour.

2.4. Evaluator's commentary on the background information

Schizophrenia is a major cause of health burden to the community and current treatments with a clear ongoing unmet need. Current treatments are imperfect in terms of both efficacy and safety and further treatments are required. The hypothesis underlying the development of brexpiprazole is logical and worthy of investigation.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

A total of 28 clinical pharmacology trials have been performed as part of the brexpiprazole oral tablet development program. There are 15 trials in healthy subjects, 2 trials in specific populations (renal impaired, hepatic impaired), 4 trials in subjects with schizophrenia, 2 trials in subjects with MDD, and 1 trial in subjects with ADHD. 4 trials (3 trials with oral tablet and one trial with an oral solution formulation) have been conducted in an Asian country.

3.2. Paediatric data

One safety, tolerability and PK trial is ongoing, in adolescents (13 to 17 years old) with schizophrenia or other related psychiatric disorders.

3.3. Good clinical practice

All trials appear to have been performed in a manner consistent with Good Clinical Practice.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier appears adequate in the number of pharmacokinetic and pharmacodynamic studies. The dossier contains an adequate, although not excessive, number of trials in the single requested indication of schizophrenia. The trials in other indications (MDD and ADHD) were reviewed but only commented on in this evaluation as relevant to the requested indication of schizophrenia.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 1, shown below, lists the submitted pharmacokinetic studies and relevant subtopics covered.

Table 1: Submitted pharmacokinetic studies

PK topic	PK Subtopic	Study
PK in healthy adults	General PK - Single dose	331-07-201[a] Arm 1
	General PK - Multi dose	331-08-206[a]
	Absolute bioavailability	331-10-241[a]
	Bioavailability compared to oral solution	331-10-005[a]
	Bioequivalence † (Single dose)	331-10-243[b]
		331-10-245[b]
		331-13-209[b]
	Bioequivalence (Multi dose)	No studies
	Food effect	331-10-246[a]
		331-07-201[a] Arm 3
	Mass balance study	331-07-201[a] Arm 2
PK in special	Target population § (Single dose/Multi	331-10-001[c]

PK topic	PK Subtopic	Study
populations	dose)	
	Major depressive disorder	331-09-221
		331-08-205[c]
	Hepatic impairment	331-09-225[a]
	Renal impairment	331-09-226[a]
	Neonates/infants/children/adolescents*	331-10-233[c]
	Elderly	331-12-291[a]
		331-10-244[a]
	Other special populations: Japanese males	331-07-002[a]
	Other special populations: Korean males	331-KOA-0701[a]
Genetic/gender related PK	Males versus females	331-10-224
	CYP2D6 genotypes	331-12-208
PK interactions	Ketoconazole, ticlopidine, quinidine, lovastatin, bupropion, fexofenadine	331-08-207[a]
	Ketoconazole, ticlopidine, quinidine	331-08-208[a]
	Rifampin	331-09-224[a]
	Activated charcoal/sorbitol	331-10-239[a]
	Omeprazole	331-10-240[a]
	Rosuvastatin (Breast Cancer Resistance Protein (BCRP) Efflux Transporter)	331-12-207[a]
Population PK analyses	Mixed population (Healthy subjects and schizophrenia)	331-12-208[a]
	Target population (exposure response)	331-13-210[a]
	Schizophrenia (validation of population PK)	331-15-214[a]

Superscript following Study signify the following: a) indicates the primary PK aim of the study; b) bioequivalence of different formulations; c) subjects who would be eligible to receive the drug if approved for the proposed indication; * indicates ongoing study

No PK results were excluded from consideration.

The following lists the studies identified by the clinical evaluator in the submission with the relevant study title:

- 10 PK studies in healthy adults:
  - Study 331-07-201 Arm 1: Ascending single oral dose PK study of brexpiprazole in healthy volunteers
  - Study 331-07-201 Arm 2: Mass balance, metabolism, rate and extent of excretion of brexpiprazole
  - Study 331-07-201 Arm 3: The effect of food on the PK of brexpiprazole and its metabolites
  - Study 331-08-206: Multiple repeated dose PK study in healthy subjects
  - Study 331-10-241: An open label, 2 period trial of absolute bioavailability of brexpiprazole oral tablets in healthy subjects
  - Study 331-10-005: Open label, bioequivalence study of brexpiprazole oral solution and tablets in healthy male subjects
  - Study 331-10-243: An open label, randomised, 2 way, crossover trial of the bioequivalence of oral doses of brexpiprazole commercial and clinical trial tablets in healthy subjects
  - Study 331-10-245: An open label, randomised, 2 way, crossover trial of dose strength equivalency of oral doses of brexpiprazole long term stability tablets in healthy subjects
  - Study 331-13-209: An open label, randomised, 2 way, crossover trial of the bioequivalence of 3 mg oral doses of brexpiprazole commercial and clinical trial tablets in healthy subjects
  - Study 331-10-246: An open label, randomised, 2 way crossover trial of the effect of a high-fat meal on the PK of brexpiprazole in healthy subjects.
- 10 PK studies in special populations (including population PK):
  - Study 331-10-001: A repeated dose study of brexpiprazole in patients with schizophrenia[9]
  - Study 331-09-221: A double blind, placebo controlled study to assess the safety, tolerability, and PK of ascending high doses brexpiprazole as adjunctive therapy in the treatment of subjects with major depressive disorder
  - Study 331-08-205: A repeated dose study of brexpiprazole in patients with schizophrenia or schizoaffective disorder
  - Study 331-09-225: A single dose, parallel group, matched study evaluating the PK of brexpiprazole tablet in subjects with normal hepatic function and hepatic impaired subjects
  - Study 331-09-226: A single dose, open label, parallel group, matched trial evaluating the PK brexpiprazole tablets in subjects with normal renal function and renally impaired subjects
  - Study 331-10-233: A dose escalation trial to assess the safety, tolerability and PK of brexpiprazole in adolescents with schizophrenia or other related psychiatric disorders[10]

[9] Conducted in Japan
[10] Ongoing study

  - Study 331-12-291: An ascending dose study of brexpiprazole adjunctive therapy in elderly patients with major depressive disorder
  - Study 331-10-244: An open label, single dose trial of the tolerability, safety, and PK of orally administered brexpiprazole tablets in healthy adult and elderly male and female subjects
  - Study 331-07-002: An ascending single dose PK study in healthy male Japanese subjects
  - Study 331-KOA-0701: An ascending single dose PK study in healthy male Korean subjects.
- 2 studies on genetic/gender PK:
  - Study 331-10-244: An open label, single dose trial of the tolerability, safety, and PK of orally administered brexpiprazole tablets in healthy adult and elderly male and female subjects
  - Study 331-12-208: A drug interaction study to assess cytochrome P450 mediated inhibition of brexpiprazole metabolism in healthy subjects.
- 6 studies on PK interactions:
  - Study 331-08-207: Potential for cytochrome P450 mediated and P-glycoprotein mediated drug interactions with brexpiprazole in healthy subjects
  - Study 331-08-208: Drug interaction study to assess cytochrome P450 mediated inhibition of brexpiprazole metabolism in healthy subjects
  - Study 331-10-239: The effect of orally administered activated charcoal on the PK of brexpiprazole in healthy subjects
  - Study 331-09-224: Drug interaction study to assess the effect of rifampin on brexpiprazole metabolism in healthy subjects
  - Study 331-10-240: The Effect of Increased Gastric pH on the Pharmacokinetics of brexpiprazole
  - Study 331-12-207: Potential for inhibition of Breast Cancer Resistance Protein (BCRP) efflux transporter by brexpiprazole in healthy subjects
- 3 studies on population PK analyses:
  - Study 331-12-208: in a mixed population (healthy subjects and patients with schizophrenia)
  - Study 331-13-210: in the target population (exposure response)
  - Study 331-15-214: in patients with schizophrenia (validation of population PK)

4.2. Summary of pharmacokinetics

The overall PK characteristics of brexpiprazole were evaluated in a series of single and repeated dose studies conducted in healthy volunteers from different ethnic groups as well as in the patient population (schizophrenia) for which the drug is intended.

Brexpiprazole was highly bioavailable; the absolute bioavailability of a single 2-mg oral dose of was 95.1%. After single and multiple dose, once daily brexpiprazole administration, brexpiprazole and one major metabolite with minimal pharmacologic activity, DM-3411, are the major analytes with > 10% exposure in the systemic circulation. Administration of brexpiprazole with food (high-fat meal) or with gastric acid pH modifiers (antacids, H_2 receptor antagonists, and PPIs) did not affect the rate or extent of brexpiprazole absorption. After multiple dose (4 mg, 21 days) once-daily administration of brexpiprazole to patients with

schizophrenia, the metabolite to parent ratio for DM-3411 was 32.6% and was similar to that observed following single dose (2 mg) administration of brexpiprazole (34.9%) to healthy subjects. Brexpiprazole and DM-3411 PK parameters (C_{max} and AUC) increase in proportion to the dose administered after single (0.2 mg to 8 mg) and multiple dose (0.5 mg to 4 mg), once daily administration. Brexpiprazole and DM-3411 are highly protein bound (> 99% and 96%, respectively). Brexpiprazole protein binding is not affected by renal or hepatic impairment.

Hepatic clearance is the major route of elimination (46.0%) followed by renal excretion (24.6%). Brexpiprazole steady state is reached after 10 to 12 days of multiple, once daily oral administration of brexpiprazole (1 mg to 4 mg), and its accumulation ratio is 3.5 to 4.1 fold (based on AUC_t). No time dependency for brexpiprazole or DM-3411 PK parameters has been observed after multiple-dose, once-daily administration.

Brexpiprazole is highly metabolised, primarily by the hepatic CYP P450 isozymes, CYP3A4 and CYP2D6, and is not a substrate or inhibitor of any other CYP isozymes or transporters. Co-administration of brexpiprazole with strong inhibitors of CYP2D6 or CYP3A4 requires dose adjustment. It is recommended that patients with known poor CYP2D6 metabolism status also have a dose adjustment of the recommended maintenance dose. Co-administration of brexpiprazole in CYP2D6 PM subjects with CYP3A4 inhibitors or CYP2D6 EM subjects with strong CYP2D6 and CYP3A4 inhibitors (population PK model simulations) is expected to yield a 4.8 and 5.1 fold increase in brexpiprazole concentrations (AUC_t), respectively, warranting a dose reduction. Co-administration of a potent CYP3A4 inducer (rifampin, 600 mg once daily) with brexpiprazole resulted in a 73% lower brexpiprazole exposure (based on AUC_t). Consequently, when administered with strong CYP3A4 inducers adjustment of the dose of brexpiprazole may be warranted. No dose adjustment is recommended based on subject age, sex, race and body weight.

In patients with moderate or severe renal impairment (creatinine clearance (CLcr) < 60 mL/minute), lower doses of brexpiprazole are recommended. In patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) lower doses of brexpiprazole are recommended.

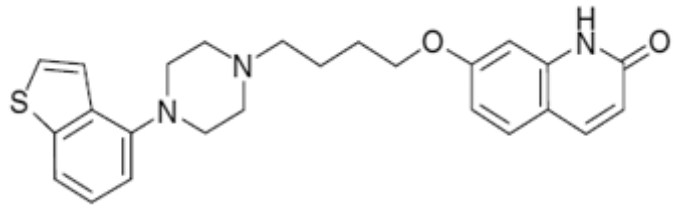
4.2.1. Physicochemical characteristics of the active substance

Brexpiprazole is 7-{4-[4-(1-benzothiophen-4-yl) piperazin-1-yl] butyloxy} quinolin-2(1H)-one. The empirical formula for brexpiprazole is $C_{25}H_{27}N_3O_2S$, and its molecular weight is 433.57. Brexpiprazole is non-hygroscopic and occurs as white to off-white crystals or crystalline powders. It has a melting point of 183°C and is physically and chemically compatible with commonly used pharmaceutical excipients. At 25°C, the solubility of brexpiprazole is 0.0024 mg/mL in water and 1.2 mg/mL in 99.5% ethanol. The pKa of brexpiprazole was determined as 7.8.

Brexpiprazole has no asymmetric centre or axis and is not optically active. The partition coefficient of brexpiprazole between n-octanol and Britton-Robinson buffer at approximately neutral pH (7.06) was >4 (Log P).

The chemical structure of brexpiprazole is as shown in Figure 1.

Figure 1: Chemical structure of brexpiprazole



4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Single oral doses of brexpiprazole from 0.2 mg to 8 mg are relatively rapidly absorbed with a T_{max} range of 1 to 8 hours reported in the clinical studies. A median T_{max} value of 4 hours was reported from a pooled analysis of brexpiprazole PK.

Administration of activated charcoal with sorbitol 1 hour after administration of a single 2 mg oral dose of brexpiprazole resulted in 5% to 23% lower C_{max} and 31% to 39% lower AUC_{∞} when compared with historical data (Study 331-10-239). In the management of overdose administration of charcoal with sorbitol may be beneficial by partially preventing brexpiprazole absorption.

Sites and mechanism of absorption

The mechanism of absorption is likely to be simple diffusion as in vitro studies with efflux transporters does not indicate that brexpiprazole is a substrate for such transporters as MDR1 (P-gp) and BCRP. Although the aqueous solubility of brexpiprazole is pH dependent (high solubility at acidic pH and decreased solubility at neutral and alkaline pH) studies with modifiers of gastric acid secretion do not affect brexpiprazole rate or extent of absorption (discussed further below).

4.2.2.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of brexpiprazole was available from a single study in healthy volunteers (Study 331-10-241). Each subject received a 0.25 mg IV solution of brexpiprazole infused over the course of 1 hour followed by a 2 mg brexpiprazole tablet administered as a single oral dose with a 9 day washout period between doses. Subjects received their assigned brexpiprazole dose after at least 8 hours of fasting. Due to the administration of a relatively low dose of brexpiprazole IV infusion (0.25 mg), 11/16 subjects had brexpiprazole plasma concentrations that were below the quantitation limit (BQL) at one or more time points in the terminal elimination phase of the brexpiprazole plasma concentration-time profile. This resulted in a possible underestimation of brexpiprazole $t_{1/2,z}$ after IV infusion compared with that of the oral dose. The result of the dose adjusted AUC geometric means and F with 90% confidence intervals (CI) for brexpiprazole was 0.951 (0.897, 1.009). The mean absolute bioavailability of brexpiprazole oral tablets was 95.1%.

Bioavailability relative to an oral solution or micronised suspension

Study 331-10-005, a single dose, crossover study examined the bioequivalence of an oral solution and brexpiprazole tablets in healthy male Japanese subjects. Each subject received either one 4 mg tablet or 4 mL of oral solution (1 mg/1 mL) of brexpiprazole on Days 1 and 31 after 10 hours of fasting. The GMR and 90% CI for brexpiprazole AUC_t and AUC_{∞} were within the 0.8 to 1.25 bioequivalence, but the GMR for brexpiprazole Cmax was 1.2236 and the 90% CI was 1.1293 to 1.3259, which was not within the bioequivalence range. Thus, the brexpiprazole oral solution was not strictly bioequivalent to the tablet.

Bioequivalence of clinical trial and market formulations

Study 331-13-209, a single pivotal bioequivalence study was conducted as a single centre, open label, 2 way crossover trial in 31 healthy male and female subjects (28 completed both treatments). The objective of the trial was to demonstrate the bioequivalence of the 3 mg Phase III clinical tablets to the 3 mg LTSS/commercial tablets. Each brexpiprazole tablet was administered after at least 8 hours of fasting. A 21 day washout period was utilised between phases. These were within bioequivalence limits of 0.8 to 1.25. Therefore, the 3 mg LTSS/commercial tablet is bioequivalent to the 3 mg Phase III clinical tablet. This study was further used to support the granting of a biowaiver for the LTSS/commercial tablets; the

manufacturing scale for the 3 mg Phase III clinical tablets used in this study was the same as that of the LTSS/commercial tablets.

An additional pivotal bioequivalence study (Study 331-10-243) was conducted in 100 healthy male and female subjects (Arm 1 = 49 subjects; Arm 2 = 51 subjects completed). Arm 1 of the trial evaluated the bioequivalence of one 3 mg LTSS/commercial tablet to 3 x 1 mg Phase II clinical tablets (48 subjects completed), and Arm 2 of the trial evaluated the bioequivalence of one 2 mg LTSS/commercial tablet to 2 x 1 mg Phase II clinical tablets (48 subjects completed). All brexpiprazole doses were administered after at least 8 hours of fasting. The GMRs and 90% CIs for both the 2 mg and 3 mg LTSS/commercial tablets versus Phase II clinical tablets were within the bioequivalence limits of 0.80 to 1.25. Thus the 3 mg LTSS/commercial tablet is bioequivalent to 3 x 1 mg Phase II clinical tablets and the 2 mg LTSS/commercial tablet is bioequivalent to 2 x 1 mg Phase II clinical tablets.

Bioequivalence of different dosage forms and strengths

A single centre, open label, randomised, 2 way, crossover trial was performed in 30 healthy male and female subjects (28 completed) to assess the dose strength equivalency of 4 x 1 mg LTSS/commercial tablets with 1 x 4 mg LTSS/commercial tablet (Study 331-10-245). Subjects were administered brexpiprazole doses after an overnight fast of at least 10 hours. The ratios were within the 0.8 to 1.25 strict bioequivalence limits. Thus the 4 x 1 mg and 1 x 4 mg LTSS/commercial tablets are dose strength equivalent and therefore interchangeable.

Bioequivalence to relevant registered products

Not applicable.

Influence of food

The effect of food on the rate and extent of absorption of brexpiprazole was evaluated in a pivotal food effect trial where 4 mg long term stability studies/commercial brexpiprazole tablets (the highest intended marketed dose) was administered to healthy volunteers (Study 331-10-246). Mean PK parameters for brexpiprazole and the major metabolite, DM-3411 were similar between the 2 states. The geometric mean ratios and 90% CIs for brexpiprazole C_{max}, AUC_t, and AUC_∞ following were calculated for the fed (high fat) versus the fasted state. The 90% CI for the ratios were within the bioequivalence limits of 0.8 to 1.25.

A second study compared 2 mg Phase II clinical tablets administered to healthy subjects in a fasted or fed (high fat) state (Study 331-07-201). PK parameters for brexpiprazole and DM-3411 were similar between the 2 conditions. The GMRs and 90% CI for the ratio of C_{max}, AUC_t, and AUC_∞ were with the accepted bioequivalence limits for brexpiprazole.

Based on the results of both studies the rate or extent of absorption of brexpiprazole was not affected by administration with a high fat meal. In the pivotal Phase III safety and efficacy trials food was not restricted with respect to brexpiprazole dosing. Both studies were adequately designed but the small number of subjects (n = 8) enrolled and completed in the second trial may have lacked statistical power to demonstrate differences should they have existed. Nevertheless, the data satisfactorily demonstrate the lack of effect of a high fat meal on the extent and rate of absorption of brexpiprazole.

Dose proportionality

The dose proportionality of brexpiprazole PK was investigated in ascending single and multiple dose studies in healthy volunteers. A single ascending dose trial of brexpiprazole was conducted in 7 cohorts of 8 healthy subjects (6 active and 2 placebo) (Study 331-07-201, Arm 1). Subjects received 0.2 to 8 mg oral doses of brexpiprazole following a minimum 10 hour fast. The 6 mg dose was the Minimum Tolerated Dose (MTD). PK parameters for brexpiprazole and metabolite DM-3411, C_{max}, AUC_t, and AUC_∞, increased proportionally with dose.

Once daily, multiple dose administration of brexpiprazole was evaluated in healthy subjects (Study 331-08-206). The trial included 3 sequential arms: Arm 1 evaluated 0.5 mg and 1 mg doses of brexpiprazole administered as a single dose (followed by a 96 hour washout) and then multiple, once-daily doses (14 days) in 2 cohorts of 12 subjects (22 completed). Arm 2 evaluated multiple, once-daily rising doses in 16 healthy subjects. Arm 3 evaluated an alternative titration schedule after achieving the MTD of 2 mg. The titration schedule for this arm was 0.5 mg for 2 days, 1 mg for 2 days, 2 mg for 2 days, and 3 mg of brexpiprazole once daily or placebo for 14 days. The MTD for multiple, once daily dosing with brexpiprazole in healthy male subjects was 2 mg. For brexpiprazole and its major metabolite, DM-3411, the C_{max} and AUC increased proportionally to the dose administered after single dose (0.5 mg to 3 mg) and multiple, once daily administration (0.5 mg to 2 mg).

A multiple ascending dose trial was performed in 48 subjects with a diagnosis of schizophrenia or schizoaffective disorder (Study 331-08-205). Details of the study are described under pharmacokinetics in the target population. For brexpiprazole and DM-3411, the C_{max} and AUC increased proportionally to the dose administered after multiple, once daily doses of 1 mg to 12 mg of brexpiprazole. In studies using multiple dose regimens in patients with major depression (Study 331-09-221) or attention deficit disorder (Study 331-09-220) dose proportionality was also established. Brexpiprazole and DM-3411 plasma PK parameters increased proportionately in the dose range of in the dose ranges of 1.5 mg to 2 mg and 3 mg to 4 mg in patients with MDD and from 3 mg to 4 mg once daily in patients with ADHD receiving stimulants concomitantly.

Based on a pooled analysis of the PK data, brexpiprazole and DM-3411 PK parameters (C_{max} and AUC) are dose proportional after single (0.2 mg to 8 mg) and multiple dose (0.5 mg to 4 mg (highest recommended dose)) once daily brexpiprazole administration.

Bioavailability during multiple dosing

The accumulation ratio of brexpiprazole following repeated single daily doses (1 mg to 2 mg) ranged from 3.44 fold to 4.43 fold (based on C_{max} and AUC) (Study 331-08-206). A similar accumulation ratio of 3.5 to 4.1 fold (based on $AUC_{0\text{-}24h}$) for brexpiprazole was noted after multiple once daily dosing (1 mg to 4 mg) in patients with schizophrenia or schizoaffective disorder (Study 331-08-205). Less than 2 fold higher brexpiprazole exposure was observed when subjects received CYP2D6 inhibitor antidepressants (fluoxetine and paroxetine) with half the dose of brexpiprazole (1.5 mg versus 3 mg and 2 mg versus 4 mg) (Study 331-09-221).

Effect of administration timing

In the single and repeated dose PK studies brexpiprazole was usually administered in the mornings after an overnight fast. No studies were conducted to examine the possibility of diurnal variation in PK parameters. Given that the half-life of elimination of brexpiprazole and its metabolite generally exceeds 40 hours it would seem unlikely that night time versus daytime administration will lead to clinically significant alterations in PK.

4.2.2.3. Distribution

Volume of distribution

Brexpiprazole is extensively distributed to tissues. The volume of distribution determined after a single dose (0.25 mg, 1 hour IV infusion) was 1.56 ± 0.418 L/kg (Study 331-10-241). The apparent volume of distribution determined after an oral dose of 2 mg in the same study was 2.2 ± 0.72 L/kg. After an oral solution of 4 mg the volume of distribution was 89.2 ± 28.1 L while after the same oral dose it was 98.7 ± 50.3 L (Study 331-10-005).

Plasma protein binding

The protein binding of ^{14}C-brexpiprazole (mouse, rat, rabbit, dog, monkey and human sera) and DM-3411 (mouse, rat, monkey, and human sera) was determined in vitro using an equilibrium dialysis method. Brexpiprazole and DM-3411 were highly protein bound in all tested species:

more than 99% for brexpiprazole and more than 90% (96% in human serum) for DM-3411. The protein binding of brexpiprazole to human albumin, human α1-acid glycoprotein, and human γ-globulin were evaluated in vitro. Brexpiprazole bound predominantly to albumin and α1-acid glycoprotein in human serum.

Brexpiprazole plasma protein binding (pre-dose plasma samples) was assessed in 3 clinical pharmacology trials: Studies 331-07-201, 331-09-225 and 331-09-226. In these studies brexpiprazole was highly protein bound in human plasma (> 99%), and its binding was not affected by the degree of hepatic or renal impairment. Furthermore, based on the results of in vitro studies, brexpiprazole is bound predominantly to albumin and α1-acid glycoprotein in human serum and its protein binding is not affected by warfarin, diazepam or digitoxin.

Erythrocyte distribution

No data reported.

Tissue distribution

The distribution of brexpiprazole was determined in the pre-clinical pharmacology studies following oral administration of ^{14}C-brexpiprazole. No studies performed in human volunteer trials. Of particular note in these pre-clinical studies were the following observations:

- highest concentrations of radioactivity was found in the intestines, stomach and liver
- concentrations in regions of the brain were lower than in plasma and were quantifiable until 24 hours post-dose in males and 8 hours post-dose in females
- in pigmented rats the highest exposure were in the eyeball and pigmented skin suggesting 14C-brexpiprazole had an affinity for melanin
- no radioactivity was found in the amniotic fluid of pregnant rats
- levels of radioactivity in the foetuses were similar to or lower than those in the blood of the dams
- ratio of milk to maternal blood concentrations of radioactivity ranged from 1.0 to 1.7 over 24 hours of measurement.

These data suggest to the evaluator that brexpiprazole might be further investigated in longer term studies for retinal pigmentation or deposits in patients (similar to what occurs with thioridazine?).[11] The evaluator suggests that the drug should be avoided in breast feeding as these ratios appear to be high compared to other antipsychotics.

4.2.2.4. Metabolism

Interconversion between enantiomers

Brexpiprazole has no isomeric forms.

Sites of metabolism and mechanisms/enzyme systems involved

Based on in-vitro metabolism studies (human liver S9, CYP isozyme specific inhibitors, recombinant human cytochrome P450s), the metabolism of brexpiprazole is primarily mediated by CYP3A4 with partial contribution from CYP2D6 and FMO3. Other enzymes that showed relatively minimal activity were CYP1A1, CYP2B6, and CYP2C19. Based on results of drug-drug interaction trials, brexpiprazole is primarily metabolised by CYP3A4 and CYP2D6. The contribution of CYP3A4 and CYP2D6 metabolic pathways to the total apparent clearance of brexpiprazole is estimated to be 46.7% and 43.3% respectively, with the balance (around 10%) attributed to other minor pathways.

[11] See Section 12 for the evaluator's comment's following the response to clinical questions, below.

Non-renal clearance

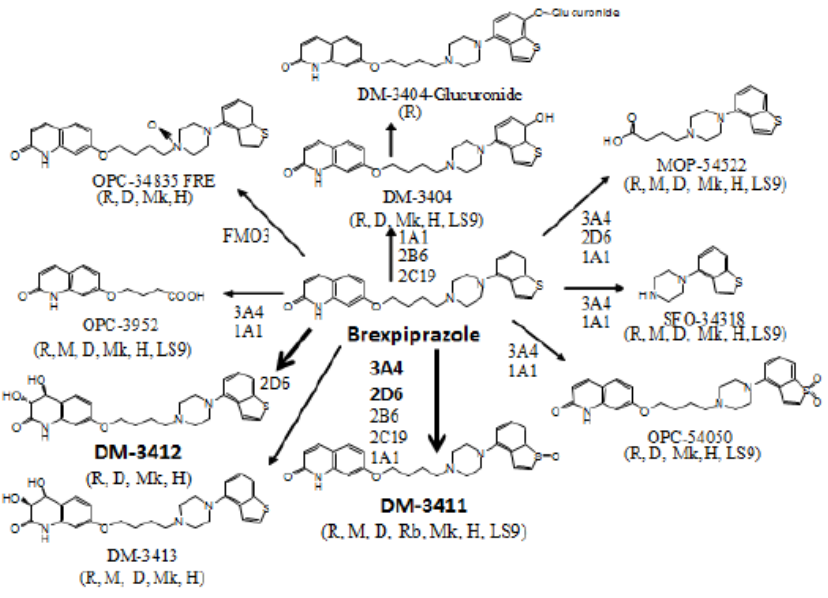
After a single oral dose of ^{14}C-brexpiprazole solution (2 mg, < 270 nCi), mean radioactivity recovery in faeces and urine was 46.0% and 24.6% of the oral brexpiprazole dose administered, indicating that brexpiprazole is primarily eliminated via hepatic metabolism followed by renal elimination. Less than 1% of an oral dose of brexpiprazole was excreted unchanged in urine; 14% was recovered unchanged in the faeces (Study 331-07-201, Arm 2.

Metabolites identified in humans: active and other

The metabolism of brexpiprazole (including metabolite profiling of plasma, urine, and faeces) has been investigated in a single dose mass balance trial ((Study 331-07-201, Arm 2) as well as in multiple dose trials). A total of 7 oxidative metabolites of brexpiprazole (DM- 3411, DM-3412, OPC-3952, SFO-34318, OPC-54050, MOP-54522, and OPC-34835) have been identified, and the human exposure to all of these metabolites has been investigated in single and multiple dose trials. After single dose (2 mg) administration of brexpiprazole (Trial 331-07-201, Arm 2), metabolite DM-3411 (34.9% of brexpiprazole exposure) was the most abundant metabolite in plasma followed by metabolite DM-3412 (6.39% of brexpiprazole exposure). After multiple dose, once daily administration of brexpiprazole (4 mg for 21 days in subjects with schizophrenia), metabolite DM-3411 (32.6% of brexpiprazole exposure) remained the most abundant metabolite observed in plasma, and metabolite DM-3412 (5.76% of brexpiprazole exposure) was the next most abundant metabolite (Trial 331-08-221). Other identified metabolites detected in plasma and urine samples were either not present or present in few subjects at consistently low concentrations across clinical trials. The metabolite to parent ratio of DM-3411 and DM-3412 metabolites was similar across trials and following single and multiple dose administration.

Figure 2, shown below, demonstrates the biotransformation pathways and subsequent metabolites proposed in humans and animals.

Figure 2: Proposed biotransformation pathways of brexpiprazole in animals and humans



Note: The major in vivo human pathways are shown in bold.

Pharmacokinetics of metabolites

Single and multiple dose once daily brexpiprazole administration results in the formation of multiple metabolites. However only brexpiprazole itself and DM-3411 are present to any significant extent in the systemic circulation. The metabolite to parent ratio of DM-3411 following 2 mg single and 4 mg multiple dose administration (21 days) was 34.9% and 32.6% of

brexpiprazole exposure (AUC), respectively, and this ratio was similar across all doses and patient populations in the clinical pharmacology trials. In all clinical pharmacology trials the PK of DM-3411 has been reported. After a single oral dose of 4 mg brexpiprazole in healthy volunteers DM-3411 maximum concentrations in plasma were achieved between 12 to 24 hours (Study 331-10-246).[12] The plasma elimination half-life was around 90 hours, similar to brexpiprazole. These parameters were little affected by administration with food (Study 331-07-201 Arm 3). After repeated doses the time to maximum concentration was considerably shorter and there was around 4 times the accumulation of the metabolite (Study 331-08-206).

The DM-3411 metabolite is not considered to contribute to the therapeutic effects of brexpiprazole due to its minimal pharmacologic activity at D_2/D_3 and 5-$HT_{2A}/_{2B}$ receptors with 9 to 17 times and 2 to 5 times lower binding affinity (in vitro) than brexpiprazole, respectively, and its poor brain penetration based on a study in rats administered high doses of radio labelled brexpiprazole. The pharmacologic activity of other metabolites of brexpiprazole has not been investigated; however, it is unlikely that these metabolites contribute to any pharmacological effects due to their minimal concentrations.

4.2.2.5. Excretion

Routes and mechanisms of excretion

Hepatic clearance is the major route of elimination of brexpiprazole followed by renal clearance.

Mass balance studies

After a single 2 mg oral dose of ^{14}C-brexpiprazole solution (< 270 nCi), mean recovery in faeces and urine was 46.0% and 24.6% of the oral brexpiprazole dose administered, respectively (total urinary and faecal radioactivity 71.1%) (Study 331-07-201, Arm 2). The percentages of unchanged brexpiprazole recovered in urine and faeces constitute less than 1% and 14% of the dose administered, respectively (Study 331-07-201, Arm 2).

Renal clearance

Following a 0.25 mg brexpiprazole 1 hour IV infusion, brexpiprazole clearance was 19.8 (± 10.0) mL/h/kg (Study 331-10-241) and was comparable to the observed apparent clearance after multiple dose, once daily (4 mg, pooled analysis) oral administration of brexpiprazole (19.8 ± 11.4 mL/h/kg). The population PK estimate of brexpiprazole apparent clearance after oral administration was 1.65 L/h, which is in line with its reported clearance after intravenous administration (1.60 L/h, assuming a typical body weight of 80.9 kg from the population PK analysis).

4.2.2.6. Intra and inter individual variability of pharmacokinetics

The inter and intrasubject variability ranges of brexpiprazole C_{max} were 19.0% to 32.0% and 11.9% to 16.0% respectively. For AUC_∞ the corresponding ranges were 40.0% to 55.0% intersubject and 10.8% to 14.6% intrasubject. The range for intersubject variability is based on pooled analysis of data at different administered brexpiprazole doses, while the range for intrasubject variability is based on the data from 3 pivotal bioequivalence trials (Studies 331-10-243, 331-10-245 and 331-13-209).

4.2.3. Pharmacokinetics in the target population

Study 331-08-205 was a multicentre, randomised, double blind, comparator controlled multiple ascending dose trial was conducted in 48 subjects with a diagnosis of schizophrenia or schizoaffective disorder. The primary objective was to determine the tolerability, safety, and steady state PK parameters of brexpiprazole and its metabolites after once daily administration (14 days) of brexpiprazole. Dosing was conducted in 6 cohorts of 8 subjects (6 active and 2

[12] Note: this is for the 'fed' treatment. The 'fasted' treatment T_{max} range is 2-24 h

control subjects). The ascending doses were 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg for the active subjects and 1 mg for the control subjects. Blood samples for PK analysis were drawn pre-dose daily from Day 1 to Day 14, and then until 168 hours after the last dose. 44 subjects completed the trial. Plasma samples were assayed for brexpiprazole and 7 metabolites (DM-3411, OPC-3952, OPC-54050, OPC-34835, DM-3412, MOP-54522, SFO-34318) using a specific validated HLPC/MS/MS assay. Based on inspection of mean pre-dose brexpiprazole concentrations (Day 2 to Day 14), steady state (1 mg to 4 mg) was reached after 10 to 12 days of dosing. For brexpiprazole and its major metabolite, DM-3411, the C_{max} and AUC increased proportionally to the dose administered after multiple, once daily doses. The brexpiprazole accumulation ratio was 3.5 to 4.1-fold (based on AUC_{0-24h}) after multiple, once daily dosing (1 mg to 4 mg). At steady state, DM-3411 was the most abundant metabolite, with its AUC_{0-24h} (pooled analysis of all doses) representing 42.2% of the AUC_{0-24h} of brexpiprazole.

Improvement symptoms were measured by the PANSS Total Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score, and CGI Severity of Illness Score. The small sample size and limited treatment duration preclude definitive efficacy conclusions, as this was primarily a PK trial. Subjects in all dose groups maintained a stable symptom profile after treatment with brexpiprazole.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Study 331-09-225 was a multicentre, open label, single dose, parallel arm trial conducted in 45 subjects to assess the effect of hepatic function on brexpiprazole kinetics. Subjects with normal hepatic function (n = 23) were matched for age (± 5years), gender and weight (± 15%) to subjects with varying degrees of hepatic impairment based on the Child-Pugh Classification scheme (8 subjects with mild, 8 subjects with moderate, and 6 subjects with severe hepatic impairment). Each subject received 2 mg of brexpiprazole in the fasted state. Protein binding was determined from a pre-dose blood sample collected from each subject and analysed using a rapid equilibrium dialysis device. No consistent trend for the effect of degree of hepatic impairment on brexpiprazole AUC was evident. There was a trend for a decrease in brexpiprazole C_{max} with increasing degree of hepatic impairment, most notably in severely impaired subjects. This suggests a reduction of brexpiprazole bioavailability with increasing degree of hepatic impairment. An increased $t_{1/2}$ for brexpiprazole of similar in magnitude (1.5 to 2-fold) across each hepatically impaired group compared to their matched controls was noted. There was no specific trend of the effect of degree of hepatic impairment on $t_{1/2}$ identified. Protein binding did not differ significantly between groups and ranged from 99.1% to 99.65%.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

The effect of renal impairment on the PK parameters of brexpiprazole following a single 3 mg oral dose was investigated in subjects with normal renal function (estimated creatinine clearance (CLcr) > 80 mL/min) and those with severe renal impairment (estimated CLcr < 30 mL/min and not requiring dialysis) (Study 331-09-226). Brexpiprazole exposure (AUC_{∞}) was increased by 68.5% (ratio: 1.685, 90% CI: 1.246, 2.277) compared with matched controls. On the other hand, brexpiprazole C_{max} was unchanged. An increase in brexpiprazole renal clearance was observed in subjects with severe renal impairment versus matched normal subjects (0.118 mL/h/kg versus 0.0439 mL/h/kg). Of note, the urinary clearance represents only a fraction of the overall clearance, even in subjects with severe renal impairment (around 0.3%). Brexpiprazole was highly protein bound in the pre-dose plasma samples, with mean value of 99.52% and 99.51% for the matched normal and severely renally impaired subjects, respectively.

4.2.4.3. Pharmacokinetics according to age and gender

An open label, single dose trial of brexpiprazole was conducted in healthy adult (18 to 45 years) and 24 elderly (≥ 65 years) subjects (Study 331-10-244). After administration of a single 2-mg

dose of brexpiprazole exposure (C_{max} and AUC_{∞}) was similar in both age groups, and brexpiprazole bodyweight adjusted apparent clearance (CL/F/Weight) was found to be similar regardless of age. For males, the GMR and 90% CIs for C_{max} and AUC_{∞} were 0.817 (90% CI: 0.672 to 0.993) and 1.048 (90% CI: 0.742 to 1.480), respectively. For females, the GMR and 90% Cis for C_{max} and AUC_{∞} were 0.880 (90% CI: 0.724 to 1.070) and 1.100 (90% CI: 0.797 to 1.518), respectively. Based on the limited data in this trial, the apparent higher brexpiprazole exposure in female subjects was deemed to be weight related rather than metabolism or elimination related because male and female subjects exhibited comparable brexpiprazole mean $t_{1/2,z}$ and weight adjusted mean apparent clearance.

A repeated, once daily, ascending dose trial (4 days titration plus 14 fixed days) was conducted in 2 cohorts of elderly subjects (70 to 85 years) with MDD (Study 331-09-221). Brexpiprazole (3 mg or 4 mg) was administered as adjunct treatment to non-CYP2D6 inhibitor antidepressants: escitalopram, sertraline, desvenlafaxine, and venlafaxine. The second cohort received brexpiprazole (1.5 mg or 2 mg) as adjunct treatment to known CYP2D6 inhibitor antidepressants: fluoxetine or paroxetine. Brexpiprazole and metabolite DM-3411 plasma PK parameters increased with increasing doses of brexpiprazole following once daily administration of brexpiprazole in the dose ranges of 1.5 mg to 2 mg and 3 mg to 4 mg in patients with MDD receiving antidepressants concomitantly. Less than 2-fold higher brexpiprazole exposure was observed when subjects received CYP2D6 inhibitor antidepressants (fluoxetine and paroxetine) with half the dose of brexpiprazole (1.5 mg versus 3 mg and 2 mg versus 4 mg).

Steady state plasma concentrations of brexpiprazole and DM-3411 were determined in 2 sequential cohorts of elderly (70 to 85 years old, inclusive) subjects with MDD (Study 331-12-291).[13] Subjects in Cohort 1 received either brexpiprazole or placebo at a starting dose of 0.5 mg/day for 7 days, which was then titrated upward to 1 mg/day for 7 days and then administered at a fixed dose of 2 mg/day for 14 days followed by 3 mg/day for 14 days. Subjects in Cohort 2 received brexpiprazole or placebo at a starting dose of 0.5 mg/day for 7 days, which was then titrated upward to 1 mg/day for 7 days and then administered as a fixed dose of 3 mg/day for 14 days. Brexpiprazole and DM-3411 plasma concentrations after once daily administration of a 3 mg dose for 14 days were comparable to the plasma concentrations observed in adult subjects with MDD who participated in previous clinical trials.

Based on the results of the population PK analysis, age was identified as a statistically significant covariate on V_c/F; the effects of age within the fifth and ninety fifth percentiles (23 years and 61 years) of the population were -19% to +14%. No dose adjustment is recommended based on age.

Administration of a single 2 mg dose of brexpiprazole to male and female subjects (stratified by age: 18 to 45 years and ≥ 65 years), female subjects had about 40% to 50% higher brexpiprazole exposure (C_{max} and AUC_{∞}) than male subjects in both adult and elderly groups. Based on the results of the population PK analysis, female subjects were predicted to have 22% smaller V_c/F and 20% lower brexpiprazole apparent CL/F, corresponding to an estimated 25% higher brexpiprazole exposure than males. No dose adjustment is recommended based on sex.

4.2.4.4. Pharmacokinetics related to genetic factors

Based on the results of the population PK analysis, CYP2D6 metabolism status was identified as a covariate for brexpiprazole apparent clearance with impact on brexpiprazole exposure; CYP2D6 PM subjects exhibited 47% higher exposure (AUC_t) to brexpiprazole compared with CYP2D6 EM subjects. To account for higher brexpiprazole concentrations in CYP2D6 PM patients a dose adjustment to one half (50%) of the label-recommended maintenance dose is recommended in patients with known poor CYP2D6 metabolism status.

[13] The sponsor commented that brexpiprazole was adjunct treatment to antidepressant therapy (ADT).

4.2.4.5. Pharmacokinetics in other special populations/with other population characteristics

The population PK analysis did not identify race as a covariate in brexpiprazole PK parameters. There was no clinically meaningful difference in the incidence of AEs due to race. No dose adjustment is recommended based on race.

Based on in vitro studies utilising human liver enzymes, brexpiprazole was not identified as a substrate for CYP1A2, the CYP isozyme involved in the metabolism of nicotine. Smoking should therefore have no effect on the PK parameters of brexpiprazole, and no brexpiprazole dose adjustment is recommended based on patient smoking status.

Based on the results of the population PK analysis, body weight was found to have a statistically significant effect on brexpiprazole V_c/F; the effect of weight within the fifth and ninety fifth percentiles (53.5 kg and 118.6 kg) of the population was less than 20% (-11% to +14%). No dose adjustment is recommended based on body weight.

4.2.5. Population pharmacokinetics

4.2.5.1. Population PK analysis

A population PK model was developed to describe brexpiprazole PK after single dose and multiple dose, once daily oral tablet administration, perform full stepwise covariate method (SCM) analyses to identify and quantify significant covariate effects on brexpiprazole population PK parameters, identify relationships between brexpiprazole exposure and selected safety endpoints and develop exposure efficacy response models to quantify placebo and brexpiprazole related effects on efficacy. The final population PK model was utilised to simulate brexpiprazole exposure in populations of clinical interest. Data from a total of 12 clinical trials were included in the analysis, which consisted of 5 Phase I trials (Studies 331-07-201, 331-09-221, 331-09-225, 331-09-226 and 331-10-244), 3 Phase II trials in subjects with MDD and schizophrenia (Studies 331-08-211, 331-09-222 and 331-07-203) and 4 Phase III trials in subjects with MDD or schizophrenia (Studies 331-10-227, 331-10-228, 331-10-230 and 331-10-231). A total of 2654 PK samples from 154 healthy subjects, 3111 PK samples from 1140 subjects with MDD, and 5072 PK samples from 1247 subjects with schizophrenia (2541 total subjects) were available for population PK analysis. The population consisted of 73.5%, 17.2%, and 5.9% Caucasian, African-American, and Asian, respectively, with the balance being other races. There were 70 (3.0%), 566 (24.0%), 911 (38.7%), 33 (1.4%) and 777 (33.0%) subjects classified as CYP2D6 PM, CYP2D6 intermediate metabolisers, CYP2D6 EM, CYP2D6 ultra-rapid, and missing/inconclusive subjects, respectively based on CYP2D6 genotype testing (Study 331-12-208).

Plasma brexpiprazole concentration-time profiles after single dose administration showed a biphasic decline, suggesting a 2 compartment disposition model. Evaluation of various structural and inter-individual variability models resulted in a base population PK model that included a first order absorption and a 2 compartment disposition model with inter-individual variability on apparent clearance (CL/F), apparent volume of distribution in the central compartment (V_c/F), and absorption rate constant (ka). The following statistically significant covariate-parameter effects were retained in the final population PK model:

- Strong CYP2D6 adjunctive inhibitor ADTs (fluoxetine and paroxetine) on CL/F
- Non-protocol mandated moderate/strong CYP2D6/CYP3A4 concomitant medications on CL/F
- Poor CYP2D6 metabolic status on CL/F
- Intermediate CYP2D6 metabolic status on CL/F
- Ultra-rapid CYP2D6 metabolic status on CL/F

- Female sex on CL/F and V_c/F
- Age on V_c/F
- Body Weight on V_c/F
- Scaling factor of MDD Phase II/III versus all other subjects (F1).

In the final population PK model, the typical values for CL/F, apparent inter-compartmental clearance (Q/F), V_c/F, apparent peripheral volume of distribution (V_p/F), and ka were estimated to be 1.65 L/hr, 0.701 L/hr, 105 L, 28.4 L, and 0.635 h^{-1}, respectively (Study 331-12-208). An intermediate SCM search identified a statistically significant covariate effect for the MDD patient population on CL/F, whereby this population showed a higher CL/F. This difference was attributed to lack of adherence to the treatment in the MDD patients as they were treated on an outpatient basis. Standard diagnostic goodness-of-fit plots indicated that the final population PK model had no significant biases and represented an adequate fit to the data.

At the fifth to ninety fifth percentiles of the population, values of the effect of age and weight on brexpiprazole V/F were estimated to be less than 20% (-19% to +14% and -11% to +14%, respectively).

In CYP2D6 PM subjects, ultra-rapid and intermediate CYP2D6 metaboliser subjects, CL/F was estimated to be -32%, +18%, and -20% than the value estimated for CYP2D6 EM subjects, corresponding to a +47%, -21%, and +25% change in brexpiprazole exposure (AUC_t) in these subjects, respectively (Study 331-12-208). Administration of adjunctive strong CYP2D6 inhibitor antidepressants (fluoxetine and paroxetine) with brexpiprazole was estimated to be accompanied by a 35% lower brexpiprazole CL/F, leading to 53% higher brexpiprazole exposure (AUC_t). This is borne out by the study examining the effect of quinidine on brexpiprazole PK (discussed in the following section).

Estimated glomerular filtration rate (eGFR) as a measure of kidney function was applied on the final population PK model and was utilised to estimate brexpiprazole exposure (AUC_t) in subjects with mild (lower limit of eGFR of 60 mL/min), moderate (lower limit of eGFR of 30 mL/min), or severe (lower limit of eGFR of 15 mL/min) renal impairment. Brexpiprazole exposure was estimated to increase by up to 5%, 13%, or 22%, respectively.

Population PK analysis was utilised to simulate the effect of co-administration of brexpiprazole with CYP2D6 and/or CYP3A4 inhibitors in the following populations of interest:

- CYP2D6 EM subjects administered brexpiprazole and strong CYP3A4 inhibitors
- CYP2D6 PM subjects administered brexpiprazole and strong CYP3A4 inhibitors
- CYP2D6 EM subjects administered brexpiprazole and strong CYP2D6 (fluoxetine and paroxetine) and strong CYP3A4 inhibitors (dual inhibition).

In CYP2D6 PM subjects, ultra-rapid and intermediate CYP2D6 metaboliser subjects, CL/F was estimated to be -32%, +18% and -20% than the value estimated for CYP2D6 EM subjects, corresponding to a +47%, -21% and +25% change in AUC_t in these subjects, respectively. Co-administration of strong inhibitors of CYP2D6 (fluoxetine, paroxetine) in CYP2D6 EM subjects reduced the CL/F by 35%, corresponding to a 53% increase in AUC_t. In subjects with schizophrenia, a relationship between brexpiprazole concentrations and changes in PANSS scores from Baseline over placebo was identified using an E_{max} model with a random effect on E_{max} but not on EC_{50}. Based on simulation, the estimated median brexpiprazole trough concentrations achieved by daily brexpiprazole administration of; 1 mg was above the EC_{50}, 2 mg was at the EC_{80}, and 4 mg was well above the EC_{80} values. In subjects with schizophrenia, no exposure-dependent increase in insomnia, percent change in body weight, or akathisia (with the possible exception of C_{max} in the highest third for akathisia) was observed during the length of the short term safety and efficacy trials (42 days) of treatment with brexpiprazole. Supportive

population PK analysis was conducted for validation of the population PK model. An exposure-efficacy analysis (Study 331-13-210) was also conducted based on the efficacy data from the Phase III maintenance efficacy trial (Study 331-10-232) in subjects with schizophrenia. A total of 744 PK samples from 415 schizophrenia subjects were available. Overall a good agreement between the simulated and observed median and ninety fifth percentile was observed, however, the model over predicted at the fifth percentile level. A further validation of the population PK model was performed using data obtained from Trial 14644A, a Phase III, randomised, double blind, parallel group, placebo controlled flexible dose study in patients with acute schizophrenia (Study 331-15-214). A total of 469 brexpiprazole plasma concentrations from 144 subjects were available. The fifth percentile and the median of the simulated data are comparable to those of the observed data. Although the ninety fifth percentile of the observed data is lower than that of the simulated, it falls within the 90% confidence interval for the ninety fifth percentile of the simulation based data. In general, external validation shows that the population PK model adequately predicts and describes the time course of brexpiprazole concentrations from Trial 14644A.

4.2.6. Pharmacokinetic interactions

4.2.6.1. Lovastatin

A pilot drug interaction study was conducted in healthy male subjects to examine the effect of brexpiprazole on substrates of CYP isozymes or P-gp (Study 331-08-207). The PK parameters of lovastatin (80 mg) were determined after single dose administration with and without brexpiprazole. A comparison of lovastatin and lovastatin hydroxyl-acid plasma PK parameters indicated that brexpiprazole did not inhibit CYP3A4. It should be noted that the conclusions of this study were not tested by a formal statistical comparison.

4.2.6.2. Bupropion

A pilot drug interaction study was conducted in healthy male subjects to examine the effect of brexpiprazole on substrates of CYP isozymes or P-gp (Study 331-08-207). The PK parameters of bupropion (150 mg) were determined after single dose administration with and without brexpiprazole. A comparison of bupropion and hydroxyl-bupropion plasma PK parameters indicated that brexpiprazole did not inhibit CYP2B6. It should be noted that the conclusions of this study were not tested by a formal statistical comparison.

4.2.6.3. Dextromethophan

A pilot drug interaction study was conducted in healthy male subjects to examine the effect of brexpiprazole on substrates of CYP isozymes or P-gp (Study 331-08-207). Following dextromethorphan administration, the amounts of dextromethorphan and dextrorphan excreted (Ae_{48h}) in urine were determined and the ratio of dextromethorphan/dextrorphan calculated. The mean (SD) dextromethorphan/dextrorphan ratio was 0.026 (0.064) and 0.025 (0.052) for 30 mg dextromethorphan alone and dextromethorphan plus brexpiprazole, respectively. This result indicated that brexpiprazole is not an inhibitor of CYP2D6. It should be noted that the conclusions of this study were not tested by a formal statistical comparison.

4.2.6.4. Fexofenadine

A pilot drug interaction study was conducted in healthy male subjects to examine the effect of brexpiprazole on substrates of CYP isozymes or P-gp (Study 331-08-207). The PK parameters of fexofenadine (60 mg) were determined after single dose administration with and without brexpiprazole. A comparison of fexofenadine plasma PK parameters indicated that brexpiprazole did not inhibit the P-glycoprotein transporter. It should be noted that the conclusions of this study were not tested by a formal statistical comparison.

4.2.6.5. Omeprazole

The effect of increasing gastric pH, using omeprazole, on the PK of brexpiprazole was examined in healthy volunteers (Study 331-10-240). Subjects received a single 4 mg dose of brexpiprazole alone and then after 5 days 40 mg omeprazole. Co-administration of omeprazole with brexpiprazole did not result in significant changes in the extent and rate of absorption of brexpiprazole, as the GMR for C_{max}, AUC_t, and AUC_∞ were 0.980 (90% CI: 0.827 to 1.160), 1.223 (90% CI: 1.102 to 1.357), and 1.180 (90% CI: 1.058 to 1.315), respectively.

4.2.6.6. Activated charcoal

An open label, single dose study was conducted in healthy volunteers to examine the effect of a single oral dose of activated charcoal and sorbitol (50 g/240 mL) on brexpiprazole PK when administered 1 hour after brexpiprazole administration (Study 331-10-239). Brexpiprazole reduced the mean C_{max} and AUC of brexpiprazole by 5% to 23% and 31% to 39%, respectively compared to historical controls. This may be useful to reduce brexpiprazole absorption in cases of accidental overdose. The mean C_{max} and AUC of DM-3411 were reduced by 27% to 44% and 35% to 47%, respectively.

4.2.6.7. Rosuvastatin

A crossover study in healthy volunteers examined the effect of a single oral dose of brexpiprazole on the PK of rosuvastatin (a BCRP transporter substrate) (Study 331-12-207). Brexpiprazole did not affect rosuvastatin exposure as the GMR and 90% CIs for rosuvastatin AUC_t and AUC_∞ were within the predefined bioequivalence limit of 0.70 to 1.43 (AUC_t and AUC_∞ GMRs were 1.05 and 1.10, respectively). A slightly lower rosuvastatin C_{max} (GMR and 90% CI: 0.76 (0.69 to 0.84)) was observed when rosuvastatin was administered with brexpiprazole, which is not considered clinically relevant, as rosuvastatin exposure (AUC) was similar to its administration without brexpiprazole.

4.2.6.8. Ketoconazole

The PK of single dose (2 mg) administration of brexpiprazole with multiple-dose co-administration of a strong CYP3A4 inhibitor (ketoconazole, 200 mg twice daily) was compared with single-dose (2 mg) administration of brexpiprazole (Study 331-08-208). There was no change in brexpiprazole C_{max} but a 97% increase AUC_∞. The results are consistent with a pilot study which that in combination with ketoconazole brexpiprazole exposure (AUC_∞) was 2.46-fold higher compared with brexpiprazole alone, and brexpiprazole $t_{1/2,z}$ was about 2-fold longer compared with brexpiprazole alone (Study 331-08-207).

4.2.6.9. Quinidine

The PK of single dose (2 mg) administration of brexpiprazole and multiple dose co-administration of a strong CYP2D6 inhibitor (quinidine, 324 mg dose once daily) resulted in no change in brexpiprazole C_{max} (either inhibitor) but a 94% increase in brexpiprazole AUC_∞ (Study 331-08-208). These results are consistent with the pilot Study 331-08-207 which showed that in combination with quinidine, brexpiprazole exposure (AUC_∞) was 2.35-fold higher, compared with brexpiprazole alone, and brexpiprazole $t_{1/2,z}$ was about 2-fold longer compared with brexpiprazole alone.

Based on population PK analysis, co-administration of brexpiprazole with strong inhibitors of CYP2D6 antidepressants (paroxetine and fluoxetine) resulted in a 53% higher brexpiprazole exposure (AUC_t) compared with other subjects.

4.2.6.10. Ticlopidine

Co-administration of a strong CYP2B6 inhibitor (ticlopidine, 250 mg, twice daily) did not affect brexpiprazole single dose PK (Study 331-08-208). Data from a pilot study showed that brexpiprazole is somewhat metabolised by CYP2B6 as the mean value of AUC_∞ was increased by around 1.4-fold by ticlopidine, and the $t_{1/2,z}$ of was unchanged (Study 331-08-207).

Co-administration with inhibitors of CYP2B6 is unlikely to require dose adjustment.

4.2.6.11. Rifampin

Co-administration of a potent CYP3A4 inducer (rifampin, 600 mg, once daily) with brexpiprazole resulted in 31% and 73% lower brexpiprazole C_{max} and AUC_{∞}, respectively (Study 331-09-224). Dose adjustment may be necessary during co-administration of brexpiprazole with strong CYP3A4 inducers.

4.2.7. Clinical implications of in vitro findings

The potential for PK drug interactions was based on results from in vitro inhibition and induction studies of CYPs and various transporters. The in vitro inhibition studies, indicated a low interaction potential of brexpiprazole and its metabolite DM-3411 acting as an inhibitor or inducer of CYP enzymes. However, assessment of mechanism-based inactivation of CYP3A4 by brexpiprazole indicated a potential CYP3A4 related drug interaction. Consequently, clinical drug interaction studies based on CYP enzymes were conducted. The clinical interaction study using lovastatin as a CYP3A4 probe showed no clinical relevant interaction.

Brexpiprazole was not a substrate for the MDR1, BCRP, OAT1B1, OAT1B3, or OCT1 transporters. When tested for inhibitory potential, brexpiprazole resulted in a C_{max}/IC_{50} ratio that was > 0.1 only for the BCRP transporter. Based on the regulatory guidance for drug interactions, a clinical drug-drug interaction study based on the BCRP transporter was conducted.

4.3. Evaluator's overall conclusions on pharmacokinetics

A broad set of PK studies have been conducted by the sponsor. These have adequately addressed the major PK issues to inform the proposed clinical use of the medication. Some minor issues were not addressed in the studies submitted. For example, there were no studies addressing potential drug-drug interactions with mood stabilisers. While the application relates to schizophrenia, brexpiprazole might be used for the treatment of schizoaffective disorder, while it seems likely that brexpiprazole may be used in bipolar disorder to treat acute psychotic relapses. Thus, either a clinical study or an in vitro investigation would seem to be warranted. Generally, the in vitro studies have been predictive of the in vivo findings with brexpiprazole. Some studies were conducted in specific Asian populations but there was no post hoc comparisons with the data obtained from Caucasian and Black populations in the comparable single dose studies. While race did not appear as a significant covariate in the population PK analysis, a post hoc comparison could reinforce the findings from the population PK analysis. The pre-clinical findings indicated that brexpiprazole seemed to accumulate in the eye as well as having an affinity for melanin. While the difficulty of studying such an effect in human populations is appreciated this potential effect did not appear to have been taken into account in the PK trials. For example, were any fundoscopic examinations conducted and what were the results of these? Given the propensity for some other antipsychotics (mainly phenothiazines) to cause retinal pigmentation and their affinity for melanin it would seem that this effect needs to be addressed in the longer term clinical trials (if it has not already been done). Information on this effect with aripiprazole (a closely related compound) might be informative. The issue is not mentioned in the PI or CMI.

The PK information in both the PI and CMI satisfactorily represents the information from the studies conducted. There are some recommendations for changes as noted [outside the scope of this document].

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Table 2 below summarises the submitted studies providing pharmacodynamic information.

Table 2: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study
Primary pharmacology	PET study healthy subjects	331-07-202
	PET study schizophrenia	331-09-219
Secondary pharmacology	Thorough QTc study	331-10-242
	Sleep polysomnography	331-08-209
Gender, other genetic and age related. Differences in PD Response	Effect of gender	
	Effect of genetic characteristic	
	Effect of age	
PD Interactions	No studies	
	Drug B	
	Drug C	
Population PD and PK-PD analyses	Target population (exposure response)	331-13-210

Note: All subtopics were the primary PD aim for each listed study.

No PD results were excluded from consideration.

5.2. Summary of pharmacodynamics

Occupancy of the D_2/D_3 receptor by brexpiprazole was investigated using positron emission tomography in healthy subjects after administration of single doses (to 6 mg). The study suggested that once daily administration of 1 mg or higher doses of brexpiprazole would result in at least 80% occupancy of the D_2/D_3 receptor. The results of the study were used to select doses for testing in the Phase II safety and efficacy trials in schizophrenia. An exploratory receptor occupancy study evaluated steady state D_2/D_3, 5-HT_{1A}, 5-HT_{2A} and serotonin transporter (SERT) occupancies of brexpiprazole (1 mg/day; 4 mg/day) in subjects with schizophrenia. There was negligible occupancy detected at 5-HT_{1A} receptors and SERT. D_2 occupancy was about 70% and 5-HT_{2A} 45% in this study.

No prolongation of corrected QT interval (QTcI) was observed in patients with schizophrenia in a Thorough QTc study. Increasing brexpiprazole doses were not associated with categorical changes in QTc. No subjects displayed QTcI or QTcF changes greater than 60 ms or new onset QTcI or QTcF of > 500 ms with brexpiprazole treatment. No clinically meaningful or statistically

significant effects of increasing brexpiprazole plasma concentrations on QTcI or QTcF were observed.

Exposure-response analyses were conducted to explore potential relationships between brexpiprazole exposure and safety endpoints. Analyses were also conducted to develop exposure-efficacy response model. In subjects with schizophrenia, there was a trend for improvement in PANSS score from Baseline over placebo. When an E_{max} model, with random effect on E_{max} but not on EC_{50}, was used to characterise this trend, the concentrations achieved by daily administration of 1 mg or more exceeded the EC_{50}. In long term treatment of schizophrenia, no plausible exposure response relationship was observed.

A pilot study to investigate the effects of brexpiprazole on sleep parameters was conducted in patients with stable schizophrenia. No statistically significant differences between 4 mg brexpiprazole and 20 mg aripiprazole were observed for any objective (polysomnographic) or subjective sleep parameters.

5.2.1. Mechanism of action

The precise mechanism of action of brexpiprazole in treating psychiatric conditions, including schizophrenia is unknown. Its effects are believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. Overall, the broad spectrum of brexpiprazole receptor binding profile shows that it has high affinity (Ki < 5nM) for multiple monoaminergic receptors including serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT7, dopamine D_2, D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Dose response occupancy and brain/plasma exposure relationship were determined in vivo or ex vivo for D_2/D_3, 5-HT_{2A}, 5-HT_{1A}, 5-HT_6 and 5-HT_7 receptors, as well as for the 5-HT transporter in preclinical studies. These results are consistent with the in vitro binding affinities and indicate that brexpiprazole may have efficient activity at several targets in the central nervous system at therapeutic plasma exposures. The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptor antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy.

5.2.2. Pharmacodynamic effects

5.2.2.1. Receptor occupancy

Results from in vitro assays have demonstrated that brexpiprazole possesses dopaminergic D_2 receptor partial agonistic activity and serotonergic 5-HT_{2A} receptor antagonistic activity, as well as high binding affinities for the dopaminergic D_3 and serotonergic 5-HT_{1A} receptors, at which it acts as a partial agonist. Occupancy at D_2/D_3 dopamine receptors (80% or higher) in humans is indicative of the potential efficacy of a compound in the treatment of schizophrenia.

Receptor occupancy for brexpiprazole was assessed in open label, single dose trial in healthy subjects (Study 331-07-202). 3 positron emission tomography (PET) scans were performed per subject: at Baseline, 4 hours post dose, and 23.5 hours post dose to reflect Baseline, maximum plasma concentration (C_{max}), and post C_{max} time points, respectively. The percent occupancy of D_2/D_3 receptor was judged by PET scan using ^{11}C-raclopride as a radio ligand. Regional (putamen and caudate nucleus) dopamine D_2/D_3 receptor occupancy was estimated at 4 hours and 23.5 hours post dose for each subject. Structural magnetic resonance imaging (MRI) of the brain was obtained for purposes of defining volumes of interest (VOIs) and for grey and white matter segmentation. Volumes of interest were manually defined for putamen, caudate nucleus, and cerebellum using locally developed VOIs and were transferred to individual PET spaces according to MRI-to-PET co-registration parameters. Correlations of dopamine D2/D3 receptor occupancy-plasma concentrations of brexpiprazole were made for putamen and caudate nucleus at 4 and 23.5 hours post-dose. After single-dose administration plasma concentrations up to 60 ng/mL corresponded to more than 80% and 90% dopamine D2/D3 receptors occupancies in the putamen and caudate nucleus, respectively. Occupancy values of dopamine

D2/D3 receptors by brexpiprazole for the putamen and caudate nucleus increased as a function of increased doses (0.25 to 6 mg) in healthy subjects.

An open label trial in subjects with schizophrenia was conducted to assess receptor occupancy in patients treated with different doses of brexpiprazole (Study 331-09-219). 3 cohorts of subjects were evaluated: Cohorts 1 and 3 received high doses of brexpiprazole (4 mg, up to 6 subjects each), and Cohort 2 received low doses of brexpiprazole (1 mg, up to 6 subjects). In Cohort 1, the binding of brexpiprazole to the D_2/D_3 (ligand: ^{11}C-PHNO) and 5-HT_{1A} (ligand: ^{11}C-CUMI) receptors was assessed by comparing the binding potential from the baseline scan to that of after 10 days treatment. In Cohort 2, the binding of brexpiprazole to the D_2/D_3 and 5-HT_{2A} (ligand: ^{11}C-MDL100907) receptors was assessed by comparing the binding potential from the baseline scan to that after 10 days of treatment. In Cohort 3, the binding of brexpiprazole to the 5-HT_{2A} receptor and SERT (ligand: ^{11}C-DASB) was assessed by obtaining a positron emission tomography (PET) scan at Baseline and comparing it to the scan obtained on Day 10. Mean ± SD occupancy for D_2 receptors following 4 mg/day brexpiprazole treatment for 10 days was 59 ± 5% (using 6 region model) or 67 ± 15% (using 8 region model); D_3 receptor occupancy was 13 ± 10% (using 6 region model) and 31 ± 8% using (using 8 region model). Mean ± SD occupancy for 5-HT_{2A} receptor following 4 mg/day brexpiprazole administration was 45 ± 7%. Clear dose and exposure occupancy relationships were observed at each of these targets, with lower occupancy observed following 1 mg/day treatment. Negligible occupancy (< 5%) was detected at serotonin 5-HT_{1A} receptors and SERT following multiple daily doses (10 day) of brexpiprazole administration of 4 mg/day for 10 days. An analysis of EC_{50} values showed that brexpiprazole was moderately D_2 preferring, with the ratio of EC_{50} (D_3)/EC_{50} (D_2) equalling approximately 4.56 when an 8 region regression model was used to separate D_2 and D_3 receptor occupancies. Occupancy at 5-HT_{2A} receptors was minimally lower than at D_2 receptors. The ratio of EC_{50} (5-HT_{2A})/EC_{50} (D_2) was approximately 1.4 when an 8 region regression model was used to separate 5-HT_{2A} and D_2 receptor occupancies.

5.2.2.2. Effect of brexpiprazole on QTc interval

A randomised, double blind, placebo and positive controlled, parallel arm trial was conducted to examine the effects of 2 dose levels of brexpiprazole on the QT/QT interval corrected for heart rate (QTc) in patients with subjects with schizophrenia or schizoaffective disorder (Study 331-10-242). Patients were randomised to 1 of 4 treatment arms (in a 2:2:1:1 ratio) as follows:

- Arm 1 was administered 4 mg brexpiprazole once daily (QD) on Days 1 to 11 and brexpiprazole placebo on Day 12
- Arm 2 was administered 12 mg brexpiprazole QD on Days 1 to 11 and brexpiprazole placebo on Day 12
- Arm 3 was administered 400 mg moxifloxacin (positive control) plus brexpiprazole placebo on Day 1 and brexpiprazole placebo QD on Days 2 to 12
- Arm 4 was administered brexpiprazole placebo QD on Days 1 to 11 and 40 mg moxifloxacin (positive control) plus brexpiprazole placebo on Day 12.

Electrocardiograms (ECGs) were performed on Days −1 (at Baseline), 1, 11, and 12. The primary endpoint was the time-matched QTcI change from Baseline (Day -1) corrected for placebo on Day 11 following brexpiprazole treatment. No QTcI prolongation after dosing with brexpiprazole was found. For the 4 mg dose, there was a single time point (6 hours) where the upper bound of the 2 sided 90% CI for the largest time matched, placebo-adjusted mean change from Baseline of the drug on the QTcI interval was greater than 10 msec. This is believed to be a false-positive result based on the fact that results for all other time points were consistent with a lack of effect of QTcI prolongation with brexpiprazole 4 mg, and no prolongation was seen at any time point with the 12-mg dose. The results for QTcF and QTcB (QT interval corrected for heart rate by Bazett's formula) were similar to those for QTcI and supported the findings of the

primary analysis. Moxifloxacin produced the expected increase in QTc interval demonstrating assay sensitivity. The largest lower bound of the 2 sided 98% CIs of moxifloxacin was greater than 5 msec. There were no subjects with QTcI or QTcF changes greater than 60 ms or with new onset of QTcI or QTcF of > 500 msec. Furthermore, there was no statistically significant relationship between changes in QTcI and QTcF and brexpiprazole plasma concentrations.

As a component of safety evaluations in the Phase II and Phase III trials, electrocardiogram (ECG) data were also recorded and monitored with no evidence of QT prolongation in these trials.

5.2.2.3. Effect of brexpiprazole on polysomnography

A pilot study to investigate the effects of brexpiprazole on sleep parameters was conducted in patients with stable schizophrenia (Study 331-08-209). Following an extensive wash out period in which cytochrome inhibitors and sedative hypnotics were tapered off, patients underwent 2 polysomnographic (PSG) screening nights. Eligible subjects after the baseline PSGs were randomised to receive 4 weeks of double blind treatment with either oral brexpiprazole (up to 4 mg) or oral aripiprazole (up to 20 mg). The double blind treatment phase consisted of a 7 day titration period and a 21 day fixed dose period. The initial titration was administered as follows:

- brexpiprazole: 2 mg x 3 days, 3 mg x 2 days, reaching 4 mg by Day 6
- aripiprazole: 10 mg x 3 days, 15 mg x 2 days, reaching 20 mg by Day 6.

Subjects were provided with an actigraph to wear on their wrist from Day -2 through the entire double blind treatment period to record movement. Subjects had PSG no. 4 and no. 5 on the nights of Day 6 and 7 (Week 1), followed by PSG no. 6 and no. 7 on the nights of Day 13 and 14 (Week 2), and PSG no. 8 and no. 9 on the nights of Day 27 and 28, respectively (Week 4). Secondary sleep, efficacy, and exploratory assessments were performed as planned at protocol specified time points during the trial. No statistically significant differences between 4 mg brexpiprazole and 20 mg aripiprazole were observed for any of the objective sleep parameters as determined by PSG (slow wave sleep (SWS), total sleep time (TST), sleep efficiency, wake after sleep onset, number of awakenings (NAW), latency to persistent sleep) at Week 1 or Week 2 (primary endpoints) or Week 4 (secondary endpoint). There was no consistent effect (from either treatment) on SWS, TST, NAW, and sleep efficiency. There were no statistically significant differences between medications in the percentage of sleep time in any of the defined stages of sleep architecture (Stage 1, Stage 2, SWS, and REM). Although an increase (from Baseline) in duration of latency to persistent REM sleep was observed in both groups at Week 4 (37.45 minutes for brexpiprazole; 25.54 minutes for aripiprazole), the treatment difference was not statistically significant (11.91 minutes; p = 0.2021). No statistically significant differences were observed treatments for subjective measures of sleep (total sleep time, number of awakenings, time to sleep onset) or sleep quality. There were no statistically significant differences between treatments for the analyses of mean change from Baseline in the Insomnia Severity Index (ISI) Total Score (-0.45 and 0.81, respectively; treatment difference =1.26; p = 0.2751) as well as the Epworth Sleepiness Scale (ESS) Total Score (=0.66 and -0.01, respectively; treatment difference -0.65; p = 0.4271) at Week 4.

5.2.3. Time course of pharmacodynamic effects

The time course of the effect of brexpiprazole on QTcI showed no consistent changes across a dosing interval.

Following single doses of brexpiprazole in healthy volunteers D_2/D_3 receptor occupancy was estimated at 4 hours and 23.5 hours post-dose for each subject (Study 331-07-202). While there was dose dependent increase in receptor occupancy, the occupancy at 4 and 24 hours after each dose was similar.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

In the Thorough QTc study no clinically meaningful or statistically significant effect of increasing brexpiprazole plasma concentrations on QTcI and QTcF was observed.

Using a population PK model established, for subjects with acute schizophrenia, a relationship between brexpiprazole concentrations and changes in PANSS scores from Baseline was identified using an E_{max} model with a random effect on E_{max} but not EC_{50} (pooled data from Study 331- 07-203, Trial 331-10-230, and Study 331-10-231) were pooled. Based on simulations from this model, the estimated median brexpiprazole concentrations achieved by daily brexpiprazole administration of 1 mg was above EC_{50}, 2 mg at EC_{80}, and 4 mg well above EC_{80} values. In long term treatment of subjects with schizophrenia (population PK model based on pooled data from the Phase III fixed dose Trials 331-10-230 and 331-10-231) no plausible exposure response relationship was observed between brexpiprazole exposure (predicted C_{trough} and C_{avg}) and impending relapse. As active brexpiprazole at the doses used (mainly 3 mg to 4 mg) was clearly more efficacious than placebo, it was concluded that the effect of brexpiprazole is maximal in the exposure range investigated. The findings are consistent with the dosing recommendations of 2 mg and 4 mg in subjects with schizophrenia in the Phase III safety and efficacy trials. No exposure dependent increase in insomnia, change in body weight, or akathisia (with the possible exception of C_{max} in the highest third for akathisia) were observed with respect to brexpiprazole exposure (C_{max} and AUC) in subjects with schizophrenia during 42 days of treatment with brexpiprazole.

The maximum obtainable receptor occupancy (O_{max}) and plasma concentration predicted to provide 50% of O_{max} (EC_{50}) were calculated in the healthy volunteer PET study (Study 331-07-202). The estimates of O_{max} and EC_{50} were 89.2% and 8.13 ng/mL, respectively, for the putamen and 95.4% and 7.75 ng/mL, respectively, for the caudate nucleus.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

There was no exploration of specific age, gender or genetic polymorphism effects on the PD parameters investigated.

5.2.6. Pharmacodynamic interactions

No PD interaction studies were conducted.

5.3. Evaluator's overall conclusions on pharmacodynamics

The PD studies focused on 3 primary areas: receptor occupancy determined by 2 PET studies, the effect on QTc interval and the effect on sleep.

The QTc study suggested a lack of significant clinical effects of brexpiprazole even at doses (12 mg) about 3 times higher than the recommended daily dose. As this study was conducted in the intended patient population it provides reassurance, along with ECG data from the PK studies, that the drug is unlikely to affect the electrical conductivity of the heart. Plasma concentrations of the drug were not related to ECG findings. This does not preclude effects as a result of an overdose of the medication.

A study in healthy volunteers suggested that doses to be used in clinical studies are likely to provide adequate receptor occupancy (> 80%) of the D_2/D_3 receptors to be effective in schizophrenia. Furthermore, this study demonstrated that receptor occupancy was dose dependent. The second PET study, conducted in patients with schizophrenia, assessed the occupancy of other receptors thought to be relevant to the drug action. Occupancy of D_2 receptors was somewhat less than the healthy volunteer study at the dose employed (4 mg) but suggests that brexpiprazole repeated dosing is likely to provide sufficient receptor occupancy for therapeutic effects. The $5\text{-}HT_{2A}$ receptors were occupied to a smaller extent than D_2 receptors. This may be relevant to a lower potential to cause extrapyramidal side effects and

tardive dyskinesia, as is seen with other antipsychotics demonstrating a similar binding profile. At the doses used there was negligible occupancy of 5-HT_{1A} and serotonin transporter. The relevance of the partial agonist effects at 5-HT_{1A} receptors identified by in vitro studies to the drug's mechanism of action is therefore dubious.

Plasma concentrations of brexpiprazole were not related to clinical outcome measures using an E_{max} modelling approach. A therapeutic drug concentration window has not been established. Plasma concentrations to achieve 50% maximum obtainable receptor occupancy in caudate and putamen were established in the healthy volunteer PET study. These concentrations are achieved in repeated dosing studies with recommended doses.

The sleep study compared the effects of 4 mg brexpiprazole with 20 mg aripiprazole in patients with schizophrenia. There was no difference between the drugs with respect to subjective or objective, polysomnographic recordings, sleep parameters. It is not clear what the relevance of this study was to the overall clinical use of the drug. A summary of significant changes induced by brexpiprazole from Baseline in sleep stages and subjective measures of sleep may have more relevance to clinical usage.

The submission did not contain any studies examining the effect of acute or repeated doses on psychomotor/cognitive performance or the effect of alcohol combined with brexpiprazole on these parameters. While it can be appreciated that this is a sedative agent and that decrements in performance are likely to occur, clinical studies can usefully examine the domains in which such decrements are likely to occur.

Some of the issues raised here are no doubt addressed in the clinical efficacy studies which are more relevant to use in the intended patient population.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The specific doses of brexpiprazole selected for investigation in Phase III were based on the results from a positron emission tomography (PET) trial in healthy subjects (Study 331-07-202) and the Phase II trial in adults with schizophrenia (Study 331-07-203).

Results from the PET trial in healthy subjects predicted steady state D_2 receptor occupancies of at least 80% to 90% at brexpiprazole doses of 1 to 2 mg/day and higher (79.3% predicted occupancy at brexpiprazole 1 mg, 88.8% at brexpiprazole 2 mg, and 95.1% at brexpiprazole 4 mg).

6.2. Phase II dose finding studies

The outcome of the Phase II trial in adults with schizophrenia suggested that the active dose range of brexpiprazole lies above 0.25 mg/day because improvement in PANSS Total Score for subjects in this fixed dose group was smaller than placebo; whereas, numerical improvements in the brexpiprazole flexible dose groups (1.0 ± 0.5, 2.5 ± 0.5, and 5.0 ± 1.0 mg/day) were greater than placebo.

6.3. Phase III pivotal studies investigating more than one dose regimen

Based on the Phase II trial in adults with schizophrenia, the efficacy objectives of the short term, placebo controlled, Phase III trials focused on brexpiprazole doses between 2 and 4 mg. The 2 fixed dose trials (Studies 331-10-231 and 331-10-230) included fixed dose arms of 4 and 2

mg/day that were included in both trials. Lower doses of brexpiprazole (1 mg/day in Study 331-10-230 and 0.25 mg/day in Study 331-10-231) were included in single trials to explore a lower dose range (1 mg/day) and minimally effective or non-effective dose (0.25 mg/day). Trial 14644A focused on a flexible dose range of 2 to 4 mg/day.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

Based on the available pharmacodynamic data the dose finding process for the pivotal studies appears appropriate. The methodology used in this process represents the best currently available, despite the obvious questions related to the lack of clarity in the relationship between specific receptor occupancy and antipsychotic efficacy.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

Three pivotal studies examining the use of brexpiprazole in schizophrenia were identified.

Study 14644A was a randomised, double blind, parallel group, placebo controlled, active reference, flexible dose study of brexpiprazole in patients with acute schizophrenia.

Study 331-10-23 was a Phase III, a Phase III, multicentre, randomised, double blind placebo controlled trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia.

Study 331-10-203 was a Phase II, 6 week, multicentre, randomised, double blind, placebo controlled study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 once daily and aripiprazole once daily for treatment of hospitalised adult patients with acute schizophrenia.

7.2. Pivotal or main efficacy studies

7.2.1. Study 14644A

7.2.1.1. Study design, objectives, locations and dates

Title: *'[An] interventional, randomised, double blind, parallel group, placebo controlled, active reference, flexible dose study of brexpiprazole in patients with acute schizophrenia'.*

This study was a trial designed to evaluate the various doses of brexpiprazole in comparison with placebo and a quetiapine arm. The allocation was randomised allocation with a 1:1:1 ratio in a double blind study design conducted over 6 weeks. It was a multicentre study with 62 centres around the world including centres in US and Eastern Europe and the trial was designed as a parallel group with an 8 day washout phase prior to start of the trial. The primary objective was to evaluate the efficacy of brexpiprazole (2 to 4 mg/day) versus placebo for the treatment of acute schizophrenia. The secondary objectives were to explore various other efficacy measures and adverse events between brexpiprazole and placebo. The study began in March 2013 and was completed in December 2014.

7.2.1.2. Inclusion and exclusion criteria

Inclusion criteria: willing to be hospitalised, has an acute exacerbation of psychotic symptoms and marked deterioration of usual function (PANSS total score ≥ 80 and score of ≥ 4 in at least 2 of the following PANSS items: hallucinatory behaviour, unusual thought content, conceptual disorganisation, or suspiciousness/persecution and CGI-S score ≥ 4.

Excluded: schizoaffective disorder and any other axis 1 or 2 disorders including but not limited to PTSD, major depression, significant suicidal ideation, pregnancy and breast feeding, treatment resistance and other medical conditions/abnormal lab values which seem reasonable.

Note: These were only inpatients and those who were willing to be admitted as inpatients and treated.

7.2.1.3. Study treatments

1. Brexpiprazole: dose 2 to 4 mg/day. N = 155 target.
2. Quetiapine XR: dose 400 to 800 mg/day. N = 155 target.
3. Placebo: N = 155 target.

The starting dose of brexpiprazole was 1 mg a day and titrated up by 1 mg a day to a maximum of 4 mg a day. Quetiapine XR was initiated at 300 mg on Day 1 and increased to 600 mg on Day 2 or 3 and then further up to 800 mg to optimise clinical effect and tolerability. Other concomitant medications allowed (rescue medications) included benzodiazepines which is reasonable clinical practice. Medication not allowed included other antipsychotics and psychotropics as well as certain dietary restriction of particular fruit juices. These were all appropriate.

7.2.1.4. Efficacy variables and outcomes

The key outcome variables assessed included the following:

Efficacy Assessments:

1. Positive and Negative Syndrome Scale (PANSS)
2. Clinical Global Impression, Global Improvement (CGI-I)
3. Clinical Global Impression, Severity of Illness (CGI-S)
4. Personal and Social Performance Scale (PSP)

Exploratory Assessments:

1. Readiness to Discharge Questionnaire (RDQ)
2. Drug Attitude Inventory, 10 Item (DAI-10)
3. CogState cognitive test battery
4. Karolinska Sleepiness Scale (KSS)
5. Schizophrenia Quality of Life scale (S-QoL)

The above rating scales are well validated as measuring instruments both for efficacy and side effects. Their use is appropriate.

7.2.1.5. Study design, objectives, locations and dates

In relation to this study methodology, the evaluator used the Cochrane Risk of Bias rating tool to ensure uniformity and consistency in rating the quality of randomisation and risk rating. The risk of rating tool has 3 risk ratings: low risk, unclear risk and high risk. The quality of the study or methodology decreases from low risk (high quality) to high risk (low quality) in terms of the bias that is potentially introduced due to methodological issues.

Table 3, below, summarises the evaluator's risk of bias estimation for Study 14644A.

Table 3: Study 14644A Risk of bias estimation

Bias	Evaluator's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients allocated a screening number and randomised using IVRS/IWRS which will randomly allocate the participant to the treatment group. This is an appropriate way of randomising for it removes the element of human bias being introduced as the system is completely automated and the recruiter does not influence allocation to the treatment arm. Low risk if protocol followed.
Allocation concealment (selection bias)	High risk	No clear documentation of allocation concealment available in the study protocol or any of the other study related documents made available, hence rated as potentially high risk of bias.[14]
Blinding of participants and personnel (performance bias)	Unclear risk	Both capsules and tablets issued and they were identical. Hence some blinding available. No details on how blinding will be tested. Hence risk of bias is unclear.[15]
Blinding of outcome assessment (detection bias)	High risk	No details recorded in protocol about how the assessors will be blind and how this will be tested. Hence rated as high risk of bias.[16]
Incomplete outcome data (attrition bias)	Unclear risk	The report indicates that various strategies were used to deal with incomplete outcome data. These included: All-patient-randomised set (APRS): all randomised patients All-patients-treated set (APTS): all randomised patients who took at least one dose of double blind IMP Full-analysis set (FAS): all patients in the APTS who had a valid baseline assessment and at least 1 valid post baseline assessment of the efficacy assessment tool PANSS total score; covering the period until withdrawal/completion Extended full-analysis set (extended FAS) all patients in the APTS who had a valid baseline assessment At least one valid post baseline assessment of the PANSS total

[14] Sponsor comment: In this and all other placebo-controlled trials, the medication was blinded and neither patients nor doctors had access to information on treatment allocation. Dispensing of randomised treatment was done on the basis of pack numbers as the only identifier of correct treatment. Link between pack number and treatment was not available to patient, investigator or study team member.
[15] Sponsor comment: Double-dummy method was used to blind the actual treatment assigned.
[16]The raters (and anyone at site and sponsor study team member) were blinded to treatment allocation as described above in Footnote 14.

Bias	Evaluator's judgement	Support for judgement
		score; covering assessments made at the completion/Withdrawal Visit or earlier as well as a completed[17] Withdrawal Follow-up Visit for patients withdrawn.[18] The report however also indicates that they utilised ANCOVA LOCF.[19] There are no universally accepted methods that are robust enough to account for all missing data. Whilst LOCF has been used in schizophrenia and other trials to account for missing data, this is increasingly discredited as a measure to account for missing data as it tends to have an overestimate of the effect of intervention. LOCF may be appropriate to use where variables are fixed and do not change over time. In a trial of this nature however, if a person withdraws from the study due to worsening of their mental state, an artificially inflated last outcome measure gets included in the final analysis for the intervention arm. Alternatives to LOCF that are statistically superior such as using all patient data by Bayesian methods or multiple imputation are considered less susceptible to bias and superior to LOCF. The National Academy of Sciences provided an advisory report to the FDA and specifically cautioned against using LOCF to account for missing data: 'Recommendation 10: Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified'. Hence in the evaluator's opinion, data derived from LOCF to account for missing participants need to be treated with caution. It is however good to note that the trialists used further sensitivity analysis. Subsequent review of a document appendix reveals that the authors did use Missing Not As Random (MNAR) analysis to further analyses and the trialists stated 'In addition the primary analysis will be repeated using LOCF and OC at Week 6 as a sensitivity analysis and to allow for comparison with legacy studies'. Whilst a large number of previous studies in schizophrenia have used LOCF, this measure should not be used for comparison for studies going forward as it provides erroneously positive results favouring the intervention arm as outlined above. If anything, data from previous high quality Cochrane systematic reviews or individual patient data comparisons should be used to compare with legacy studies. Placebo based imputation models and Delta Adjusted Patten Imputation are less familiar to this reviewer. It is encouraging however to see that sensitivity analyses performed using all of the above models (listed in the protocol document). Subgroup analyses

[17] Sponsor comment: The main method used for handling missing data was MMRM. Under assumptions of missing data being MAR.
[18] Sponsor comment: LOCF was only used as primary analysis method in the Phase II Study 331-07-203. The Phase III studies used MRM as primary statistical analysis method with LOCF as one of the sensitivity methods. For the comparison across trials the Phase II data were also analysed using MMRM. The limitations of LOCF are acknowledged.
[19] Sponsor comment: LOCF was only used as sensitivity analysis.

Bias	Evaluator's judgement	Support for judgement
		incorporate all expected confounders. Number of previous admission could be another subgroup analysis that should be assessed; however, the evaluator was not able to find any details of this. Details of all adverse events and how they will be evaluated recorded in detail.
Selective reporting (reporting bias)	Unclear risk	Most of the data have been reported. The data on continuous variables such as change in PANSS scores, efficacy measures are reported in individual patient data and not as summated data with means and standard deviations. For the ones where standard error and means were reported, analysis was performed on the outcome measures.
Other bias	Unclear risk	Potential selection bias based on the sample chosen. As mentioned above, the participants were chosen only if willing to be hospitalised.
Comment	The study was designed according to principles of Declaration of Helsinki, availability of dummy tables. Ethics handling was adequate. All raters received appropriate training as outlined in detail how they would be trained in administering the rating scales. Amendments to protocol reviewed no concerns.	

7.2.1.6. Analysis populations

The analysis of the primary outcome was conducted in patients which schizophrenia who were hospitalised. The primary outcome was appropriately chosen: change in baseline PANSS total score at Week 6. The population were chosen such that the results from this study would only be generalisable to inpatients (voluntarily) admitted and treated for 6 weeks. The study was multicentre and spanned 2 continents and generalisable to inpatients around the world as such, however the duration of the study was only 6 weeks and for a condition such as schizophrenia which requires longer term treatment, this one study in itself if not generalisable. Efficacy analyses were based on the Full Analysis Set (FAS) and the safety analyses were based on the All-Patients-Treated Set (APTS).

7.2.1.7. Sample size

The authors stated that 'The sample size calculation was based on the comparison of brexpiprazole and placebo using a significance level of 5%, and assuming a standard deviation of 20 for the primary endpoint (change from Baseline to Week 6 in PANSS total score). A total of 450 patients (150 per treatment group) were needed for an LOCF analysis to provide a power of approximately 90% for finding brexpiprazole statistically significantly superior to placebo if the effect was an improvement of 7.5 points. To account for 3% of the patients not contributing to the analysis, a total of 465 patients (155 per treatment group) were to be enrolled in the study'.

They were able to recruit the required number of participants; however the sample size was not sufficiently large enough to power subgroups analyses adequately. It was adequate for primary outcome based on recruitment. There was however high dropout rates even within a 6 week inpatient study that one needs to consider whilst interpreting the results.

7.2.1.8. Statistical methods

The statistical analysis plan is provided in detail within both the protocol and full report for the study. For the endpoint measures for the primary outcome, a continuous outcome is

appropriate. They have also chosen to report an improvement classed as ≥ 30% improvement in PANSS which is laudable compared to trials of the past which would report ≥ 20% improvement as a standard measure for defining improvement. The statistical analysis plan included in the appendix for this study clarifies the following analyses:

- All patients randomised set (APRS): all randomised patients
- All patients treated set (APTS): all patients in the APRS who took at least one dose of double blind IMP
- Full analysis set (FAS): all patients in the APTS who had a baseline assessment and at least one post baseline assessment of the PANSS total score; covering the period until withdrawal/completion.

Baseline characteristics assessed and adequately reported. As stated above in Table 3, there are many limitations to using the LOCF methodology.[20] The TGA recommended EMA Guideline on Missing Data in Confirmatory Clinical Trials states 'Only under certain restrictive assumptions does LOCF produce an unbiased estimate of the treatment effect. Moreover, in some situations, LOCF does not produce conservative estimates. However, this approach can still provide a conservative estimate of the treatment effect in some circumstances'. The use of LOCF hence may be considered not an appropriate measure as the statistical assumptions are too many to generalise it into day to day clinical situations.

7.2.1.9. Major protocol violations/deviations

None of concern

7.2.1.10. Baseline data

The treatment groups were similar with respect to age, sex, and race distribution: the mean age of the patients was 41 years, there were slightly more men than women (overall 57% versus 43%), and approximately 3 quarters of the patients in each treatment group were White.

Overall, the demographics of the patients who were withdrawn from the study was similar to that of the patients who completed the study, with the exception that slightly more men and African Americans withdrew from the study than completed the study.

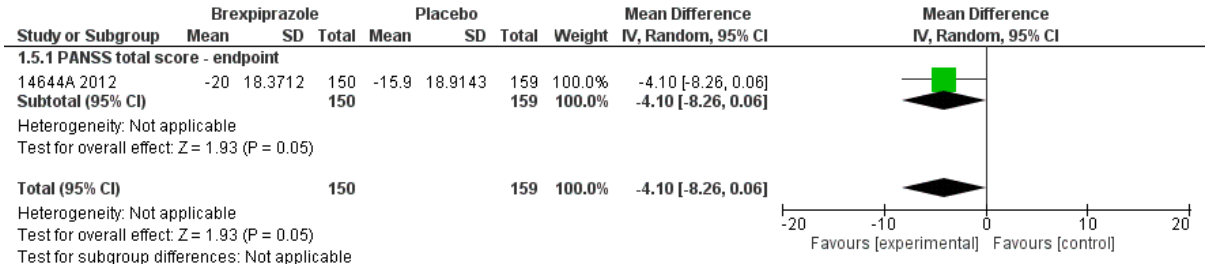
There were no clinically relevant differences between the treatment groups; the mean height, weight, BMI, and waist circumferences were approximately 171 cm, 79 kg, 27 kg/m^2, and 92 cm, respectively. Schizophrenia history at Baseline was similar across the treatment groups. Overall, the mean time (years) since the first diagnosis for schizophrenia was 13.6 years and the mean time (years) since the first antipsychotic treatment was 14.1 years. The majority (> 77%) of the patients had had the schizophrenia diagnosis for at least 5 years. Overall, the baseline schizophrenia history of the patients who were withdrawn from the study was similar to that of the patients who completed the study. The most common (> 5% in any treatment group) family psychiatric history comprised (placebo, brexpiprazole, and quetiapine): alcohol/substance abuse, father (11%, 9%, and 10%), schizophrenia, mother (6%, 8%, and 5%), and depression, mother (7%, 3%, and 5%).

7.2.1.11. Results for the primary efficacy outcome

Analysis of brexpiprazole versus placebo is outlined below in Figure 3. Tools used: Review Manager (Cochrane RevMan tool) analysis of continuous outcome data.

[20] The sponsor commented that the primary analysis for the Phase III placebo controlled short-term trials was done using MMRM. MMRM was used for analysis of all continuous efficacy endpoints. LOCF was used as a conservative measure for calculation for sample size.

Figure 3: Study 14644A Brexpiprazole versus placebo, primary outcome



Based on the analysis above, the brexpiprazole arm showed a tendency towards being beneficial compared with placebo; however the results were not statistically significant. In addition, based on the results reported, for the comparison of brexpiprazole versus quetiapine, the evaluator has outlined below the analyses as reported using the LOCF data as reported by the authors and using Intention to Treat (ITT) the evaluator provided analyses based on the assumption of 'once randomised always analyse method'. There is no statistically significant difference between the 2 analyses shown in Table 4.

Table 4: Study 14644A Brexpiprazole versus quetiapine on primary outcome

Efficacy data	Participants	Measure used	Effect estimate
Efficacy data (LOCF)	237	Mean Difference (IV, Fixed, 95% CI)	1.79 (-2.04, 5.62)
Efficacy data (ITT)	300	Mean Difference (IV, Fixed, 95% CI)	1.79 (-1.60, 5.18)

See the sponsor's comments/corrections in the following footnote.[21]

7.2.1.12. Results for other efficacy outcomes

The trial defined ≥ 30% improvement on PANSS total score as 'improvement'. When this was evaluated in the trial, at Week 6, it did not show statistical significance when comparing brexpiprazole to placebo (p = 0.056).[22] Other efficacy outcomes for this study included CGI-S which showed statistically significant improvements compared with placebo (< 0.05) and similar improvements comparing CGI-I and PSP total scores compared with placebo.

Leaving the study early is not an efficacy outcome, however can be considered an indication of tolerability and if people left the study early due to lack of efficacy, that in itself is an important outcome.

7.2.1.13. Evaluator commentary

Overall, for the primary outcome, 'treatment with brexpiprazole did not reach statistical significance in the primary efficacy variable, the change from Baseline in PANSS total score at Week 6, compared to placebo'. It showed some improvements in other outcomes, however were only brief lasting within analyses of data in Weeks 2 to 4 and did not have any benefit over 6 weeks, which would be important in the clinical context of treating schizophrenia over longer periods as happens in clinical practice.

[21] Study 14644A included quetiapine only as an active reference to confirm assay sensitivity and was not designed or powered with the purpose to compare brexpiprazole versus quetipine.It is not clear what analysis method was used to generate the estimate of effect presented in this table.
[22] The sponsor added that for the response analysis the p-value was 0.003, in favour of brexpiprazole. This p-value is the primary endpoint mean change in PANSS.

7.2.2. Study 331-10-232

7.2.2.1. Study design, objectives, locations and dates

The evaluator marked this as a pivotal study because it is the study that provides longer term data which is applicable for maintenance treatments. The study is described as a long term, maintenance, controlled trial but the design is more complex, suggesting potential enrichment in sampling as is common in this area of study. It is basically done in 3 phases. In the first phase or Phase A, other study medications are washed out based on what they are between 2 and 15 days. In phase B, brexpiprazole is gradually titrated upwards. Until this point, it is open label and there is no randomisation or blinding. Once titrated and symptoms of schizophrenia stabilised, then patients enter a randomisation phase where they are given either a placebo or the IMP.

7.2.2.2. Inclusion and exclusion criteria

See Figure 4, below.

7.2.2.3. Study treatments

Phase B: converted from current antipsychotic to brexpiprazole 1 to 4 mg/day. Discontinued if did not tolerate 1 mg/day.

Phase C: all subjects received single blind brexpiprazole 1 to 4 mg/day for at least 12 weeks and up to 36 weeks, based on the individual subject's response and tolerability considerations.

7.2.2.4. Efficacy variables and outcomes

Time from randomisation to impending relapse was the key outcome. Other outcomes included change in PANSS scores; total, negative and positive as well as CGI-S and GAF scores were evaluated.

7.2.2.5. Randomisation and blinding methods

Is described in detail in Table 5 below under 'Evaluator's comments'.

7.2.2.6. Analysis populations

Is described in detail in Table 5 below under 'Evaluator's comments'.

7.2.2.7. Sample size

N = 230, however appears trial was terminated when N = 202.[23]

7.2.2.8. Statistical methods

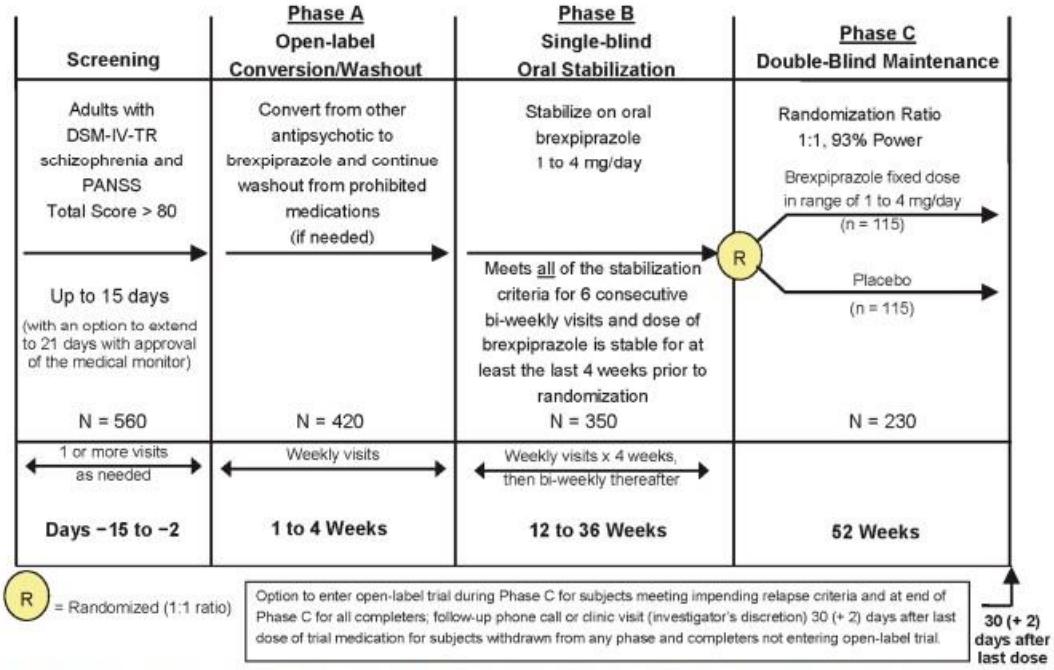
For the main outcome of hazard ratios was provided using cox proportional hazard model. For key secondary outcomes in the double blind phase, the usual models analysed in other studies using MMRM for observed data and LOCF for missing data was used. The analysis seemed appropriate.

7.2.2.9. Participant flow

The following image is taken from the trial report which demonstrates flow of participants through the trial across the different phases. As described later on, the trial was terminated early as the interim analysis outcomes were met and it was predominantly a time to discontinuation or time to relapse study.

[23] The sponsor added that the study termination was due to pre-planned interim analysis that achieved pre-specified criteria for efficacy.

Figure 4: Study 331-10-232 Trial design



DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision;
PANSS = Positive and Negative Syndrome Scale.
Note: Subjects who did not need a washout period of other antipsychotic treatments or prohibited medications could enter the Single-blind Stabilization phase directly.

7.2.2.10. Major protocol violations/deviations

No issues identified.

7.2.2.11. Baseline data

Within the double blind phase, demographic and baseline characteristics of the subjects were well balanced between the groups. The results report that of the 202 subjects randomised in the double blind Maintenance phase, the majority were male (60.9%), White (62.9%), and non-Hispanic (81.7%), and ranged in age from 18 to 62 years. Subjects were representative of an acutely ill schizophrenia population prior to entry into the Stabilisation phase, with mean baseline PANSS Total Score of 84.4 and a mean CGI-S score of 4.3. At Baseline in the double blind Maintenance phase, subjects were representative of a symptomatically stable population, with a mean PANSS Total Score of 56.5 and 58.1 for the brexpiprazole and placebo groups, respectively. Overall it appears that the demographics had been matched and confounders potentially equally distributed. The randomisation process appears to have been reasonably successful.

7.2.2.12. Results for the primary efficacy outcome

The authors used time to impending relapse as a key outcome. For this measure, they stated that time to impending relapse was significantly delayed with brexpiprazole compared with placebo in both the interim and final analyses ($p = 0.0008$ and $p < 0.0001$, respectively; log rank test). For the final analysis, the hazard ratio was reported as 3.420 (95% CI = 1.825, 6.411). The evaluator has been unable to independently perform these analyses, however it appears to be accurate and compared to placebo, brexpiprazole does appear to reduce relapse and thereby rehospitalisation rates (final analysis: 13.54% versus 38.46%, $p < 0.0001$)

7.2.2.13. Results for other efficacy outcomes

Other secondary outcomes also favoured brexpiprazole over placebo. These were the proportion of subjects meeting stability criteria, improvement in clinical symptomology (as

assessed by PANSS, CGI-S, and CGI-I), improved functioning (as assessed by PSP and GAF scales), and prolonged time to trial discontinuation, as compared with placebo.

7.2.2.14. Evaluator's commentary

Although a frequently required methodology, the evaluator would like to note some concerns about the ethical aspects of changing a patient whose mental state has stabilised into a placebo arm and essentially not treating them for up to a year. This is something the ethics approval bodies and institutional review boards have considered and is probably a requirement for the FDA, nevertheless sits uneasy in terms of not treating someone with a known and available medication when the risks of non-treatment and cognitive deficits and risks are known to increase. The results however indicate that the trial was terminated because the interim analyses stopping rules had been met.

The first phase is appropriate where there is a washout period to ensure there is no cross contamination of the medications and the effects of the intervention drug can be attributed to it alone and not previous antipsychotics. Phase B is relatively straightforward as it is titrating the medication upwards and ensuring tolerability. The evaluation of the quality of the study is summarised in detail below. The efficacy data do appear to show that brexpiprazole delayed the onset of relapse compared to placebo and some improvements were noted compared to placebo when measured using PANSS and CGI-S scales for mental state data. Safety data appeared to show that there were no deaths in either of the groups and TEAEs were not statistically significant between the 2 groups and were minimal.

Table 5 below gives an overview of the design, methodology and outcomes of Study 331-10-232.

Table 5: Study 331-10-232 Characteristics

Study 331-10-232 Characteristics	
Methods	*Title*: A Phase III, multicentre, randomised, double blind placebo controlled trial of 3 fixed doses OPC-34712 in the treatment of adults with acute schizophrenia allocation: randomised in Phase C to 1:1 ratio. *Blindness*: Double blind. *Duration*: Phase C duration was 52 weeks. *Design*: Multi-centric, 50 sites around the world, with 3 phases to the study. The screening was for 2 to 15 days. Eligible patients entered conversion phase (Phase A) where other medications were washed out. Then they entered Phase B, or the single blind stabilisation phase where the dose of brexpiprazole was titrated from 1 mg a day up to a maximum of 4 mg a day that would maintain stability of psychotic symptoms over 12 consecutive weeks (within a maximum of 36 weeks), while minimising tolerability issues. Then the subjects entered Phase C or double blind phase where they were randomised to receive a stabilisation dose of brexpiprazole or placebo.
Participants	*Diagnosis*: Diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). *History*: Informed consent, ill for at least 3 years experiencing a relapse. N = 202 in double blind phase. Total N = 524. *Sex*: Male and Female *Age*: 18 to 65 years *Setting*: Outpatients for double blind phase (C) *Inclusion criteria*: Those able to provide informed consent, living in a stable environment, diagnosis of schizophrenia DSM-IV-TR and confirmed by MINI, requiring ongoing

Study 331-10-232 Characteristics	
	management for schizophrenia, PANSS score > 80, history of relapse and/or exacerbation of symptoms when they were not receiving antipsychotic treatment, willing to discontinue medications, and for the Phase C, had to be outpatients, with PANSS <70, CGI-S < 4 and no risk history to self or others. *Excluded*: Schizoaffective disorder and any other axis 1 or 2 disorders, , other major mental health disorders, including but not limited to PTSD, major depression, significant suicidal ideation, pregnancy and breast feeding, treatment resistance and other medical conditions/abnormal lab values which seem reasonable.
Interventions	*Phase B*: Converted from current antipsychotic to brexpiprazole 1 to 4 mg/day. Discontinued if did not tolerate 1 mg/day. *Phase C*: All subjects received single blind brexpiprazole 1 to 4 mg/day for at least 12 weeks and up to 36 weeks, based on the individual subject's response and tolerability considerations.
Outcomes	*Primary outcome*: Time from randomisation to exacerbation of psychotic symptoms/impending relapse in the double blind maintenance phase, defined as meeting any of the following 4 criteria: Clinical Global Impression Improvement scale (CGI-I) score ≥ 5 *and* an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of > 4 with an absolute increase of ≥ 2 on that specific item since randomisation *or* an increase on any of the following individual PANSS items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of > 4 and an absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) since randomisation. Hospitalisation due to worsening of psychotic symptoms (including partial hospitalisation programs), but excluding hospitalisation for psychosocial reasons (for example homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition); or Current suicidal behaviour as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) (that is, an answer of 'yes' to any of the questions on the Suicidal Behaviour section of the C-SSRS); or Violent or aggressive behaviour resulting in clinically significant self-injury, injury to another person, or property damage. *Secondary outcomes*: Percentage of subjects meeting impending relapse criteria. *Other secondary outcomes*: Proportion of subjects meeting stability criteria at endpoint in each treatment group: Change from Baseline to endpoint in PANSS Total Score Change from Baseline to endpoint in PANSS Positive Subscale score Change from Baseline to endpoint in PANSS Negative Subscale score Change from Baseline to endpoint in Clinical Global Impression Severity of Illness scale (CGI-S) score CGI-I score at endpoint Change from Baseline to endpoint in Personal and Social Performance scale (PSP) score Change from Baseline to endpoint in Global Assessment of Functioning scale (GAF) score

Study 331-10-232 Characteristics	
	Time to discontinuation due to all causes Change from Baseline to endpoint in PANSS Excited Component (PEC) score Change from Baseline to endpoint in PANSS Marder Factor scores. *Pharmacokinetic endpoints*: Plasma concentrations were determined for brexpiprazole and its major metabolite, DM 3411. The pharmacokinetic (PK) data was summarised graphically with descriptive statistics. The collected PK samples were used for population PK modelling. *Other outcomes*: Changes in composite score for the CogState computerised cognitive test battery and results for the individual test domains were examined as other outcomes. The proportion of subjects with remission was examined as an exploratory endpoint. Remission was defined as a score of ≤ 3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganisation (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6).
Notes	Company funded trial.

Table 6, below, summarises the evaluator's assessment of the risk of bias in Study 331-10-232.

Table 6: Study 331-10-232 Risk of bias[24]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were assigned to IMP via an IVRS/IWRS according to a computer generated randomisation code provided by the sponsor. The appearance of the IMP in the double blind maintenance phase was identical to the stabilisation phase.
Allocation concealment (selection bias)	High risk	Allocation concealment not described[25], presumed not to have happened.
Blinding of participants and personnel (performance bias)	Unclear risk	Decision on breaking blinding documented. Blindness maintained in double blind phase of the study, however not earlier. Hence could have led to some degree of selection bias. Hence rated unclear.
Blinding of outcome assessment (detection bias)	High risk	Testing of blinding not done. Hence risk rated as high.
Incomplete outcome data (attrition bias)	Unclear risk	As with other study designs, LOCF and OC used to account for missing data.
Selective reporting	Low risk	Most data reported.

[24] See also the sponsor's comments in the footnotes attached to Table 3 above.
[25] The sponsor commented that blinding of treatment allocation is described in the study protocol.

Bias	Authors' judgement	Support for judgement
(reporting bias)		
Comment	Unclear risk	Company funded trial.

7.2.3. Study 331-10-203

7.2.3.1. Study design, objectives, locations and dates

Outlined in Table 7 below in the Evaluator commentary.

7.2.3.2. Inclusion and exclusion criteria

Outlined in Table 7 below in the Evaluator commentary.

7.2.3.3. Study treatments

Outlined in Table 7 below in the Evaluator commentary.

7.2.3.4. Efficacy variables and outcomes

Outlined in Table 7 below in the Evaluator commentary.

7.2.3.5. Randomisation and blinding methods

Outlined in Table 7 below in the Evaluator commentary and in the associated risk of bias table (Table 8).

7.2.3.6. Analysis populations

Outlined in Table 7 below in the Evaluator commentary.

7.2.3.7. Sample size

The total number randomised was 459. There were in total 6 groups including the one placebo group. Aripiprazole was considered an active reference. In order to maintain a nominal alpha level at 0.05 (2 sided) after accounting for multiple comparisons, the Hochberg procedure was used. To power the sample size to achieve at least 80% power at an alpha level of 0.0167 (2 sided) to detect a difference of -11.5 points in the mean change from Baseline in PANSS Total Score at Week 6 (LOCF) between an individual brexpiprazole treatment group (except the 0.25 mg QD fixed dose group) and placebo using a 2 sided z-test.

They calculated the resulting the resulting sample size was 90 subjects in each of these 3 brexpiprazole groups and 90 subjects in the placebo group. The total sample size was calculated as 450 to adequately power the study at all arms and they were able to recruit adequate numbers to the study.

7.2.3.8. Statistical methods

Similar to other studies in this genre (Study 14644A), this study used MMRM[26] for evaluating its primary outcomes. The authors defined it as 'Used treatment, study centre, visit, and treatment visit interaction as fixed effects and Baseline as covariate with an unstructured variance covariance matrix structure to the visits, and was applied to the change from Vaseline in PANSS Total Score at Week 6 (OC) data in each of the 3 OPC-34712 flexible dose group comparisons versus placebo (sensitivity analysis for ANCOVA-1[27])'.

[26] The sponsor commented that this was the only study that used LOCF for the primary outcome, but MMRM was also calculated for the across study comparison.
[27] The sponsor commented that as this study was older, it used ANCOVA LOCF to assess the primary endpoint, as opposed to 146644A that used MMRM. In 203, MMRM was a sensitivity analysis.

In addition, similar to Study 14644A, they used LOCF and OC analysis to account for missing data/variables and have its associated disadvantages as outlined previously.

7.2.3.9. Participant flow

See Table 7, below.

7.2.3.10. Major protocol violations/deviations

No concerns.

7.2.3.11. Baseline data

Baseline characteristics were evenly matched across the different variables. There was no concern in terms of baseline characteristics influencing the eventual outcome due to selection bias. The results report that 'The trial population had a mean age of 39.1 years, weight of 75.2 kg, and BMI of 26 kg/m^2. The trial population was 62.5% male, 62.5% White, 20% Asian, 16.8% Black or African American, and 5.2% of subjects were of Hispanic or Latino ethnicity'. Baseline scores were similar across treatment groups, with the authors reporting 'The trial population as a whole had the following baseline scores (mean (± SD)): PANSS Total Score, 97.5 (± 10.2); PANSS Positive Subscale Score, 25.5 (± 3.7); PANSS Negative Subscale Score, 24.9 (± 4.5); CGI-S score, 4.9 (± 0.6); and PSP score, 45.8 (± 11.2)'.

7.2.3.12. Results for the primary efficacy outcome

The overall treatment compliance for the medications including the placebo groups was good. The primary efficacy outcome was Change from Baseline to Week 6 in PANSS Total Score. For this outcome, the authors used change data with least square means. There were no standard errors or standard deviations readily available in the study report (Study 331-07-203) to perform independent calculations. The evaluator was however able to find the standard deviations on the ClinicalTrials.gov website which was used for the analysis. The data was reanalysed for the dose of Brexpiprazole 4 mg a day[28], which seems to be the most efficacious dose and the results demonstrate that for the primary outcome, the mean difference effect score was -6.47 with a 95% CI of -10.63 to -2.31. This does demonstrate statistically significant superiority over placebo, although the confidence intervals are rather narrow. Similarly the brexpiprazole arm demonstrated superiority over the placebo arm in all other dose ranges apart from perhaps what might be expected in the 0.25 mg dose range.[29] For this dose, the placebo arm fared better.

When compared with aripiprazole[30] however, there was no statistically significant difference between the 2 arms. The mean difference was -0.27 with a 95% CI of between -7.51 and 6.97. Further details of these analyses are presented under Section 7.4, below.

7.2.3.13. Results for other efficacy outcomes

When the trialists performed a further sensitivity analysis on the observed case data set, although the results supported the primary analysis, the magnitude of the placebo effect for Mean Change from Baseline in PANSS Total Score at Week 6 was quite big and no significant differentiation from placebo was observed for any of the OPC-34712 flexible dose groups or for the aripiprazole group, and the 0.25 mg/day dose was shown to be less effective than placebo.

7.2.3.14. Evaluator commentary

The quality of the study and its characteristics are summarised in Table 7, below. Risk of bias is outlined in Table 8, also below.

[28] These results refer to Study 230. Trial 331-10-203 did not include a 4 mg dose arm.
[29] The 0.25 arm refers to Trial 331-10-231, the estimate above to Trial 331-10-230, and the sample size calculation to trial 331-10-203.
[30] Only in Trial 331-10-203

Table 7: Study 331-07-203 Characteristics

Study 331-07-203 Characteristics	
Methods	*Title*: A Phase II, 6 week, multicentre, randomised, double blind, placebo controlled study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 once daily and aripiprazole once daily for treatment of hospitalised adult patients with acute schizophrenia. *Allocation*: Randomly assigned 1:2:2:2:2:1 ratio. *Blindness*: Double blind. *Duration*: 6 weeks. *Design*: Multicentre, this trial was conducted at 74 centres in 12 countries (Bulgaria, Croatia, India, the Philippines, Romania, Russian Federation, Serbia, Slovakia, South Korea, Taiwan, Ukraine, and the US)
Participants	*Diagnosis*: schizophrenia (DSM-IV-TR) and confirmed by the Mini International Neuropsychiatric Interview (MINI). *History*: informed consent obtained. N = 459. *Sex*: Male and female. *Age*: 18 to 65 years. *Setting*: Inpatients. *Inclusion criteria*: Recently hospitalised or willing to be hospitalised, has an acute relapse of schizophrenia and marked deterioration of usual function (PANSS total score ≥ 80 and score of ≥ 4 at screening and Baseline and willing to discontinue all prohibited psychotropic. *Excluded*: Hospitalised for ≥ 14 days, schizoaffective disorder and any other axis 1 or 2 disorders including but not limited to PTSD, major depression, significant suicidal ideation, pregnancy and breast feeding, treatment resistance and other medical conditions/abnormal lab values. A list of drugs prohibited prior to assessments, certain fruit juices prohibited 72 hours prior to dosing and ECT prohibited 60 days prior to trial.
Interventions	*Brexpiprazole*: Dose 0.25 mg/day. N = 42. *Brexpiprazole*: Dose 1 mg/day. N = 89. *Brexpiprazole*: Dose 2.5 mg/day. N = 90. *Brexpiprazole*: Dose 5 mg/day. N = 93. *Placebo*: N = 95. *Aripiprazole*: Dose 15 mg/day. N = 50.
Outcomes	*Efficacy Assessments*: Positive and Negative Syndrome Scale (PANSS) (primary outcome) Clinical Global Impression, Global Improvement (CGI-I) (secondary outcome) Clinical Global Impression-Severity of Illness (CGI-S) (primary outcome) Personal and Social Performance Scale (PSP) (primary outcome).

Table 8: Study 331-07-203 Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned through an IWR or IVRS to one of the 6 double blind treatment groups. Computer generated randomisation codes provided by the OPDC Biometrics Department with block of size 10 were generated for this 1:2:2:2:2:1 randomisation. Within each block of size 10, there were 2 sub-blocks. A copy of random allocation schedule is made available.
Allocation concealment (selection bias)	High risk	No details on allocation concealment, hence potentially rated as high risk of bias.[31]
Blinding of participants and personnel (performance bias)	Low risk	Some details about blinding available. Investigator not to request details of blinding unless required for clinical care and safety. Documentation of breaking blinding to be made. Matched placebo and investigational medical compounds. Medications stored securely.
Blinding of outcome assessment (detection bias)	High risk	No details on testing if blinding was effective provided.
Incomplete outcome data (attrition bias)	High risk	In order to assess sensitivity of results due to missing data, 2 types of analyses were performed: LOCF and Observed Case (OC).
Selective reporting (reporting bias)	Unclear risk	Most available data appear to have been reported.
Comment	Unclear risk	Sponsor funded study.

As outlined above, there are a few risks of bias issues to consider with this study and other similar studies in terms of lack of description around allocation concealment, further steps to test blinding and other biases that may have crept in as a result. The baseline characteristics are matched evenly. The study appears to be powered adequately. The issues with using LOCF have been highlighted previously in accounting for missing data. Based on the available evidence presented, apart from the 0.25 mg dose of brexpiprazole, all the other dose ranges were efficacious compared to placebo but not significantly better compared to aripiprazole.

7.3. Other efficacy studies

The following 2 studies (Study 331-10-230 and Study 331-10-231) are very similar in their methodology and design.

[31] See Table 3 for sponsor comments on risk of bias.

7.3.1. Study 331-10-230

In Table 9, below, is a summary of the above study along with its risk of bias table as Table 10, assessing the quality of the study.

Table 9: Study 331-10-230 Characteristics

Study 331-10-230 Characteristics	
Methods	*Title*: A Phase III, multicentre, randomised, double blind, placebo controlled trial of fixed dose OPC-34712 (4, 2, and 1 mg/day) in the treatment of adults with acute schizophrenia. *Allocation*: Randomised in a 3:3:2:3 ratio. *Blindness*: Double blind. *Duration*: 6 weeks. *Design*: Multicentre (68 sites received investigational medicinal product; 64 sites screened subjects; 59 sites randomised subjects); Multinational (Colombia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan, and the United States. Subjects who completed all trial visits through the Week 6 visit may have been offered entry into an optional open label rollover Trial 331-10-237.
Participants	*Diagnosis*: Schizophrenia as diagnosed by DSM-IV-TR. *History*: Those who could consent and would benefit from hospitalisation or continued hospitalisation for treatment of a current acute relapse of schizophrenia. N = 674. *Sex*: Male and female. *Age*: 18 to 65 years. *Setting*: Inpatients only. *Inclusion criteria*: Willing to be hospitalised, an acute exacerbation of psychotic symptoms and marked deterioration of usual function as demonstrated by meeting *all* of the following criteria at the screening and Baseline visits: Total BPRS score ≥ 40; *and* Score of ≥ 4 on 2 or more of the following BPRS items: hallucinatory behaviour unusual thought content conceptual disorganisation, or suspiciousness; *and* 3. CGI-S score ≥ 4 (moderately ill). *Excluded*: Schizoaffective disorder and any other axis 1 or 2 disorders, those who had ≥ 30% improvement in PANSS rating between screening and baseline scores, other major mental health disorders, including but not limited to PTSD, major depression, significant suicidal ideation, pregnancy and breast feeding, treatment resistance and other medical conditions/abnormal lab values which seem reasonable.
Interventions	*Brexpiprazole*: Dose = 4 mg/day, N = 184.

Study 331-10-230 Characteristics	
	Brexpiprazole: Dose = 2 mg/day, N = 186. *Brexpiprazole*: Dose = 1 mg/day, N =120. *Placebo*: N = 184.
Outcomes	*Efficacy assessments*: Positive and Negative Syndrome Scale (PANSS; total, positive and negative); Clinical Global Impression - Severity of Illness (CGI-S) scale; Personal and Social Performance (PSP) scale; Clinical Global Impression, Improvement (CGI-I) scale; and PANSS Excited Component (PEC) and PANSS Marder Factor scores, which were derived from the PANSS.
Notes	*Enrolment distribution across countries was as follows*: Colombia, 57 subjects; Croatia, 38 subjects; Mexico, 37 subjects; Philippines, 11 subjects; Russia, 266 subjects; Slovakia, 5 subjects; Taiwan, 17 subjects; and the US, 243 subjects.

Table 10: Study 331-10-230 Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An IVRS/IWRS was used to obtain the subject identification and to assign trial medication for randomised subjects. Treatment assignments were based on a computer generated permuted-block randomisation schedule provided by the OPDC Biometrics Department. A copy of the randomisation report available.
Allocation concealment (selection bias)	High risk	Allocation concealment not outlined. [32]
Blinding of participants and personnel (performance bias)	Unclear risk	Double blind trial. Some detail outlined as to how blinding was done.
Blinding of outcome assessment (detection bias)	High risk	Robustness of the blinding process and success not evaluated.
Incomplete outcome data (attrition bias)	High risk	LOCF and OC analysis used for missing data.[33] As reported in previous studies, this approach has shortcomings.
Selective reporting	Low risk	Most available data appear to have been reported.

[32] See Table 3 for the sponsor's comments on risk of bias.
[33] The sponsor commented that LOCF was only used for sensitivity. MMRM was used for the primary analysis. Under assumption of missing data being MAR, the MMRM analysis is considered valid. Sensitivity analyses under MNAR were provided in the studies.

Bias	Authors judgement	Support for judgement
(reporting bias)		
Comment	Unclear risk	Overall risk rated as unclear as there are some strengths and weaknesses to the study as outlined above.

7.3.1.1. Results for the primary efficacy outcome

This study demonstrated an improvement in PANSS Total Score from Baseline to Week 6. Brexpiprazole 4 mg/day group fared better compared with the placebo group (LS mean difference = -6.47, p = 0.0022).

7.3.1.2. Results for other efficacy outcomes

Improvements in the brexpiprazole arm compared to the placebo arm were noted for all dose ranges across the trial Weeks 1 to 6. The brexpiprazole 4 mg a day group also fared better than placebo on measures of change in PSP score, CGI-S, CGI-I and all subscales of PANSS scores at endpoint. Detailed values obtained and reviewed from the Study 331-10-230 report.

7.3.1.3. Evaluator commentary

No deaths occurred in this study during the study period or for 30 days after. This is a placebo controlled study and brexpiprazole particularly the 4 mg a day arm fared well compared to placebo on all primary and secondary efficacy outcome measures.

Approximately 30% of patients left the study early in the brexpiprazole arms with similar numbers in the placebo arm. This continues to remain on the higher side for a 6 week inpatient study. The evaluator is not sure what the explanation for this is.

7.3.2. Study 331-10-231

This study is quite similar to the study above and appears to be 1 of 3 studies using exactly the same methodology and design, with slightly different doses of brexpiprazole. Table 11 below summaries the key study characteristics along with a risk of bias rating for this particular study.

Table 11: Study 331-10-231 Characteristics

Study 331-10-231 Characteristics	
Methods	*Title*: A Phase III, multicentre, randomised, double blind placebo controlled trial of 3 fixed doses OPC-34712 in the treatment of adults with acute schizophrenia. *Allocation*: Randomised in a 2:2:1:2 ratio *Blindness*: Double blind *Duration*: 6 weeks *Design*: Multicentre, mainly in USA, also Canada, 7 subjects; Japan, 19 subjects; South Korea, 15 subjects; Latvia, 31 subjects; Malaysia, 21 subjects; Poland, 16 subjects; Romania, 109 subjects; Serbia, 75 subjects; Ukraine, 115 subjects; United States, 228 subjects.
Participants	*Diagnosis*: Schizophrenia as diagnosed by DSM-IV-TR and confirmed by MINI History: Those who could consent and would benefit from hospitalisation or continued hospitalisation for treatment of a current acute relapse of schizophrenia.

Study 331-10-231 Characteristics	
	N = 636 *Sex*: Male and Female *Age*: 18 to 65 years *Setting*: Inpatients *Inclusion criteria*: Willing to be hospitalised, an acute exacerbation of psychotic symptoms and marked deterioration of usual function as demonstrated by meeting *all* of the following criteria at the screening and baseline visits: Total BPRS score ≥ 40 *and* Score of ≥ 4 on 2 or more of the following BPRS items: hallucinatory behaviour, unusual thought content, conceptual disorganisation, or suspiciousness CGI-S score ≥4 (moderately ill). *Excluded*: schizoaffective disorder and any other axis 1 or 2 disorders, those who had ≥ 30% improvement in PANSS rating between screening and baseline scores, other major mental health disorders, including but not limited to PTSD, major depression, significant suicidal ideation, pregnancy and breast feeding, treatment resistance and other medical conditions/abnormal lab values which seem reasonable.
Interventions	*Brexpiprazole*: Dose = 4 mg/day, N = 180 *Brexpiprazole*: Dose = 2 mg/day, N = 182 *Brexpiprazole*: dose = 0.25 mg/day, N = 90 *Placebo*: N = 184
Outcomes	*Efficacy*: Positive and Negative Syndrome Scale (PANSS; total, positive and negative), Clinical Global Impression, Severity of Illness scale, PANSS Excited Component (PEC) scores, PANSS Marder Factor scores, Clinical Global Impression, Improvement (CGI-I) scale, and Personal and Social Performance Scale (PSP).
Notes	Company funded trial.

Table 12: Study 331-10-231 Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were randomly assigned through an IVRS or IWRS to receive brexpiprazole or matching placebo. Blocks of randomisation numbers based on a permuted-block randomisation schedule pre-generated by the sponsor (OPDC Biometrics Department) were assigned to trial sites by the IVRS or IWRS. Subjects who satisfied the eligibility criteria were assigned a randomisation number by the IVRS or IWRS in a 2:2:1:2 ratio from a block of

Bias	Authors judgement	Support for judgement
		randomisation codes within the trial site. This number corresponded to one of the following treatment groups: Brexpiprazole 2 mg/day Brexpiprazole 4 mg/day Brexpiprazole 0.25 mg/day Placebo A copy of the computer generated permuted block randomisation schedule was made available.
Allocation concealment (selection bias)	High risk	No allocation concealment described.[34]
Blinding of participants and personnel (performance bias)	Unclear risk	The investigator was instructed to not access or to reveal the treatment assignment code for an individual subject except in case of emergency. Any blinding that was broken was documented. Double blind trial. Some detail outlined as to how blinding was done.
Blinding of outcome assessment (detection bias)	High risk	Robustness of the blinding process and success not evaluated.
Incomplete outcome data (attrition bias)	High risk	LOCF and OC analysis used for missing data.[35] As reported in previous studies, this approach has shortcomings.
Selective reporting (reporting bias).	Low risk.	Most available data appear to have been reported.
Comment	Unclear risk	Other psychotropic including antipsychotics excluded similar to other studies of this design. Sponsor funded study.

7.3.2.1. Results for the primary efficacy outcome

Similar to other studies in this genre, this study used the primary efficacy measure as change from Baseline to Week 6 on the PANSS total score. There were statistically significant improvements in the brexpiprazole 2 mg and 4 mg arm compared to placebo, but no difference between brexpiprazole 0.25 mg arm and placebo. They also used the Hochberg approach to

[34] See Table 3 for the sponsor's comment on blinding risk.
[35] The sponsor commented that LOCF was only used for sensitivity. MMRM was used for the primary analysis. Under assumption of missing data being MAR, the MMRM analysis is considered valid. Sensitivity analyses under MNAR were provided in the studies.

recalculate data and the results were no different. The significant results seem to arise from Week 3 onwards and remained through to Week 6.

7.3.2.2. Results for other efficacy outcomes

Other key secondary measures, again similar to other studies measured CGI-I, CGI-S and PSP scores. The brexpiprazole 2 mg and 4 mg arms were superior to placebo but not the 0.25 mg arm. PANSS subscale data are reported as being superior for the same outcomes.

7.3.2.3. Evaluator commentary

Handling of missing data is an issue to note across all the trials as outlined in more detail within Study 14644A. Risk of bias is an issue similar to other studies of this nature outlined previously. Brexpiprazole appears to prevent relapse compared to placebo in adequate doses and it is reasonably clear that the dose range of 4 mg/day is much more optimal compared with the smaller doses, for example 0.25 mg a day.[36]

7.3.3. Study 331-10-002

This is a protocol for 'A dose-finding trial of OPC-34712 in patients with schizophrenia'. It is planned to be a multicentre study utilising approximately 140 sites in Japan. The objective is to investigate the efficacy and safety brexpiprazole at 1, 2, and 4 mg in comparison with placebo in subjects with schizophrenia. The details of the study design are very similar to Study 331-10-230 in that there is a 2 week wash out phase, will run for a 6 week period and will only be conducted on inpatients. This is study protocol for an ongoing study and no results available yet.

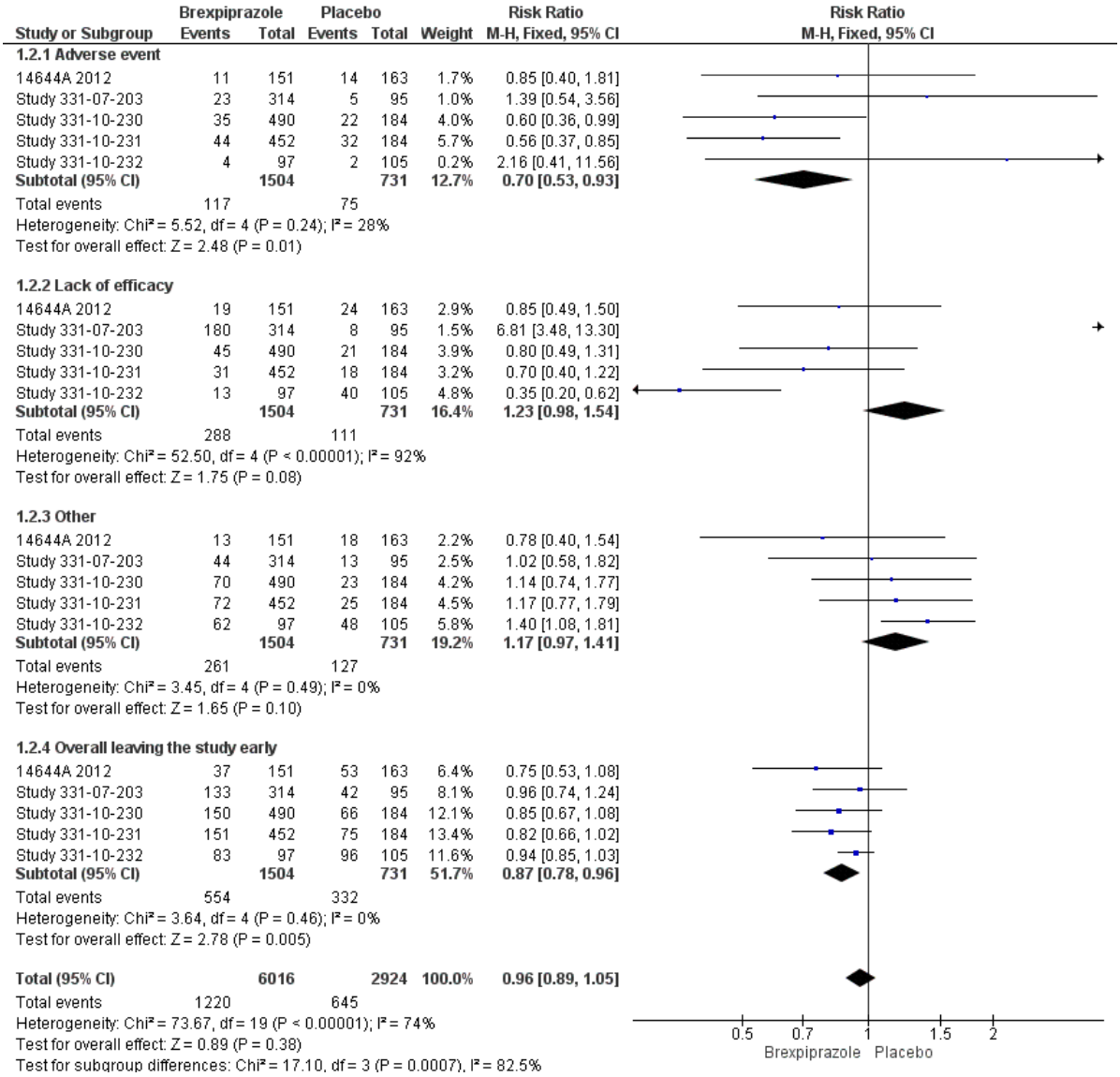
7.4. Analyses performed across trials: pooled and meta analyses

There were no specific meta-analyses available; however the evaluator performed their own pooled meta-analyses from the available data. These were conducted using data available from the documents provided and for only the key efficacy outcomes. Additional data was gathered, such as standard deviations from the ClinicalTrials.gov website when they were not clearly reported in the study reports. Please note that these are not fully conducted systematic reviews of literature that supported the meta-analysis as that was outside the scope of this review. Key efficacy measures and dichotomous outcomes on leaving the study early due to the various reasons listed in the respective studies were included. There were only 2 studies that compared brexpiprazole versus other antipsychotics for schizophrenia. Efficacy analysis from these are analysed as well.

[36] The sponsor commented that Prevention of relapse was shown in Trial 331-10-232, but was not an objective this Trial 331-10-231. This trial showed efficacy in the acute setting up to 6 weeks for brexpiprazole 2 and 4 mg/day.

7.4.1. Analysis 1

Table 13: Analysis 1 Reasons for dropout (All studies)



See the sponsor's comments on potential discrepancies in the data in the following footnote.[37]

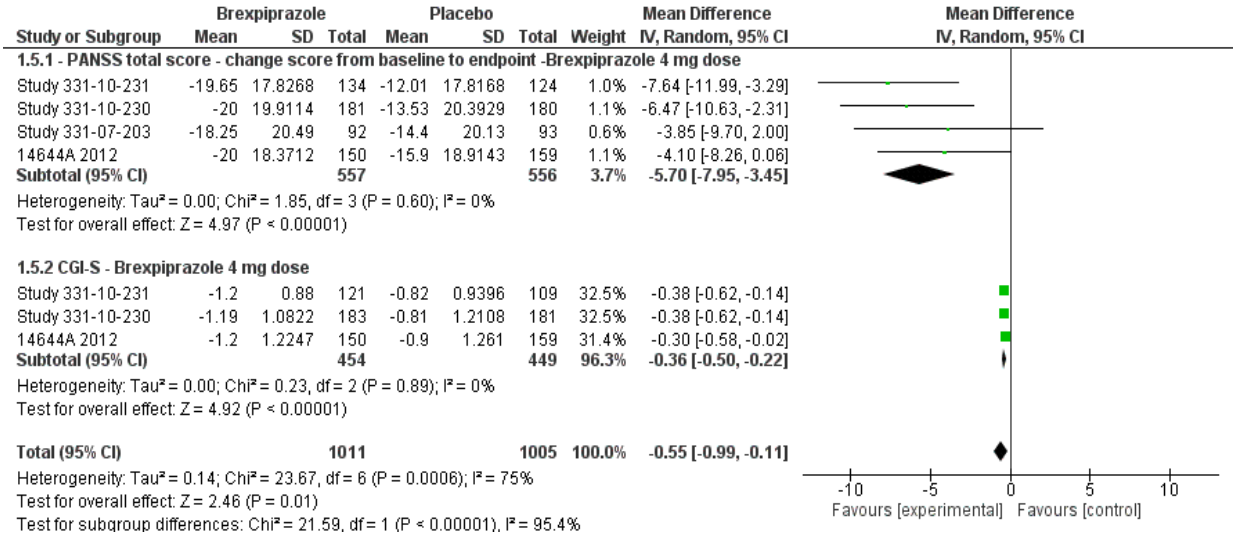
For the individual outcomes of overall leaving the study early, brexpiprazole arm was superior to placebo. Similarly, brexpiprazole appeared to be superior to placebo for the outcome of adverse events. On the other hand, for other outcomes which included things such as protocol deviations, investigator led discontinuation and lack of efficacy, the trends seemed to favour placebo however were not significant. When all of these outcomes are pooled using risk ratios, fixed effect model, there was no difference between the 2 groups. The overall pooled effect score was RR 0.96, 5 RCTs, 95% CI (0.89, 1.05).

[37] The sponsor commented with the following: under heading 1.2.2 Lack of efficacy: Withdrawal due to lack of efficacy occurred in 18 subjects across the 4 brexpiprazole arms, not 180. This will change the result of this part of the meta-analysis; under heading 1.2.3 Other: Withdrawal rate due to other reasons was 14 subjects for placebo arm. Withdrawal rate due to other reasons was 46 subjects for placebo arm; and under heading 1.2.4 Overall leaving the study early: Overall withdrawal rate was 97 subjects for brexpiprazole arms. Overall withdrawal rate was 27 subjects for placebo arm.

7.4.2. Analysis 2

Analysis from 4 RCTs providing data on continuous variables reporting change in PANSS total score, which has been the primary efficacy score across the trials.

Table 14: Analysis 2 Primary efficacy outcome (All studies)



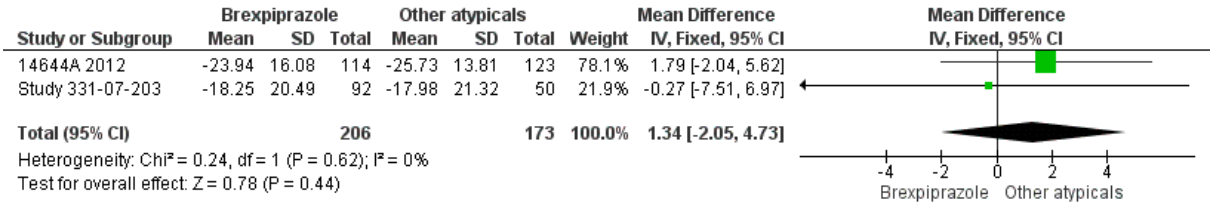
For the key outcome of change in PANSS score from Baseline to endpoint, which has been considered as a measure of efficacy against both placebos and other atypical antipsychotics, the data available has been largely skewed as noted in the graphs above. If we were to apply the reliable formula that data are skewed when the mean < 2 x SD, then it is numerically obvious as well. Hence comparing these data should be interpreted with caution. The trend seems to favour brexpiprazole compared with placebo. The pooled mean difference is -5.70 (95% CI -7.95 to-3.45) for 4 RCTs with a total population of 1113 participants.

The efficacy was a bit more robust for the measures of CGI-S and the confidence intervals were narrower favouring brexpiprazole: MD -0.55 (-0.99, -0.11).[38]

Heterogeneity for both the outcomes is low, however higher when pooled as expected.

7.4.3. Analysis 3

Table 15: Analysis 3 Efficacy data based on PANSS score change comparing with other atypical antipsychotics (LOCF data)

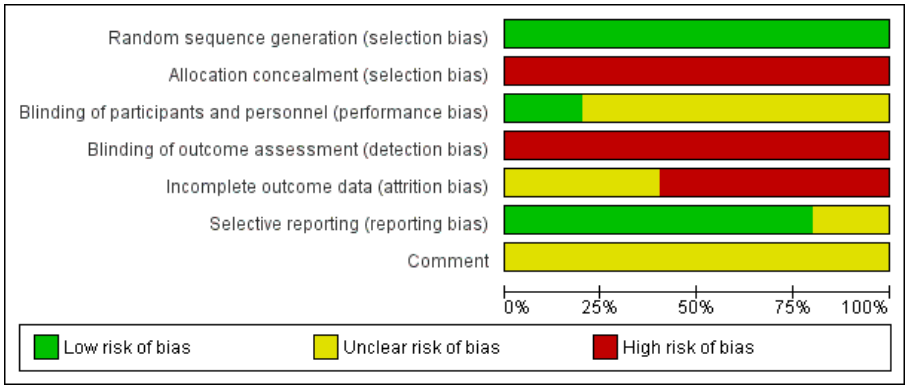


The Study 14644A related to comparison between brexpiprazole and quetiapine and the second study related to comparison between brexpiprazole and aripiprazole. These need to be interpreted with caution. There were no statistically significant differences between the 2 groups.

[38] The sponsor commented that this mean difference seems to be calculated by averaging the mean differences of the PANSS and CGI-S scores. As these scales have different ranges of scoring, averaging the means do not seem to give an interpretable value. A more usual approach in such analysis would be to use the standardised effect sizes for each of the scales and average those.

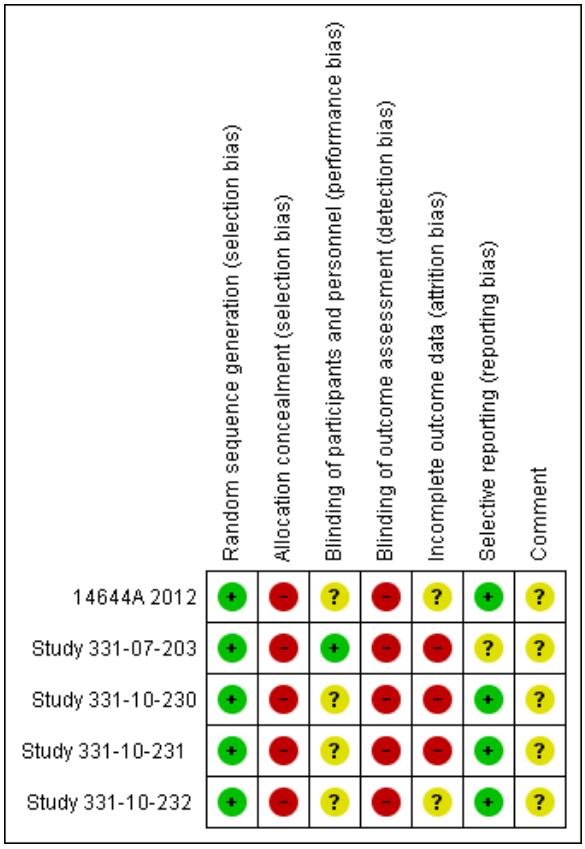
Overall risk of bias ratings from all included RCT studies are outlined in 2 ways below in Figures 5 and 6.

Figure 5: Risk of bias graph



Note: Please review the clinical evaluator's judgements about each risk of bias item presented as percentages across all included studies)

Figure 6: Risk of bias summary



Note: Please review the clinical evaluator's judgements about each risk of bias item for each included study.

Other studies evaluated are largely uncontrolled studies, the majority of which are open label studies that followed on from previous RCTs, some longer term up to 2 weeks. Due to high risk of bias inherent in the trial design, these have not been evaluated in detail for risk of bias.

7.5. Evaluator's conclusions on clinical efficacy

From the evidence available, there some good quality data available from randomised controlled studies evaluating the efficacy, side effects and tolerability of brexpiprazole

compared with placebo and within 2 trials comparing with aripiprazole and quetiapine respective.

All but one of the RCTs was of short duration, conducted within 6 weeks. The 1 longer term study was conducted over 52 weeks, an evaluation of relapse rates and time to discontinuation rates evaluated brexpiprazole in various doses versus placebo.

7.5.1. Limitations

These are short terms trials, mostly conducted in acute inpatient setting where the patient was able to provide consent. Despite these short term trials, the dropout rates although not very different from other intervention or placebo groups were around the 30% mark which is a bit high. There are some methodological limitations as outlined in the individual study risk of bias tables, especially in relation to allocation concealment, testing blinding and accounting for missing data using OC and LOCF measures.[39] Thus, the overall results need to be interpreted with caution.

7.5.2. Overall comments

A positive attribute amongst these trials is to note that ≥ 30% reduction in PANSS score was noted as a criterion for improvement which is an improvement over trials in this nature historically which defined ≥ 20% as improvement. The authors have been able to demonstrate improvement versus placebo on this measure. It is interesting to note that there have been significant response rates to placebos throughout these trials. The reasons for this should be explored further. The dose ranges studied seemed to be appropriate and the dose of 0.25 mg clearly comes across as sub-therapeutic. Majority of the optimal efficacy appears to occur in the 4 mg a day dose range although the lower dose ranges have been effective. Brexpiprazole seems to work compared with placebo in reducing PANSS scores most of the time, however only in the higher dose range and it was not much different to quetiapine or aripiprazole.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.1.2. Pivotal and/or main efficacy studies

As outlined above under efficacy, 3 studies evaluating the efficacy of brexpiprazole in the treatment of schizophrenia were identified by the evaluator as pivotal.[40] These were:

- Study 14644A: A Phase III, multicentre, randomised, double blind, parallel group, placebo controlled, active reference, flexible dose study of brexpiprazole in patients with acute schizophrenia;
- Study 331-10-232: A Phase III, multicentre, randomised, double blind, placebo controlled trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia; and
- Study 331-07-203: A Phase II, 6 week, multicentre, randomised, double blind, placebo controlled study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 once

[39] This seems to be based on the assumption that LOCF was used for primary analysis. This was the case only for Phase II trial 331-10-203, but not for the Phase III trials.
[40] The sponsor considers Trials 331-10-231 and 331-10-230 as pivotal. Trial 331-10-203 was a Phase II trial which failed to show assay sensitivity and therefore not considered pivotal.

daily and aripiprazole once daily for treatment of hospitalised adult patients with acute schizophrenia.

8.1.3. Other studies

8.1.3.1. Other efficacy studies

2 other controlled efficacy studies relating to the use of brexpiprazole in the treatment of schizophrenia were identified in the submission, as outlined under efficacy, above. These were:

- Study 331-10-230; A Phase III, multicentre, randomised, double blind, placebo controlled trial of fixed dose OPC-34712 (4, 2, and 1 mg/day) in the treatment of adults with acute schizophrenia; and
- Study 331-10-231; A Phase III, multicentre, randomised, double blind, placebo controlled trial of 3 fixed doses of OPC-34712 in the treatment of adults with acute schizophrenia.

Within the safety data set, several open label trials of brexpiprazole in schizophrenia, not previously discussed in the evaluation, were also identified.

Trial 331-08-210 is a completed Phase II, 52 week, open label trial that assessed the long term safety and efficacy of brexpiprazole in 244 adults with schizophrenia. Subjects could enrol in this trial after completing the Week 6 visit in parent Trial 331-07-203 during which they had received treatment with brexpiprazole, aripiprazole, or placebo. Initially, the protocol was approved as a 6 week trial and was extended to be a 52 week trial with Amendment 2. Of the 244 subjects who entered the trial, 216 subjects were part of the original protocol specified 6 week enrollers and 28 were part of the Amendment 2 permitting 52 week enrollers. The dose range of brexpiprazole was 1 to 6 mg/day.

Trial 331-10-237 is an ongoing Phase III, open label trial that assessed the long term safety and efficacy of brexpiprazole in adults with schizophrenia. Trial 331-10-237 was originally 52 weeks in duration, but has been amended in certain countries to be 26 weeks in duration. Subjects were eligible to enrol in this trial after completing the Week 6 visit in parent Trials 331-10-230 or 331-10-231, or the Week 52/early termination (ET) visit in Trial 331-10-232; or could be de novo subjects. Rollover subjects received prior treatment with either brexpiprazole or placebo. The dose range of brexpiprazole was 1 to 4 mg/day during the Phase B treatment period; rollover subjects from Trials 331-10-230, 331-10-231, and 331-10-232 may have received a starting dose of 2 mg/day brexpiprazole, and de novo subjects received a starting dose of 1 mg/day brexpiprazole. Dose adjustments were then made based upon the clinical judgment of the investigator as it related to tolerability and therapeutic response.

Trial 14644B is an ongoing Phase III, 52-week, open label extension of Trial 14644A to assess the long term safety and efficacy of brexpiprazole in adult subjects with schizophrenia. Subjects were eligible to enrol in the open label extension after completing Trial 14644A. The dose range of brexpiprazole in the extension trial was 1 to 4 mg/day.

Taken together, the pivotal, additional completed efficacy studies and open label studies were pooled in the submission as the 'schizophrenia trials' and this data was mainly utilised by the evaluator as the most relevant data set to the requested indication.

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

The following studies were identifiable as part of the dose finding and pharmacology development of the molecule that provided evaluable safety data:

- Study 331-07-201: Arm 1; Healthy subjects; single rising dose, safety, tolerability, and PK; brexpiprazole dose 0.2, 0.5, 1, 2, 4, 6, and 8 mg.
- Study 331-08-206: Healthy subjects; multiple rising dose safety, tolerability, and PK; brexpiprazole dose 0.5, 1, 2, and 3 mg.

- Study 331-08-205; Subjects with Schizophrenia; Multiple rising dose safety, tolerability, and PK; brexpiprazole dose 1, 2, 4, 6, 8, 10 and 12 mg.
- Study 331-09-221: Subjects with MDD; Multiple dose safety, tolerability, and PK; brexpiprazole dose 1.5, 2, 3, and 4 mg.
- Study 331-09-220: Subjects with ADHD; Multiple dose safety, tolerability, and PK; brexpiprazole dose 3 and 4 mg.
- Study 331-12-291: Subjects with MDD; Multiple dose safety, tolerability, and PK in elderly; brexpiprazole dose 2 mg
- Study 3331-09-226: Healthy subjects; Effect of severe renal impairment; brexpiprazole dose 3 mg.
- Study 331-10-244: Healthy Subjects; Effect of age and gender on brexpiprazole; brexpiprazole dose 2 mg.

These studies have been discussed under pharmacokinetics and pharmacodynamics of this evaluation and will only be further referred to in this section when they provide significant addition to the safety data.

8.1.3.3. Studies evaluable for safety only

Several ongoing studies of brexpiprazole in schizophrenia were also identified. 2 were of particular interest. Study 331-10-002 is a dose finding trial of OPC-34712 in patients with schizophrenia. It is planned to be a multicentre study utilising approximately 140 sites in Japan. Whilst final data is not available, safety data was identified in the submission. Study 331-10-233 is a Phase I, open label, dose escalation trial to examine safety, tolerability and pharmacokinetics of brexpiprazole in adolescents with schizophrenia. An early synopsis was available in the submission. Whilst this in the adolescent population is of great interest, at this point, only 4 subjects had been enrolled and safety data was only available for 3 subjects. No deaths, serious adverse events or drop outs due to safety issues were noted at this point. This data can thus only be considered very preliminary and will not be discussed further, but would be valuable to ultimately review.

In addition, there are a number of studies that looked at the use of brexpiprazole for other clinical indications, primarily MDD and ADHD. Whilst these are not related to the requested indication, it is clear that the data they contain in relation to safety is of relevance generally. The completed studies in this indication were collected together with the schizophrenia trials under the heading 'All Brexpiprazole Trials group'. This dataset was also reviewed to look for any new issues within the larger data set.

8.2. Studies that assessed safety as the sole primary outcome

Not applicable.

8.3. Patient exposure

As of 15 May 2015 (data cut-off date), the number of subjects with schizophrenia who have been exposed to 1 dose of brexpiprazole was 1406 in the short term, controlled trials, 97 in the long term controlled trial and 1265 in the long term, open label trials. In the long term, open label trials, 604 subjects were exposed to brexpiprazole for 26 weeks (6 months) and 372 subjects for 52 weeks (1 year) from long term Baseline, not including possible exposure in the parent trial. An overview of exposure across studies is shown in Table 16, below.

Table 16: Exposure to brexpiprazole and comparators in clinical studies in schizophrenia

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Brex
	Brex	Placebo	Quetiapine	Aripiprazole	Brex	
Schizophrenia						
Short term, controlled	1406	624	154	50		1406
Long term	97	104				97
Open label					1265	1265
Total:	1503	728	154	50	1265	2768

Looking at duration of exposure, from the long term and open trials, a total of 681 subjects with schizophrenia had exposure longer than 6 months, and 413 longer than 12 months. The mean dose of brexpiprazole exposure was 2.4 (± 1.3), 3.6 (± 0.7), and 3.1 (± 0.8) mg in the short term controlled, long term controlled and open label studies respectively.

In the 4 short term, controlled trials, the mean duration of treatment was slightly shorter at sites in North America (31.7 days) compared with sites in Europe (35.7 days), Asia, (35.0 days) and Latin America (39.3 days). The mean duration of treatment was similar across treatment groups for the different age groups, genders, and race groups.

Exposure to longer duration controlled treatment in the single long term controlled study is made slightly more complex by the nature of the design. It is however noteworthy that only 77 subjects with schizophrenia have had more than 6 months exposure to brexpiprazole in a controlled trial. This number could reasonably be considered at the lower end of the range for safety evaluation. This point is counterbalanced by the relatively large amount of longer term exposure in the open label studies. The mean duration of exposure to brexpiprazole was 197.1 days in the long term, open label trials group. Of the 1265 subjects with schizophrenia exposed to brexpiprazole in the long term, open label trials, 604 subjects (47.7%) were exposed to ≥ 26 weeks of treatment and 372 subjects (29.4%) were exposed to ≥ 52 weeks of treatment. The overall level of exposure to the compound in subjects with schizophrenia could thus be considered adequate for safety evaluation.

Although containing subjects with other indications including MDD and PTSD, the broader 'All brexpiprazole trials group' contained, as of the data cut-off date of 15 May 2015, 5636 subjects who had been exposed to at least 1 dose of brexpiprazole across the Phase II/III trials for schizophrenia, MDD, and ADHD. Overall, 1504 subjects (26.7%) have been exposed to brexpiprazole for 52 weeks. Overall, 2048 subjects were exposed to 1 mg (< 1.5 mg) brexpiprazole across indications (schizophrenia, MDD, ADHD). The majority of subjects (n = 3501) were exposed to brexpiprazole within the proposed therapeutic dose range (2 to 4 mg/day); 1619 subjects were exposed to 2 mg (1.5 to < 2.5 mg) doses, 1158 subjects were exposed to 3 mg (2.5 to < 3.5 mg) doses, and 724 subjects were exposed to 4 mg (3.5 to 4.5 mg) doses of brexpiprazole. A total of 87 subjects received doses of brexpiprazole > 4 mg (> 4.5 mg). This thus constituted an important supplementary set of exposure and safety data.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

Treatment emergent adverse events (TEAE) were reported by exposure for the short term controlled studies as below. The percentage of subjects reporting ≥ 1 TEAE was similar in the brexpiprazole 2 to 4 mg/day group and placebo group (58.4% and 59.3% respectively). No TEAE satisfied the reasonable sponsor's predefined criteria for 'common, i.e., incidence ≥ 5% in the all brexpiprazole group and ≥ 2 x placebo'. The most frequently experienced (5% of subjects) TEAEs in the brexpiprazole 2 to 4 mg/day group were headache, insomnia, agitation, akathisia, and schizophrenia; of which, only akathisia was reported by a higher percentage of subjects in the all brexpiprazole group than in the placebo group. Events reported by 2% of subjects in the brexpiprazole 2 to 4 mg/day group with an incidence higher than in the placebo group were diarrhoea, nausea, dyspepsia, toothache, weight increased, blood CPK increased, back pain, akathisia, tremor, dizziness, sedation, and headache.

The majority of TEAEs were classified as mild (29.9% and 29.6% of subjects in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively) or moderate (23.5% and 23.4% of subjects in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively). Most of the severe TEAEs reported by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were in the 'Psychiatric Disorders' SOC and included schizophrenia (21 subjects (2.2) and 20 subjects (3.2%) in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively), agitation (8 subjects (0.8%) and 4 subjects (0.6%), respectively), psychotic disorder (3 subjects (0.3%) and 4 subjects (0.6%), respectively), insomnia (4 subjects (0.4%) and 1 subject (0.2%), respectively), and schizophrenia, paranoid type (2 subjects (0.2%) and 2 subjects (0.3%), respectively). Other severe TEAEs experienced by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were blood CPK increased (3 subjects (0.3%) and 1 subject (0.2%), in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively), psychomotor hyperactivity (2 subjects (0.2%) and 1 subject (0.2%), respectively), and rhabdomyolysis (2 subjects (0.2%) and 0 subjects, respectively).

For the single long term controlled study, in the single blind stabilisation phase of Trial 331-10-232 (Phase B) a total of 464 subjects were treated with brexpiprazole (1 to 4 mg/day). Of these subjects, 277 (59.7%) had TEAEs during the stabilisation phase). The most frequently occurring TEAEs (≥ 5% of subjects) were insomnia (12.1%), akathisia (9.1%), agitation (6.5%), schizophrenia (6.0%), weight increased (5.2%), and headache (5.0%). During the double blind maintenance phase of Trial 331-10-232, 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. The most frequently occurring TEAEs in the placebo group were headache (9.6%), insomnia (7.7%), schizophrenia (6.7%), nasopharyngitis (6.7%), and psychotic disorder (5.8%). Events reported in ≥ 2% of subjects in the brexpiprazole group with a higher incidence relative to placebo, included tremor, pruritus, decreased appetite, musculoskeletal pain, muscle spasm, and toothache. Again, no TEAE in the double blind maintenance phase satisfied the sponsor's criteria for 'common' TEAEs, that is, incidence > 5% in the brexpiprazole group and ≥ 2 x placebo. The incidence of TEAEs in the 'Psychiatric Disorders' SOC was 9.3% in the brexpiprazole group compared with 24.0% in the placebo group.

In the single blind stabilisation phase of Trial 331-10-232 (Phase B) and in the double blind maintenance phase, the majority of TEAEs were mild to moderate in severity, with severe TEAEs occurring infrequently. During the double blind maintenance phase, the number of subjects reporting severe TEAEs was low in both treatment groups (2 (2.1%) brexpiprazole, 3 (2.9%) placebo). Severe psychotic disorder (1 subject (1.0%)) and severe insomnia and decreased appetite (1 subject (1.0%)) were reported in the brexpiprazole group, and severe

psychotic disorder, suicidal ideation, and hypertension were reported in the placebo group (1 subject (1.0%) each).

Finally, in the open label long term studies, the percentage of subjects reporting 1 TEAE in the long term, open label schizophrenia trials was 59.1%. The most frequently experienced TEAEs in the all brexpiprazole group were schizophrenia, insomnia, weight increased, and headache, similar to the short term trials. The incidence of subjects with weight increased was higher in the population of subjects who completed 52 weeks of treatment (15.0% of completers versus 8.0% of safety sample) than in the pooled population that included subjects who were treated for a shorter time period. The significance of the higher rate of weight gain in those exposed to brexpiprazole for more than 12 months in this group is highlighted by the relatively low numbers exposed to brexpiprazole for that duration of time in the single longer term controlled trial.

Most subjects had events that were mild (27.4%) or moderate (24.4%) in severity in the open long term trials, the percentage of subjects who reported ≥ 1 TEAE that was severe was 7.4%. Most severe TEAEs were related to the underlying condition: schizophrenia (44 subjects, 3.5%), agitation (5 subjects, 0.4%), and psychotic disorder (9 subjects, 0.7%). The only other severe TEAEs that occurred in more than 1 subject were weight increased (2 subjects), suicidal ideation (2 subjects), and peritonitis (2 subjects, 0.2%). The severe peritonitis was fatal in 1 of the 2 subjects in which it occurred.

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.1.3. Other studies

Studies evaluable for safety only

Of note, in the broader 'All brexpiprazole trials' dataset reported in the submission, 5636 subjects (schizophrenia 2579, MDD 2902, and ADHD 155) who were treated with one or more doses of brexpiprazole through 15 May 2015. Of these subjects, 4218 (74.8%) had TEAEs, with the highest incidence of TEAEs occurring in subjects with MDD (82.4%), followed by schizophrenia (67.2%), and ADHD (61.3%). Overall, nervous system disorders (35.4%) and psychiatric disorders (31.3%) were predominant across indications. Headache (9.7%), akathisia (9.2%), and somnolence (6.2%) were the most frequently occurring TEAEs within the nervous system disorders SOC; insomnia (10.3%) and anxiety (5.1%) were the most frequently occurring TEAEs within the psychiatric disorders SOC. For subjects with schizophrenia in the 'All brexpiprazole trials' group, the incidences for the following frequently occurring TEAEs were: insomnia (12.3%), headache (10.0%), schizophrenia (9.3%), weight increased (7.7%), and akathisia (7.4%). Of some note, the rate of weight increase as a TEAE was even higher in the MDD group at 21.8%.

Overall, the TEAE data suggests that akathisia, insomnia and headache are relatively frequent early problems. The akathisia is unsurprising given the mode of action of the compound. It was not fully clear if the rates of headache and insomnia are greater than placebo. Although there is some conflict in the results between the controlled and open label longer term studies, the data could reasonably be construed to suggest that the risk of weight gain with prolonged treatment is real although the extent of the issue unclear.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

In the short term controlled studies, the percentage of subjects with TEAEs assessed by the investigator as potentially related to IMP was 36.2% in the brexpiprazole 2 to 4 mg/day group compared with 32.5% in the placebo group. The most frequently experienced TEAEs (> 2% of subjects in the brexpiprazole 2 to 4 mg/day group) that were assessed as potentially related to

IMP were headache (6.3%), akathisia (5.5%), insomnia (5.2%), weight increased (4.0%), nausea (2.7%), agitation (2.6%), tremor (2.6%), constipation (2.2%), sedation (2.1%) and somnolence (2.2%).

Of these potentially related events, akathisia, weight increased, nausea, tremor, insomnia, and sedation were reported at rates higher in brexpiprazole-treated subjects than in placebo treated subjects.

In the long term controlled pivotal Study 331-10-232, in the single blind stabilisation phase, a third of all subjects (33.2%) had potentially drug related TEAEs, most of which were associated with the nervous system disorders (20.5%) or psychiatric disorders (9.5%) SOC. Akathisia (8.2%) and insomnia (5.8%) were the most frequently occurring potentially drug related TEAEs. Overall, 19.4% of subjects had potentially treatment related TEAEs in the double blind maintenance phase of Trial 331-10- 232. Subjects treated with brexpiprazole had a lower incidence of potentially treatment-related TEAEs (14.4%) compared with subjects who received placebo (24.0%), primarily due to a lower incidence of potentially treatment related nervous system disorders (7.2% versus 12.5%) and psychiatric disorders (4.1% versus 7.7%).

The most frequently occurring potentially treatment related TEAEs for the brexpiprazole group were tremor (3 (3.1%)), headache (2 (2.1%)), and insomnia (2 (2.1%)); all other TEAEs occurred in ≤ 1 brexpiprazole treated subject. The most frequently occurring potentially treatment related TEAEs for the placebo group were headache (4 (3.8%)), dizziness (3 (2.9%)), extrapyramidal disorder, insomnia, psychotic disorder, and schizophrenia (all reported in 2 (1.9%) subjects).

The percentage of subjects in the long term, open label trials who reported an event that was assessed by the investigator as potentially related to IMP was 32.3%. Weight increased (7.1%), akathisia (4.5%), insomnia (3.7%), headache (2.6%), somnolence (1.8%), schizophrenia (1.7%), tremor (1.7%), agitation (1.2%), dyskinesia (1.0%), and extrapyramidal disorder (1.0%) were the most frequently reported (≥ 1% of subjects) TEAEs assessed as potentially related to IMP.

8.4.2.2. Other studies

[41]Overall, 5636 subjects (schizophrenia 2579, MDD 2902, and ADHD 155) were treated with one or more doses of brexpiprazole through 15 May 2015. Of these subjects, 4218 (74.8%) had TEAEs, with the highest incidence of TEAEs occurring in subjects with MDD (82.4%), followed by schizophrenia (67.2%), and ADHD (61.3%). Overall, nervous system disorders (35.4%) and psychiatric disorders (31.3%) were predominant across indications. Headache (9.7%), akathisia (9.2%), and somnolence (6.2%) were the most frequently occurring TEAEs within the nervous system disorders SOC; insomnia (10.3%) and anxiety (5.1%) were the most frequently occurring TEAEs within the psychiatric disorders SOC. Over half of all subjects (55.4%) had potentially drug related TEAEs, most of which were associated with the nervous system disorders (30.1%) or psychiatric disorders SOCs (19.4%).

For subjects with schizophrenia in the 'All brexpiprazole trials' group, the incidences for the following frequently occurring TEAEs were: insomnia (12.3%), headache (10.0%), schizophrenia (9.3%), weight increased (7.7%), and akathisia (7.4%). Potentially drug-related TEAEs were reported for 41.6% of subjects with schizophrenia, the most frequent of which (incidence ≥ 5% for the events listed above) were akathisia (7.0%), weight increased (6.9%), insomnia (5.8%), and headache (5.4%).

In summary, the adverse event data is consistent with a relatively favourable general tolerability profile. The evidence is strongly suggestive of akathisia as a treatment related event. This is unsurprising given the receptor binding profile of the agent and its close chemical relationship to aripiprazole, which is noted for this issue. A somewhat lower frequency than is

[41] The first sentence describes TEAEs while the second sentence only describes related TEAEs.

seen in the initial trials with aripiprazole in schizophrenia may be related to a more gentle titration regime than was seen in the initial trials with aripiprazole in that condition.[42] Insomnia and headache also appear relatively frequent, although not meeting the threshold for excess frequency relative to placebo. The adverse event data in relation to weight gain from both the short term, and more significantly the longer term data is somewhat conflicting. In particular, the finding of increased likelihood of weight gain as an adverse event with greater duration of exposure suggests this may be an important issue. It is however noteworthy that weight gain with other atypical antipsychotic agents is often noted as an adverse event within the first few months of therapy.

These impressions, particularly in relation to extrapyramidal side effects, were supported by a useful table exploring TEAEs of interest in the schizophrenia trials, reproduced below. It is noteworthy that this does not explore metabolic issues.[43] It is also noteworthy that the above mentioned abnormalities such as rhabdomyolysis and raised CK that may suggest neuroleptic toxicity do not necessarily meet full criteria for a diagnosis of neuroleptic malignant syndrome, which would be anticipated to be a rare but serious complication.

Table 17: Summary of incidence for selected safety topics of interest (safety sample: short term, controlled, long term, controlled, and long term, open label trials in schizophrenia)

Topic	Percentage of Subjects						
	Short-term,controlled				Long-term, Controlled a		Long-term, open-label
	BREX (N=1406)	Placebo (N=624)	ARI (N=50)	QUET (N=153)	BREX (N=97)	Placebo (N=104)	BREX (N=1265)
Metabolic syndrome b	1.2	1.2	0.0	2.4	0.0	0.0	2.94
Any EPS event c	11.9	8.7	12.0	9.2	6.19	4.81	8.93
Akathisia	6.3	4.3	4.0	3.9	1.03	0.96	4.66
Dyskinetic	0.3	0.6	0.0	0.0	1.03	0.96	1.11
Dystonic	1.6	1.9	4.0	0.7	2.06	0.96	1.19
Parkinsonian-like	4.9	2.6	6.0	5.2	3.09	1.92	3.08
Residual effects	0.2	0.2	0.0	0.7	--	--	--
Seizures	0.1	0.2	2.0	0.0	0.00	0.00	0.16
Somnolence	5.0	4.3	4.0	26.1	0.00	0.00	3.3
Suicidality TEAEs	0.3	0.2	0.0	0.0	0.00	1.92	1.03
Completed suicide	--	--	--	--	0.00	0.00	0.08
Intentional overdose	--	--	--	--	0.00	0.00	0.08
Intentional self-injury	0.1	0.0	0.0	0.0	0.00	0.00	--
Suicidal ideation	0.1	0.2	0.0	0.0	0.00	01.92	0.79
Suicide attempt	0.1	0.0	0.0	0.0	0.00	0.00	0.16
NMS	0.0	0.0	0.0	0.0	0.00	0.00	0.0
Hypersensitivity	2.0	0.8	2.0	1.3	1.03	1.92	0.87
VTEs	0.0	0.0	0.0	0.0	0.00	0.00	0.0

[42] The sponsor believes that lower incidence of akathisia may have to do with the pharmacology profile, not because of a more gentle titration. The faster titration was not associated with high incidence of akathisia.
This issue was further addressed through a clinical question to the sponsor. For details of this question, and the evaluator's response, see Section 12, Question 8: *'Would the sponsor consider some expansion of the wording around akathisia within the PI and CMI, noting that higher dose and rapid dose escalation is likely despite their appropriate advice not to.'*

[43] Metabolic issues were explored elsewhere in the submitted data.

Note: Subjects with multiple EPS TEAE were only counted once in total EPS row. a Double blind, Maintenance phase. b Ne is the total number of subjects who did not meet the criteria at Baseline and had a post baseline result (Ne is the denominator for the percentage calculation). For the treatment groups: Ne = 1125 (brexpiprazole), Ne = 507(placebo), Ne = 42(aripiprazole), Ne = 127(quetiapine) in short term, controlled trials; Ne = 72 (brexpiprazole) and Ne = 67 (placebo) in the long term controlled trial; Ne = 987 (brexpiprazole) in long term, open label trials.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

In relation to the short term controlled trials, serious adverse events, reported by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were in the psychiatric disorders SOC and included schizophrenia (21 subjects (2.2%) and 20 subjects (3.2%) in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively), agitation (8 subjects (0.8%) and 4 subjects (0.6%), respectively), psychotic disorder (3 subjects (0.3%) and 4 subjects (0.6%), respectively), insomnia (4 subjects (0.4%) and 1 subject (0.2%), respectively), and schizophrenia, paranoid type (2 subjects (0.2%) and 2 subjects (0.3%), respectively). Other severe TEAEs experienced by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were blood CPK increased (3 subjects (0.3%) and 1 subject (0.2%), in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively), psychomotor hyperactivity (2 subjects (0.2%) and 1 subject (0.2%), respectively), and rhabdomyolysis (2 subjects (0.2%) and 0 subjects, respectively).

In relation to the long term controlled trial, in the stabilisation phase, serious TEAEs were reported for 7.3% of subjects, most of which were associated with the psychiatric disorders SOC (6.3%). Schizophrenia (4.7%), psychotic disorder (0.6%), and suicidal ideation (0.6%) were the only serious TEAEs that occurred in more than 1 subject during the stabilisation phase. 1 subject had a fatal serious TEAE (non-self-inflicted gunshot wound) during the stabilisation phase that was considered by the investigator to be unrelated to brexpiprazole therapy. Overall, 7.0% of subjects had a serious TEAE during the double blind maintenance phase of Trial 331-10-232. Subjects treated with brexpiprazole had a lower incidence of serious TEAEs (3 subjects, 3.1%) than subjects who received placebo (11 subjects, 10.6%) primarily due to the lower incidence in the psychiatric disorders SOC. Each serious TEAE in the brexpiprazole group occurred in only 1 subject.

The overall incidence of serious TEAEs in the long term, open label trials was 12.2%. Similar to results seen in the short term trials, the highest incidence of serious TEAEs in the long term trials (10.2% of subjects) occurred in the psychiatric disorders SOC, reflective of the underlying schizophrenia specific symptoms. Most other serious TEAEs in other SOCs were experienced by only 1 subject. Most serious TEAEs were not considered by the investigator to be related to IMP. 13 subjects had schizophrenia reported as serious TEAEs that were considered related to IMP; other serious TEAEs assessed as related or possibly to IMP were akathisia (2 serious TEAEs), psychotic disorder (4 serious TEAEs) and 1 serious TEAE each of anxiety, cardiac failure, grand mal convulsion, aggression, panic attack, and diabetic ketoacidosis.

7 deaths were noted in the schizophrenia short term and long term controlled and open label studies. All of the deaths were judged as not related to the IMP. 2 of the deaths were due to violent means; homicide by gunshot wound and suicide particularly in the latter case that failure of treatment may be considered relevant. A further death judged unrelated to IMP also occurred in a still blinded subject in one of the ongoing open label schizophrenia trials.[44] There were no trends noted in the cause of deaths.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

[44] This is the case from the ongoing short term study, a non-blinded, open label trial.

8.4.3.3. Other studies

There were 4 serious TEAEs reported by 4 subjects (3 subjects with schizophrenia and 1 subject with MDD) in the Clinical pharmacology trials group. All 4 subjects who reported a serious TEAE recovered from their respective events; 2 subjects continued in their respective trials and 2 were discontinued due to their respective serious TEAE. Noticeably, these events included an episode of allergic response to the study medication, which does not appear to have been seen in later studies, in a subject with schizophrenia and an episode of extrapyramidal side effects in a subject with MDD judged likely to be related to study medication. No deaths were recorded in the clinical pharmacology trials.

The overall incidence of serious TEAEs in all Phase II/III brexpiprazole trials was 5.7% (323/5636 subjects). The highest incidence of serious TEAEs occurred in the psychiatric disorders SOC (4.1% of subjects), with 2.6% of subjects reporting schizophrenia. Serious TEAEs were reported in 0.3% of subjects in each of the following SOCs: nervous system disorders, infections and infestations, and injury, poisoning and procedural complications.

The percentage of subjects who reported ≥ 1 serious TEAE was 9.5% for subjects with schizophrenia (246/2579) and 2.7% for subjects with MDD (77/2902); none of the subjects with ADHD (0/155) experienced a serious TEAE. The investigator considered the majority (> 80%) of serious TEAEs to be not related to IMP.

In the entire brexpiprazole clinical development program across Phase I through Phase III trials for all indications (schizophrenia, MDD, agitation in AD, ADHD, and PTSD overall, there have been 26 deaths in the brexpiprazole CDP as of the data cut-off date of 15 May 2015: 8 subjects with schizophrenia as above, 10 subjects with MDD, and 8 subjects with agitation in AD. Of the 26 deaths, 13 occurred in subjects who were treated with brexpiprazole (either concurrent with death or prior to death), 8 deaths occurred in subjects whose treatment remains blinded in ongoing trials, and 5 deaths occurred prior to randomisation to IMP. All deaths were considered unrelated or unlikely related to IMP by the investigator, with the exception of the death of a subject with a long history of MDD (completed suicide (possibly related)).

A medical review (blinded in the cases of deaths in placebo controlled trials) by the sponsor identified confounding information (that is, a variable that interferes with, or distorts the association being studied between 2 other variables because of a strong relationship with both of the other variables) or alternative contributing aetiology in all but 1 of the 26 deaths. Overall, the investigator assessed 23 deaths as not related and 2 as unlikely related to IMP; 1 of the deaths due to completed suicide (MDD) was assessed as possibly related to IMP. The incidence of death in the completed short term, controlled schizophrenia trials was 0.1% (1/1406 subjects). The incidence of death in the long term, open label schizophrenia trials was 1.4% (5/1265 subjects). The incidence of death in the long term, open label MDD trials was 0.2% (5/2084).

Overall, the data related to serious TEAEs were broadly consistent with the overall AE data in suggesting a relatively good tolerability profile. Whilst akathisia, other extrapyramidal symptoms and insomnia were reported, their frequency as severe events is not particularly high in the opinion of the evaluator. The presence of reports of rhabdomyolysis and raised CK amongst the serious adverse events raises the possibility of neuroleptic toxicity syndromes although the overall rate is low. This possibility is again consistent with the receptor binding profile of the drug. The deaths do not appear excessive in number or suggestive of any specific issues. It is noted that the ongoing schizophrenia trial data or ongoing trials for other conditions did not significantly alter these impressions.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

In the short term trials, the percentage of subjects reporting TEAEs leading to discontinuation of IMP was 7.8% (76 subjects) in the brexpiprazole 2 to 4 mg/day group and 12.2% (76 subjects) in the placebo group. As with serious TEAEs, AEs leading to discontinuation of IMP were predominately in the psychiatric disorders SOC and were likely related to the underlying condition (for example: schizophrenia, psychotic disorder, agitation or hallucination). The incidence of these events was similar to or greater in the placebo group than in the brexpiprazole groups. Other TEAEs that led to discontinuation in > 1 subject in the brexpiprazole 2 to 4 mg/day group were hepatic enzyme increased (3 subjects, 0.3%), psychomotor hyperactivity, tremor, and rhabdomyolysis (2 subjects each, 0.2%). The incidence of these events was greater in the brexpiprazole group than in the placebo group.

In the stabilisation phase of the long term controlled trial the most frequently occurring TEAEs resulting in discontinuation of brexpiprazole therapy were related to the subject's underlying disease. Discontinuations of IMP due to TEAEs occurred at less than half the rate in the brexpiprazole group (5.2%) compared with the placebo group (11.5%) in the double blind maintenance phase of Trial 331-10-232. This was due to a lower incidence of discontinuations due to psychiatric disorders (schizophrenia, psychotic disorder, and suicidal ideation) for subjects in the brexpiprazole group. During the DB Maintenance phase of Trial 331-10-232, no subject discontinued due to weight gain or akathisia.

A total of 178 subjects (14.1%) had a TEAE leading to discontinuation of IMP in the long term, open label trials group as of 15 May 2015. Most subjects who discontinued IMP because of a TEAE had events in the Psychiatric Disorders SOC (140 subjects, 11.1%), such as schizophrenia (103 subjects, 8.1%), psychotic disorder (18 subjects, 1.4%), and agitation (3 subjects, 0.2%). Other events leading to discontinuation of more than 2 subjects in the long term, open label trials were weight increased (5 subjects, 0.4%), akathisia (4 subjects, 0.3%), alanine aminotransferase increased (3 subjects, 0.2%), pregnancy (3 subjects, 0.2%), and agitation (3 subjects, 0.2%).

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.4.3. Other studies

Other efficacy studies

A total of 706 subjects (12.5%) had a TEAE leading to discontinuation of IMP in the all Phase II/III All brexpiprazole trials group as of 15 May 2015. Most subjects who discontinued IMP because of a TEAE had events in the psychiatric disorders SOC (365 subjects, 6.5%), such as schizophrenia (191 subjects, 3.4%), psychotic disorder (43 subjects, 0.8%), depression (30 subjects, 1.5%), suicidal ideation (16 subjects, 0.3%), and anxiety (16 subjects, 0.3%). Other events leading to discontinuation of more than 10 subjects were weight increased (80 subjects, 1.4%), akathisia (36 subjects, 0.6%), somnolence (18 subjects, 0.3%), fatigue (12 subjects, 0.2%), and insomnia (11 subjects, 0.2%). A listing of all TEAEs for subjects who were discontinued from IMP due to a TEAE was presented in the Summary of Clinical Safety [not included here].

The percentage of subjects who discontinued IMP due to a TEAE was 13.4% for subjects with schizophrenia (360/2579), 11.9% for subjects with MDD (344/2902), and 1.3% for subjects with ADHD (2/155). The most frequent TEAE that led to discontinuation of IMP was schizophrenia for subjects with schizophrenia (191/2579, 7.4%) and weight increased for subjects with MDD (75 subjects, 2.6%).

Studies with evaluable safety data: dose finding and pharmacology

In the clinical pharmacology trials, in the safety sample, 27 of 982 subjects (2.7%) (included in the safety sample, 27 of 982 subjects (2.7%) (including 24 brexpiprazole subjects (6 healthy, 4 MDD, and 14 schizophrenia and 3 placebo subjects (1 MDD, 2 schizophrenia)) were discontinued from IMP due to a TEAE. The TEAEs that led to discontinuation of IMP for more than 2 brexpiprazole subjects were extrapyramidal disorder (5 subjects (0.6%); 3 schizophrenia and 2 MDD) and akathisia (4 subjects (0.5%); 2 healthy and 2 schizophrenia). In the placebo group, agitation led to discontinuation of IMP for 2 subjects (1.9%). There were no TEAEs leading to discontinuation of IMP reported in other populations (subjects with hepatic or renal impairment) or ADHD trials.

Overall, discontinuation rates across the completed trial program are relatively low, with a pattern consistent with that noted previously in relation to TEAEs in terms of the most likely issues.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

Small mean changes from Baseline were observed for hepatic parameters for the all brexpiprazole group and the placebo group in the short term and long term, controlled trials and in the long term, open label trial. No subject in any of these trials met criteria for Hy's Law. Potentially clinically relevant changes in hepatic parameters were infrequent and the incidence of TEAEs related to hepatic function was low. Of specific no serious TEAE judged as related to IMP was reported. Whilst it is conceivable this could represent misattribution, the overall rates of abnormalities and TEAEs related to hepatic dysfunction were low and do not appear to indicate the need for active monitoring.

8.5.2. Renal function and renal toxicity

Changes in baseline chemistry and any clinically meaningful changes are discussed elsewhere. There does not appear to be any signal suggestive of IMP induced laboratory changes or clinical events.

8.5.3. Other clinical chemistry

Mean changes from Baseline to last visit in the short term and long term, controlled trials and in the long term, open label trial were similar among treatment groups for all electrolyte and other parameters (albumin, bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, protein (total), and sodium) and were small across all treatment groups; none were considered to be clinically meaningful. The frequencies of PCR values for calcium, chloride, potassium, and sodium were low and similar across brexpiprazole dose groups. The incidence of PCR values was also low and was similar in the all brexpiprazole and placebo groups. There were no TEAEs associated with electrolytes reported by brexpiprazole-treated subjects in the short term or long term, controlled trials and only 1 subject in the long term, open label trial had a TEAE associated with electrolytes (blood potassium increased).

The mean change from Baseline at last visit for each haematology parameter (basophils, eosinophils, haematocrit, haemoglobin, lymphocytes, monocytes, neutrophils, red blood cell count, and white blood cell count) was small across all treatment groups in the short term and long term trials, and none was considered to be clinically meaningful. The mean change from Baseline to last visit for each coagulation parameter (platelets, activated partial thromboplastin time, prothrombin time, and international normalised ratio) was also small and similar among treatment groups, and none was considered to be clinically meaningful. Few subjects had PCR values for any of the haematology and coagulation parameters.

8.5.3.1. Prolactin

In the short term trials, median changes in prolactin from Baseline to last visit across all treatment groups were small and none of the changes were considered to be clinically meaningful. The median change from Baseline to last visit in prolactin in the all brexpiprazole group was higher than in the placebo group (2.73 ng/mL versus -1.46 ng/mL, respectively);[45] and was higher in female subjects than male subjects across all treatment groups. There was no apparent dose effect for changes from Baseline in prolactin for either male or female subjects in the fixed-dose trials. Values of PCR for prolactin (> 1 x upper limit of normal (ULN)) were more frequently observed in the all brexpiprazole group compared with the placebo group for both females and males. The incidence of TEAEs related to prolactin (blood prolactin increased or hyperprolactinemia) was less than 1% in the brexpiprazole treated groups and the placebo group. All of these TEAEs were mild or moderate in severity. The dose of IMP was not changed for any of these subjects due to the increase in prolactin and none had a prolactin level > 3 x ULN. In the long term, controlled trial, median prolactin values decreased from Baseline to the last visit in all treatment groups. None of these changes were reported as TEAEs. In the double blind maintenance phase of this trial, PCR values for prolactin occurred infrequently in both treatment groups. No TEAE meeting the PCR criteria for prolactin was reported. The pattern of median changes from Baseline in the long term, open label trials was similar to the short term trials with larger median changes noted in females than in males. The incidence of PCR values for prolactin was higher for both male and female subjects in the long term, open label trials than in the short term trials. A total of 7 subjects (0.6%) reported TEAEs of blood prolactin increased, 2 of which had an elevation of > 3 x ULN. None of the subjects were discontinued from IMP due to the increase. A search of the clinical database for TEAEs in the SOCs of reproductive system and breast disorders and psychiatric disorders (sexual function related AEs; for example, decreased libido, anorgasmia) for the 7 subjects with TEAEs related to prolactin revealed none with these types of TEAEs in these SOCs. Given the potential relevance of prolactin related side effects in the use of atypical antipsychotic medications with significant dopaminergic activity, these are generally pleasingly low levels of problem, and further specific monitoring does not appear to be required.

8.5.4. Other laboratory tests

8.5.4.1. Creatine kinase

Consistent with known toxicity of atypical antipsychotics, rises in CK and evidence of neuroleptic malignant syndrome like episodes was extensively investigated.

The evaluation of CPK elevation and rhabdomyolysis included a review of TEAEs as well as an assessment of change from Baseline and PCR values for CPK. The TEAEs that were included in the search for rhabdomyolysis and CPK elevation were based on the SMQ for rhabdomyolysis and were the following: blood CPK abnormal, blood CPK increased, blood CPK MM increased, muscle necrosis, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinaemia, myoglobinuria, myopathy, myopathy toxic, and rhabdomyolysis.

The mean change in creatine phosphokinase (CPK) from Baseline to last visit in the short term or long term, controlled trials were similar between brexpiprazole and placebo groups. Few subjects had PCR changes (> 3 x ULN) in CPK. The incidence of PCR changes in the short term trials was 8.8% in the all brexpiprazole group and 6.1% in the placebo group. In the long term, open label trials, the incidence of PCR changes in CPK was similar to the all brexpiprazole group in the short term trials (8.9%). A total of 5 subjects had PCR changes in CPK during the double blind maintenance phase in the long term, controlled trial: 1in the brexpiprazole group and 3 in the placebo group.

[45] These results are from females only.

Rhabdomyolysis was reported as a TEAE associated with CPK in 3 brexpiprazole treated subjects in the short term trials. All 3 events were serious and 2 led to discontinuation of IMP. None of the subjects with TEAEs of rhabdomyolysis were symptomatic, thus there was no objective confirmation of rhabdomyolysis in these subjects. No TEAEs of rhabdomyolysis were reported during the double blind maintenance phase of the long term, controlled trial and the long term, open label trials. Blood CPK increased was reported as a TEAE in 34 subjects in the short term trials, of whom 19 were in the brexpiprazole 2 to 4 mg/day group. One subject in the 2 to 4 mg/day group was discontinued from IMP due to a TEAE of increased blood CPK. There were no TEAEs associated with CPK elevations during the double blind Maintenance phase of the long term, controlled trial. A total of 14 subjects (1.1%) were reported to have blood CPK increased in the long term, open label trials. None were serious, 1 was severe, and 2 resulted in discontinuation of IMP. Half of the subjects had TEAEs of CPK increased that were assessed as possibly related (6 subjects) or related (1 subject) to brexpiprazole.

Although uncommon, these changes lack a current clear explanation and may require further evaluation. The views of the sponsor should be sought, although it is noteworthy in the below section that frank NMS was not reported. It is likely that NMS represents the extreme end of a range of dopamine blockade related neurotoxic reactions and the CK signal may suggest that NMS could occur with the IMP, all be it at a frequency that is extremely low.

8.5.4.2. Neuroleptic malignant syndrome

The TEAEs that were included in the search for NMS were based on the SMQ for NMS and were the following: hyperthermia malignant, neuroleptic malignant syndrome, and serotonin syndrome. There were no subjects in the short term, controlled trials, in any treatment group during the stabilisation or double blind maintenance phase of Trial 331-10-232, or in the long term, open label trials who reported a TEAE related to NMS.

8.5.4.3. Metabolic indices

Metabolic parameters of interest include elevations in glucose and changes in lipids over time, potentially clinically relevant (PCR) changes, and treatment emergent shifts and associated AEs. The emergence of metabolic syndrome (meeting ≥ 3 of the following criteria at a visit: central obesity, dyslipidaemia (elevation in triglycerides and/or decrease in high-density lipoprotein (HDL)), cholesterol, hypertension, and elevated fasting glucose) is also evaluated. There were no remarkable findings for any of the metabolic parameters in either the short term or long term trials. Results were broadly comparable between brexpiprazole and placebo in both the short term and long term, controlled trials.

Mean changes from Baseline to last visit in serum glucose and lipid parameters were small and not clinically relevant across treatment groups and similar between the long term and short term trials. Incidences of PCR values for metabolic parameters were similar between the brexpiprazole groups and the placebo group in the short term, controlled trials, and lower than or comparable to placebo in the long term, controlled trial. The incidences of PCR values for metabolic parameters in the long term trials were generally higher than in the short term trials.

The percentage of subjects with shifts from normal in fasting glucose and lipids from Baseline to the last visit was similar between the brexpiprazole and placebo groups in the short term, controlled trials. There were no patterns observed in the incidence of treatment-emergent shifts in fasting glucose or lipid levels in the short term fixed-dose trials that might indicate a dose effect. The incidence of shifts was generally higher in the long term, open label trials than in the short term trials or the Double blind Maintenance phase of the long term, controlled trial. In the long term, controlled trial, the incidences for all metabolic parameters were higher at the last visit of the Stabilisation phase than at the last visit of the double blind Maintenance phase, except for HDL-cholesterol which was lower.

The incidence of TEAEs associated with blood glucose and lipid parameters was low in the short term and long term, open label trials and 1 subject in each of these trials groups discontinued

from IMP due to a TEAE associated with glucose (long term) or lipids (short- term). In the double blind maintenance phase of the long term, controlled trials, there were no TEAEs related to lipid and glucose parameters in the brexpiprazole group; however, in the stabilisation phase, diabetes mellitus, hyperglycaemia and hypoglycaemia were reported in 1 subject each, and type 2 diabetes mellitus was reported in 4 subjects.

The percentage of subjects with metabolic syndrome was small and similar between brexpiprazole and placebo groups in the short term, controlled trials. In the long term, controlled trials, no subject in either the brexpiprazole or placebo groups developed metabolic syndrome during the double blind maintenance phase. In the long term, open label trials, the percentage of subjects meeting the criteria for metabolic syndrome was low, but higher than in the short term, controlled trials.

In summary the findings in relation to metabolic parameters were essentially consistent with those seen with weight; a relatively low level of concern overall but with some incongruity between the long term controlled studies and the open label studies. It is particularly relevant to note here that the number of subjects exposed to the IMP in the controlled long term study for more than 6 months was relatively low and changes in metabolic parameters may reasonably be expected to take longer to emerge slowly, noting no time analysis was available. There was also no analysis identified that looked at these changes in those who gained a significant amount of weight (≥ 7% increase in body weight).

8.5.5. Electrocardiograph findings and cardiovascular safety

Mean changes from Baseline to last visit were small in magnitude and similar across treatment groups in the short term and long term trials. None of the changes observed in the ECG parameters in any of the trials were considered to be clinically relevant. Other than QT interval increases, the most frequently reported PCR changes overall were ST/T morphological changes, including myocardial ischemia, and symmetrical T-wave inversions, which were reported in a comparable proportion of subjects in the brexpiprazole 2 to 4 mg/day, all brexpiprazole, and placebo groups.

In addition, the effects of brexpiprazole at therapeutic (4 mg) and supratherapeutic (12 mg) doses on QT interval were evaluated in subjects with schizophrenia or schizoaffective disorder in a randomised, double blind, placebo and positive controlled (moxifloxacin), parallel arm Trial 331-10-242. The design of this trial followed the Food and Drug Administration (FDA) 'Guidance for Industry on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Arrhythmic Drugs' and was reviewed by the FDA QT Interdisciplinary Review Team. Design recommendations from the FDA were incorporated into the protocol prior to commencing the trial. The subjects randomised to brexpiprazole received active IMP for 11 days and placebo on Day 12; the subjects randomised to moxifloxacin received moxifloxacin on Day 1 and placebo on Days 2 to 12. While moxifloxacin produced the expected significant changes in individually corrected QT interval (QTcI), none of the changes in QTcI for the supratherapeutic dose of 12 mg brexpiprazole exceeded 5 ms, and none of the associated upper 1 sided 95% confidence intervals (CIs) exceeded the limit of 10 ms. For the lower dose of 4 mg brexpiprazole, none of the associated upper 1 sided 95% CIs in QTcI exceeded the limit of 10 ms except for Hour 6, which was considered a false positive finding. The results in this trial demonstrated no QTc prolongation following therapeutic (4 mg) or supratherapeutic (12 mg) doses of brexpiprazole. In addition, no symptomatic or statistically significant effect of increasing brexpiprazole plasma concentrations on QTcI and QTcF was observed.

Overall, there appeared no specific concerns about significant or occasional major changes in ECG with the IMP.

8.5.6. Vital signs and clinical examination findings

Mean changes from Baseline to last visit for all vital signs measured (heart rate, SBP, and diastolic blood pressure) in the short term and long term trials were unremarkable and none were clinically meaningful. The percentages of subjects with PCR changes in vital signs were low across treatment groups.

In particular, as shown in Table 18 below, changes in blood pressure appeared to be minimal across all schizophrenia trials. In short term, controlled trials, the percentages of subjects with PCR changes in vital sign measurements were low (≤ 1.5%) and similar across groups. No patterns indicative of a dose effect were observed in the fixed dose trials. The percentages of subjects with PCR changes in vital signs (heart rate, SBP, and DBP) were low during the double blind maintenance phase of Trial 331-10-232. No PCR changes in vital signs were reported in more than 1 (1.0%) subject, with the exception of an increase in standing SBP of ≥ 20 mmHg concurrent with an SBP of > 180 mmHg in 2 (1.9%) subjects in the placebo group. There were no reports of orthostatic hypotension during the double blind maintenance phase of the trial. The percentages of subjects with PCR vital sign changes during long term, open label treatment were generally similar to those observed for the brexpiprazole group during double blind treatment in the short term trials.

Table 18: Summary of supine vital signs parameters (safety sample: short term, controlled, long term, controlled and long term, open label trials in schizophrenia)

	Short-term,controlled		Long-term,control		Long-term, open-label
	Brexpiprazole (N=1406)	Placebo (N=624)	Brexpiprazole (N=97)	Placebo (N=104)	Brexpiprazole (N=1265)
Systolic blood pressure (mmHg)					
Mean (SD) Baseline	120.3 (10.6)	121.3 (10.9)	119.6 (10.6)	122.0 (10.2)	120.6 (10.9)
Mean Change (SD) at Last Visit	0.7 (9.6)	0.7 (9.7)	0.7 (7.3)	0.9 (9.7)	1.1 (10.4)
Incidence of subjects meeting PCR criteria for systolic blood pressure (%)					
< 90 mmHg + decrease of ≥ 20 mmHg	0.1	0.0	0.0	0.0	0.16
> 180 mmHg + increase of ≥ 20 mmHg	0.0	0.0	0.0	0.0	0.16
Diastolic blood pressure (mmHg)					
Mean (SD) Baseline	75.8 (7.8)	75.7 (7.6)	74.0 (8.2)	74.7 (8.1)	75.2 (8.2)
Mean Change (SD) at Last Visit	-0.1 (7.5)	0.6 (7.4)	-0.5 (6.9)	0.4 (7.4)	0.6 (8.2)
Incidence of subjects meeting PCR criteria for diastolic blood pressure (%)					
< 50 mmHg + decrease of ≥ 15 mmHg	0.1	0.0	0.0	0.0	0.16
> 105 mmHg + increase of ≥ 15 mmHg	0.1	0.0	0.0	0.0	0.24
Heart rate (bpm)					
Mean (SD) Baseline	73.6 (10.4)	73.4 (10.8)	69.8 (9.7)	72.0 (11.2)	73.4 (10.5)
Mean Change (SD) at Last Visit	1.0 (10.6)	2.1 (11.4)	3.1 (9.3)	2.4 (10.5)	0.1 (10.5)
Incidence of subjects meeting PCR criteria for heart rate (%)					
< 50 bpm + decrease of ≥ 15 bpm	0.1	0.0	0.0	0.96	0.40
> 120 bpm + increase of ≥ 15 bpm	0.0	0.7	0.0	0.0	0.0
Incidence of subjects meeting PCR criteria for orthostatic hypotension (%)					
≥ 20 mmHg decrease in SBP and ≥ 25 bpm increase in heart rate from supine to sitting/standing	0.9	1.5	0.0	0.0	0.67

8.5.7. Weight

The incidence of TEAEs associated with weight increase in the brexpiprazole 2 to 4 mg/day group was 4.7% in the short term, controlled trials, and approximately twice the rate of placebo

(2.4%); however, no subjects were discontinued from IMP due to these TEAEs. Most of the brexpiprazole treated subjects who reported a TEAE associated with weight increase in these trials met the PCR criterion for weight increase. No apparent dose-related increase in weight was noted in the fixed-dose trials. TEAEs associated with weight increase were reported infrequently during the double blind maintenance phase of the long term, controlled trial. Weight increased was the only TEAE associated with weight gain reported in the brexpiprazole group in the maintenance phase of this trial; there were no subjects in the placebo group who had TEAEs associated with weight gain. The percentage of subjects in the brexpiprazole group with a weight increase meeting the PCR criterion (≥ 7% from Baseline) was 5.2% in the double blind maintenance phase compared with 1.0% in the placebo group; 11.3% of subjects met the PCR criterion for weight increase during the stabilisation phase.

In the long term, open label trials, TEAEs associated with weight increase were reported for 8.1% of subjects; however, few subjects discontinued IMP because of these TEAEs. An increase of 2.2 kg in body weight was observed at Week 52 for subjects who completed 52 weeks of treatment. There were no notable differences in the changes in body weight over time in groups by prior treatment, although the increase in weight in the group who received prior treatment with placebo was greater than in the other groups. The percentage of subjects who had a weight increase that met the PCR criterion in long term, open label trials was higher than in both the short term and long term, controlled trials. Most of the subjects who experienced a TEAE associated with weight increase met the criterion for a PCR weight gain. The magnitude of the change in weight from Baseline to last visit was similar between the short term, controlled and long term, open label trials (1.2 kg and 1.1 kg, respectively), and decreased by a small amount of 0.3 kg in the double blind maintenance phase of the long term, controlled trial after an increase of 0.8 kg during the stabilisation phase. A small increase of 0.2 kg in weight was observed in the placebo group in the short term trials, and a decrease of 2.2 kg was noted in the placebo group in the long term, controlled trial.

The conflict between these findings in longer term trials does leave some reservation about the scale of any potential weight gain with the IMP, although the level of weight gain seen in the longer term uncontrolled studies was only a mean of 2.2 kg.[46] Of note, a time analysis suggested the majority of this weight gain occurred in the first 6 months of therapy. When looked at in term of clinically significant weight gain, this discrepancy becomes a bit more obvious. The percentage of subjects who had a weight increase that met the PCR criterion (increase of ≥ 7% in body weight) in the long term open label trials (18.0%) was higher than that in the short term and long term controlled trials (9.8% and 5.2%, respectively, of subjects in the all brexpiprazole group).

Changes in bodyweight parameters from Baseline and last visit for Trial 331-10-232 are shown below in Tables 19 and 20.

[46] Overall the sponsor believes there is an overall moderate weight increase associated with treatment with brexpiprazole. The apparent conflict between the controlled long term data and the open label uncontrolled trials is likely due to the difference in design between these trials. The controlled maintenance Trial 331-10-232 randomised an enriched population of responders to initial brexpiprazole treatment, given the randomised withdrawal design on this trial. The open label trials have a broader inclusion of schizophrenia patients.

Table 19: Mean (SD) change from Baseline in weight, waist circumference, and BMI at last visit in the double blind maintenance phase of Trial 331-10-232 (safety sample)

Parameter (Units)	Timepoint	Mean (SD)	
		Brexpiprazole	Placebo
Weight (kg)	Baseline	81.8 (21.8)	85.9 (23)
	Change at last visit	-0.3 (4.9)	-2.2 (3.6)
Waist circumference (cm)	Baseline	93.4 (17.1)	96.4 (17.4)
	Change at last visit	0.2 (4.9)	-1.1 (3)
BMI (kg/m^2)	Baseline	28.1 (6.7)	29.1 (6.9)
	Change at last visit	-0.1 (1.7)	-0.8 (1.3)

Note: Baseline was defined as last value prior to treatment start. Last visit was defined as the last evaluable value at a scheduled visit.

Table 20: Mean (SD) change from Baseline in weight, waist circumference, and BMI at last visit (safety sample: long term, open label trials in schizophrenia)

Parameter (unit)	Timepoint	Brexpiprazole		
		N	Mean (SD)	Median (Min, Max)
Weight (kg)	Baseline	1255	81 (20.9)	77.8 (39.3, 179.2)
	Change at Week 14	882	1.2 (3.7)	0.8 (-12.7, 26.5)
	Change at Week 26	601	1.6 (5.1)	1.1 (-13.8, 27.7)
	Change at Week 52	377	2.2 (7)	1.6 (-22.8, 30.9)
	Change at last visit	1255	1.1 (5.4)	0.7 (-29.3, 30.9)
Waist circumference (cm)	Baseline	1254	93.1 (16.6)	91 (58, 158)
	Change at Week 14	881	0.7 (4)	0 (-15, 20)
	Change at Week 26	600	1.1 (6.7)	1 (-91, 30)
	Change at Week 52	378	1.7 (6.8)	1 (-21, 27)
	Change at last visit	1254	0.7 (6)	0 (-91, 29)
BMI (kg/m^2)	Baseline	1255	27.7 (6.5)	26.6 (16.1, 69)
	Change at Week 14	882	0.4 (1.3)	0.3 (-4.3, 8.9)
	Change at Week 26	601	0.6 (1.8)	0.4 (-5.1, 9.2)
	Change at Week 52	377	0.8 (2.5)	0.6 (-8.3, 10.3)
	Change at last visit	1255	0.4 (1.9)	0.3 (-10.4, 10.3)

Note: Baseline was defined as last value last value obtained at the visit. Last visit prior to treatment start. Visit analysis value was defined as was defined as the last evaluable value at a scheduled visit.

8.5.8. Extrapyramidal symptoms

There were 2 components of the analysis of EPS: 1) analysis of TEAEs associated with EPS and 2) analyses of assessments using EPS scales: Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

The percentage of subjects who reported ≥ 1 TEAE associated with EPS in the fixed dose, short term controlled trials was higher in the brexpiprazole 2 to 4 mg/day group than in the placebo group. The most frequently reported TEAEs associated with EPS in the brexpiprazole 2 to 4 mg/day dose group were akathisia (5.8%) and tremor (2.8%). Most of the TEAEs associated with EPS were mild or moderate in severity, and few subjects discontinued because of these TEAEs. No subjects in any treatment group had a serious TEAE of EPS.

Treatment emergent akathisia was observed in a small percentage of subjects in both the brexpiprazole 2 to 4 mg/day and placebo groups in the fixed dose trials. No brexpiprazole treated subjects had a serious TEAE or discontinued IMP because of a TEAE of akathisia. There were no reports of tardive dyskinesia in brexpiprazole treated subjects. No clear dose dependency was observed for the incidence of akathisia and parkinsonian events in the brexpiprazole groups. For other types of EPS (dyskinetic events, dystonic events, and total

residual events), the incidence was low (< 2% of subjects) with no difference noted across treatment groups. In the double blind maintenance phase of the long term, controlled trial, TEAEs associated with EPS occurred infrequently in the brexpiprazole group and were generally similar in type and frequency to those reported in the placebo group. Symptoms of akathisia, involuntary movement, or tremor at Baseline were infrequent in both the brexpiprazole group and placebo group. The percentage of subjects who reported ≥ 1 TEAE associated with EPS in the long term, open label trials was lower (8.9%) than in the short term, controlled trials (11.9%). The incidence of EPS related TEAEs in the long term, open label trials was predominantly driven by a higher percentage of subjects with events (mostly akathisia) with no previous exposure to brexpiprazole, the prior placebo (11.8%) and de novo groups (11.2%), compared with the prior brexpiprazole group (7.4%).

Mean scores at Baseline in EPS evaluation scales were similar across brexpiprazole and placebo groups in the short term and long term, controlled trials, and mean changes from Baseline to last visit were small and similar across treatment groups. In the long term, open label trials, mean changes from Baseline for all 3 EPS evaluation scales were small and were similar to mean changes from Baseline in the brexpiprazole treatment groups in both the short term and long term, controlled trials.

A summary of EPS associated TEAEs in the short term controlled trials is shown below in Table 21. Mean change from Baseline in the relevant scales is shown in Table 22.

Table 21: Summary of incidence of TEAEs associated with EPS (safety sample: short term, controlled trials in schizophrenia)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects						
	Brexpiprazole				Placebo (N=624)	ARI (N=50)	QUET (N=153)
	< 2 mg (N=341)	2-4 mg (N=972)	> 4 mg (N=93)	All (N=1406)			
At least one TEAE	28 (8.2)	116 (11.9)	23 (24.7)	167 (11.9)	54 (8.7)	6 (12.0)	14 (9.2)
Total Akathisia Events	13 (3.8)	60 (6.2)	15 (16.1)	88 (6.3)	27 (4.3)	2 (4.0)	6 (3.9)
Akathisia	12 (3.5)	56 (5.8)	14 (15.1)	82 (5.8)	25 (4.0)	2 (4.0)	6 (3.9)
Psychomotor hyperactivity	1 (0.3)	4 (0.4)	1 (1.1)	6 (0.4)	2 (0.3)	0 (0.0)	0 (0.0)
Total Dyskinetic Events	1 (0.3)	3 (0.3)	0 (0.0)	4 (0.3)	4 (0.6)	0 (0.0)	0 (0.0)
Dyskinesia	1 (0.3)	3 (0.3)	0 (0.0)	4 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Tardive dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Total Dystonic Events	4 (1.2)	16 (1.6)	3 (3.2)	23 (1.6)	12 (1.9)	2 (4.0)	1 (0.7)
Dystonia	0 (0.0)	5 (0.5)	0 (0.0)	5 (0.4)	5 (0.8)	0 (0.0)	0 (0.0)
Muscle contractions involuntary	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle rigidity	2 (0.6)	4 (0.4)	2 (2.2)	8 (0.6)	2 (0.3)	2 (4.0)	0 (0.0)
Muscle spasms	2 (0.6)	7 (0.7)	0 (0.0)	9 (0.6)	6 (1.0)	0 (0.0)	1 (0.7)
Total Parkinsonian Events	12 (3.5)	48 (4.9)	9 (9.7)	69 (4.9)	16 (2.6)	3 (6.0)	8 (5.2)
Bradykinesia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Extrapyramidal disorder	4 (1.2)	16 (1.6)	6 (6.5)	26 (1.8)	10 (1.6)	2 (4.0)	1 (0.7)
Parkinsonism	0 (0.0)	4 (0.4)	0 (0.0)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor	8 (2.3)	27 (2.8)	3 (3.2)	38 (2.7)	6 (1.0)	2 (4.0)	7 (4.6)
Total Residual Events	2 (0.6)	1 (0.1)	0 (0.0)	3 (0.2)	1 (0.2)	0 (0.0)	1 (0.7)
Muscle twitching	1 (0.3)	1 (0.1)	0 (0.0)	2 (0.1)	1 (0.2)	0 (0.0)	1 (0.7)
Myoclonus	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Subjects with multiple EPS TEAE were only counted once in total EPS

Table 22: Mean (SD) change from Baseline at last visit, EPS evaluations (safety sample: short term, controlled trials in schizophrenia)

Evaluation	Timepoint	Mean (SD)						
		Brexpiprazole				Placebo	ARI	QUET
		< 2 mg	2-4 mg	> 4 mg	All			
SAS	Baseline	0.7 (1.4)	0.6 (1.5)	1 (2.2)	0.7 (1.5)	0.7 (1.9)	0.9 (1.6)	0.5 (1.4)
	Change at last visit	-0.2 (1.3)	-0.1 (1.4)	0.2 (2.3)	-0.1 (1.4)	-0.1 (1.4)	-0.1 (1.6)	-0.1 (1)
BARS	Baseline	0.1 (0.36)	0.12 (0.43)	0.18 (0.53)	0.12 (0.42)	0.15 (0.5)	0.3 (0.65)	0.1 (0.32)
	Change at last visit	0 (0.43)	0.01 (0.48)	0.23 (0.76)	0.02 (0.5)	0 (0.5)	0 (0.64)	-0.03 (0.38)
AIMS	Baseline	0.36 (1.06)	0.32 (1.08)	0.58 (1.56)	0.35 (1.12)	0.33 (1.21)	0.54 (1.13)	0.23 (0.9)
	Change at last visit	-0.16 (0.83)	-0.06 (0.94)	-0.13 (1.18)	-0.09 (0.93)	-0.01 (0.84)	-0.04 (0.99)	-0.08 (0.61)

Note: The SAS Total Score can range from 0 to 40. The BARS global clinical assessment of akathisia ranges from 0 to 5. The AIMS Total Score can range from 0 to 28. Baseline was defined as last value prior to treatment start. Last visit was defined as the last evaluable value at a scheduled visit.

The lack of correlation between the reported TEAE of akathisia and any change in the BARS scores is of note and could be interpreted as consistent with either the lack of severity of the symptom, its overall frequency or even the difficulties inherent in its subjective rating. The minimal rate of discontinuation because of akathisia is noteworthy, likely to be attributable to the titration regime and this is highly relevant to the potential clinical place of the compound.

8.6. Other safety issues

8.6.1. Safety in special populations

Apart from the previously discussed ongoing trial in adolescents, the only specific utilisation data of IMP in special populations was considered within the pharmacokinetics section of this report.

The planned analysis of the effect of intrinsic factors (age, gender, and race) on TEAE Incidence from the schizophrenia short and long term data set, which included a Breslow-Day test of the homogeneity of the TEAE odds, ratios, was not performed because no TEAE in the schizophrenia short term trials satisfied the predefined criteria for 'common', that is incidence ≥ 5% in the all brexpiprazole group and at an incidence ≥ 2 x placebo. Visual inspection of the available data did not suggest many meaningful clinical differences despite the pharmacokinetic data suggesting potential differences in overall exposure in women and those aged over 55 years old on a dose equivalent basis.

8.6.2. Drug-drug interactions

Results of drug-drug interaction trials have confirmed that CYP3A4 and CYP2D6 isozymes are primarily responsible for the metabolism of brexpiprazole, and thus results of trials related to inhibition of these isozymes are presented in this section. A complete summary of all drug-drug interaction trials conducted with brexpiprazole are provided in SCP, and is discussed in the above pharmacodynamics section of this report.

8.7. Post-marketing experience

The dossier did not contain any specific information on post-marketing experience, noting that the IMP has thus far only been made available in the USA. An update could be sought from the sponsors.

8.8. Evaluator's overall conclusions on clinical safety

Overall the dossier demonstrates an appropriate level of information on clinical safety, evaluated utilising adequate and contemporary methodology. The overall exposure to the compound in the population with the requested indication of schizophrenia is adequate with the caveat that the longer term exposure (particularly ≥ 6 months) in the controlled trials is somewhat limited. This is offset by the availability of data from a number of longer term, open label trials in schizophrenia.

The most likely impact of this relative weakness in the dataset in terms of safety is the evaluation of safety issues more likely to become relevant with long term exposure. Of these, the most likely relevant is the metabolic issues which are in general, one of the major safety concerns with this class. Indeed, there does appear to be some conflict between the weight gain and metabolic parameter data between the longer term controlled data and the open label data, with the latter suggesting a small metabolic signal whereas the former suggest essentially none. Any concern in this area could be added to by the clearly higher rates of weight gain in particular seen in the adult MDD trials. This does need to be interpreted with some caution however: this is not the requested indication, rates of weight gain seen in affective disordered patients are higher with most atypical antipsychotics trialled in such populations than in those with schizophrenia and even the strongest interpretation of the available data does not suggest this IMP has a concerning metabolic signal relative to the worst agents in the atypical class. The reviewer noted the occurrence of 1 case of diabetic ketoacidosis in the available dataset that was judged as potentially related to the IMP although after reviewing the available information, this level of attribution does appear reasonable and the single case not sufficient to warrant further concern at this time. Indeed, it would have been surprising had that been found given its close chemical relationship to aripiprazole, clearly one of the metabolically safest of the atypical antipsychotics.

Within the TEAE data the presence of akathisia as an early treatment phase issue is relatively clear, and this is supported by the formal measurement.[47][48] Again, given the relatively high frequency of this issue with the related compound aripiprazole, this is not surprising and indeed consistent with the suggested receptor profile. Overall the rates of akathisia as a serious TEAE are not particularly high, and rates of discontinuation due to akathisia also not particularly high. This could be seen to suggest that the dose titration regime recommended in the PI and utilised in many but not all of the trials is appropriate and probably reduces this rate. Although not a direct criterion for evaluation, an underestimation of the impact of early treatment akathisia and an aggressive initial titration recommendation with aripiprazole had a significant impact on the utilisation of that compound, despite the very important long term value of its metabolic safety.

The presence of a small signal with events of rhabdomyolysis and/or elevation of CK suggest that the compound is capable of inducing neuromuscular reactions that could be considered part of the full spectrum of neuroleptic toxicity, even in the absence of any confirmed cases of full blown NMS. This is entirely consistent with the receptor binding profile of the compound and the available safety and post marketing data with other compounds within class that have a similar binding profile and the overall rate is low. It would be of some value never the less to

[47] This issue was further addressed through a clinical question to the sponsor. For details of this question, and the evaluator's response, see Section 12, Question 8: 'Would the sponsor consider some expansion of the wording around akathisia within the PI and CMI, noting that higher dose and rapid dose escalation is likely despite their appropriate advice not to.'

[48] Sponsor comment: Akathisia is reported at higher incidence after 6 weeks of treatment with brexpiprazole as compared to placebo. However, in early phase of treatment, for exampleafter 1 week, the incidence is actually comparable to placebo. The relatively lower level of akathisia seen with brexpiprazole demonstrated in the clinical programme, even with faster titration, is believed to be related to the pharmacological profile as described in the non-clinical pharmacology documents.

request an update from the sponsor about all post marketing experience in the USA and particularly ask if there is any further signal in this area.

Other aspects of note include what appears to be a very low level of electrocardiographic impact and pleasingly low levels of prolactin elevation with this compound. Elevations of hepatic enzymes overall appear low, despite the presence of 3 discontinuations of IMP due to such irregularities in the short term trials, and the evaluator does not think they constitute sufficient reason to recommend further monitoring.

Given this overall positive interpretation of the safety data, it is also worth reiterating the obvious fact that the available safety data in schizophrenia is almost entirely in adults and conclusions about safety in children and adolescents and the elderly with schizophrenia cannot be drawn.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The first round assessment of benefits, and the strengths and uncertainties of the data, is shown below in Table 23.

Table 23: First round assessment of benefits

Benefits	Strengths and uncertainties
Schizophrenia is an uncommon but not rare disease effecting 1% of the population. Currently available treatments are somewhat effective, with most sharing a similar rate of improvement in positive symptoms of illness but modest impact on negative and cognitive symptoms. Any new treatment should at least share this efficacy, noting that the predictive capacity to identify which individual agent will benefit which patient is currently limited. Rates of relapse in schizophrenia are high, presumably partly reflective of the neurobiology of the disease, risk factors such as substance abuse but also poor adherence to otherwise effective antipsychotic therapy. New therapies should thus be not just acutely effective (the usual basis for judgement) but show evidence of relapse prevention and the capacity through good tolerability to potentially contribute to improving adherence. With increasing evidence of the reduced life expectancy in patients with schizophrenia (approximately 15 to 20 years in Australia) that is predominantly due to metabolic diseases, new agents should also show a strong profile in this area.	Brexpiprazole has been demonstrated to show appropriate levels of efficacy in a number of acute trials in schizophrenia. The trials are of a standard design, apart from the setting of a 30% improvement in PANSS scores as being indicative of response, arguably a tougher test than is sometimes used. These positive findings come despite a relatively high placebo response rate in some of the trials. The controlled, longer term data is also supportive of efficacy and although only one long term controlled study is available, such data is difficult to obtain. Brexpiprazole also appears to have a relatively favourable safety profile, with expected rates of akathisia which led to few withdrawals when using the standard titration regime. Its metabolic profile also appears generally favourable, although not completely clean certainly amongst those atypical antipsychotics with a more favourable profile.

9.2. First round assessment of risks

The first round assessment of benefits, and the strengths and uncertainties of the data, is shown below in Table 24.

Table 24: First round assessment of risks

Risks	Strengths and uncertainties
Central to treatment risk in this population is the often acute nature of presentation which may frequently involve polypharmacy, rapid dose escalation in individuals with schizophrenia and multiple comorbidities. The risks of overdose are real with any pharmacotherapy in this setting. The other longer term risk with the atypical antipsychotics is the underestimation of the level of metabolic risk due to the relatively short term nature of pre-release data for a condition that will often involve very long term therapy.	The available dataset with brexpiprazole shares the usual weaknesses and strengths in this regard. There is little data on comorbid populations currently available. One of the particular risks that may occur with this compound will be more rapid dose escalation than recommended in the PI, particularly given the 'lowish' level of sedation seen with the compound. This is highly likely to produce higher rates of akathisia and intolerability and ultimately this may limit the acute utility of the drug. The uncertainty around the level of metabolic impact when comparing the 2 forms of longer term data available [49](controlled or open) does leave some room for uncertainty about the exact level of concern re metabolic impact.

9.3. First round assessment of benefit-risk balance

On the above basis, the dossier contains evidence that indicates brexpiprazole has an adequate risk benefit ration that is comparable to that of other currently available atypical antipsychotics. Importantly, the probably quite favourable metabolic profile is desirable as the emphasis on better long term physical health in individuals with schizophrenia is increasingly reflected in contemporary guidelines where agents such as olanzapine are now considered second line therapy.

10. First round recommendation regarding authorisation

The recommendation of the evaluator is to authorise brexpiprazole for the indication of schizophrenia.

[49] Given the proposed titration in the PI which allows for a high level of tolerance, and given supplementary evidence that even a faster titration would not adversely impact the tolerability profile, the sponsor believes this is not likely to be a factor limiting the acute utility of the drug.
This issue was further addressed through a clinical question to the sponsor. For details of this question, and the evaluator's response, see Section 12, Question 8: *'Would the sponsor consider some expansion of the wording around akathisia within the PI and CMI, noting that higher dose and rapid dose escalation is likely despite their appropriate advice not to.'*

11. Clinical questions

11.1. Pharmacokinetics

1. It would seem likely that brexpiprazole will be used off label for the treatment of manic/hypomanic symptoms in bipolar disorder. Therefore, studies on the effect of the drug on the PK of lithium and other mood stabilisers and vice versa would seem to of interest. Does the sponsor have such studies or any in vitro data that would suggest an interaction or otherwise with such medicines?
2. There was no PK study or combined PK/PD study of the potential for an interaction between brexpiprazole and alcohol. What are the specific recommendations for the use of alcohol? Is this based on any PK/PD study?

11.2. Pharmacodynamics

3. There were no studies of ascending single doses of brexpiprazole reporting on the psychomotor or cognitive effects, on the ability to drive, or to operate machinery either in healthy volunteers or patients with schizophrenia. Does the sponsor have any data with respect to the effects on standardised tests of psychomotor, cognitive performance or specific tasks related to the ability to drive after single or repeated doses?

11.3. Efficacy

4. Does the sponsor have any thoughts as the reason(s) behind the higher placebo response rate seen in a number of the trials, obviously examining the question as to whether this makes any comment about quality of trial that is not immediately obvious?
5. Does the sponsor have any further long term data available since data lock given the availability of only one long term controlled study in subjects with schizophrenia in the dossier?

11.4. Safety

6. Is there any update from post marketing surveillance in the USA or the Adolescent trail that was not complete at the time of submission? Although not likely to be critical to approval, the post marketing surveillance may inform further about uncommon but serious issues such as NMS and the adolescent trial is clearly of interest.
7. The pre-clinical findings indicated that brexpiprazole seemed to accumulate in the eye as well as having an affinity for melanin. While the difficulty of studying such an effect in human populations is appreciated this potential effect did not appear to have been taken into account in the PK trials. For example, were any fundoscopic examinations conducted and what were the results of these? Given the propensity for some other antipsychotics (mainly phenothiazines) to cause retinal pigmentation and their affinity for melanin it would seem that this effect needs to be addressed in the longer term clinical trials (if it has not already been done). Information on this effect with aripiprazole (a closely related compound) might be informative. The issue is not mentioned in the PI or CMI.

11.5. PI and CMI

8. Would the sponsor consider some expansion of the wording around akathisia within the PI and CMI, noting that higher dose and rapid dose escalation is likely despite their appropriate advice not to.

11.6. Additional expert input

No further advice recommended at this point.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics

12.1.1. Question 1: Pharmacokinetic effect of brexpiprazole on mood stabilisers

'It would seem likely that brexpiprazole will be used off label for the treatment of manic/hypomanic symptoms in bipolar disorder. Therefore, studies on the effect of the drug on the PK of lithium and other mood stabilisers and vice versa would seem to be of interest. Does the sponsor have such studies or any in vitro data that would suggest an interaction or otherwise with such medicines?'

12.1.1.1. Evaluator's comments

The applicant acknowledges the lack of specific studies. A description is given of relevant metabolic pathways for both brexpiprazole and the major mood stabilisers that provide a credible explanation as to the low likelihood of interaction. Given the indication applied for this is considered an adequate response but the issue may require further examination if a subsequent application is made for other indications such as bipolar disorder related indications or MDD.

12.1.2. Question 2: Potential for interaction between brexpiprazole and alcohol

'There was no PK study or combined PK/PD study of the potential for an interaction between brexpiprazole and alcohol. What are the specific recommendations for the use of alcohol? Is this based on any PK/PD study?'

12.1.2.1. Evaluator's comments

The applicant acknowledges there is no direct data available which, it should be acknowledged, is not uncommon in this situation. The applicant describes the plan to place an appropriate warning against taking alcohol whilst using brexpiprazole in the PI and CMI. This represents an adequate response.

12.2. Pharmacodynamics

12.2.1. Question 3: Ability to drive and operate machinery

'There were no studies of ascending single doses of brexpiprazole reporting on the psychomotor or cognitive effects, on the ability to drive, or to operate machinery either in healthy volunteers or patients with schizophrenia. Does the sponsor have any data with respect to the effects on standardised tests of psychomotor, cognitive performance or specific tasks related to the ability to drive after single or repeated doses?'

12.2.1.1. Evaluator's comments

The applicant acknowledges the lack of specific data in this area, which does appear an unfortunate omission. The applicant provides a summary of data on relevant treatment emergent adverse events and cognitive data but these cannot be considered entirely equivalent. The applicant describes the plan to provide an appropriate caution in the PI and CMI as well as additional information consistent with the US PI related to somnolence and related adverse events. The only alternative actions available are to insist on the availability of such data, which

would seem to constitute an unreasonable delay at this point, or argue for a more definite warning. On balance, this would also appear unreasonable given the TEAE data.

12.3. Efficacy

12.3.1. Question 4: Placebo response

'Does the sponsor have any thoughts as the reason(s) behind the higher placebo response rate seen in a number of the trials, obviously examining the question as to whether this makes any comment about quality of trial that is not immediately obvious?'

12.3.1.1. Evaluator's comments

The applicant provides a broad but appropriate response, suggesting that the higher placebo response seen in some of the trials is consistent with a trend towards higher placebo response in schizophrenia trials over the last decade. The applicant does not describe any specific factors relevant to the brexpiprazole trials. As the benefit of brexpiprazole in schizophrenia is accepted, there appears little need for further enquiry.

12.3.2. Question 5: Long term data

'Does the sponsor have any further long term data available since data lock given the availability of only one long term controlled study in subjects with schizophrenia in the dossier?'

12.3.2.1. Evaluator's comments

The applicant does not add any data. Whilst further controlled data would be valuable, the efficacy of brexpiprazole in schizophrenia is accepted based on the available data.

12.4. Safety

12.4.1. Question 6: Post-marketing surveillance

'Is there any update from post marketing surveillance in the USA or the adolescent trial that was not complete at the time of submission? Although not likely to be critical to approval, the post marketing surveillance may inform further about uncommon but serious issues such as NMS and the adolescent trial is clearly of interest.'

12.4.1.1. Evaluator's comments

The applicant has helpfully provided the 5 Periodic Adverse Drug Experience Reports available since brexpiprazole became available in the USA, still the only country in which it is approved. These reports do not yield any data that changes the risk estimation provided in the first round evaluation. The applicant also indicates that there is no significant data available from the adolescent trial at this point. This information does thus not materially influence the risk benefit analysis outlined in the first evaluation.

12.4.2. Question 7: Effect on eye

The pre-clinical findings indicated that brexpiprazole seemed to accumulate in the eye as well as having an affinity for melanin. While the difficulty of studying such an effect in human populations is appreciated this potential effect did not appear to have been taken into account in the PK trials. For example, were any fundoscopic examinations conducted and what were the results of these? Given the propensity for some other antipsychotics (mainly phenothiazines) to cause retinal pigmentation and their affinity for melanin it would seem that this effect needs to be addressed in the longer term clinical trials (if it has not already been done). Information on this effect with aripiprazole (a closely related compound) might be informative. The issue is not mentioned in the PI or CMI.'

12.4.2.1. Evaluator's comments

The applicants largely explain the ocular findings in the non-human studies as an artefact of ageing animals being studied (further explained in the response to the Nonclinical report). However, they acknowledge there are no human ophthalmologic studies, particularly in relation to longer term use which might be more likely to show any issue of retinal pigmentation. This question thus remains a somewhat open one, all be it with only a hypothetical risk identifiable.

12.5. PI/CMI

12.5.1. Question 8: Akathisia

'Would the sponsor consider some expansion of the wording around akathisia within the PI and CMI, noting that higher dose and rapid dose escalation is likely despite their appropriate advice not to.'

12.5.1.1. Evaluator's comments

The applicants present previously identifiable data showing more clearly a relatively small increase in rates of akathisia relative to placebo for doses within the recommended dose range. They also compare those trials with faster titration to those with more gradual titration, as implied in the question, and demonstrate there is relatively little difference. In the single study looking at doses above the recommended dose range, the rates of akathisia are significantly higher but it would appear unreasonable to utilise this data to create a higher level of warning.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of brexpiprazole in the proposed usage are unchanged from those identified in Section 9, above.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of brexpiprazole in schizophrenia are largely unchanged from those identified previously in Section 9, above, with the exception of the concerns stated in relation to the risk of the akathisia. Based on the interpretation of the previously outlined data contained in the applicant's response (see Question 8, above) this risk is considered of lower concern.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of brexpiprazole, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

Approval of brexpiprazole is recommended for adult patients with schizophrenia.

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